Effects of maternally administered immunoglobulin on platelet counts of neonates born to mothers with autoimmune thrombocytopenia: re-evaluation

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Summary

Objective: Since immunoglobulin is transported across the placenta, maternal administration of it theoretically seems attractive as an antenatal treatment for a fetus. However, the effects of antenatally administered intravenous immunoglobulin (IVIG) on fetal platelet counts have been controversial. Our series of 11 cases of idiopathic thrombocytopenic purpura (ITP) and a review of previous reports are presented. A combined retrospective analysis to know whether maternal response to IVIG is associated with improvement of fetal thrombocytopenia was conducted.

Methods: IVIG was given to 11 steroid refractory pregnancies with ITP. Good maternal response to the therapy was defined as an increase in the platelet count to greater than 50 x 10^9/L after completion of the IVIG infusion. Neonatal platelet counts of the umbilical cord were performed just after birth and followed-up for at least the first week of life.

Results: Seven of the 11 neonates had thrombocytopenia of less than 100 x 10^9/L, and two of them had severe thrombocytopenia of less than 50 x 10^9/L. Two out of two neonates born to mothers with a good response to IVIG were thrombocytopenic; whereas five out of nine neonates born to mothers with a poor response were thrombocytopenic. The combined retrospective analysis of our results and published reports have shown that fetal thrombocytopenia was not associated with the maternal response to IVIG but with the level of immunoglobulin G of neonates at birth. Passive thrombocytopenia was more frequently observed in neonates with normal levels of immunoglobulin G than those with elevated levels.

Conclusion: This combined analysis confirmed the proposed hypothesis that the lack of effect of maternally administered IVIG on fetal platelet counts may mainly be attributed to the insufficient therapeutic level of transferred immunoglobulin G in the cord blood.

Key words: Immunoglobulin; Thrombocytopenia; Pregnancy.

Introduction

In autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura; ITP), the autoantibody is formed against specific platelet surface glycoproteins, including IIb/IIIa and Ib/IX complexes [1]. This has special relevance in pregnancy because the placenta has receptors for the constant fragmenting (Fc) of the IgG immunoglobulin molecule facilitating active transport of immunoglobulin across the placenta to the fetal circulation [2]. There is a risk of intracerebral hemorrhage and consequent neurological impairment or death during the thrombocytopenic period in fetuses or neonates. Thus, the identification of a fetus at risk of thrombocytopenia has been a major concern in the obstetric management of women with ITP. Potential predictors of fetal/neonatal thrombocytopenia include the maternal platelet count, maternal antiplatelet antibody, maternal platelet associated IgG level, previous maternal splenectomy, and steroid therapy. However, the diagnostic value of these predictors remains controversial [3-7]. Such uncertainty has led to the introduction of invasive procedures for direct estimation of fetal platelet counts, such as percutaneous cordocentesis or fetal scalp sampling. When a fetus is found to be severely thrombocytopenic, a cesarean section is usually done. If antenatal treatment can be shown to consistently increase fetal platelet counts, the number of cesarean sections due to fetal thrombocytopenia would be reduced.

The antenatal treatment of choice might be maternally administered intravenous immunoglobulin (IVIG). IVIG has been shown to be effective in the treatment of mothers with ITP [8] and neonates with passive immune thrombocytopenia [9-11]. Since immunoglobulin is transported across the placenta, maternal administration is theoretically attractive as an antenatal treatment for the fetus. Although several case reports have shown the efficacy of IVIG given to mothers with ITP in preventing passive immune thrombocytopenia in the fetus [12-22], others have failed to show this [23-28]. Since most of the case reports have been anecdotal with less than three cases in each report, the effects of antenatally administered immunoglobulin on fetal platelet counts has remained controversial.

Recently, we had a case of neonatal death soon after delivery where passive immune thrombocytopenia might have been a contributing factor. The mother was steroid refractory and received IVIG before the delivery. This case led us to analyze and re-evaluate the effects of maternally administered IVIG on platelet counts of neonates born to mothers with ITP in our hospital. Our series of 11 cases of ITP and a review of previous reports are presented.

Materials and Methods

Pregnant women were included for the analysis if they had a previous diagnosis of ITP or had platelet counts of less than 100 x 10^9/L on more than one occasion with adequate or abundant megakaryocytes on bone-marrow aspiration. Subjects were excluded if there was evidence of preeclampsia, infection, thrombotic thrombocytic purpura or systemic lupus erythematosus. Most of the patients were treated by hematologists according to the following regimen. Corticosteroid (predonisone) was started if the maternal platelet count was less than 50~80 x 10^9/L or there was evidence of a bleeding diathesis. The usual dose of oral predonisone was 0.5 to 1.0 mg/Kg with tapering as soon as possible to a dose that maintained the platelet count at 50 x 10^9/L. For steroid refractory cases, monomeric polyvalent immunoglobulin was administered intravenously seven days before the planned induction of vaginal delivery or elective cesarean section near term. The usual dose was 400 mg/Kg/day for five consecutive days. A good response to therapy was defined as an increase in the platelet count to greater than 50 x 10^9/L after completion of the IVIG infusion [8]. For immunoglobulin refractory cases, platelet transfusions were given if the maternal platelet count was less than 20 x 10^9/L before a vaginal delivery and 50 x 10^9/L before a cesarean section. Neonatal platelet counts of the umbilical cord were performed just after birth and followed-up for at least the first week of life. Platelet counts between 50 to 99 x 10^9/L were defined as neonatal thrombocytopenia and a count of less than 50 x 10^9/L as severe thrombocytopenia.

The English and Japanese literature were reviewed using medical databases (EMBASE, MEDLINE, and JOIS) to select articles which reported the use of IVIG in mothers with ITP.

We extracted the reports in which the dose of IVIG given to mothers, maternal and neonatal platelet counts, and other demographic data were described in detail.

Results

The maternal response: From July 1982 to December 1995, 27 women with ITP delivered 36 babies in our hospital. According to the regimen mentioned above, IVIG was given to 11 pregnancies in 9 women with ITP. The details of these pregnancies are described in Table 1 (Cases 1 through 11). Two of the nine mothers had two pregnancies and delivered two babies each (Cases 1 and 7; Cases 9 and 10). Eight women had a history of ITP antedating the index pregnancy and two women had undergone a splenectomy. All the mothers had been given oral corticosteroids before the infusion. The median interval between completion of the infusion and delivery was two days (range: 0-15 days). The median maternal platelet count before and after the IVIG therapy was 22.5 (range: 4-340) and 73.0 (range: 15-200) x 10^9/L, respectively. Good response to the infusion was observed in two out of eleven cases.

The neonatal response: The median platelet count was 72 x 10^9/L at birth (range: 28-178). Seven out of 11 neonates had thrombocytopenia of less than 100 x 10^9/L, and two of them were severely thrombocytopenic. Although a postnatal decrease in the platelet count was observed in five neonates, corticosteroid or IVIG was not required and spontaneous recovery was observed in all cases. There was one neonatal death (case 6) because of intracranial bleeding which was considered to have occurred during labor. The platelet count of the fetal scalp sampling was 80 x 10^9/L in this case.

The relation of the maternal and neonatal response to IVIG: Two out of two neonates born to mothers with a good response were thrombocytopenic: 71 and 53 x 10^9/L (Case 4 and 7). Five out of nine neonates born to mothers with a poor response were thrombocytopenic.

Discussion

It is well known that maternal endogenous immunoglobulin is transported across the placenta. Immunoglobulin infused into the mother has also been shown to be able to cross the placenta from maternal to fetal circulation [29]. Therefore, high-dose IVIG therapy could theoretically treat the fetus at risk of passive thrombocytopenia. The proposed mechanisms of the action of immunoglobulin include: (1) a decrease in platelet antibody synthesis; (2) an interference or decrease in antiplatelet antibody transfer across the placenta; (3) a decrease in platelet binding to any platelet antibodies based on a competitive inhibition or steric hindrance; (4) and an interference with phagocyte-mediated immune clearance by the reticuloendothelial system [30].

However, our results failed to show the efficacy of IVIG on fetal platelet counts since the response rate at birth was 36% (4 out of 11 cases) in our series. If the published report [12-28] and our series are combined, the overall response rate is as low as 53% (17 out of 36 cases). As shown in Table 2, the combined retrospective study also failed to demonstrate a significant relation of the maternal response to IVIG and fetal/neonatal thrombocytopenia (risk ratio 1.06, 95% confidence interval 0.48-2.35). In other words, it was shown that the maternal response to IVIG cannot be a predictor of fetal/neonatal platelet counts.

The possible explanation for these results might be as follows. Immunoglobulin might not have been sufficiently transported across the placenta. The levels of immunoglobulin G in the maternal and cord blood had been measured in nine cases in the published reports and two cases in our series. In these cases, the levels of immunoglobulin G in the mothers were all elevated to as high as >1900 mg/dl (normal range: 640 to 1350 mg/dL), whereas the levels in the cord at birth were less than normal range (normal range: 830 to 1230 mg/dL) in 5 out of 11 cases. Figure 1 shows the relation of the cord level of immunoglobulin G and neonatal platelet counts in the combined retrospective analysis. There were significant differences in the neonatal platelet counts between two different levels of immunoglobulin G in the cord blood. Four out of five neonates with normal levels of immunoglobulin G were thrombocytopenic. However, only one out of six neonates with elevated immunoglobulin G level was thrombocytopenic. This phenomena can be partly explained by the possibility [27] that although maternally derived antiplatelet IgG crossed the placenta and caused passive ITP in the babies, exogenous IgG did not cross the placenta significantly, despite reaching pro-

Table 1. — *Effects of maternally administered IVIG on maternal and fetal platelet counts in cases of autoimmune thrombocytopenia.*

	MOTHER										NEONATE					
						Platelet count (10^9/L)			IV-Deliv.	Maternal	Platelet count (10^9/L)			Cord-		
Case	History of ITP	steroids	splen-ectomy	PA-IgG	Dose of IVIG g/Kg/Day (course)	before IVIG	after IVIG	Mode of Delivery	interval (day)	IgG (mg/dl)	at birth	nadir	therapy (response)	IgG (mg/dl)	PA-IgG	Ref
1	+	+	+		0.4/K/Dx5	17	39	VD	2		72	27(5)				
2	+	+	–	+	0.4/K/Dx5	10	15	CS	0		50	27(1)				
3	+	+	–		0.4/K/Dx5	35	72	VD	1		178					
4	+	+	+		0.4/K/Dx5	17	70	VD	15	2021	71	27(3)		820		
5	–	+	–	+	0.4/K/Dx5	56	85	CS	1		77	74(1)				
6	+	+	–	+	0.4/K/Dx5	20	32	CS	6		42					
7	+	+	+		0.4/K/Dx5	16	105	VD	3		53	29(3)				
8	+	+	+	+	0.4/K/Dx5	15	17	CS	1	2680	28			650		
9	+	+	–	+	0.4/K/Dx5	25	55	VD	1		106					
10	+	+	–		0.4/K/Dx5	28	36	VD	2		141	106(5)				
11	+	+	–	+	0.4/K/Dx5	42	35	VD	14		200					
12	–	+	–	+	0.4/K/Dx5	5	111	VD	0		251					24
13	+	+	–	+	0.4/K/Dx5(x2)	16	67	CS			201	15(4)	IVIG(+)		+	24
14	+	+	–		0.4/K/Dx5	71	113	VD	4		142					20
15	–	+	–		0.4/K/Dx5	18	130	CS	140		>100					20
16	–	+	–		0.4/K/Dx5	8	200	CS	1		129					15
17	+	+	–	+	0.4/K/Dx5	17	180	VD	14		normal			1200	+	14
18	–	+	–		25g/Dx5	5	73	CS	2		158					16
19	+	+	+	–	24g/Dx5	34	98	CS	1		115				–	16
20	+	+	+	–	0.49/K/Dx5(x6)	60	65	CS	70	3370	200			744	+	19
21	+	+	–	+	0.4/K/Dx5	87	175	VD	1		254				+	12
22	–	–	–	–	0.4/K/Dx5	50	200	CS	0		253					13
23	+	+	–	+	0.4/K/Dx5	30	ND	CS			30	10			–	23
24	+	–	–	–	0.4/K/Dx5(x2)	140	ND	CS			5	10			+	23
25	+	–	–	+	0.4/K/Dx5(x5)	340	ND	CS			80	1			+	23
26	–	+	–		0.3/K/Dx7	4.1	70	VD	6	2100	23	49		752		26
27	+		–		0.4/K/Dx5	50~100	194	CS		2397	34					27
28	+		–		0.4/K/Dx5	50~100	187	CS		2415	22	2(3)	IVIG(+)			27
29	–	+	–		0.4/K/Dx3	81	121	CS	3		50	10(3)	steroid			28
30	+	–	–		0.4/K/Dx3	50	184	CS	2		10	10	str+IVIG(+)			28
31	+	+	+		0.22/K/Dx5	11	90	CS	5	1900	44	20(3)	steroid	570		25
32	+	+	–	–	0.4/K/Dx5	10	25	VD	1	4350	93	75		1660		22
33	+	+	–	+	0.4/K/Dx5	10	30	VD	6	4500	100	55(4)		1540	+	22
34	+	+	–		0.4/K/Dx5(x4)	7	51	CS	2	3200	256	250		1461		18
35	+	–	–		0.4/K/Dx5	4	17	VD	1	3024	309	265(4)		1500		17
36	–	+	–	+	0.4/K/Dx5	29	166	VD	2	2190	450			1360	+	2

Abbreviations: ND, not described; Ref, reference number; CS, cesarean section; VD, vaginal delivery; IV-Deliv.interval, interval between delivery and completion of IVIG treatment. Cases 1 through 11, our series; Cases 12 through 31, the English literature; Cases 32 through 36, the Japanese literature.

tective IgG levels in a mother. The slow transfer of immunoglobulin across the placenta might be another postulated mechanism [13]. These explanations can be supported by the fact that a severely thrombocytopenic neonate born to a mother give IVIG showed a good and rapid response to postnatal administration of IVIG with remarkable elevation of the serum level of immunoglobulin G to 2345 mg/dL (Case 28).

Additionally, IVIG therapy may not always be effective in all cases even though the level of immunoglobulin G is sufficiently elevated. In case 32, for example, the neonate had thrombocytopenia (93 x 10^9/L) although the cord level of immunoglobulin G was as high as 1660 mg/dL. In their experience of the treatment of neonates with passive thrombocytopenia, Ballin *et al.* [9] reported an overall response rate of 75% (12 out of 16 cases of passive immune thrombocytopenia). In fetuses, therefore, it is likely that the expected response rate is similar to that of neonates if the fetal level of immunoglobulin G is sufficiently high in utero.

Similar results of the unreliable effects on maternal IVIG to fetuses have been reported in other types of immune disorders. For example, maternal administration of IVIG to decrease fetal hemolysis in Rh(D) disease has been reported with good [31] or poor results [32]. In an attempt to treat alloimmune thrombocytopenia, some investigators have reported their experience with successful results [33] and poor results [34, 35]. Therefore the effects of maternal administration of IVIG on such immune disorders still remains controversial. As an alternative treatment, direct administration of immunoglobulin to fetuses has recently been advocated to raise the fetal platelet count in alloimmune thrombocytopenia [36] or to prevent progressive hemolysis in Rh(D) disease [37]. Although they are anecdotal at present and not controlled-randomized studies, these reports indicate that in

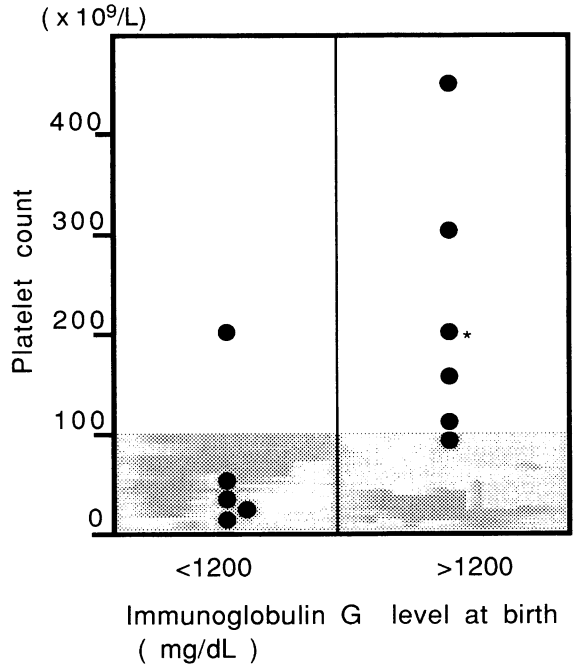

Figure 1. — The relation of the level of cord immunoglobulin at birth and neonatal platelet counts in the combined retrospective analysis. There were significant differences in the neonatal platelet counts between the two groups (Student *t* test; $p<0.05$). *: The platelet count was reported as normal in this case (Reference 14).

utero administration of immunoglobulin would be associated with an improved fetal platelet count in passive thrombocytopenia in ITP.

It has recently been reported that the risk of passive thrombocytopenia in ITP is much lower than previously thought [4, 38]. Furthermore, some authors have definitively concluded that cesarean section should only be performed for obstetrical indications [4, 39].

Nevertheless, cesarean sections are still performed in many institutions when the fetus is shown to be severely thrombocytopenic before delivery since there is no guarantee that serious morbidity caused by thrombocytopenia will not occur; although the estimated risk for serious consequences of the disease is likely to be 1-2% [40]. As shown in the combined retrospective analysis in this paper, the neonatal level of immunoglobulin G in the cord blood was sufficiently elevated in only half of the cases even though the maternal level was sufficiently elevated in all the cases after maternal administration of IVIG. Passive thrombocytopenia was more frequently observed in neonates with normal levels of immunoglobulin G than those with elevated levels. On the basis of these results, it would appar that the number of thrombocytopenic neonates would have been reduced if the fetal level of immunoglobulin had been raised sufficiently in such cases, including our case of neonatal death. In this regard, it is tempting to speculate that in utero administration of immunoglobulin would be an effective antenatal treatment for a consistent increase of fetal platelet counts and the reduction of cesarean sections. However, the decision to carry out the in utero treatment should be thoroughly weighed as to the relatively low risk of this disease versus the procedure itself.

Table 2. — *Relation between passive thrombocytopenia and maternal response to IVIG in the combined retrospective analysis*

	PIT (+)	PIT (–)	Total
Maternal response (–)	7	9	16
Maternal response (+)	7	10	17

A good response to therapy was defined as an increase in the maternal platelet count to greater than 50 x 10^9/L after completion of the IVIG infusion. Neonatal platelet counts of less than 100 x 10^9/L were defined as passive immune thrombocytopenia (PIT).

Conclusion

This combined analysis confirmed the proposed hypothesis that the lack of effect of maternally administered IVIG on fetal platelet counts may mainly be attributed to the insufficient therapeutic level of transferred immunoglobulin G in the cord blood.

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