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CASE REPORT

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Clinical response to therapeutic plasmapheresis and intravenous immunoglobulin in pregnancies complicated by alloimmunization despite persistently high titers: Report of two cases

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Key Clinical Message

Plasmapheresis and IVIG use in cases of alloimmunization during pregnancy are effective strategies when severe early fetal anemia is anticipated. Despite no change in antibody titer levels before and after plasmapheresis, clinical response was observed in both fetuses, and both had an excellent obstetrical outcome.

Abstract

Hemolytic disease of the fetus and newborn is a potentially lethal complication of alloimmunization, and intrauterine fetal blood transfusion (IUBT) is the standard treatment and care plan for severe fetal anemia. However, IUBT is technically unattainable before 20 weeks of gestation. Plasmapheresis and intravenous immunoglobulin (IVIG) are the two treatment modalities described in the literature that postpone the need for transfusion until after 20 weeks. Here, we present two cases of alloimmunization (one with anti-Kell and the other with anti-D). Both had poor outcomes in previous pregnancies because of the early development of severe fetal anemia and hydrops before 24 weeks of gestation. Both patients underwent three sessions of plasmapheresis before 18 weeks, followed by weekly IVIG infusion, which continued until 23–27 weeks of pregnancy. Antibody titers were measured before and after plasmapheresis. In addition, weekly MCA Doppler was performed to monitor the development of severe fetal anemia requiring blood transfusion, which was diagnosed when the peak systolic velocity (PSV) was 1.5 multiples of the median or more. The first patient underwent IUBT at 24 weeks and the second at 28 weeks, as indicated by the MCA Doppler. Both patients were delivered by cesarean section, the first at 34 weeks and the second at 36 weeks, for different obstetrical indications. Both pregnancies resulted in a live birth. We conclude that the use of plasmapheresis and IVIG in alloimmunization during pregnancy is an effective treatment strategy when severe early fetal anemia is anticipated before 20 weeks of gestation. Despite no change in antibody

titer levels before and after plasmapheresis, a clinical response was observed in both fetuses, and both had excellent obstetrical outcomes.

KEYWORDS

alloimmunization, antibody titer, case report, hemolytic disease of the fetus and newborn, plasmapheresis

1 | INTRODUCTION

Intrauterine blood transfusion (IUBT) is an essential part of treatment for patients with hemolytic disease of the fetus and newborn (HDFN).[1] Patients who develop anemia before the gestational age of 20 weeks present a significant challenge, given higher rates of complications with IUBT at that gestational age. Therapeutic plasmapheresis and intravenous immunoglobulin (IVIG) have been used in similar cases to delay the need for IUBT. The American Society of Apheresis guidelines suggest that alloimmunization in pregnancy is a recognized indication of plasmapheresis.[2] Given the strength of the evidence, the guidelines recommend providing it based on the assessment of individual cases (as a category III indication). The immunomodulatory effects of plasmapheresis and IVIG in these conditions are not entirely clear but are likely partially explained by antibody removal from maternal plasma. Some previous publications observed antibody titer reduction along with the clinical response.[3,4]

We report two cases of alloimmunized pregnant women against different red cell antigens who had previous pregnancies affected by HDFN at an early gestational age. We describe the protocol used for management, antibody titration, fetal monitoring results, and fetal/neonatal outcomes.

2 | CASE REPORT/CASE PRESENTATION

2.1 | Case 1

A 31-year-old woman (gravida 4 para 2+1 miscarriage) was referred to our center on the 13th week of gestation for management of pregnancy complicated by alloimmunization against antigen K. Her obstetrical history is reported as follows: The first pregnancy was uncomplicated and delivered at 37 weeks of gestation by cesarean section due to cephalopelvic disproportion; she had a healthy newborn with no evidence of anemia or jaundice. The second pregnancy was complicated by a spontaneous miscarriage at 8 weeks of gestation with no known etiology identified. Her third pregnancy was complicated by hydrops that was diagnosed at 27 weeks. Unfortunately, at the time of diagnosis, the fetus had severe fetal anemia with MCA-PSV at 1.9 multiples of the median (MoM) and severely impaired cardiac function with poor cardiac contractility consistent with long-standing fetal anemia. She had inconsistent prenatal care before diagnosis, and her latest obstetrical visit was almost 4 weeks prior to the presentation. Screening the mother for red cell antibodies revealed she was alloimmunized against the K antigen. She underwent two sessions of IUBT procedures at 27 and 29 weeks with subsequent improvement in fetal anemia and hydrops, albeit the fetal cardiac function did not recover. A cesarean section had to be performed at 30 weeks due to breech presentation in active preterm labor and preterm premature rupture of the membrane. The newborn had a hemoglobin of 8 g/dL, and the direct antiglobulin test was positive. The female newborn was admitted to the neonatal intensive care unit and required an exchange transfusion and phototherapy. She eventually died at 2 months of age from complications of heart failure.

Upon referral to our center for management of her fourth pregnancy at 13 weeks, investigations were performed and showed the mother's blood group was A Rh(D) positive. Red cell phenotyping showed her red cells were negative for K antigen. Antibody screening was positive, and antibody identification revealed the presence of anti-K with a titer of 1:512. The fetus's father was tested for the K antigen and was found to be K+, as expected. Given the previous obstetric history, we anticipated the development of severe fetal anemia before 20 weeks. We agreed on using plasmapheresis and IVIG per institutional protocol to delay the onset of severe anemia and the need for IUBT. At the gestational age of 17 weeks, she had three sessions of plasmapheresis (using the Spectra Optia apheresis system) on alternating days, processing 1.5 plasma volumes in each session and using 5% albumin as replacement fluid. The antibody titer dropped to 1:256 after plasmapheresis, then increased again to 1:2048 before IVIG use. Weekly IVIG was administered at a dose of 1 gram per kg of body weight from weeks 19–23. MCA-PSV reached 1.7 MoM at 21 weeks and 6 days. IUBT was offered to treat fetal anemia; however, the mother declined fetal transfusion due to the associated risks of early IUBT. She agreed to weekly monitoring and IVIG until 24 weeks. The fetal

MCA-PSV dropped temporarily to 1.3 MoM after IVIG and increased again, reaching 1.7 MoM at 24 weeks. The fetus did not develop signs of fetal hydrops throughout the follow-up period. Four IUBT procedures were performed at 24, 27, 29, and 31 weeks. Transfused blood was allogeneic O Rh(D) negative and K negative and met all requirements for IUBT.[5] The nadir fetal hemoglobin level before transfusion was 7.3 g/dL, and the titer of anti-K fluctuated throughout the pregnancy, reaching 1:512 at the time of delivery. Table S1 in the Data S1 details the patient's diagnostic and therapeutic data. The mother delivered by cesarean section at 34 weeks of gestation due to the onset of preterm labor. Apgar's score was six at 1 min and seven at 5 min. The female newborn weighed 2.2 kg, and her hemoglobin was 15.4 g/dL. The forward grouping of the cord blood sample showed that blood group A. Rh(D) typing was positive. Passively transmitted anti-K was identified. Both phenotyping for the K antigen and direct antiglobulin test were negative. The newborn was jaundiced and required triple phototherapy but did not require any transfusions. She was discharged at the age of 10 days in good condition. At 1 month of age, the newborn had a hemoglobin of 11 g/dL, and the reticulocyte count was 8%. She remained clinically well upon follow-up at 6 months, with hemoglobin of 11.7 g/dL. Repeated investigations at 6 months of age confirmed the infant's blood group was A Rh(D) positive, and the phenotyping for K antigen was positive. The antibody screening of the infant and direct antiglobulin tests were negative.

2.2 | Case 2

A 31-year-old woman (gravida 5 para 3+1 miscarriage) was referred to our center for management of pregnancy complicated by alloimmunization with anti-D at high titer. Her blood group was O Rh(D) negative, and her husband's blood group was O Rh(D) positive. The first pregnancy was complicated by intrauterine fetal death at 32 weeks, secondary to fetal hydrops with unknown etiology. Rh immunoglobulin prophylaxis was administered within 24 h after delivery. During the second pregnancy, anti-D antibodies were detected, and weekly MCA Doppler followed the fetus to detect fetal anemia. At 32 weeks of gestation, the fetus was found to have severe fetal anemia and developed mild ascites and pleural effusion. IUBT was unavailable at the treating hospital, and referral to another institution was not feasible due to logistical reasons, so a cesarean section was performed at 32 weeks to facilitate postnatal treatment. The male newborn had anemia and jaundice, which required neonatal intensive care, and he received red cell transfusions and phototherapy. The newborn was eventually discharged home in good condition. The third pregnancy was

TABLE 1 Summary of patient's diagnostic and therapeutic data.

Case	Gestational age during TPE	Maternal alloantibody	Pre-TPE titer	Post-TPE titer	Duration of IVIG	Gestational age at first IUBT	MCA-PSV before the first IUBT (MoM)	Fetal hemoglobin before 1st IUBT (g/dL)	Total number of IUBTs	Gestational age at delivery (weeks)
1	17 weeks	Anti-K	1:1024	1:256	5 weeks	24	1.7	7.3	4	34
2	15 weeks	Anti-D	1:1024	1:2048	10 weeks	28	1.86	5.6	4	36

complicated by a miscarriage at 7 weeks of gestation. The fourth pregnancy was complicated by the development of fetal hydrops at 22 weeks, and four intrauterine transfusions were performed with trivial improvement in fetal condition. At 26 weeks, the patient developed intrauterine fetal death and was delivered by cesarean section.

Upon referral to our center for management of the fifth pregnancy at 12 weeks, the initial assessment identified an anti-D titer of 1:1024. Given the poor obstetric history, plasmapheresis and IVIG use were planned to delay the need for IUBT as per our institutional protocol. She had three sessions of plasmapheresis at 15 weeks of gestation (using the Spectra Optia apheresis system) on alternating days, processing 1.5 plasma volumes in each session, and albumin was used as replacement fluid. IVIG was then administered weekly from Week 15 to Week 25 of gestational age at a dose of 1 gram per kg. The antibody titer was 1:2048 and did not change until delivery. The MCA-PSV remained below 1.5 MoM until 28 weeks, when the first IUBT was performed, and then repeated at 30, 32 and 34 weeks. Table S2 in the Data S1 presents details of the patient's diagnostic and therapeutic data. The patient was delivered through elective cesarean section at 36 weeks of gestation. Forward ABO grouping from the cord was O. Rh(D) typing of the newborn was negative. Antibody screening and identification revealed anti-D antibodies and the direct antiglobulin test was negative. The female newborn had a hemoglobin of 10.9 g/dL, bilirubin of 5.7 mg/dL, and direct bilirubin of 0.7 mg/dL. She required a transfusion of red cells, phototherapy, and intensive care. The newborn was discharged after 7 days in good condition. Repeat laboratory testing at 5 months of age revealed that the blood group was O Rh(D) positive; antibody screening and direct antiglobulin test were negative.

A summary of both patients' diagnostic and therapeutic data is presented in Table 1.

3 | DISCUSSION/CONCLUSION

Plasmapheresis and IVIG have been used as immunomodulatory measures in many conditions. Several case reports, case series, and case–control studies support the effectiveness and safety of their use, separately or in combination, in patients at risk of early HDFN to delay the need for the first IUBT.[3,4,6–14] A Cochrane review search for randomized clinical trials evaluating the effect of IVIG in pregnancies affected by HDFN failed to identify any trials,[15] and we could not identify any such trials in our literature search. Such a trial is eagerly awaited, given the risk of publication bias and the various regimens described.

In women with clinically significant red cell alloantibodies, titration of alloantibodies during pregnancy is recommended to allow physicians to identify those pregnancies with the highest risk of fetal anemia.[16] A titer of 1:16 (or a rising titer) is usually considered critical and indicates the need for more frequent clinical/radiological fetal monitoring.[16] An exception is anti-K, where the risk of HDFN is high at any titer. Once the need for frequent fetal monitoring is established during pregnancy with high alloantibody titer, further antibody titration is rarely required. However, in the setting of clinical studies and case reports, antibody titration is frequently monitored. One of the essential findings among our patients was that clinical response was achieved despite the lack of a significant drop in antibody titer. In other studies, antibody titer dropped significantly after plasmapheresis and remained low during IVIG therapy.[3–13]

Although anti-D and anti-K are both IgG antibodies recognized to have the potential for causing severe HDFN, anti-K has a unique suppressive effect on fetal erythroid progenitors, in addition to antibody-mediated hemolysis. Despite the difference in characteristics between anti-D and anti-K and the differences between our patients' past obstetric history and antibody titers, successful obstetric outcomes were achieved using our current protocol in both patients.

Patients may require plasmapheresis during pregnancy for many indications, and the procedure is associated with a high safety profile. However, a group of common complications may be encountered by all patients undergoing plasmapheresis, including central venous access complications (e.g., thrombosis, bleeding, and infection), citrate toxicity (presenting with hypocalcemia), hypotension (mostly vasovagal etiology), and transfusion reactions (when plasma is used as replacement fluid). The risks of these complications are similar in pregnant women, with a higher risk of hypotension and resultant fetal distress.[17] Normal saline infusion is usually effective in improving blood pressure during the procedure.

Our cases also serve as a good reminder that cord or neonatal blood testing results after IUBT may not be valid since testing may be reflective of transfused units.[18] In both of our patients, cord blood testing revealed negative results when red cells were phenotyped for the implicated antigen (K antigen for the first patient and D antigen for the second patient). Accurate results were obtained when the infant was beyond 120 days from the last transfusion. The recent IUBT may also explain the negative results on direct antiglobulin testing of the cord blood since the red cells in the cord samples were negative for the D or K antigen and were not coated by maternal antibodies.

In conclusion, based on the available literature, plasmapheresis and IVIG are effective measures to delay the need for IUBT in pregnant women with alloimmunization at risk of early HDFN. However, the published regimens are widely variable, and further studies are required

to determine the most effective strategy. Nevertheless, a successful pregnancy may be achieved despite persistently high antibody titers.

3.1 | Patient perspective

Although patients were initially worried about having plasmapheresis and its potential side effects, they were willing to have it in order to achieve a good pregnancy outcome. Both were very grateful after having live births.

AUTHOR CONTRIBUTIONS

Nedaa Bahkali: Writing – review and editing. **Ebtihal Alhawsawi:** Writing – original draft. **Kholoud Althakafi:** Writing – original draft. **Kholoud Arab:** Writing – review and editing. **Almotasimbellah Rayes:** Writing – review and editing. **Maha A. Badawi:** Supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical approval is not required for writing a case report by the ethical committee at King Abdulaziz University Hospital (KAUH).

CONSENT

Written informed consent was obtained from the patients for publication of the details of their medical case for this case report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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