Article published online: 2024-04-04

Double-Filtration Plasmapheresis and High-Dose Intravenous Immunoglobulin Therapy in a Case of Anti-M Alloimmunization

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AJP Rep 2024;14:e101–e105.

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Abstract

Hemolytic disease is a common cause of fetal morbidity and mortality. The anti-M blood cell alloantibodies are one of the most severe causes of fetal anemia and intrauterine death. Since no standard treatment method has been established for pregnant women, the management of this pathology is through conventional methods used for treating Rh blood-type alloimmunization. For the first time, we report a unique case wherein a pregnant woman who had intrauterine fetal death in two previous pregnancies with very low titers of anti-M antibodies had negative effects during very early pregnancy, which were successfully managed in her third pregnancy with a novel protocol. We aggressively managed the blood type (anti-M antibody) and blood platelet incompatibilities (anti-HPA-4b antibody) through combination therapy twice a week (46 cycles between 12 and 34 weeks) of double filtration plasmapheresis (DFPP) and high-dose γ-globulin (20–40 g/wk). An elective cesarean section was performed at 34 weeks, and a healthy neonate was born without detection of alloantibodies in the umbilical cord blood. Our report suggests that the combination of DFPP and intravenous immunoglobulin should be considered for the treatment of anti-M alloimmunization in pregnant women.

Keywords
- alloimmunization
- anti-M non-Rh antibody
- anti-HPA-4b antibody
- DFPP
- high-dose IVIG

Anti-M red blood cell (RBC) alloantibodies are observed in 0.3% of pregnant women,[1] in which it causes hemolytic disease of the fetus/newborn; currently, no standard treatment method has been established. It is managed by plasmapheresis and high-dose intravenous immunoglobulin (IVIG) therapy that are conventionally used for treating Rh blood-type alloimmunization during pregnancy. We report a unique case of a pregnant woman who had intrauterine fetal death (IUFD) in two previous pregnancies; the detected titers of anti-M antibodies were very low. Informed consent was obtained from the mother for publication of this case report.

Case Report

A 25-year-old woman presented to us at 8 weeks of pregnancy with a history of IUFD in two previous pregnancies. Following blood testing, a 16-fold increase in immunoglobulin (Ig)G-type anti-M antibody titer was observed during her *first pregnancy* (age, 21 years), which ended in IUFD at 36 weeks. In her *second pregnancy* (age, 23 years), anti-M antibodies were detected at 12 weeks, which increased 64-fold at 15 weeks, and resulted in hydrops fetalis and IUFD at 19 weeks. Blood type analysis revealed type O ccDEE

received
April 10, 2020
accepted
October 22, 2023

DOI https://doi.org/10.1055/s-0043-1777995.
ISSN 2157-6998.

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NN in the patient and type O CCDee MM in her husband. IgG-type anti-M antibody titers were observed to be increased 32 times postpartum until 3 months.

In her *current (third) pregnancy*, IgG-type anti-M antibodies were elevated by eight times from 6 to 11 weeks. Owing to her history of IUFD at relatively low anti-M antibody titers, antibody depletion by a twice-weekly course of double filtration plasmapheresis (DFPP) was initiated at 12 weeks of pregnancy. Fresh frozen plasma was used as replacement solution but was changed to 5% albumin solution during the second round when she displayed allergy symptoms. After DFPP, fibrinogen levels decreased, but not below 70 mg/dL. The reduced Ig levels during DFPP were replenished with γ-globulin preparations (20–25 g/wk, increased to 40 g/wk from 22 weeks) (►**Fig. 1**). The IgG-type anti-M antibody titers decreased from 128 times at 12 weeks to 2 to 16 times at 15 weeks before DFPP administration, with a further drop after each DFPP administration (►**Fig. 2**).

As RBC alloimmunization is sometimes accompanied by platelet alloimmunization,[2] screening for HPA and HLA antibodies was conducted at 22 weeks. Thus, anti-HLA antibody was negative, but anti-HPA antibodies (anti-HPA4b) were confirmed in her serum. HPA typing showed type 1/a 2a/a 3a/b 4a/a 5a/a 6a/a 7a/a 15a/a in the patient and type 1a/a 2a/a 3b/b 4a/b 5a/a 6a/a 7a/a 15a/a in her husband. The same treatment was continued for platelet alloimmunization owing to the risk of neonatal alloimmune thrombocytopenia (NAIT), and anti-HPA4b levels were monitored (►**Table 1**). Fetal middle cerebral artery peak systolic velocity (MCA-PSV) was also measured from 16 weeks to monitor for fetal anemia (►**Fig. 3**) to guide the decision to continue pregnancy.

Uterine contractions and cervical length shortening were encountered at 24 weeks and immediately managed using oral nifedipine. The fetus did not show signs of hydrops fetalis, remained well, and had an estimated fetal weight of −0.8 to −1.3 standard deviation (SD) for gestational age on the growth curve. Owing to the significant burden imposed by frequent DFPP, an elective cesarean section was planned at 34 weeks. After the 46th DFPP session (16-fold increase in IgG-type anti-M antibodies and an MCA-PSV of 1.39 multiple of the median), a course of antenatal corticosteroid therapy was administered and a male neonate (birth weight, 1,822 g; Apgar scores, 7 [1 minute] and 9 [5 minutes]; umbilical artery pH 7.34) was delivered. At 1-month postpartum follow-up, the mother had a 128-fold increase in IgG-type anti-M antibody titer.

The newborn was admitted to the neonatal intensive care unit for urgent care. Blood test revealed hemoglobin (Hb) levels of 12.6 g/dL, platelet count of 121,000/μL, O Rh(+) type, type 4a/band HPA type, and eightfold increase in IgG-type anti-M maternal antibodies. Although his antibody disassociation test was positive, he possessed antibodies with anti-M specificities, and his direct globulin test was negative. The newborn had HPA-4b positive platelets, but no anti-HPA antibodies, so the possibility of NAIT was excluded. The newborn was discharged 6 weeks after birth and developed normally over 2 years of follow-up.

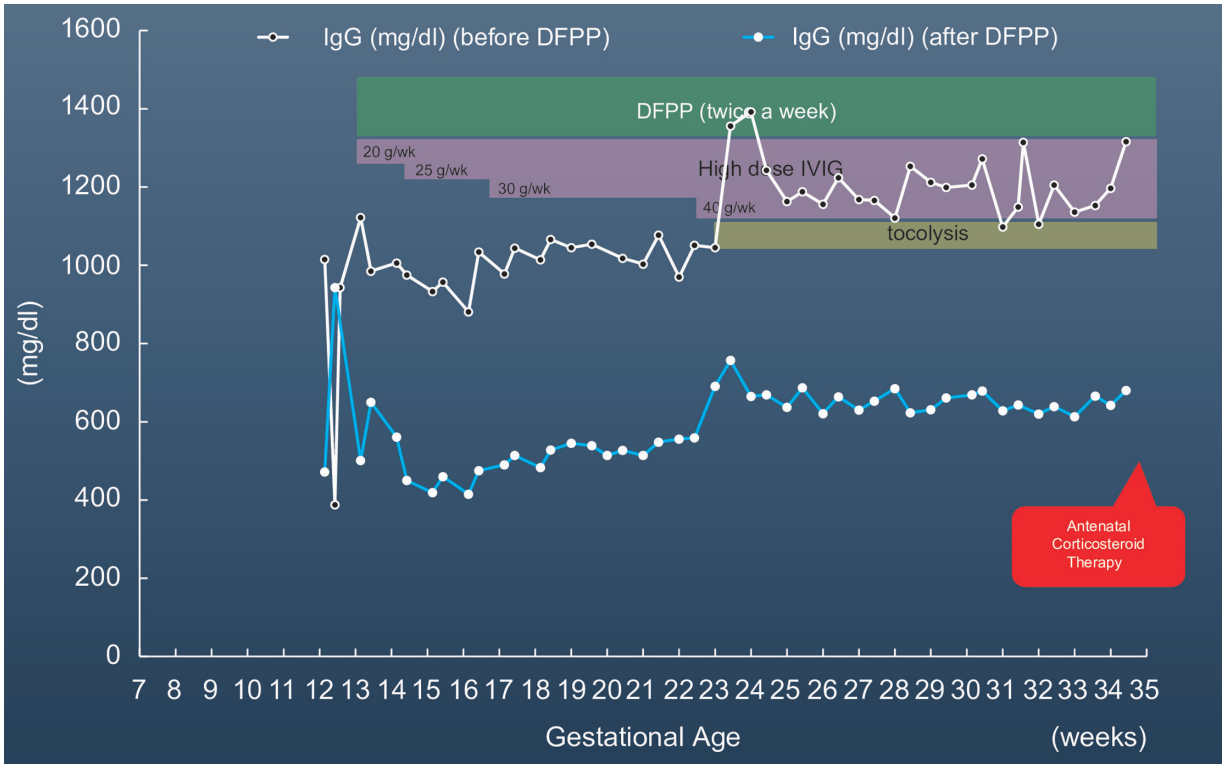

Fig. 1 IgG concentration in the bloodstream also decreased after DFPP treatment. DFPP, double filtration plasmapheresis; Ig, immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity.

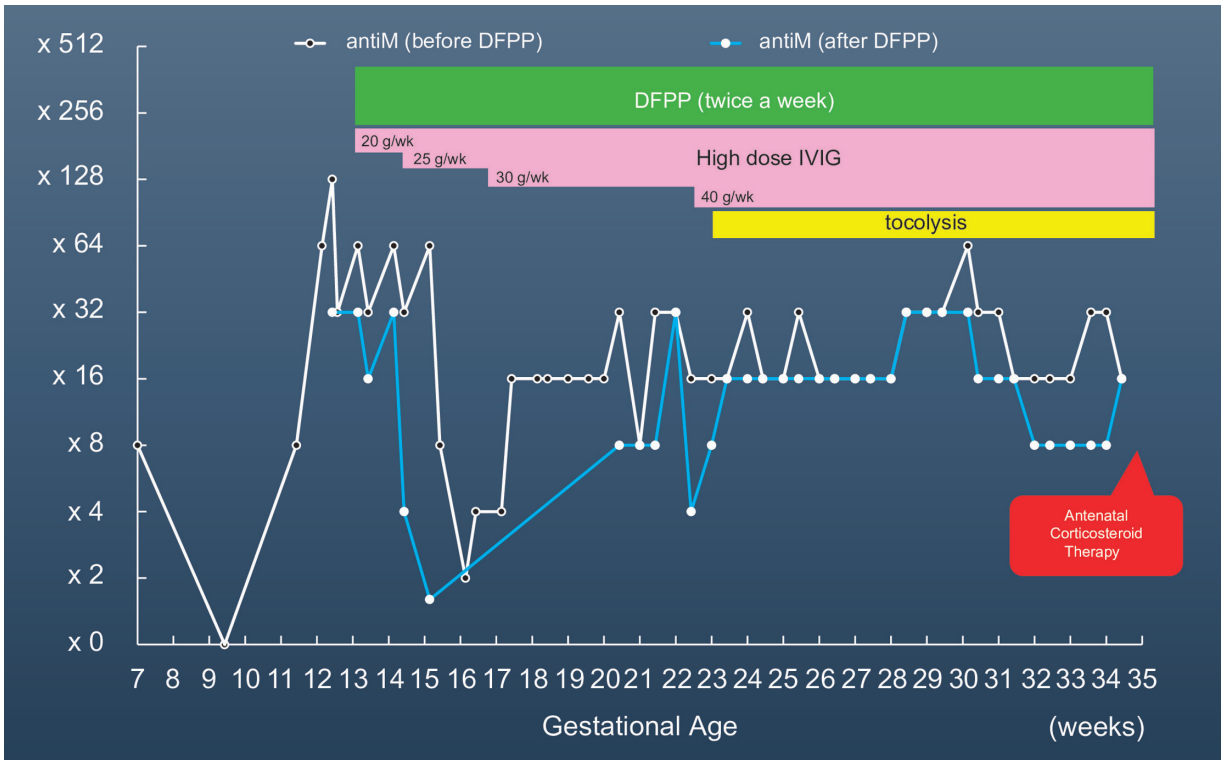

Fig. 2 Changes in IgG-type anti-M antibody levels with DFPP treatment. DFPP, double filtration plasmapheresis; Ig, immunoglobulin; IVIG, intravenous immunoglobulin.

Discussion

The anti-M blood cell alloantibody is one of the most severe causes of fetal anemia and intrauterine death, and no standard treatment has been established for this pathology.[3] Currently, there are three different types of approaches to deal with this pathology: an A1—*Conservative approach*, such as ultrasonographic measurement of MCA-PSV or direct measurement of Hb level through umbilical cordocentesis, is often adopted in milder cases. However, if severe fetal anemia or hydrops fetalis is observed, newborns are delivered preterm. 2—*Interventional approach*, such as intraperitoneal fetal blood transfusion or neonatal exchange transfusion and fetal intraperitoneal injections of Ig, is adopted if symptoms of anemia are present.[4] 3—*Preventative methods*, such as plasmapheresis and high-dose IVIG therapy are adopted to prevent such symptoms from emerging. As intrauterine transfusion via intravascular is possible from 18 to 20 weeks of gestation, and prior to 18 weeks (from 16 weeks of gestation), intraperitoneal transfusion can be performed.[5,6]

Table 1 Gestational age and changes in anti-HPA-4b antibody titer

Pregnancy (wk)	Anti-HPA-4b antibody titer	
	Before DFPPa	After DFPPa
24	×256	×256
26	×128	–
28	×256	×256
30	×128	×128
31	×64	×64
32	×32	×16
33	×128	×128
34	×512	×256

Abbreviation: DFPPa, double filtration plasmapheresis administration.

Since we have demonstrated that DFPP can achieve approximately 70% antibody depletion rate, a twice-weekly regimen of DFPP was chosen to achieve a satisfactory depletion in antibody levels.[7] Owing to the history of recurrent IUFD at relatively low titers of anti-M antibodies, we supplemented DFPP with high-dose IVIG therapy. High-dose IVIG therapy and administration of anti-D globulins have been previously shown to prevent allosensitization by negative feedback and reduce the transfer of erythrocyte antibodies to the newborn by saturating villus IgG Fc receptors. In addition, the treatment reduces fetal erythrocyte lysis by the reticuloendothelial system.[8,9] To be effective, high-dose IVIG therapy such as plasmapheresis must be started when the mother is 10 to 12 weeks pregnant.[10] Reports have suggested an IVIG dosage of 400 mg/kg (mother's weight) for 5 days for 3 to 6 weeks.[10]

However, in the current case, we applied a twice-weekly DFPP regimen that could decrease Ig levels, and administrated a higher dosage of IVIG, which started at 12 weeks of gestations with 400 mg/kg (mother's weigh) and gradually increased to 800 mg/kg (mother's weight), taking into account that the mother's weight before pregnancy was 50 kg. The patient

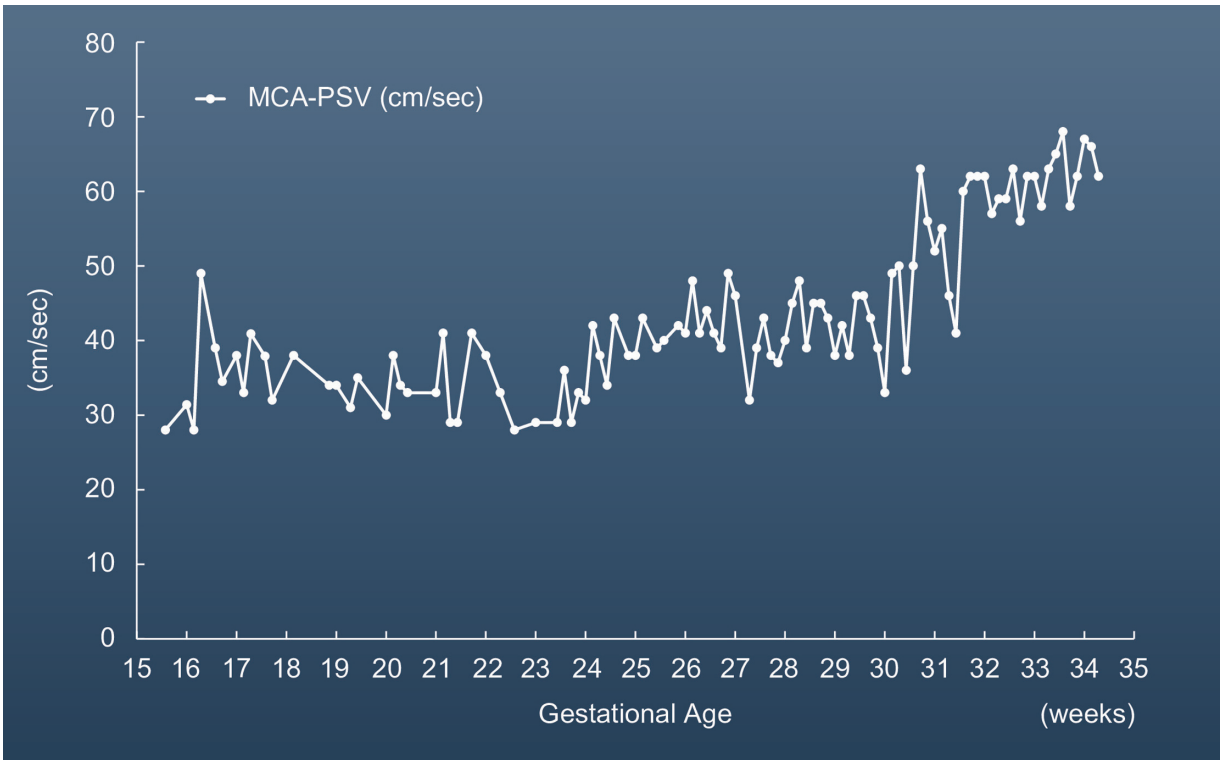

Fig. 3 The MCA-PSV level was 1.24 MoM at 30 weeks but was consistently > 1.50 MoM after 32 weeks. DFPP, double filtration plasmapheresis; IVIG, intravenous immunoglobulin; MCA-PSV, middle cerebral artery peak systolic velocity; MoM, multiple of the median.

tested positive for anti-HPA-4b antiplatelet antibodies, the most common type of anti-HPA antibody in Japanese individuals.[11] Anti-HPA antibodies are observed in 0.6 to 0.8% of pregnancies and may manifest as NAIT in 10% of these cases,[12] which is why DFPP and IVIG were continued while monitoring the fetal status. As uterine contractions are a potential cause of fetomaternal transfusion and further sensitization by increased fetal blood inflow to the mother's bloodstream, the increased production of anti-M antibodies was a concern. Tocolytics were therefore immediately administered when uterine contractions occurred in the 22nd week.

Conclusion

This report showed that a combination of DFPP and IVIG achieved a successful outcome in a pregnant patient with anti-M and anti-HPA alloimmunizations, and a history of recurrent IUFD. We strongly recommend that a combination of DFPP and IVIG as in these cases should be considered the first option as a preventive method in the treatment of anti-M alloimmunization in pregnant women.

Ethical Approval and Informed Consent

Data for this retrospective study were obtained from the medical records of the patients treated until delivery at the Fukushima Medical University (FMU) Hospital, Japan. Informed consent was obtained from the patient, and this human subject research complied with all the relevant national regulations and institutional policies and was conducted in accordance with the tenets of the Declaration of Helsinki. The study was approved by the ethics committee of FMU (No. 29368).

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

Editorial support, in the form of medical writing, assembling tables and creating high-resolution images based on the authors' detailed directions, collating author comments, copy editing, fact checking, and referencing, was provided by Editage, Cactus Communications.

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