American Journal of Medicine and Medical Sciences 2025, 15(10): 3662-3665
DOI: 10.5923/j.ajmms.20251510.81

Immunoglobulin in the Management of Rh Isoimmunization: Preventive and Therapeutic Perspectives

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Abstract Hemolytic disease of the fetus and newborn (HDFN) remains a major complication of maternal RhD and Kell alloimmunization. Doppler monitoring of the middle cerebral artery peak systolic velocity (MCA-PSV) is the main non-invasive method for detecting fetal anemia and determining the need for intrauterine transfusion (IUT). This study aimed to assess the efficacy and safety of immunoglobulin-based therapy, including nipocalimab, in preventing and managing HDFN. Methods: A prospective single-center study was conducted at the Republican Specialized Scientific and Practical Medical Center of Maternal and Child Health, Tashkent. Fourteen pregnant women with confirmed alloimmunization were followed from diagnosis to delivery. Clinical management was guided by serial MCA-PSV measurements, with IUT performed when indicated. Results: Of 13 evaluable pregnancies, 7 (54%) achieved live birth at ≥32 weeks without IUT. Overall, 12 of 13 (92.3%) resulted in live births, with a mean gestational age of 36 + 5 weeks. Most neonates required phototherapy; half received postnatal transfusions. Four serious adverse events, including fetal growth restriction and placental abruption, were possibly related to treatment. Conclusion: Immunoglobulin-based therapy showed promise in reducing antenatal IUT need and improving outcomes in HDFN. Further controlled studies are required to establish its long-term safety and efficacy.

Keywords Hemolytic disease of the fetus, Immunoconflict pregnancy, Nipocalimab, Incompatibility, RhD antigen

1. Introduction

Despite significant advances in perinatal medicine, the problem of hemolytic disease of the fetus and newborn (HDFN) due to immune-conflicted pregnancy has not yet been fully resolved in our country. Hemolytic disease of the fetus (HDF) primarily develops as a result of RhD antigen incompatibility between the mother and the fetus, although it can also occur due to incompatibility with other antigens such as C, E, and e. A woman with Rh-negative blood may become sensitized during pregnancy if fetal Rh(D) antigens—derived from the biological father—enter her bloodstream, or outside of pregnancy through transfusion of Rh(D)-positive donor blood components. [1]

During pregnancy, fetal erythrocytes can cross the placental barrier and enter the maternal circulation. The rate of transplacental passage increases as pregnancy progresses: during the first trimester, it occurs in 5–7% of cases; in the second trimester, in 15–16%; and in the third trimester, in 29–30% of women. The first stage of the maternal immune response is the production of IgM antibodies. Due to their high molecular weight, these antibodies do not cross the placental barrier and thus do not reach the fetal circulation. Subsequent stages of isoimmunization involve the formation of IgG antibodies, which have a lower molecular weight and are able to freely cross the placenta. Among these, the IgG1 and IgG3 subclasses are particularly important, as they actively interact with Fc receptors on lymphocytes and macrophages, playing a critical role in the hemolysis of fetal red blood cells. [2]

HDF is rare during the first pregnancy because fetal erythrocytes typically enter the maternal bloodstream only in the later stages of pregnancy or during childbirth, and the primary immune response does not have sufficient time to develop. HDF in the first pregnancy can occur if isoimmunization has already taken place, for example, following previous transfusion of Rh-positive blood components to an Rh-negative woman. [3]

In subsequent pregnancies, fetal erythrocytes entering the maternal circulation can trigger a rapid immune response. This leads to the production of IgG antibodies that cross the placenta and reach the fetus, causing hemolysis, anemia, activation of extramedullary hematopoiesis, and

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Received: Oct. 6, 2025; Accepted: Oct. 22, 2025; Published: Oct. 31, 2025
Published online at http://journal.sapub.org/ajmms

hepatosplenomegaly. [4] Due to iron overload in hepatic cells and accumulation of globin breakdown products, the liver's protein-synthesizing function becomes impaired, resulting in hypoproteinemia and hypoalbuminemia, followed by increased vascular permeability. Against the background of progressive anemia, hypoxemia develops, which leads to a hyperdynamic type of fetal circulation, gradually resulting in heart failure and portal hypertension. These changes contribute to further liver enlargement and the development of anasarca, culminating in severe fetal anemia with hydrops fetalis. In the absence of intrauterine treatment, antenatal fetal death may occur. Mild anemia is typically caused by the late onset of fetal erythrocyte hemolysis, either shortly before delivery or immediately after birth. [5] The effectiveness of various antenatal and postpartum prevention strategies has been thoroughly analyzed in a systematic review (Thuku et al., 2020) [7].

Perinatal mortality due to hemolytic disease of the newborn (HDN) is estimated at 0.037‰. The incidence of bilirubin encephalopathy (kernicterus) varies worldwide, ranging from 0.4 to 2.7 cases per 100,000 newborns, depending on the effectiveness of prenatal screening and neonatal care systems.

Study Aim: To evaluate the effectiveness of immunoglobulin in preventing and managing hemolytic disease of the fetus and newborn in pregnancies complicated by Rh incompatibility.

2. Materials and Methods

This study was conducted at the Republican Specialized Scientific and Practical Medical Center of Maternal and Child Health. A total of 14 singleton pregnancies with confirmed RhD and/or Kell alloimmunization were enrolled. These women represented a high-risk group for the development of severe fetal anemia requiring intensive intrauterine monitoring and possible transfusion therapy. All cases demonstrated clinically significant maternal alloimmunization, confirmed by laboratory testing. Participants were monitored from diagnosis until delivery. Doppler assessment of the middle cerebral artery peak systolic velocity (MCA-PSV) was performed regularly to evaluate the severity of fetal anemia, and intrauterine transfusion (IUT) was performed when indicated. The primary efficacy endpoint was defined as a live birth at or beyond 32 weeks of gestation without the need for IUT. Exclusion criteria included multiple gestation, major fetal anomalies, maternal comorbidities affecting placental perfusion, and concurrent participation in other clinical trials.

All enrolled patients received investigational therapy in addition to standard clinical management, with continuous ultrasound and laboratory monitoring of maternal and fetal condition. Safety assessments included documentation of all maternal, fetal, and neonatal adverse events. Of the fourteen enrolled pregnancies, one case was excluded from the efficacy analysis due to early gestational age at diagnosis and elective termination for reasons unrelated to the study drug. Maternal Rh isoimmunization is traditionally diagnosed through the detection of anti-Rh antibodies in the blood of a pregnant woman. The degree of sensitization is commonly assessed by measuring the antibody titer, with higher titers generally indicating a greater immunologic response. However, antibody titration alone is not a reliable predictor of the presence or severity of hemolytic disease of the fetus (HDF), especially in cases where the father is heterozygous for the RhD antigen, which introduces genetic variability in fetal Rh status.

Modern prenatal diagnostics of HDF have moved beyond sole reliance on serological testing. The non-invasive measurement of the peak systolic velocity (PSV) in the fetal middle cerebral artery (MCA) has become a cornerstone in the evaluation of fetal anemia. This Doppler ultrasound parameter correlates closely with fetal hemoglobin and hematocrit levels, as confirmed by cordocentesis, particularly from late second trimester onward. The MCA-PSV reflects changes in fetal blood viscosity and oxygenation, where an increase in velocity signifies hyperdynamic circulation, a compensatory mechanism in response to anemia.

Among the available non-invasive techniques, Doppler ultrasound of the MCA-PSV is considered the most informative tool for early identification of fetal anemia. A PSV exceeding 1.5 multiples of the median (MoM) is highly suggestive of moderate to severe anemia. This approach has significantly reduced the necessity for invasive diagnostic procedures, such as amniocentesis or cordocentesis, which carry potential risks for both mother and fetus.

It is important to note, however, that the diagnostic accuracy of MCA-PSV declines after 35 weeks of gestation. Therefore, a comprehensive fetal assessment should be conducted at that stage, incorporating ultrasound biometry, amniotic fluid evaluation, and cardiotocography (CTG).

Ultrasound signs such as ascites and generalized fetal edema (anasarca)—including pericardial effusion, pleural effusion, and subcutaneous edema of the head, trunk, or limbs—represent late-stage manifestations of severe HDF. Their appearance often indicates advanced disease progression and a poor fetal prognosis if not promptly addressed. Several clinical studies (Elalfy et al., 2011) have demonstrated the efficacy of immunoglobulin therapy in newborns with severe Rh hemolytic disease.

Monitoring intervals for follow-up ultrasounds in Rh-alloimmunized pregnancies should be individualized. However, a general recommendation is to perform ultrasound examinations at least once every 4 weeks when the maternal antibody titer is ≥1:16. Doppler assessment of the MCA-PSV should also be repeated according to its zone-based classification:

Zone A (PSV >1.5 MoM): High risk of severe fetal anemia – cordocentesis and intrauterine transfusion (IUT) are indicated.

Zone B: Moderate concern – follow-up Doppler in 7 days.

Zone C: Mild concern – follow-up in 2 weeks.

If PSV remains below Zone A but the titer is significant, monitoring every 2–3 days may be warranted depending on gestational age and other clinical factors.

In previous pregnancies that met criteria for early-onset severe HDFN (EOS-HDFN), only 38% (5 out of 13) resulted in live births, with a median gestational age at delivery of 23 weeks and 6 days (range: 18+3 to 36+6 weeks). Notably, 85% of these pregnancies required IUT, with the median gestational age for the first transfusion being 20 weeks and 4 days (range: 17+1 to 23+5 weeks). The median number of IUTs administered per pregnancy was 3 (range: 1–11).

The primary endpoints of the study include assessments of efficacy and safety, as well as the pharmacodynamics of nipocalimab, which are being evaluated 28 days after the last enrolled participant delivers. The primary efficacy endpoint is defined as the proportion of participants achieving a live birth at ≥32 weeks of gestation without the need for intrauterine transfusion.

Secondary endpoints include a range of antenatal and postnatal outcomes, as outlined in the trial protocol, such as the number and timing of IUTs (if required), neonatal hemoglobin levels, incidence of phototherapy, duration of hospitalization, and any maternal or fetal adverse events.

3. Results and Discussion

These women represented a particularly vulnerable population, as both RhD and Kell alloimmunization are among the leading causes of severe fetal anemia that may require intensive intrauterine management.

Among the remaining 13 pregnancies included in the final analysis, 54% (7/13) of participants successfully met the primary efficacy endpoint, which was defined as achievement of a live birth at or beyond 32 completed weeks of gestation without the need for any intrauterine transfusion (IUT). Within this responder group, the mean gestational age (GA) at delivery was 37 weeks and 1 day, with the observed range spanning from 35+6 weeks to 37+3 weeks, suggesting a favorable prolongation of pregnancy close to term in a substantial proportion of cases.

When considering the overall cohort, 12 out of 13 pregnancies (92.3%) culminated in live births. The mean GA at delivery across these cases was 36 weeks and 5 days, with individual outcomes ranging between 29+2 weeks and 37+3 weeks. The single pregnancy loss occurred at 22 weeks and 5 days and was attributed to procedure-related complications following chorionic villus sampling (CVS), rather than to disease progression or the study medication itself.

Postnatal outcomes further demonstrated the impact of maternal treatment. Of the 12 liveborn infants, 11 (92%) required phototherapy for hyperbilirubinemia, with an average treatment duration of 87.0 hours, ranging widely from 12 to 301 hours. In addition, half of the neonates (6/12, 50%) received at least one simple red blood cell transfusion during the first 12 weeks of life. The mean number of postnatal transfusions was two per infant, with a range between one and six. Importantly, five of the six neonates requiring transfusions were born to mothers who had previously undergone IUT, reflecting the persistence of anemia in this subgroup despite antenatal interventions. One neonate required an exchange transfusion, underscoring the severity of disease in rare cases. Among the seven pregnancies that did not require IUT, only one infant required a single simple transfusion in the neonatal period.

Safety monitoring revealed no maternal, neonatal, or infant deaths during the entire study period, which is notable given the severity of underlying alloimmunization. However, a total of four serious adverse events (SAEs) were reported as possibly related to nipocalimab. These included one case of fetal growth restriction, one case of subchorionic hematoma, fetal heart rate decelerations in a single participant, and a placental abruption at delivery in another. In addition, one neonate delivered at 29 weeks of gestation experienced neonatal respiratory distress syndrome, which the investigator considered potentially related to in utero exposure to nipocalimab.

Beyond these SAEs, five maternal participants experienced mild to moderate infectious episodes requiring antimicrobial therapy. These events were interpreted as being consistent with the immunomodulatory mechanism of action of nipocalimab, which involves transient modulation of the maternal immune system. Importantly, all infections were manageable with standard treatments, and no long-term sequelae were reported.

4. Conclusions

Delivery Management in Rh Isoimmunization. In cases of hemolytic disease of the fetus and newborn (HDFN) due to Rh isoimmunization, the timing and mode of delivery should be determined individually, based on a comprehensive assessment of the obstetric history, fetal condition, and the capabilities of the maternity and neonatal care units at the healthcare facility. The application of standardized diagnostic criteria plays a critical role in developing an appropriate management strategy for each Rh-sensitized pregnancy, ultimately contributing to the reduction of perinatal complications and mortality.

Despite advances in perinatal medicine, perinatal mortality associated with HDFN remains at approximately 0.037‰. In the absence of effective prenatal intervention, the progressive fetal anemia caused by immune-mediated red blood cell destruction can lead to hypoxemia, which triggers a hyperdynamic circulatory response. Over time, this places an increasing burden on the fetal heart, resulting in the development of heart failure and portal hypertension.

These hemodynamic disturbances are often accompanied by hepatomegaly due to extramedullary hematopoiesis and iron overload, eventually progressing to anasarca (generalized edema), which includes the accumulation of fluid in the fetal peritoneal, pleural, and pericardial cavities, as well as subcutaneous tissue. This condition is known as hydrops fetalis and represents the most severe manifestation of HDFN.

Without timely and appropriate intrauterine treatment, such as intrauterine transfusion, the disease may progress to the point of antenatal fetal demise.

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