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Review

Rh Isoimmunization in the Newborn: Current Prevention

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ABSTRACT

Rh isoimmunization remains one of the main causes of hemolytic disease of the newborn (HDN) and adverse perinatal outcomes in pregnant women sensitized to the Rh-D antigen. Although its incidence has fallen dramatically in recent decades thanks to anti-D immunoglobulin prophylaxis, cases still arise in populations with limited prenatal care or inconsistent protocols. This article reviews the immunological basis of isoimmunization, risk criteria, indications and dosing schemes for pre- and post-exposure prophylaxis, as well as new strategies based on individualized immunoglobulin dosing and non-invasive fetal monitoring. Challenges in implementing programs in middle- and low-income countries including logistical and educational issues are highlighted, and future perspectives such as tolerogenic vaccines and high-affinity monoclonal antibodies are discussed. Current prevention, combining evidence-based guidelines with technological advances, offers effective control of Rh isoimmunization but requires stronger integration between health professionals and public-health systems to ensure equitable access.

Keywords: Rh isoimmunization; Anti-D immunoglobulin; Perinatal hemolytic disease; Prenatal prophylaxis; Fetal monitoring

Introduction

Rh isoimmunization refers to the process by which an Rh-D–negative pregnant woman becomes sensitized to Rh-D antigens present on Rh-positive fetal erythrocytes, triggering a maternal immune response that produces antibodies capable of crossing the placental barrier and causing fetal or neonatal hemolysis[1-5]. Historically, before systematic prophylaxis was introduced, the resulting perinatal hemolytic disease was responsible for high morbidity, mortality, and neurological sequelae in survivors. Understanding the immunological mechanisms initiated by the work of Landsteiner and Wiener in the early 20th century enabled the development of anti-D sera and dosing protocols that transformed perinatal prognosis. Yet Rh isoimmunization remains a public-health problem in regions with insufficient prenatal coverage or cold-chain failures, leading to delayed diagnosis and inadequate immunoglobulin administration[6-10]. Fetomaternal Rh incompatibility arises not only in first pregnancies but also after miscarriage, abdominal trauma, amniocentesis, and previous deliveries without proper prophylaxis. Recent technological advances have enabled non-invasive fetal monitoring methods such as free fetal DNA testing in maternal plasma, allowing accurate determination of fetal Rh status and tailored prophylaxis. Parallel research on monoclonal antibodies and tolerogenic vaccines seeks alternatives to human immunoglobulin, aiming to reduce infectious-transmission risks and batch variability.

Objectives

This integrative review summarizes current aspects of Rh isoimmunization prevention, focusing on contemporary epidemiology, immunobiological mechanisms, prophylaxis indications and dosing, fetal monitoring techniques, and implementation challenges across diverse health-care settings.

Materials and Methods

This narrative literature review was conducted using PubMed, Scopus, and SciELO databases, covering articles published from 2015 to 2024.

Discussion

Prophylaxis for Rh isoimmunization represents one of the greatest successes in maternal–infant health, drastically reducing perinatal hemolytic disease in countries with well-structured programs. Conventional regimens rely on a fixed 300 µg dose of anti-D immunoglobulin administered routinely around 28 weeks' gestation and immediately after delivery of an Rh-positive newborn. Alternative protocols recommend additional doses after invasive procedures or fetomaternal hemorrhage events such as amniocentesis, vaginal bleeding, or trauma. In high-income settings, free fetal DNA testing in maternal plasma enables non-invasive identification of fetal Rh status, preventing unnecessary prophylaxis in Rh-negative fetuses, optimizing costs, and reducing maternal exposure to immunoglobulin. However, applying these tests in middle- and low-income countries is limited by laboratory infrastructure and high costs. Additional challenges include variable adherence to protocols, with reports of immunoglobulin documentation failures and cold-chain lapses that may compromise product potency. Ongoing professional training and patient education are critical to reinforce the importance of prophylaxis and ensure universal coverage. Recent research explores recombinant anti-D monoclonal antibodies and tolerogenic vaccines that could, in theory, provide more stable immunoprotection without blood-borne risks. Pre-clinical trials show promising results in inducing specific anergy but remain far from clinical use[11,12].

Implementation of electronic records and automatic alert systems has improved tracking of Rh-negative pregnant women, enabling timely interventions[13-14]. International cooperation for donating and distributing anti-D immunoglobulin is also strategic in shortage regions.

Conclusion

Prophylaxis with anti-D immunoglobulin is undeniably one of the most significant advances in preventing perinatal hemolytic disease, having markedly reduced its incidence in countries with well-structured health programs. Nonetheless, residual cases persist in vulnerable populations due to socioeconomic barriers, cold-chain failures, and gaps in prenatal follow-up. Incorporating non-invasive fetal monitoring methods, such as free fetal DNA analysis, increases precision in identifying women truly needing additional immunoglobulin doses, avoiding unnecessary exposure and optimizing resources. Yet the applicability of these tests is constrained by laboratory infrastructure and high costs, underscoring the need for investment in context-appropriate technologies for middle- and low-income settings. Electronic registry systems and automated alerts for Rh-negative pregnant women have proven effective in reducing protocol failures and improving prophylaxis adherence. Expanding equity requires continuous professional training and targeted information campaigns for pregnant women, emphasizing prophylaxis and postpartum care. Simultaneously, research on recombinant anti-D monoclonal antibodies and tolerogenic vaccines offers promising alternatives to human immunoglobulin, with potential for reduced batch variability and elimination of serologic sourcing risks. Ultimately, consolidating evidence-based guidelines alongside accessible technologies and robust public-health policies is essential to eradicate Rh isoimmunization as a public-health issue. Synergy among biotechnological innovation, professional capacity building, and integrated health-information systems is central to ensuring universal coverage and ever safer perinatal outcomes. Only through these combined efforts can all pregnant women regardless of socioeconomic status or geographic location receive timely and effective prophylaxis, safeguarding the health and well-being of future generations.

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