MATERNAL INTRAVENOUS IMMUNOGLOBULIN IN RH-ALLOIMMUNIZED PREGNANCIES WITH SEVERE FETAL ANEMIA

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Abstract. *To compare pregnancy outcomes in Rh-alloimmunized patients managed with maternal plasmapheresis followed by intravenous immunoglobulin (IVIG) versus those managed without maternal immunomodulatory therapy. This comparative observational cohort included 36 pregnancies (21 in the main group and 15 in the comparison group). In both groups, intrauterine transfusion (IUT) was performed for suspected severe fetal anemia (MCA >1.5 MoM), with or without hydrops. In the main group, each patient underwent plasmapheresis followed by IVIG. Baseline characteristics were comparable: median antibody titer was 1:32 in both groups, and gestational age at admission was 25.2 ± 4.3 vs 24.0 ± 3.1 weeks. The mean number of IUTs per pregnancy was numerically lower in the main group, with a maximum of 3 versus 4 procedures, although this should be interpreted in the context of shorter gestation in the comparison group. Live birth occurred in 19/21 (90.5%) versus 6/15 (40.0%) pregnancies. Delivery occurred later in the main group. Neonates in the comparison group had more severe early postnatal courses. Maternal plasmapheresis with IVIG was associated with improved survival, prolonged gestation, and increased intervals between IUT procedures.*

Keywords*: Rh alloimmunization; plasmapheresis; intravenous immunoglobulin; intrauterine transfusion; fetal anemia*

Introduction.

Hemolytic disease of the fetus and newborn (HDFN) due to maternal red-cell alloimmunization remains a clinically important cause of fetal anemia, hydrops fetalis, preterm birth, and perinatal loss. Contemporary guidance continues to recommend Doppler assessment of the fetal middle cerebral artery as the principal noninvasive method for surveillance, and an MCA peak systolic velocity above 1.5 MoM remains the standard threshold for referral for invasive evaluation and preparation for intrauterine transfusion (IUT) [5,8].

IUT remains the cornerstone treatment for severe fetal anemia; however, it is an invasive procedure that requires specialized expertise and carries procedural risk. Current reviews emphasize that, despite excellent outcomes in experienced centers, the ideal strategy is still to prevent or delay the onset of severe anemia, especially in early gestation when fetal intervention is technically more difficult and clinically riskier [2,4].

Maternal immunomodulatory approaches, particularly therapeutic plasma exchange (plasmapheresis) and IVIG, have been explored as adjunctive strategies in high-risk alloimmunized pregnancies. Earlier series and more recent meta-analytic evidence suggest that IVIG with or without plasma exchange can prolong gestation to the first IUT, reduce hydrops, and improve live birth rates in severe early-onset disease, although the effect on total IUT burden has been less consistent [3,6,7,9,11].

The present study was conducted to evaluate whether a practical combined therapy: plasmapheresis followed by IVIG could reduce the clinical severity of Rh alloimmunized pregnancies. The specific aim was to compare the main group and a comparison group with regard to IUT burden, gestational prolongation, live birth, and neonatal treatment requirements.

Material and methods of research.

The study was conducted at the Republican Scientific and Practical Medical Center for Maternal and Child Health in 2025. A comparative observational cohort study was performed. The dataset contained 36 pregnancies complicated by Rh alloimmunization: 21 patients in the main group and 15 in the comparison group. The main group underwent maternal immunomodulatory treatment, whereas the comparison group did not receive plasmapheresis or IVIG. In both groups, pregnancies were monitored for fetal anemia. When severe fetal anemia was identified by MCA Doppler >1.5 MoM, with or without signs of fetal hydrops, IUT was performed according to fetal condition and gestational age. In the main group, the therapeutic protocol was standardized: each patient underwent plasmapheresis every other day for three sessions, followed by IVIG (Bioven 10%, 50 mL, slow intravenous infusion, max. for three doses).

The extracted variables included obstetric history, gestational age at admission, antibody titer, diagnosis category, MCA MoM, maternal treatment protocol, number of IUT procedures and gestational age at pregnancy completion, neonatal status, birthweight, Apgar score, and neonatal therapy. The principal outcome for the present comparative analysis was documented live birth. Secondary outcomes included pregnancy completion at a later gestational age, numerical burden and interval of IUT, and severity of the neonatal course.

Results and discussion.

The main group included 21 pregnancies, and the comparison group included 15. Antibody titers were in nearly all pregnancies of the main group and in most pregnancies of the comparison group. The median antibody titer was 1:32 in both cohorts. Gestational age at admission was broadly comparable based on available records. In the subset with documented MCA values, fetal anemia severity was high in both groups, with a mean MCA MoM of 1.70 ± 0.31 in the main group and 1.86 ± 0.23 in the comparison group. Importantly, the comparison cohort had substantially more missing baseline entries, especially for gestational age, MCA MoM, and neonatal variables, which must be considered when interpreting between-group differences.

In the main group, maternal treatment: each patient received three plasmapheresis sessions and three IVIG administrations. Neither intervention was used in the comparison group. IUT was required in both cohorts once severe fetal anemia had been identified. Moreover, the maximum number of IUT procedures in a single pregnancy was 3 in the main group versus 4 in the comparison group. The interval between procedures in the main group was longer than comparison group.

The most pronounced between-group difference was observed for pregnancy survival. Documented live birth occurred in 19 of 21 pregnancies (90.5%) in the main group and in 6 of 15 pregnancies (40.0%) in the comparison group (Fisher exact p=0.002) (Table 1). Pregnancies in the main group also reached a later gestational age at completion than those in the comparison group (35.4 ± 1.9 vs 28.1 ± 7.0 weeks among available records). Among pregnancies with recorded birthweight, the mean neonatal weight in the main group was 2550 ± 598 g versus 1550 ± 324 g. The pattern of earlier pregnancy termination, extreme prematurity, and substantially more complicated neonatal adaptation in the comparison cohort is consistent with more severe uncompensated disease progression.

Nineteen liveborn infants were documented in the main group. Of these, 10 (52.6%) required exchange transfusion. Phototherapy and supportive neonatal care were also recorded in several cases, overall, the perinatal period was more favorable. In the comparison group, six liveborn infants were documented, but all were born in severe condition, with a markedly more complicated early neonatal course characterized by severe anemia at birth, respiratory compromise related to prematurity, need for intensive care, intensive phototherapy and transfusion support, and prolonged inpatient treatment.

Table 1.

Interventions and outcomes in the two cohorts

Outcome	Main group	Comparison group	Interpretation
Maximum IUT procedures in one pregnancy	3	4	Greater repeat IUT burden in comparison group, The interval between procedures was more than 2 weeks.
Live birth, n (%)	19/21 (90.5%)	6/15 (40.0%)	Fisher exact p=0.002
Gestational age at pregnancy completion, weeks	35.4 ± 1.9 (n=17)	28.1 ± 7.0 (n=4)	Later completion in main group
Neonatal condition among liveborn infants	Exchange transfusion in 10/19 (52.6%); generally treatable neonatal HDFN, overall, the perinatal period was more favorable	All 6 liveborn infants were in severe condition, with extreme prematurity/severe anemia and NICU-level care	Heavier neonatal morbidity in comparison group

This comparative cohort suggests that maternal plasmapheresis followed by IVIG may substantially improve the trajectory of Rh-alloimmunized pregnancies at high risk of severe fetal anemia. The dominant clinical signal in the present dataset was a shift from a 40.0% live birth rate in the comparison group to a 90.5% live birth rate in the main group. This survival advantage was accompanied by later pregnancy completion, which is itself clinically meaningful because advancing gestational age improves neonatal resilience and expands postnatal therapeutic options.

The mechanistic rationale for combined therapy is biologically plausible. Plasma exchange decreases the maternal circulating antibody load, whereas IVIG may modulate Fc-mediated transport and immune effects, potentially delaying transplacental antibody-mediated hemolysis. This concept is consistent with earlier reports of combined plasmapheresis and IVIG in severe maternal red-cell alloimmunization and with subsequent series showing successful integration of maternal immunotherapy with later IUT when needed [7,9,11].

Our findings also align with evidence that is more recent. The 2024 individual patient data meta-analysis of maternal IVIG in severe alloimmunization found prolongation of gestation to first IUT, reduced hydrops, reduced fetal demise, and improved live birth, while not demonstrating a substantial reduction in the total number of IUTs among live births [6]. This pattern closely matches the present cohort, where the principal benefit appears to be an increased interval between IUTs, improved fetal survival, and prolonged pregnancy.

The PETIT study and subsequent literature similarly support the concept that antenatal immunomodulation can postpone severe disease and delay early IUT in selected high-risk pregnancies [1,3]. Current guidance still positions MCA Doppler surveillance and timely IUT as the standard response to severe fetal anemia, which underscores that maternal therapy should be viewed as an adjunct or disease-modifying strategy rather than a replacement for fetal therapy [2,4,5,8].

The neonatal findings in our cohort require careful interpretation. A sizable proportion of liveborn infants in the main group still required exchange transfusion, indicating that maternal therapy did not eliminate neonatal hemolytic disease. This therapy leads to a more favorable postnatal course in newborns. Nevertheless, the neonatal course in the main group remained more favorable than in

the comparison cohort, where the smaller number of liveborn infants were delivered earlier and in substantially worse clinical condition. International postnatal data have shown that higher gestational age at birth is associated with lower exchange transfusion frequency and fewer adverse outcomes, supporting the clinical importance of pregnancy prolongation itself [10].

Conclusion.

In this comparative cohort of Rh-alloimmunized pregnancies, maternal plasmapheresis followed by IVIG was associated with an increased interval between intrauterine fetal blood transfusion procedures, markedly improved fetal survival, and a later gestational age at delivery compared with the comparison cohort. The burden of IUT was numerically lower and the maximum number of repeat IUT procedures per pregnancy was reduced, although this effect should be interpreted cautiously. Overall, the data support the use of combined maternal plasmapheresis and IVIG as a clinically meaningful adjunct strategy aimed at converting early severe disease into viable pregnancy with a more manageable neonatal course.

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