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MINIREVIEWS

Weak D phenotype in transfusion medicine and obstetrics: Challenges and opportunities

Prasanna Bharathi Sainath, Velmurugan Ramaiyan

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Prasanna Bharathi Sainath, Department of Pharmacology, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Chennai 602105, Tamil Nādu, India

Velmurugan Ramaiyan, Department of Pharmacy, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Chennai 602105, Tamil Nādu, India

Corresponding author: Velmurugan Ramaiyan, PhD, Professor, Department of Pharmacy, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, NH 48, Chennai 602105, Tamil Nādu, India. ramaiyan.dr@gmail.com

Abstract

The Rh blood group system, especially the D antigen, is crucial in transfusion medicine and obstetrics. Weak D phenotypes, caused by mutations in the Rhesus D antigen (RhD) blood group (*RHD*) gene, result in reduced antigen expression, posing challenges in serological testing and clinical management. Variability in detection methods leads to inconsistent results, making accurate classification difficult. Molecular techniques like polymerase chain reaction and DNA sequencing have significantly improved the identification of weak D variants, offering more reliable transfusion strategies and reducing the risk of alloimmunization. However, challenges such as lack of standardized protocols, cost constraints, and population-specific variations remain. In obstetrics, proper management of pregnant women with weak D is essential to prevent hemolytic disease of the fetus and newborn. Non-invasive prenatal testing using cell-free fetal DNA shows promise in predicting RhD incompatibility and minimizing unnecessary Rh immune globulin administration. Future advancements in high-throughput genotyping and discovery of novel *RHD* alleles could enhance RhD testing accuracy and efficiency. Standardizing *RHD* genotyping and adopting genotype-based management strategies for Rh immune globulin therapy and red blood cell transfusions will improve patient safety and clinical outcomes. This review examines the molecular basis, challenges, and future prospects in weak D phenotype management.

Key Words: Weak D phenotype; Rhesus antigen; RhD blood group genotyping; Allele; Transfusion; Allo-immunization; Pre-natal; Non-invasive prenatal testing; Rhesus immunoglobulin

Core Tip: In this review, we explore the weak D phenotype, caused by Rhesus D antigen (RhD) blood group allele variations, which reduces RhD expression on red blood cells, impacting transfusion strategies and anti-D immunization risks. Molecular and novel genotyping techniques may be necessary for exact identification, and mitigate the risk of alloimmunization in these weak D traits. Implementation challenges such as standardization and financial constraints are quite prevalent in several countries. Hence it emphasizes the importance of accurate weak D phenotype identification and the potential of inculcating molecular techniques in transfusion medicine and obstetrics.

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INTRODUCTION

Recently a 50-year enigma surrounding the AnWj antigen has led to the discovery of a new system, myelin and lymphocyte protein, thereby modifying the overall blood group system to 47. This breakthrough unraveled the unsolved antigen's function and importance in the diagnostic typing of blood groups[1]. Clinically, the Rh blood group system is one of the quite significant among the discovered 36 systems of blood groups following ABO[2]. The Rh system of blood groups is intricate and consists of over 40 antigens, of which the following five C, c, D, E, and e are clinically relevant. A couple of the autosomal dominant genes on chromosome 1, Rhesus D antigen (RhD) blood group (*RHD*) and RhCE blood group, express these five Rh antigens. Among these, the D antigen is exceptionally ubiquitous and susceptible to immunity. As a result, it plays an integral role in immunohematology and blood processing[3]. It is well-known that the existence or missing of the D antigen on the outer layer of erythrocytes was determined as Rh-positive or negative, respectively[4].

A keen interest in Rh antigen took importance in a RhD-negative woman who builds anti-D in forthcoming conception with an RhD-positive newborn, which encompasses the potential for death and disability termed as erythroblastosis fetalis. After introducing the concept of advancing anti-D [Rh□(D) immune globulin (RhIG)] in those mothers either at 28 weeks of gestation or within 72 hours of parturition anticipated the likelihood of illness. Therefore, in cross-matching any blood groups, Rh compatibility is of great importance to rule out the chance of Rh-isoimmunization reactions[5,6]. Then the possibility of infusing D + red blood cells (RBCs) in a dire circumstance becomes obsolete if a RhD-negative person has been pre-sensitized, and transfer of solely D-RBCs remains mandatory forever[7].

Weak D antigen expression is associated with hemolytic disease of the fetus and newborn (HDFN); however, its impact on clinical outcomes in RhD-negative individuals is not well understood. Additional research is required to assess the influence of weak D antigen expression on immune responses and antibody development, along with the possible long-term health implications for RhD-negative individuals. The main aim of this literature-based review was to seek the mode of inheritance of weak D antigen in the RhD blood group system and how despite the challenges, *RHD* genotyping and weak D detection have the potential to improve patient outcomes and safety in transfusion medicine.

POLYMORPHISM IN THE D VARIANT OF RH ANTIGEN

Though several antigens of this system are yet unexplored, the clinically recognized 5 agglutinin which shows polymorphisms has transiently deep-rooted in our community transfusion risk. Therefore, thoroughly researching the practical implications involved in managing such variant agglutinin would be essential. Substantial heterogeneity was noted in the D phenotype due to deletions and missense mutations[4,8-10]. Perhaps the regular custom wasn't successful after encountering a case in 1946 where erythrocytes failed to aggregate using the usual anti-D, rather agglutinated with alternative anti-D sera. From then, the traits with this newer version of D agglutinin were designated as Du by Stratton [11,12]. What if a Rh-ve mother or any Rh-ve recipient receives blood from a Du donor? They will be easily prone to unwanted RhD alloimmunization. This questioned the credibility of routine antigen testing and the probability of managing the complication in those individuals. In the United States, regulations were established concerning Rh-ve mothers, necessitating that erythrocytes from donors who at first examined negative for anti-D undergo reconfirmation employing antiglobulin, referred to as an "indirect anti-globulin test or Coomb's test"[11,13-15].

However, this policy was in clinical practice only for donors and not applied to recipients who preliminarily tested to be D-ve by anti-D as it ensures that they were not pre-sensitized. In due course, certain novel developments in biological research techniques have enabled the delineation and molecular classification of D^U antigens into three phenotypes: Weak D, partial D, and DEL variants. Among them, the weak D variant acquired prominence in certain cases of transfusion and did not omit to underplay its part in obstetric medicine as well[11]. "Weak D" simply implies the quantitative decline of the D agglutinin. The weak D phenotype is caused by various *RHD* alleles encoding aberrant RhD proteins, resulting in reduced RhD expression in RBCs[16,17]. Molecular studies have revealed that most if not all, weak D phenotypes carry altered RhD proteins, which contradicts the previous belief that they express complete D antigens[18]. This genetic diversity has significant implications for transfusion strategies and anti-D immunization risks.

MOLECULAR BASIS OF WEAK D PHENOTYPE

Studies suggest that D agglutinin is an assembly made up of numerous antigenic determinants (epitopes). The Rh factors are peptides (12-pass on transmembrane proteins with 6 extracellular/intracellular turns) coded by the *RHD* and RhCE blood group genes at the proerythroblastic stage. This D peptide comprises 417 amino acids[19]. Wagner *et al*[18] in 1999 demonstrated that point modifications within the *RHD* gene lead to amino acid alterations across the membrane and inner domains of the D antigen, impacting its inclusion and consequently its surface population density, often below 5000 D antigens per RBC[18,20]. A study utilizing flow cytometry found that weak D individuals exhibited an antigen expression preferably tenfold fewer than that of D people[21].

Hence, the biologically defined weak D subtype is a form of the RhD peptide characterized by a change in amino acid sequence in the structure, resulting in a reduced expression of D antigen, as illustrated in Figure 1[11]. The occurrence of altered levels of D agglutinin has been postulated by three genetic mechanisms: Inheritance of the *RHD* gene by the individual, who encodes for a poorly transcribed D agglutinin; existence of the C agglutinin in the trans orientation on contrary genomes, exemplified by the Dce/dCe genotype. It was rather prevalent among individuals of African descent; Could have emerged while any of the epitopes of the D antigen are lost, commonly referred to as the "partial D antigen", and may become alloimmunized if infused with D-positive blood that has the lost epitope[19].

Initially, a cohort of 16 unique weak D types was identified; however, the cumulative sum of it, right from their subgroups ranging, currently surpasses 80. The alterations are believed to elicit conformational complications during the assembly of the peptide into the erythrocyte membrane, perhaps hindering peptide convergence, palmitoylation, or the attachment of the peptide to the proerythroblast framework. Consequently, the quantity of D antigen presented on the surface of the erythrocyte diminished, although the D agglutinin on it stays mostly unaltered in volume. Out of more than 50 possible mutations, the particularly prevalent being the Val270Gly variant classified as type 1, resulting in reduced D expression[22].

CHALLENGES IN WEAK D DETECTION

The immediate spin tube approach is commonly used in finding the D antigen employing anti-human globulin, notably polyspecific Coomb's serum (anti-human globulin and monoclonal anti-C3d), in the indirect agglutination test[4]. Weak D traits in serology are typically identified if a gestational mother, probable infusion beneficiary, or donor of blood undergoes regular RhD typing. In such cases, a less effective degree of erythrocyte aggregation (≤ 2 +) than anticipated when utilizing potent anti-D antisera (Monoclonal IgM or a combination of IgG and IgM) reagents (3 + to 4 +) is revealed. When a medical laboratory labels a specimen of blood as D (+), despite previous evidence indicating a RhD type of D (-), weak D serological traits are kept tested[11].

Technically, detecting weak D by serology is tough. Traditional serological techniques may fail to reliably identify weak D variations, misclassifying individuals as RhD negative when they are actually weak D positive. Studies have demonstrated that regular serological typing might miss weak D types, especially in cases of mixed-field agglutination, complicating results interpretation[23,24]. Furthermore, using different monoclonal antibodies can result in inconsistent results, since certain reagents may not detect the weak D antigen due to the presence or absence of specific epitopes[25,26]. This inconsistency necessitates the use of molecular genotyping approaches, which can provide a more precise classification of weak D symptoms while reducing the hazards associated with inaccurate typing[27,28].

Molecular techniques have significantly advanced the detection and characterization of weak D variants in the Rh blood group system. Polymerase chain reaction (PCR) and DNA sequencing have become essential tools for identifying specific mutations in the *RHD* gene responsible for weak D phenotypes. These methods have allowed researchers to classify weak D types more accurately and discover new variants, such as weak D types 31, 71, 72, and 82 as well as weak D types 122 and 149[29-31].

Interestingly, the prevalence and distribution of weak D types varies among populations as shown in Table 1[32-37]. In Taiwanese individuals, four types of weak D have been identified, with mutations at codons 10, 174, 270, and specifically GGT to GAT mutation at 282[16]. In contrast, a study in Southwestern Germany found that more than 90% of weak D were types 1, 2, or 3, with distribution differences between regions[38]. Similarly, a study in South Egypt found that weak D Type 4 was the most common, followed by Type 3[27]. Novel weak D types continue to be discovered, such as weak D59 in a Chinese individual and weak D54 in another study[30,39]. This highlights the importance of population-specific molecular studies for accurate typing and transfusion strategies. Molecular advancements have greatly improved our understanding of weak D variants and their genetic basis. These techniques complement serological methods and provide more precise identification of weak D types, which is crucial for safe blood transfusion practices and prevention of alloimmunization[31].

GENOTYPING IN HAEMATOLOGY

Genotyping has emerged as a valuable tool in managing weak D phenotypes. Molecular testing can accurately identify the weak D type, allowing for more informed transfusion decisions. For instance, genotyping can differentiate between weak D types that are unlikely to cause immunization (such as types 1, 2, and 3) and those that may pose a risk (such as types 4.2 and 7)[40,41]. Techniques such as PCR and multiplex ligation-dependent probe amplification have been developed to identify specific *RHD* alleles, allowing for a more precise classification of RhD status[42,43]. The imple-

Table 1 Clinical Interpretation of widespread weak D in distinct groups

Number	Ethnic group	Weak D subtypes	Clinical interpretation	Ref.
1	Caucasian	Weak D types 1, 2, 3	Can be treated as D-positive for RhIG administration and transfusion	[32, 34]
2	Asian	Asia type DEL (*RHD* 1227 G > A)	Appears D-negative in conventional serology but can be treated as D-positive	[34]
3	Iranian	Weak D type 15	Most prevalent; weak D types 1, 2, and 3 account for 15% of cases	[33]
4	Brazilian	Weak D types 1, 2, 3, 4	Most frequent in descending order; presence of both caucasian and arican D variants	[35]
5	Australian	Weak D types 1, 2, 3	Found in 75% of weak D samples; some other types (1.1, 5, 15, 17, 90) showed partial D-epitope profiles	[36]
6	Chinese	Various	45 *RHD* alleles were identified, including 11 novel variants; 3.5% carried DEL alleles	[37]

RHD: Rhesus D antigen blood group.

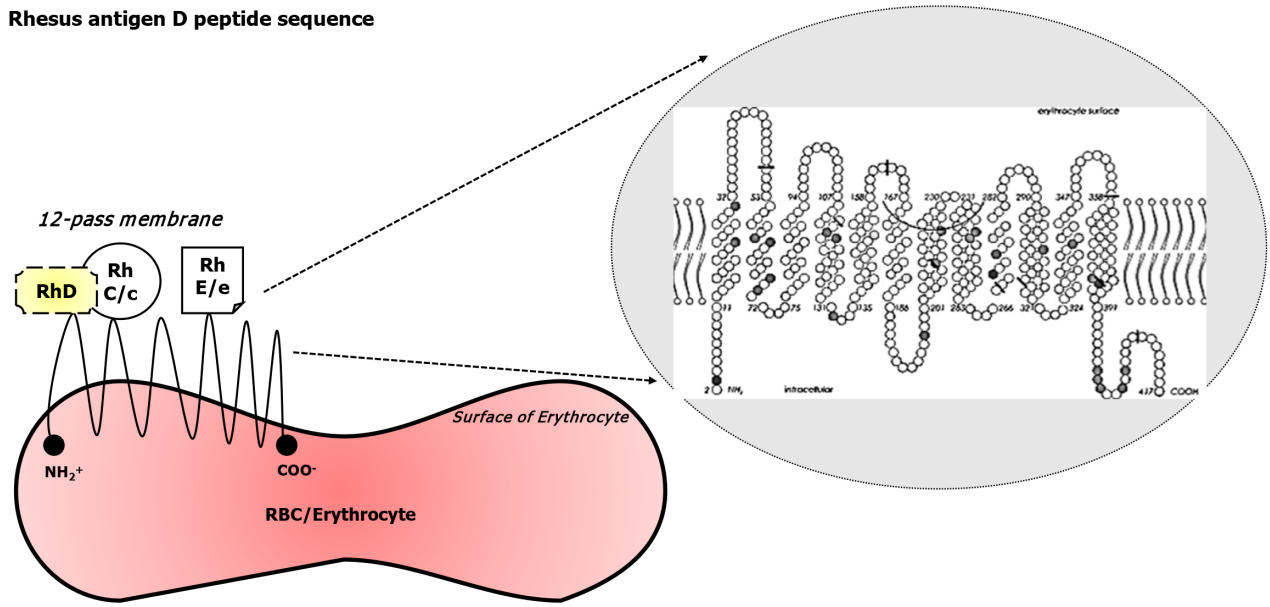

Figure 1 Rhesus antigens locus in the 12-pass membrane of the erythrocyte and its amino acid sequence[11]. Citation: Sandler SG, Chen LN, Flegel WA. Serological weak D phenotypes: a review and guidance for interpreting the RhD blood type using the *RHD* genotype. *Br J Haematol* 2017; 179: 10-19. Copyright © The Authors 1999-2025. Published by John Wiley and Sons, Inc. RhD: Rhesus D antigen; RBC: Red blood cell.

mentation of *RHD* genotyping in clinical practice has been shown to reduce unnecessary RhIG administration in pregnant women with weak D phenotypes, thus improving patient care and reducing healthcare costs[44,45]. Furthermore, the systematic genotyping of pregnant women with weak D phenotypes has been recommended to optimize RhIG prophylaxis and minimize the risk of HDFN as shown in Table 2[11,32,45-53].

One significant development is the application of *RHD* genotyping to help determine whether D-positive RBC units can be transfused to patients who have developed unexpected anti-D antibodies. This approach is particularly beneficial for patients with sickle cell disease, who frequently require transfusions and may develop anti-D antibodies due to exposure to altered Rh proteins. Studies suggest that after anti-D alloantibodies become undetectable in plasma for at least six months, some D-positive patients can safely receive D-positive transfusions. This finding could help reduce the demand for Rh-negative units, which are limited in availability. Moreover, high-throughput sequencing and advanced molecular techniques are improving the identification and classification of weak D variants, allowing for more personalized transfusion strategies. New assays can identify a broader range of weak D types, including rare variants that were previously challenging to detect[46].

OBSTACLES IN *RHD* GENOTYPING

Despite the clear benefits of *RHD* genotyping, several challenges hinder its widespread adoption in clinical practice. One

Table 2 Summary of the challenges and opportunities in managing weak D phenotypes and the importance of Rhesus D antigen blood group genotyping and standardized practices for improved patient care and resource management

Number	Aspect	Challenge	Opportunities	Ref.
1	Serological testing	Variable results and interpretations across laboratories. Discrepancies between automated gel and manual tube testing	Standardization of testing methods and interpretation guidelines. Use of multiple testing methods to improve accuracy	[32, 50]
2	RhD interpretations	Inconsistent reporting terms are used to interpret weak D-reactive maternal RhD types. Risk of misclassification of partial D as weak D	Development of consistent immunohematologic terminology. Integration of *RHD* genotyping for accurate classification	[32, 49,50]
3	RhIG management	Unwarranted antiglobulin testing leads to recommendations against giving RhIG in some cases. Unnecessary RhIG administration for certain weak D types	*RHD* genotype-guided management of RhIG therapy. Early pregnancy *RHD* genotyping to optimize RhIG use	[11, 32,48]
4	Fetomaternal hemorrhage testing	Use of contraindicated fetal rosette test for weak D-reactive newborns, risking false-negative results	Implementation of appropriate testing methods for accurate assessment of fetomaternal hemorrhage	[32]
5	RBC transfusion	Unnecessary use of D-negative RBCs for patients with certain weak D types	Conservation of D-negative RBC units through *RHD* genotyping and appropriate management of weak D types 1, 2, and 3 as D-positive	[11, 48]
6	Population differences	Variation in *RHD* allele distribution among different populations	Population-specific genotyping strategies and transfusion policies	[47, 56]
7	Novel alleles	Continuous discovery of new *RHD* alleles	Ongoing research to characterize new alleles and their clinical significance	[51, 52]
8	Timing of genotyping	Delayed genotyping leads to complicated clinical management	Early *RHD* genotyping, preferably during early pregnancy, to guide patient management	[48, 53]

RhD: Rhesus D antigen; RhIG: Rh immune globulin; *RHD*: Rhesus D antigen blood group; RBCs: Red blood cells.

significant barrier is the lack of standardized protocols for testing and interpreting weak D phenotypes across different healthcare settings[47,54]. Barriteau *et al*[32] in 2022 highlight inconsistencies in reporting terminology, with nine different terms used to interpret weak D-reactive maternal RhD types. This lack of standardization can lead to confusion and potentially impact patient care. Additionally, there may be resistance from healthcare providers who are accustomed to traditional practices and may be hesitant to change established protocols[11]. Moreover, the technical aspects of genotyping, such as the potential for cross-contamination during sample processing and the need for multiple amplification runs, can pose challenges in laboratory settings[55]. Education and training on the importance of genotyping and the implications of weak D phenotypes are essential to overcome these challenges and improve patient outcomes.

The financial implications of *RHD* genotyping are significant. While the initial cost of genotyping may be perceived as a barrier, studies have demonstrated that it can lead to long-term savings by reducing the unnecessary use of Rh-negative blood and RhIG[44,48]. Kacker *et al*[44] highlighted that the financial benefits of genotyping pregnant women with weak D phenotypes could outweigh the costs associated with the testing itself, particularly in subsequent pregnancies. Additionally, the integration of genotyping into routine transfusion practices can help avoid the wastage of Rh-negative blood, which is often in high demand[56].

Transfusion-related acute lung injury is a serious complication of blood transfusion that has emerged as a leading cause of transfusion-related morbidity and mortality[57,58]. A "two-hit" model has been proposed, where the patient's underlying condition acts as the first insult, and the transfusion serves as the second trigger[58,59]. The condition is diagnosed based on clinical criteria, including the temporal association with transfusion, absence of pre-existing acute lung injury, and exclusion of other causes of pulmonary edema[58,60]. Further research would be needed to explore the specific relationship between RhD genotyping, weak D phenotypes, and transfusion-related acute lung injury.

EXPLORING PROSPECTS TO IMPROVE OUTCOME AND SAFETY IN WEAK D INDIVIDUALS

Ongoing research into identifying novel *RHD* alleles and developing high-throughput genotyping methods could enhance the accuracy and efficiency of RhD testing[61]. Barriteau *et al*[32] in 2022 recommend implementing consistent immunohematologic terminology and *RHD* genotype-guided management for RhIG therapy and RBC transfusions. A study examining the impact of *RHD* genotyping on obstetrical patients and transfusion candidates found that genotyping changed RhD management in 43% of cases, resulting in net conservation of D-negative RBCs and RhIG[32]. A study in Croatia found that *RHD* genotyping confirmed weak D alleles in 92.4% of serologically weak D samples, with weak D type 1 being the most common variant (49.7%)[62]. Similarly, a study in Iran identified weak D type 15 as the most prevalent variant, accounting for 43% of the samples tested[33]. A study in Quebec, Canada, found that weak D type 42 was the most prevalent variant, representing 17.5% of all individuals tested[45].

While most studies focus on exons 4, 5, 7, and 10 of the *RHD* gene, some researchers have developed algorithms to solve discordant results due to *RHD* variant alleles. A study in Belgium identified 247 women with *RHD* variant alleles out of 11630 tested, with *RHD* × 08N.01 is the most frequent variant[63]. As the understanding of RhD genetic diversity expands, particularly in underrepresented populations, the refinement of genotyping protocols will be crucial for ensuring equitable access to accurate blood typing and transfusion practices[49,64]. The standardization of *RHD* genotyping techniques is crucial for their widespread clinical implementation. External quality assessment workshops have demonstrated that despite different methodological approaches, fetal *RHD* genotyping is a reliable laboratory assay [65,66]. However, there is still a need for well-established strategies including standardized high-throughput protocols and specific bioinformatic tools to make the most of the latest technical developments in this field[67].

The future prospects must elaborate studies incorporating the following solutions such as for standardizing *RHD* genotyping techniques and terminology, improving molecular detection methods with high-throughput genotyping and refined artificial intelligence-algorithms, integrating *RHD* genotyping into routine transfusion and obstetric practices, expanding non-invasive prenatal testing (NIPT) for fetal RhD status. conducting cost-effectiveness studies for genotyping implementation like CRISPR-based, providing education on weak D phenotypes and genotyping interpretation, developing population-specific genotyping strategies and continuing research on novel *RHD* alleles and their clinical significance[67].

OBSTETRIC CONSIDERATIONS

In obstetrics, the management of pregnant women with weak D phenotypes is crucial to prevent HDFN. If a weak D mother carries a Rh-positive fetus, there is a risk of sensitization, which can lead to severe complications in subsequent pregnancies[68,69]. The administration of RhIG is a standard practice to prevent sensitization; however, the necessity of RhIG in women with weak D phenotypes remains a topic of debate. Current guidelines suggest that women with weak D types 1, 2, and 3 may not require RhIG prophylaxis, while those with more immunogenic weak D types should be closely monitored[11,69].

NIPT for fetal RhD status using cell-free fetal DNA from maternal plasma genotyping has emerged as a reliable technique for predicting RhD incompatibility between pregnant women and fetuses and has shown promise in reducing unnecessary RhIG administration[70,71]. Initially, the maternal blood was withdrawn as early as 10 weeks of gestation and isolated to obtain cell-free fetal DNA from the placenta. It will be genetically analyzed using advanced PCR techniques that identify abnormal chromosomal sequences. This approach not only alleviates the physical and psychological burden on pregnant women but also minimizes the risk of exposure to potential contaminants associated with RhIG[70]. Several studies have demonstrated high accuracy, sensitivity, and specificity of this method across different trimesters[72]. Real-time PCR and endpoint quantitative fluorescent PCR have shown excellent ability to predict the *RHD* genotype, with accuracies of 98.6% and 99.4% respectively[73]. NIPT for RhD status can be combined with other non-invasive prenatal tests to provide comprehensive fetal assessment. This nuanced approach underscores the importance of accurate phenotyping and genotyping in obstetric care.

FOR CLINICIANS IN-PRACTICE

Developing genotyping strategies tailored to specific populations to account for genetic variations and improve accuracy. Use genotyping information to guide individualized patient care, including transfusion strategies and RhIG administration in pregnancy. Foster collaboration between transfusion medicine specialists, obstetricians, geneticists and policy-makers is essential to overcoming current challenges in enhancing transfusion safety. This might improve overall management of patients with weak D phenotypes[73].

CONCLUSION

RHD genotyping offers a more reliable alternative to serotyping for transfusion management by preventing misclassification and unnecessary RhIG administration. However, high costs remain a barrier in resource-limited settings, necessitating affordable molecular testing solutions. Given the genetic diversity of weak D variants across ethnic groups, comprehensive sequencing strategies are crucial for safe transfusion practices. Clinicians should integrate molecular testing into routine RhD assessment to minimize alloimmunization risks and ensure precise patient care decisions. Understanding the molecular basis of weak D phenotypes is essential for optimizing transfusion strategies and obstetric management.

FOOTNOTES

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Country of origin: India

ORCID number: Prasanna Bharathi Sainath 0000-0002-4179-7744; Velmurugan Ramaiyan 0000-0002-9399-3579.

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