CASE REPORT

Journal of International Surgery and Clinical Medicine (*JISCM)* 2025, Volume 5, Number 2: 43-48
E-ISSN: 2807-7008

Published By :
Surgical Residency Program
Universitas Syiah Kuala

The Effects of Prednisone and Aspirin Administration on Pregnancy Outcomes in Mothers with RhD Isoimmunization and a History of Recurrent Pregnancy Loss: A Case Report

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Received: 2024-09-16
Accepted: 2025-11-18
Published: 2025-12-12

ABSTRACT

Introduction: Rhesus incompatibility arises when an Rh-negative mother becomes sensitized to the D antigen of an Rh-positive fetus, triggering the production of anti-D antibodies, a process known as isoimmunization. This condition is associated with severe obstetric complications, including Recurrent Pregnancy Loss (RPL) and Hemolytic Disease of the Fetus and Newborn (HDFN). Clinical management remains challenging, as no single therapeutic modality can comprehensively eliminate the adverse effects of isoimmunization. A targeted and integrated management approach is therefore imperative to optimize pregnancy outcomes. Emerging evidence suggests that corticosteroids combined with aspirin may confer beneficial effects in patients with rhesus incompatibility.

Case Presentation: A 27-year-old woman, G5P0A4, with RhD-negative status, experienced recurrent pregnancy loss and was managed with prednisone (10 mg/day), aspirin, and Rh immunoglobulin (RhIg) at appropriate gestational intervals. The patient successfully carried the pregnancy to 36 weeks and six days, resulting in the birth of a healthy neonate.

Discussion: Rhesus incompatibility is a clinically significant condition in which Rh-negative mothers develop isoimmunization following exposure to Rh-positive fetal blood, producing antibodies against fetal red blood cell antigens. This immunological response contributes to adverse pregnancy outcomes, most notably RPL and HDFN, both carrying substantial maternal and neonatal morbidity. Effective management continues to pose considerable clinical challenges due to limited therapeutic interventions capable of mitigating the immunological consequences of isoimmunization. Evidence from published case reports indicates that combined prednisone and aspirin administration may represent a promising adjunctive therapeutic strategy alongside RhIg prophylaxis.

Conclusion: The integrated management incorporating RhIg prophylaxis as the cornerstone of therapy alongside adjunctive prednisone and aspirin was associated with a successful pregnancy outcome in this RhD-negative mother with a history of RPL. The relative contribution of each therapeutic component cannot be determined from a single case report. Further prospective studies with larger sample sizes are needed to evaluate the independent efficacy of corticosteroids and aspirin in this clinical context.

Keywords: Recurrent pregnancy loss, prednisone, aspirin, rhesus incompatibility, isoimmunization, hemolytic disease.
Cite This Article: Susanty, D., Marhadisony, R., Indirayani, I., Aditya, R., Fuad, M. 2025. The Effects of Prednisone and Aspirin Administration on Pregnancy Outcomes in Mothers with RhD Isoimmunization and a History of Recurrent Pregnancy Loss: A Case Report. *Journal of International Surgery and Clinical Medicine* 5(2): 43-48. DOI : 10.51559/jiscm.v5i2.83

INTRODUCTION

Rhesus incompatibility during pregnancy occurs when the immune system of an Rh-negative mother becomes sensitized following exposure to the D antigen derived from an Rh-positive fetus. In response, the maternal immune system recognizes the D antigen as a non-self substance and consequently initiates the production of specific antibodies directed against it. This immunological process, whereby the mother develops antibodies in response to fetal red blood cell antigens, is clinically defined as rhesus isoimmunization.[1,2] Rhesus isoimmunization can result in serious conditions. Continuous exposure to anti-D will trigger maternal IgG production to destroy fetal red blood cells via the transplacental route.[3,4]

The occurrence of Rhesus incompatibility is substantially influenced by the proportion of individuals carrying the Rh-negative blood type within a given population, a figure that demonstrates considerable variation across different ethnic and geographical groups.[1] Generally, this condition has a higher prevalence in Caucasian populations (approximately 15%–17% in North America and Europe) and a much lower prevalence in Asian populations (0.1%–0.3%).1,5 There are currently

no epidemiological data on Rhesus incompatibility or isoimmunization in Indonesia. Nevertheless, data released by the Central Statistics Agency (Badan Pusat Statistik/BPS) revealed that as of 2010, individuals with Rh-negative blood type accounted for less than one percent of the total Indonesian population, representing approximately 1.2 million people.[6]

The United States Preventive Services Task Force (USPSTF) strongly recommends blood type and Rh(D) antibody screening for all pregnant women at their initial prenatal visit (Grade A). Furthermore, repeat antibody testing is recommended for all unsensitized Rh-negative mothers at 24 to 28 weeks of gestation, unless the father is confirmed to be Rh-negative (Grade B).[3] The diagnosis of rhesus isoimmunization is established based on the quantification of anti-D antibody titers in maternal blood, whereby the detection of anti-D antibodies bound to maternal red blood cells yields a positive Direct Coombs test result.[7,8]

One of the primary principles in managing Rhesus incompatibility is the prevention of maternal sensitization.[3] Current clinical guidelines recommend the routine administration of Rhesus immunoglobulin to all Rh-negative pregnant women as a prophylactic measure against anti-D isoimmunization.[9,10] Despite the approval of anti-D IgG for routine antepartum prophylaxis since 1976, the risk of isoimmunization has not been entirely eliminated, underscoring the continued need for vigilant monitoring and comprehensive management strategies in affected pregnancies.[2,3] Several reports indicate a reduction in isoimmunization incidence with immunosuppressants, including steroids. Patients treated with steroids or other immunosuppressive agents have shown a decreased risk of isoimmunization.[11,12] In their report on 12 mothers with rhesus isoimmunization, Tamer and Yasser concluded that oral prednisolone therapy significantly helps in preventing fetal anemia and should be considered for use.[13]

Aspirin has also been reported to have the potential to prevent pregnancy-related complications. Ruan et al. noted that aspirin can improve pregnancy outcomes complicated by autoimmune diseases.[14] Ou et al. reported that the combined use of aspirin, prednisone, and triple multivitamin therapy was associated with successful pregnancy maintenance up to 12 weeks of gestation.[15] Nevertheless, the efficacy of combining corticosteroids with aspirin in the management of rhesus incompatibility remains a subject of ongoing debate, and further robust scientific evidence is warranted to comprehensively evaluate the therapeutic effectiveness of this regimen.[14,15] In light of this, the present report aims to describe a case of an Rh-negative pregnant woman with a history of recurrent pregnancy loss who was managed with a combination of corticosteroids and aspirin, with the intention of contributing to the growing body of evidence surrounding this therapeutic approach.

CASE PRESENTATION

A 27-year-old mother with RhD-negative blood type, was aware of her RhD status prior to marriage. She has been married for four years and experienced four consecutive miscarriages. The first pregnancy ended in an incomplete abortion at 13-14 weeks of gestation, requiring curettage, followed by an injection of Human Rho(D) Immune Globulin. Both direct and indirect Coombs' tests were non-reactive. TORCH screening revealed Anti-Toxoplasma IgG positive with a concentration of 48 and IgM negative (indicating past exposure or infection with toxoplasma), Anti-Rubella IgG positive with a concentration of 54 and IgM negative, Anti-CMV IgG positive with a concentration of 30 and IgM negative (suggesting past exposure or infection with CMV), and both Anti-HSV2 IgG and IgM were negative.

The second pregnancy occurred four months after the first and resulted in a miscarriage at seven weeks. The patient experienced bleeding from early pregnancy, and the ultrasound showed an anembryonic pregnancy; she received misoprostol therapy but no Human Rho(D) Immune Globulin injection. The third pregnancy, occurring six months later, also ended in miscarriage. Ultrasound revealed an anembryonic pregnancy at ten weeks, treated with misoprostol. Again, Coombs' tests were non-reactive, and no Human Rho(D) Immune Globulin was administered.

The fourth pregnancy occurred one month after the third, and an ultrasound detected a fetal pole. During this pregnancy, the patient was treated with Chorionic Gonadotropin (250 mcg, six times), Dydrogesterone, Mefenamic Acid, Progesterone (2x400 mg), Tranexamic Acid, and folic acid. However, she experienced a spontaneous miscarriage at 13 weeks, with pathology indicating a retained placenta. No Human Rho(D) Immune Globulin was given. Subsequently, the patient underwent screening for autoimmune disorders, hormonal abnormalities, and infections, all of which were normal. Laboratory tests for estradiol, progesterone, and estrogen were within normal limits. ACA IgG was <2, ACA IgM was 3, Anti-Beta2-Glycoprotein 1 IgG and IgM were negative, fasting blood glucose was 78, fasting insulin was 4.3, ANA profile was negative, TSHs was 1.28, Anti-Mullerian Hormone was 6.79, Prolactin was 10.09, and lupus tests were negative.

The fifth pregnancy occurred one year after the fourth. Ultrasound revealed a fetal pole. The patient was treated with folic acid (1 gram), prednisone (10 mg), vitamin D3, progesterone, aspirin, and micronutrients. Early in the pregnancy, Coombs' tests were positive (1+). At 13 weeks, she experienced bleeding and received an injection of Human Rho(D) Immune Globulin.

The pregnancy continued, and therapy was maintained until 20 weeks when Coombs' tests were rechecked and found to be non-reactive. At 24-28 weeks, screening indicated no maternal or fetal abnormalities. At 28 weeks, another Human Rho(D) Immune Globulin injection was administered. At 36 weeks and six days, the patient experienced premature rupture of membranes and fetal tachycardia, leading to an emergency cesarean section. Ai female infant weighing 2400 grams was delivered, with apgar scores of 8 and 9 at 1 and 5 minutes, respectively. No congenital abnormalities were observed. The patient received another Human Rho(D) Immune Globulin injection 24 hours post-cesarean section. Both mother and baby are currently healthy.

Table 1. Serial Maternal Anti-D Antibody (Coombs Test) Titers Throughout the Fifth Pregnancy

Gestational Age	Direct Coombs Test	Indirect Coombs Test	Clinical Notes
Initial visit (5th pregnancy)	Positive (1+)	Positive (1+)	Prednisone 10 mg/day + Aspirin initiated
13 weeks	Not re-checked	Not re-checked	Bleeding episode; RhIg injection administered
20 weeks	Non-reactive	Non-reactive	Effective antibody suppression observed
28 weeks	Not re-checked	Not re-checked	Routine RhIg injection administered per protocol
36 weeks 6 days	N/A	N/A	Emergency C-section; healthy neonate 2400g, Apgar 8/9

RhIg = Rh immunoglobulin; N/A = not applicable

DISCUSSION

When an Rh-negative mother is partnered with an Rh-positive father, the fetus is likely to inherit the Rh-positive status from the paternal side. Should the Rh-negative mother become exposed to Rh-positive red blood cells, whether through the process of childbirth or any other form of fetomaternal hemorrhage, she is at considerable risk of developing anti-D antibodies in response to the presence of the D antigen. This exposure may subsequently lead to maternal D isoimmunization, a condition that arises as a direct consequence of the maternal immune system mounting a response against RhD-positive red blood cells.[1] Recurrent miscarriages in pregnant women with Rh-negative blood type can be associated with isoimmunization due to Rh incompatibility.[3,8] It is important to acknowledge, however, that Rh isoimmunization classically causes complications in the 2nd and 3rd trimesters, most notably hydrops fetalis and severe fetal anemia, rather than early first-trimester pregnancy loss. The early miscarriages in this patient (7-13 weeks) may not be directly attributable to Rh isoimmunization, as anti-D titers during previous pregnancies were not systematically documented. Other contributing etiologies, including chromosomal abnormalities, uterine structural factors, or coagulation disorders, cannot be entirely excluded based on the available data. The relationship between Rh isoimmunization and early RPL in this patient therefore remains a plausible hypothesis rather than a confirmed causal association.

Maternal isoimmunization can be caused by several conditions, including transplantable fetomaternal bleeding during pregnancy, injections using needles contaminated with RhD-positive blood, accidental blood transfusions with the RhD-positive, and allogenous hematopoietic stem cell transplants that do not match RhD. Transplacental fetomaternal bleeding is known to be the main cause of isoimmunization D in the mother, in which the mother's blood components can be mixed with the fetal blood, increasing the risk of maternal sensitization.[7,16]

Isoimmunization during pregnancy should be considered as a potential underlying etiology in cases of recurrent miscarriage. This immunological condition exerts a significant impact on fetal well-being by substantially elevating the risk of several serious complications, including Hemolytic Disease of the Fetus and Newborn (HDFN), hydrops fetalis, as well as fetal thrombocytopenia and neutropenia.[14] These conditions are often observed in mothers experiencing recurrent miscarriages and stillbirths. In this case, the mother was known to have an Rh-negative blood type before marriage.[17] The patient also experienced recurrent miscarriages four times, raising suspicion of maternal isoimmunization, although the exact causal mechanism in the early weeks of pregnancy warrants further investigation.

Isoimmunization to the Rh factor occurs as a result of sensitization when an Rh-negative pregnant woman is exposed to the D antigen present on fetal red blood cells. During the initial encounter with the D antigen, the maternal immune system produces high molecular weight Immunoglobulin M (IgM) antibodies, which are unable to cross the placental barrier and therefore exert no adverse effect on the fetus at this stage. However, upon subsequent exposure, the mother mounts a rapid anamnestic immune response, stimulating the synthesis of low molecular weight IgG antibodies that are capable of traversing the placental barrier and gaining access to the fetal circulation. Once antibody synthesis has been initiated, it cannot be suppressed, and with each successive pregnancy involving an Rh-positive fetus, the maternal anti-Rh antibody response becomes increasingly amplified. Maternal B cells recognize the RhD antigens expressed on fetal red blood cells and initiate a cascading immune response, beginning with the transient production of IgM anti-D immunoglobulins, followed by a rapid class switch to IgG immunoglobulins. This immunological process simultaneously generates long-lived memory B cells that remain quiescent until provoked by renewed antigenic exposure in subsequent pregnancies. Upon re-exposure to the Rh antigen, these memory B cells become reactivated, rapidly producing IgG antibodies at progressively increasing titers, thereby posing an escalating threat to fetal well-being with each successive Rh-incompatible pregnancy.[7,18]

Maternal IgG antibodies that successfully traverse the placental barrier

are capable of targeting and destroying RhD-positive fetal erythrocytes, leading to the development of fetal anemia or a condition clinically recognized as Hemolytic Disease of the Fetus and Newborn (HDFN), also referred to as erythroblastosis fetalis. In its most severe manifestation, this condition can progress to hydrops fetalis or culminate in intrauterine fetal death. In the context of the present case, the authors hypothesize that the patient's history of recurrent miscarriages may be partially related to repeated maternal exposure to fetal antigens, though it must be acknowledged that this association is speculative given the limitations of a single case report and the absence of documented anti-D titers in earlier pregnancies.[2]

The United States Preventive Services Task Force (USPSTF) strongly recommends Rh blood typing and antibody testing for all pregnant women at their initial prenatal visit (Grade A), with repeat antibody testing advised for unsensitized Rh-negative mothers at 24 to 28 weeks of gestation, unless the father is confirmed to be Rh-negative (Grade B).[3,19] The diagnosis of Rh isoimmunization is established through the detection of anti-D antibodies in maternal blood, with the Direct Coombs test serving as the principal diagnostic tool for determining antibody titers, whereby a positive result is indicative of maternal sensitization. Rosette testing is further indicated for the detection of D-positive red blood cells in Rh-negative patients, and is typically followed by Kleihauer-Betke testing to quantify the extent of fetomaternal hemorrhage. In the present case, both the direct and indirect Coombs tests yielded positive results at a titer of 1, while rosette and Kleihauer-Betke testing were unavailable at the treating facility.[20,21]

Management of Rh isoimmunization focuses on preventing sensitization in mothers. The cornerstone of management in this case was the administration of Rh immunoglobulin (RhIg), which represents the standard of care for Rh-negative pregnant women. RhIg was administered at 13 weeks following a bleeding episode, at 28 weeks per routine antepartum protocol, and postpartum following delivery. RhIg contains antibodies against Rh(D) antigen, blocking maternal immune recognition to prevent isoimmunization with approximately 99.8% effectiveness. It is most plausible that the successful pregnancy outcome in this case was primarily attributable to timely and appropriate RhIg administration. Serial plasmapheresis and intravenous immunoglobulin therapy are also promising approaches to reduce fetal disease severity with significant antibody titers (>1024) or severe previous hemolytic disease history.[13,21]

In addition to RhIg, the patient received adjunctive therapy with prednisone (10 mg/day) and aspirin. Several studies have reported decreased isoimmunization incidence with immunosuppressants, including steroids. Patients treated with steroids or other immunosuppressive agents show a reduced risk of isoimmunization. The fundamental concept underlying this therapy is the suppression of maternal anti-Rh antibodies crossing the placental barrier, thereby preventing hemolysis in fetal red blood cells.[11,12] Studies by Tamer and Yasser on 12 Rh-immunized mothers concluded that oral prednisolone effectively prevents fetal anemia and should be considered for treatment. Another study by Abdeldayem et al. evaluated three cases of Rh-negative multiparous women treated with oral prednisolone, demonstrating its ability to suppress antibodies and maintain adequate fetal cardiovascular function and tissue oxygenation. Tamer and Yasser documented significant reductions in maternal anti-Rh antibody titers as well as Middle Cerebral Artery Peak Systolic Velocity (MCA-PSV) among mothers who received oral prednisolone at a dose of 40 mg commencing from the 10th week of pregnancy, with deliveries occurring at a mean gestational age of 33.18±1.2 weeks and mean fetal birth weights averaging 1978.5±232.5 grams. Corroborating these findings, Abdeldayem et al. reported that the administration of oral prednisolone at 40 mg successfully prevented adverse fetal outcomes attributable to maternal isoimmunization in two cases, with both deliveries achieved at 34 weeks of gestation and no documented occurrence of hydrops fetalis.[13]

It is noteworthy that the prednisone dose employed in the present case (10 mg/day) is considerably lower than the doses cited in the referenced studies (40 mg/day). The decision to use a reduced dose in this patient was guided by a risk-benefit assessment specific to her clinical context. Given the patient's negative autoimmune and thrombophilia screening results, and considering the potential risks associated with higher-dose corticosteroid therapy including susceptibility to infection, gestational hyperglycemia, and glucose intolerance the clinical team opted for the lowest effective dose. The favorable Coombs test conversion from positive (1+) to non-reactive at 20 weeks suggests that antibody suppression was achieved at this reduced dose. However, it cannot be determined with certainty whether this outcome was attributable to the prednisone, the aspirin, the RhIg, or their combined effect. Prospective dose-comparison studies are needed to establish the optimal corticosteroid dosing regimen in this clinical context.

Dysregulation of the coagulation cascade has been established as a critical pathological mechanism underlying Recurrent Pregnancy Loss (RPL), with prior investigations demonstrating that approximately 78% of women affected by RPL exhibit identifiable hemostatic abnormalities. In this regard, low-dose aspirin (LDA) has been increasingly recognized as a potentially effective therapeutic intervention for pregnancy-related complications, particularly in the context of unexplained recurrent spontaneous abortion (URSA). Accumulating evidence from multiple studies has substantiated the efficacy of LDA in augmenting uterine artery perfusion and mitigating the rate of spontaneous abortion in RPL patients. Ou et al. demonstrated successful pregnancy continuation up to 12 weeks of gestation through the concurrent administration of aspirin (100 mg/day), prednisone (5 mg/day), and triple multivitamin therapy. Consistent with these findings, Wang et al. and Qi Yu independently reported markedly improved birth outcomes in women presenting with idiopathic recurrent abortion following treatment

with a combined regimen of prednisone, aspirin, folate, and progesterone. The pathogenesis underlying these conditions is predominantly attributed to placental dysfunction, which may be mechanistically linked to the enzymatic targets of aspirin. Since arachidonic acid metabolism is primarily mediated through COX-1 enzyme activity in the biosynthesis of prostanoids, encompassing prostacyclin, prostaglandins (PGs), and thromboxanes (TXs), aspirin exerts its pharmacological effect by suppressing this enzymatic activity, consequently attenuating the inflammatory response. Beyond its anti-thrombotic effects, aspirin's anti-inflammatory properties are also relevant in the context of Rh isoimmunization. By inhibiting COX-mediated prostanoid synthesis, aspirin may modulate the pro-inflammatory microenvironment at the maternal-fetal interface that is exacerbated by anti-D antibody-mediated immune activation, thereby potentially reducing placental inflammation and improving trophoblast function. This mechanistic link underscores the rationale for including aspirin as part of the integrated management approach in this case, though direct evidence specific to Rh isoimmunization remains limited.[14,15,22]

CONCLUSION

In this case, successful pregnancy outcome in an RhD-negative mother with a history of four consecutive miscarriages was achieved through an integrated management approach comprising Rh immunoglobulin (RhIg) prophylaxis as the standard of care, supplemented by adjunctive prednisone (10 mg/day) and aspirin therapy. RhIg remains the most plausible primary contributor to the favorable outcome. While the reduction in anti-D antibody titers observed at 20 weeks is encouraging, the independent contribution of prednisone and aspirin to preventing RPL cannot be definitively established from a single case report. The lower dose of prednisone used (10 mg/day versus 40 mg/day in referenced studies) was a deliberate clinical decision based on risk-benefit assessment for this patient, yielding an apparent suppressive effect without documented adverse effects. Further well-designed prospective studies with larger sample sizes and consistent antibody titer documentation are essential to more definitively evaluate the role of corticosteroids and aspirin as adjuncts to RhIg in the management of Rh-incompatible pregnancies with a history of RPL.

DISCLOSURES

Funding

Funding for this case report was neither sought nor received from any public institution, commercial body, or nonprofit organization.

Conflict of Interest

The authors declare that there are no conflicts of interest pertaining to the publication of this work.

Author Contribution

Devi Susanty contributed to the conception, patient data collection, and drafting of the manuscript. Regina participated in the literature review and clinical documentation. Ima Indirayani supervised the case management and provided critical revisions of the manuscript. Rizka Aditya supervised the case management and provided critical revisions of the manuscript. M. Fuad contributed to hematologic consultation and provided expert input during manuscript preparation. All authors reviewed and approved the final version of the manuscript for submission to the Journal of International Surgery and Clinical Medicine.

Acknowledgments

The authors wish to extend their sincere appreciation to the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Syiah Kuala, as well as to the dedicated medical staff of Dr. Zainoel Abidin General Hospital for their invaluable assistance and support throughout the management of this case. The authors also gratefully acknowledge the patient and her family for their cooperation and willingness to provide informed consent for the publication of this case report.

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