OBSTETRICS

Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization

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OBJECTIVE: The objective of the study was to report the maternal and perinatal outcome in patients with severe red cell alloimmunization in pregnancy who were treated with immunomodulation therapy.

STUDY DESIGN: This was a retrospective multicenter case series. Patients with a history of early second-trimester fetal loss secondary to severe maternal red cell alloimmunization or patients with markedly elevated maternal antired cell titers felt to be consistent with poor fetal outcome were offered treatment. Therapy consisted of serial plasmapheresis followed by weekly infusions of intravenous immune globulin (IVIG). Maternal titers were measured before and after plasmapheresis.

RESULTS: Pregnant patients with either a history of a previous perinatal loss (n = 7) or markedly elevated maternal antibody titers (n = 2) were treated with combined plasmapheresis and IVIG. All 9 fetuses subsequently required intrauterine transfusions (median 4; range 3-8). All infants survived with a mean gestational age at delivery of 34 weeks (range 26-38 weeks). Maternal antired cell titers were significantly reduced after plasmapheresis ($P < .01$) and remained decreased during IVIG therapy. Serial peak middle cerebral artery velocities remained below the threshold for moderate to severe fetal anemia during therapy.

CONCLUSION: Combined immunomodulation with plasmapheresis and IVIG represents a successful approach to the treatment of severe maternal red cell alloimmunization.

Key words: hemolytic disease of the fetus and newborn, intravenous immune globulin, plasmapheresis, red cell alloimmunization

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Although anti-D immune globulin, introduced in 1968, has reduced the frequency of Rhesus alloimmunization, fetal anemia remains a problem for patients with anti-D as well as other antired cell antibodies. Hemolytic disease of the fetus/newborn (HDFN) is characterized by severe fetal anemia leading to increased cardiac output, tissue hypoxia, lactic acidosis, fetal hydrops, and eventual in utero death.[1]

Since its introduction in the 1960s, intrauterine transfusion (IUT) has markedly improved the perinatal outcome in cases of maternal red cell alloimmunization. Refinement in technique to include the use of cordocentesis and intravascular transfusion has allowed for the salvage of even hydropic fetuses. The treatment of HDFN prior to 20 weeks' gestation is limited by technical aspects inherent in gaining fetal intravascular access in conjunction with tenuous fetal physiology secondary to severe anemia.

Plasmapheresis is a known historical treatment for HDFN.[1] With the development of IUT techniques that have been associated with an 85-90% perinatal survival, plasmapheresis has been abandoned as a treatment modality.[2] In some case series, intravenous immune globulin has resulted in a prolongation in gestation prior to the need for IUT.[3] Combination treatment with plasmapheresis and IVIG for the treatment of red cell alloimmunization in pregnancy has also been reported in the literature. A MEDLINE literature review from 1989 to 2005 located only 2 articles reporting a total of 7 patients receiving both plasmapheresis and intravenous immune globulin (IVIG) in these pregnancies.[4,5]

We sought to describe our experience with a combined immunomodulation therapy of plasmapheresis and IVIG in cases of very severe maternal red cell alloimmunization. The treatment was performed in an attempt to deter the development of fetal anemia and prolong pregnancy to a gestational age at which IUT was technically possible and more likely to be successful.

Materials And Methods

This retrospective multicenter study reviewed cases of severe maternal red cell alloimmunization treated between the years 1996 and 2005 at the University of North Carolina School of Medicine, Duke University Medical Center, the Hutzel Women's Hospital at Wayne

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State University, Providence St. Vincent Medical Center, Lehigh Valley Hospital, and Baylor College of Medicine. Institutional review board approval for the abstraction of the patients' medical records was obtained at the University of North Carolina at Chapel Hill.

Patients included in this study were all treated in consultation with 1 of the authors (K.J.M.). The therapy was considered innovative rather than experimental in these severe cases, and therefore local institutional review board therapy at each center was not sought prior to treatment. Inclusion criteria included a history of a previously affected pregnancy associated with fetal hydrops, anemia, or intrauterine fetal demise (IUFD) presenting prior to 24 weeks' gestation. Because subsequent pregnancies are usually associated with even more severe HDFN earlier in gestation, it was felt that these patients were candidates for this salvage therapy. In addition, in a minority of cases, a markedly elevated maternal antibody titer for a red cell antibody known to be associated with severe HDFN and believed to result in early fetal anemia and possible fetal demise was also considered an inclusion criterion.

Standardized data abstraction forms were sent to the physicians who treated each patient. These forms requested the following information: history of previous pregnancy, antibody involved, initial antibody titer prior to plasmapheresis, estimated gestational age (EGA) at onset of treatment, number of plasmapheresis sessions, antibody titer after plasmapheresis, EGA at onset of IVIG dosing, number of IVIG doses, fetal hematocrit prior to the first intrauterine transfusion, EGA at time of first IUT, number of IUTs, EGA at delivery, pregnancy outcome, and neonatal treatment required for anemia including phototherapy and simple or exchange transfusions.

The consultation provided to the 6 centers involved the following protocol: single volume plasmapheresis was to be initiated every other day for 3 procedures after the 12th week of gestation, depending on the clinical scenario. Volume replacement consisted of 5% albumin. After the third plasmapheresis exchange, a 1 g/kg loading dose of IVIG diluted in normal saline was administered after premedication with 25 mg of intravenous diphenhydramine HCl and 1000 mg of oral acetaminophen. The 10% IVIG infusion was begun at a rate of 60 ml/hour and increased by 30 ml/hour every 30 minutes to achieve a maximum rate of 240 ml/hour. The following day, a second dose of 1 g/kg IVIG was given. A weekly dose of 1 g/kg IVIG was provided to the patient until 20 weeks' gestation.

In cases of a heterozygous paternal phenotype, amniocentesis was performed at 15-16 weeks' gestation to confirm the fetal antigen status. Noninvasive or invasive fetal testing was then used to determine whether IUT was required for further treatment. Some centers utilized cordocentesis, whereas others measured middle cerebral artery (MCA) Doppler peak systolic velocities (PSV) plotted on the curve as described by Mari et al[6] to determine whether the fetus was at risk for anemia. If severe fetal anemia was present at the time of the initial cordocentesis, IUTs were performed as per the protocol for the treating center. The timing of delivery was left to the discretion of the maternal-fetal medicine specialist involved in each case.

The primary objective evaluated by this study was the comparison of perinatal outcome from the previous pregnancy with that in the current pregnancy after treatment with combined plasmapheresis and IVIG. Secondary objectives included the assessment of changes in antibody titer before and after plasmapheresis. The trends in serial maternal antibody titers and MCA-PSV values were also evaluated during the course of treatment.

An exact binomial test was used to compare perinatal outcomes between successive pregnancies in each patient. Red blood cell antibody titers are routinely reported as the reciprocal of the last tube in serial dilutions with a positive agglutination reaction.[1] To compare the antibody titer levels before and after plasmapheresis, the titers were compared using a Wilcoxon signed-rank test. A P value of less than .05 was considered statistically significant. Analyses were performed with SAS 8.2 software (SAS Institute Inc, Cary, NC).

RESULTS

Nine patients from 6 different centers were enrolled in the study from 1996 to 2005. Of the patients included, 3 received their care at the University of North Carolina, 3 at the Baylor College of Medicine, and 1 at each of the other medical centers participating in this series. Seven patients were enrolled for previous perinatal loss (IUFD, n = 6 and neonatal death at 28 weeks on the first day of life, n = 1), whereas 2 were included for markedly elevated maternal antibody titers at first presentation. The demographic data for the study population is described in Table 1.

All 9 patients received plasmapheresis, every other day, for 3 treatments upon initial presentation. These patients subsequently underwent IVIG treatments. The number of IVIG treatments ranged from 5 to 18 for each individual patient and were given from as early as 6 to as late as 30 weeks of gestation. Four patients (44%) experienced side effects from IVIG treatment. Side effects in these patients included headache in 2, chest congestion in 1, and mild flushing and pruritus in 1. One of the patients with headaches required oral narcotics for pain relief. No complications were reported during plasmapheresis treatments.

All 9 patients subsequently required intrauterine transfusions during their pregnancies. The mean gestational age at first IUT was 24 weeks (range 18-28 weeks). A median of 4 IUTs (range: 3-8) was performed on each fetus. The mean fetal hematocrit prior to the initial IUT was 22.7% (range 11-33%). Patient #7 underwent an emergency cesarean section secondary to prolonged fetal bradycardia during the fourth IUT of the pregnancy (Table 2). No other IUT complications were reported.

All 9 fetuses survived the treatment regimen. The mean gestational age at delivery after treatment with plasmapheresis and IVIG was 34 weeks (range 26-38 weeks). Five infants (56%) required simple transfusions and 2 (22%) needed phototherapy.

When compared with a previous pregnancy with IUFD, survival was markedly

TABLE 1
Patient demographics

Pt.	Age	G&P	Ab	Enrollment Ab titer	Enrollment GA
1	30	2-1101	Kell	512	14
2	35	11-5336	D	*	10
3	37	4-2112	Kell	256	13.1
4	20	5-0321	D	1,024	5.2
5	31	4-2022	Kell	512	9.6
6	41	4-2202	D	512	9
7	43	7-3223	D	4,096	8
8†	43	6-3123	D	8,192	10.5
9†	28	2-2002	Kell	16,384	16

Ab, maternal antibody; *GA*, gestational age (weeks); *G&P*, gravidity & parity (term, preterm, abortion, living children); *Pt*, patient.

* Antibody titer not drawn.

† Included secondary to markedly elevated antibody titer.

improved in the treated pregnancies (0 of 7 vs 7 of 7; $P < .01$). IUTs in the treated pregnancy were performed later than in the prior pregnancy (21.7 ± 3.1 vs 24.2 ± 3.3 weeks), although this difference was not statistically significant ($P = .06$). Fetal hematocrit at first IUT was also higher at the first IUT in the treated pregnancies (13.6 ± 7.2 vs 22.3 ± 8.2%); however, this trend was again not statistically significant ($P = .13$) (Table 2).

One patient (patient #2) failed to have an initial antibody titer performed prior to initiation of the treatment protocol. Maternal antibody titers after plasmapheresis treatment were significantly lower than prepheresis titers ($P < .01$; Table 3). In 5 patients, maternal antibody titers drawn after treatment with IVIG could be compared with postpheresis titers. In these patients, there were no statistical differences between antibody titers, with all remaining within 1 dilution of their titer after plasmapheresis ($P = .5$) (Table 3 and Figure 1).

In 6 patients, fetal MCA-PSV measurements were obtained during treatment with plasmapheresis and IVIG. Although statistical analysis could not be performed secondary to a lack of normative data for gestational ages of less than 18 weeks' gestation, serial MCA-PSV values remained below the extrapolated

TABLE 2
Prior and current pregnancy outcomes

	Prior pregnancy					Current pregnancy				
Pt	Titer	GA at IUT#1	Pre-IUT#1 Hct	# of IUTs	Outcome (GA at delivery)	Titer	GA at IUT#1	Pre-IUT#1 Hct	# of IUTs	Outcome (GA at delivery)
1	256	23.4	17	3	Neo death (28)	512	27	27	4	Survival (33)
2	512	20.5	6	1	IUFD (20)	*	23.5	16.8	6	Survival (34)
3	512	†	n/a	n/a	IUFD (25)	256	24.5	27	5	Survival (35)
4	1024	18	9.5	1	IUFD (18)	1024	18.2	‡	8	Survival (36)
5	2048	§	§	§	IUFD (19)	512	22	12	6	Survival (38)
6	2048	25	22	4	IUFD (31)	512	28.6	26	3	Survival (35)
7	1024	†	n/a	n/a	IUFD (17)	4096	21.2	29	4	Survival (27)
8	1028	§	§	§	Survival (31)	8192	26.4	11	3	Survival (34)
9	8192	§	§	§	Survival (37)	16,384	26.3	33	4	Survival (37)

GA, gestational age (weeks); *Hct*, fetal hematocrit (percent); *IUFD*, intrauterine fetal demise; *IUT*, intrauterine transfusion; *n/a*, not applicable; *Pt*, patient.

* Antibody titer not drawn.

† IUFD prior to IUT.

‡ Fetal hematocrit not obtained at time of IUT.

§ No IUT performed.

TABLE 3
Pre- and postplasmapheresis and post-IVIG antibody titers

Patient	Preplasmapheresis titer*	Postplasmapheresis titer*†	PostIVIG titer†
1	512	512	512
2	‡	‡	1024
3	256	128	‡
4	1024	256	124
5	512	128	‡
6	512	256	256
7	4096	512	‡
8	8192	256	512
9	16,384	256	256

* $P < .01$.

† $P = .5$, Wilcoxon signed-rank test.

‡ Antibody titer not drawn.

moderate to severe anemia threshold during the course of plasmapheresis and IVIG treatment. By evaluating the MCA-PSV values available for the patients in this study, it appears that plasmapheresis and IVIG maintain the fetus in a nonanemic state long enough to achieve a gestational age at which IUT was technically feasible (Figure 2).

Comment

Treatment of HDFN in the early second trimester is associated with poor perinatal outcomes.[7,8] Technically, the clinician faces a daunting challenge of targeting umbilical cord vessels measuring less than 3-5 mm. Even if successful in completing an IUT at this extremely premature gestational age, many fetuses cannot tolerate transfusion because of acute hemodynamic changes and consequently die in utero. Of severely anemic, hydropic fetuses, in utero fetal death after IUT has been reported to be as high as 36.8%.[7]

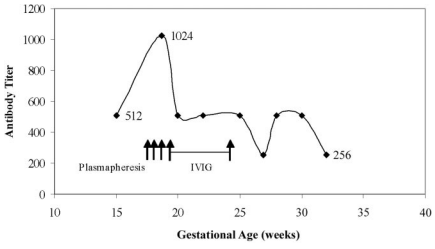
In more recent years, van Kamp et al[8] illustrated an overall IUT procedure-related fetal loss rate of 5.6% when performed at less than 20 weeks' gestation. These difficulties gave us a reason to search for a noninvasive treatment for the fetus in these circumstances.

Both plasmapheresis and IVIG have been utilized individually in the treatment of maternal red cell alloimmunization. Angela et al[9] presented a series of 14 cases of anti-D alloimmunized patients treated with intensive plasma exchange alone. The patients underwent plasmapheresis for a mean duration of 13.5 weeks with successful perinatal outcomes in 75% of the cases. Voto et al[3] retrospectively compared IVIG combined with intrauterine transfusion with IUT alone. Severe fetal anemia was less common and gestational age at first IUT was greater in the IVIG/IUT group, compared with those treated with IUT only. Their study also demonstrated that fetal mortality was reduced by 36% in the IVIG/IUT group.[3]

Similarly in the current study, universal perinatal survival was achieved with a combined treatment of plasmapheresis, IVIG, and IUT. When compared with the previous pregnancy, incremental increases in fetal hematocrit at the first IUT in conjunction with a later gestational age at the time of the first IUT were also achieved with this therapy.

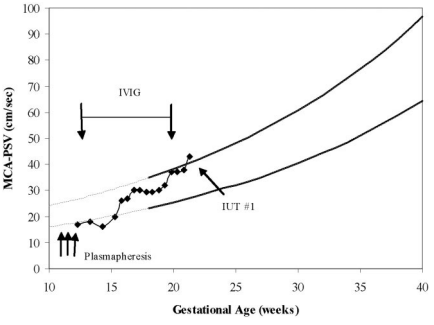
Combined plasmapheresis and IVIG therapy has been utilized in a variety of antibody-mediated diseases. In Sjogren's syndrome, systemic lupus erythematosus, and Guillain-Barré syndrome, clinicians have utilized combined plasmapheresis and IVIG in their treatment.[10–12] Combined therapy with both plasmapheresis and IVIG has been evaluated in randomized trials for the treatment of Guillain-Barré syndrome. The Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group showed that plasmapheresis followed by IVIG had a small advantage over plasma exchange or IVIG alone in the interval to return of neurological function.[13]

FIGURE 1
Maternal antibody titer from patient #1 during plasmapheresis and intravenous immune globulin treatment is shown.



Individual plasmapheresis is indicated (*vertical arrows*). The period of weekly intravenous immune globulin infusions (IVIG) (*connected arrows*) is also indicated.

FIGURE 2
Serial MCA velocities from patient #7 are shown.



Normal (1.0 MoM) serial MCA velocities (*lower curve*) are represented. Moderate to severe fetal anemia (1.5 MoMs) (*upper curve*) is represented. Serial MCA velocities from 18 to 40 weeks' gestation, as described by Mari et al[6] (*solid curve lines*) and extrapolated with exponential trend line from 10 to 18 weeks' gestation (*dashed curve lines*) are shown. Individual plasmapheresis (*vertical arrows*) is indicated. The period of weekly intravenous immune globulin infusions (IVIG) (*connected arrows*) is indicated. *MCA-PSV*, middle cerebral artery Doppler peak systolic velocities; *IUT*, intrauterine transfusion; *MoM*, multiples of the median.

Combined treatment in maternal red cell alloimmunization has been reported in 7 patients in the literature. Zhao et al[5] treated 5 patients with poor obstetrical history with plasmapheresis followed by IVIG administration every 7-20 days according to their antibody titers. All 5 patients had live-born infants without undergoing intrauterine transfusion therapy. Fernández-Jiménez et al[4] described 2 other cases treated with both plasmapheresis and IVIG. One patient had a history of 6 first-trimester spontaneous abortions and the other had a history of 2 second-trimester intrauterine fetal demises. Both patients underwent plasmapheresis and IVIG weekly to 3 times weekly throughout gestation, and neither had IUTs performed. With treatment, both patients had successful pregnancy outcomes with delivery at 36 weeks.

Plasma exchange has been reported to reduce the maternal antibody titer; however, a rebound to levels higher than the prepheresis titer has been seen.[14,15] Indeed, our study showed that plasmapheresis was successful in acutely lowering the maternal antibody titer. Margulies et al[16] treated 24 patients with severe Rh disease with IVIG alone and noted a decline in antibody levels in the majority of the patients in their series. We therefore hypothesized that replacing the loss of immunoglobulin removed by plasmapheresis with IVIG would prevent the rebound phenomenon that was previously reported.

Available data from our patients indicated that the antired cell titer remained at postpheresis levels during the course of IVIG. IVIG may also function through other mechanisms to delay the onset of severe HDFN. Transplacental passage of the putative antibody may be inhibited by competition for Fc receptors. Alternatively, transplacental passage of the IVIG may effect an Fc blockade of the fetal reticuloendothelial system, thereby reducing the degree of phagocytosis of sensitized fetal red cells. The exact mechanism by which combined plasmapheresis/IVIG therapy can ameliorate the effects of maternal red cell antibody could not be determined by the present study.

Our study is limited by a variety of factors. This is a retrospective analysis of 9 patients, which included variations in protocol as decided on by the individual clinicians caring for the patients in the study. Another shortcoming is inherent in the therapy itself. IVIG costs approximately $6000/week of treatment.[17] For this reason in our protocol, we limited IVIG therapy to 20 weeks' gestation in the majority of cases. Our rationale was that IUTs could then be technically performed and more successful after this gestational age. In our study, patients received an average of 11 weeks of IVIG before the addition of plasmapheresis and IUT costs as well as physician and hospital facility charges, making the treatment regimen costly. These factors may play an important role in the decision to proceed with combined therapy of plasmapheresis and IVIG for maternal red cell alloimmunization.

In conclusion, the enhanced rate of perinatal survival reported in this series along with the lack of rise in the MCA peak velocity in those fetuses that were monitored in a serial fashion lend credence to combined plasmapheresis/IVIG as a useful treatment in patients with severe red cell alloimmunization in pregnancy. Because 4 of the 9 patients in our series involved Kell alloimmunization in which the onset of fetal anemia can be rapid, the combined immunomodulation used in this study may be particularly suited for this subset of patients. Our series represents preliminary data that should be substantiated in a larger, prospective, randomized trial. With additional research, the future of therapy for severe HDFN may one day include directed maternal immunomodulation to prolong the development of fetal anemia and delay or eliminate the need for invasive procedures such as IUT.[18,19] ■

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