Fetal and neonatal alloimmune thrombocytopenia : towards implementation of screening in pregnancy

Kamphuis, M.M.

Citation

Version:	Not Applicable (or Unknown)
License:	[Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)
Downloaded from:	https://hdl.handle.net/1887/49219

Cover Page

Universiteit Leiden

CHAPTER 8

LOWER-DOSE INTRAVENOUS IMMUNOGLOBULINS FOR THE TREATMENT OF FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA, A COHORT STUDY

MM Kamphuis
NP Paridaans
D Winkelhorst
A Wikman
E Tiblad
E Lopriore
M Westgren
D Oepkes

ABSTRACT

Background:

Intravenous immunoglobulins (IVIG) are the cornerstone in the treatment of pregnancies at risk for fetal and neonatal alloimmune thrombocytopenia (FNAIT). The most commonly used dose is 1.0 g/kg per week, not based on any dose finding study. IVIG is an expensive multidonor human blood product with dose-related side effects. Our aim was to describe the amount of severe thrombocytopenia according to two different doses of IVIG.

Study design and Methods

We performed a cohort study, where two dosage regimes of IVIG were evaluated in the treatment of pregnant women suffering from FNAIT with a previous affected child without intracranial hemorrhage (ICH). Cases, treated with 0.5 or 1.0 g/kg per week, were selected from the international multicenter No IntraCranial Hemorrhage (NOICH) registry. Outcome was neonatal platelet (PLT) count at birth and amount of severe thrombocytopenia. Furthermore the appearance of ICH was analyzed.

Results

A total of 109 women were included in the study, 46 in the 0.5 IVIG and 63 in the 1.0 IVIG group. There was no difference in PLT count at birth (mean, 112 vs. 119, crude difference 7; confidence interval [CI], -37.4-23.7) and incidence of severe thrombocytopenia (<30x109/L; n = 7/46 versus n = 7/63; odds ratio, 1.43 [CI 0.46-4.42]). No ICH occurred.

Conclusion

In pregnancies with FNAIT with a previous affected child without ICH, treatment with IVIG in a weekly dose of 0.5g/kg or 1.0 g/kg results in comparable neonatal PLT count at birth and degree of thrombocytopenia.

8

INTRODUCTION

Fetal or neonatal alloimmune thrombocytopenia (FNAIT) is a rare but devastating disease caused by platelet (PLT) destruction in the fetus or neonate through maternal (Ig)G allo-antibodies. In Caucasians, FNAIT is most commonly caused by the human platelet antigen (HPA)-1a.[1] Two percent of the Caucasian population is (HPA)-1a negative (HPA-1bb), thus, one in 50 Caucasian pregnant women is at risk to develop FNAIT. Actual sensitization occurs in 6 to 12% of HPA-1bb mothers, of whom one in three deliver a child with severe thrombocytopenia ($<50 \times 10^9$/L).[2] The most feared complication is ICH (intracranial hemorrhage), often leading to death or severe, irreversible neurologic damage, which occurs in 10% of newborns with severe thrmobocytopenia.[2,3] Unlike in the pathophysiologically similar red blood cell (RBC) alloimmunization, fetuses in a first pregnancy can be severely affected. In the absence of screening programs, the disease is virtually always only detected after birth of an affected child. Preventive measures can then be taken in the next pregnancy.

Until recently, repeated fetal blood sampling and intrauterine PLT transfusions were the choice of treatment for fetuses with alloimmune thrombocytopenia. Bussel and colleagues were the first, in 1988, to report beneficial effects of maternal administration of immunoglobulins (IVIG) in pregnancies with FNAIT.[4] The conventional dose of 1.0 g IVIG/kg per week was not based on any dose-finding studies. The dose originated from studies in patients with idiopathic thrombocytopenic purpura and in neonates with alloimmune thrombocytopenia.[5-8]

In the past decade, several studies have been published supporting the safety and efficacy of non-invasive, IVIG-only treatment in FNAIT.[9-11] Currently, our standard treatment of pregnant women at risk for a child with FNAIT with a previous affected child without ICH is a weekly dose of 1 g/kg per week. Radder and coworkers reported that placental antibody transfer is not further increased with increasing IgG concentrations in the mother.[12] This suggests a limitation of the placental transfer via the Fc-receptor, likely due to saturation.

To test the hypothesis that a lower dose of 0.5 g/kg per week IVIG might be equally effective in the treatment of FNAIT, an international, open-label randomized controlled trial (RCT) in women with FNAIT, with an affected sibling without ICH was performed.[13] Unfortunately this trial was prematurely ended due to lack of inclusion and we therefore had to conclude that we had insufficient data to show equivalence between the two treatment regimens. The aim of this study was to describe the neonatal PLT count and clinical outcome of two different dosages of IVIG in a large cohort of pregnancies affected by FNAIT.

8

MATERIAL AND METHODS

Study design and participants

We performed a cohort study of pregnant women affected by FNAIT treated with two different dosages of IVIG (0.5 g/kg per week vs. 1.0 g/kg per week).

Because of the limited evidence for any particular dose we decided, after prematurely ending the RCT in 2007, comparing 0.5 g versus 1.0 g of IVIG for FNAIT, to continue offering 0.5 g of IVIG /kg per week to FNAIT women, with a previous child without ICH. These cases were collected in our international Web-based No IntraCranial Hemorrage (NOICH) database (http://www.NOICH.org), initially started to gather data for the RCT but kept open for caregivers to collect and share data of FNAIT cases from 2000 to 2010. From that same database, women were treated with 1.0 g/kg per week were selected. Inclusion period ranged from 2007 to 2015. The timing of starting IVIG treatment in pregnancy differed per center according their local protocol.

All cases were women with singleton pregnancies, who previously gave birth to an affected sib, with a PLT count of fewer than $150x10^9$ /L but without an ICH. HPA alloimmunization was confirmed by the presence of maternal anti-HPA antibodies, and either a homozygous father or detection of the offending HPA antigen in the fetus by amniocentesis or cfDNA testing in maternal plasma in case of a heterozygous father.

Women with autoimmune thrombocytopenia, multiple pregnancies, fetuses and neonates with major congenital anomalies or chromosomal abnormalities, and women with a previous child with FNAIT and ICH were excluded. Patients with immunoglobulin-A deficiency were only excluded if they had a severe allergic constitution, and so were patients who ever had an allergic reaction to blood product due to anti-IgA anti. Finally cases that participated in the NOICH trial were left out.[13]

Medication and management protocol

Eligible women were offered the lower dose of 0.5 g/kg IVIG, to be started at 28 weeks of gestation. The brand of IVIG used in Leiden was Freeze-dried Immunoglobulin (CLB Sanquin) and Gamma Gard (Baxter International, Inc) .The medication was administered weekly until delivery over a period from 3 to 6 hours, according to the amount required and tolerance. Ultrasound was used to rule out fetal ICH just before start of the treatment and repeated monthly. No fetal blood samplings were performed at any time. The choice for type of delivery, elective cesarean section or intended vaginal delivery, was left to the obstetrician with consent from the patient. Standard recommendations at vaginal delivery were not to use fetal scalp electrodes or fetal scalp blood samplings and to refrain from ventouse or forceps application. As in other alloimmunized pregnancies, we aim for a delivery around 37 weeks of gestation.

Baseline demographics, medical and obstetric history were recorded in the MedSciNet NOICH database (http://www.NOICH.org). Directly after birth the PLT count in umbilical blood was tested, first automatically and in case of a count $<100x10^9$/L, a manual count was done. HPA compatible platelets were available within 12 hours after

birth. A neonatologist examined the child directly after birth. Treatment was left to the discretion of the neonatologist. Within the first days after birth a cranial ultrasound of the neonate was performed, and all signs or suspicions of bleedings were recorded.

Statistical analysis

Patient characteristics are presented as medians with interquartile range (IQR) or numerical values in numbers with percentages or categories. Data analysis was generated using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). A p value of 0.05 was considered significant. As data were not normally distributed data were analyzed using a Mann Whitney U test. Categorical data were analyzed using a chi-squared test. Correlation was analyzed using Spearman's correlation.

Outcome variables were reported as medians (PLT count at birth) with crude difference or numbers (severe thrombocytopenia) with percentages and odds ratio (OR). Confounding was prevented using regression analysis.

RESULTS

After ending of the trial in 2007, 46 cases were collected who received the lower-dose IVIG of 0.5 g/kg per week. Sixty-three cases could be selected from the NOICH database that were treated with 1.0 g/kg per week.

Baseline characteristics of the included cases and controls are shown in table 8.1, showing both groups to be equal for most relevant parameters, besides gestational age at start of IVIG treatment and total amount of IVIG per patient

Perinatal survival was 100%; no ICH was observed. Neonatal PLT count at birth did not differ significantly (112×10^9/L vs. 119×10^9/L; crude difference 7, confidence interval [CI], -37.4 to 23.7). Furthermore the number of cases of severe thrombocytopenia (<30×10^9/L) was not significantly different between the 0.5 IVIG group and the 1.0 IVIG group (n= 7 [15%] vs. n=7 [11%]; OR 1.43; CI 0.46-4.42). Neonatal PLT count at birth or amount of severe thrombocytopenia and gestational age at start IVIG were not correlated (p= 0.175 in Spearman's correlation).

Likewise regression analysis showed no significant difference in outcome. The outcome is given in table 8.2.

8

Table 8.1 *Demographic characteristics of patients with FNAIT treated with low-dose or higher dose-IVIG*

	0.5 g/kg IVIG (n= 46)	1.0 g/kg IVIG (n=63)	p value
Gravidity	3	3	
Parity	2	2	
Anti HPA-1a	36 (78)	52 (82)	0.41
5b	3	2	
1a/5b	1	2	
Other: 3a,15a (N)	6	7	
PLT count of sib	17 (8-30)	18 (13-35)	0.84
GA at start IVIG treatment	28 (28)	32 (27-34)	0.001 #
Total number of IVIG treatments	10 (9.5-11)	7 (5-10)	0.53
Total amount of IVIG, g (dose × no. IVIG)	5 (4,75-5,5)	7 (5-10)	0.002
Mode of delivery			
Vaginal	25 (56)	30 (48)	0.39
Cesarean	20 (44)	31 (49)	
GA age at birth	38 (37-38)	38 (37-38)	

GA gestational age, IVIG immunoglobulins
continuous variables are reported as median (IQR), and categoric variables as numbers (%)
Spearman showed no correlation

Table 8.2 *Primary and secondary outcome*

	0.5 g/kg IVIG (n= 46)	1 g/kg IVIG (N=63)	Crude difference	Adjusted* difference
ICH	0	0		
PLT at birth (x10⁹/L), mean (CI)	112 (87-138)	119 (102-137)	7 (-37,4-23,7) OR	0,349 (-31,2-31,9) Adjusted OR*
Severe thrombocytopenia (<30 x10⁹/L)	7 (15%)	7 (11%)	1,43 (0,46-4,42)	1,15 (0,76-4,52)
Severe thrombocytopenia (<50 x10⁹/L)	14 (30%)	12 (19%)	1,86 (0,76-4,52)	1,61 (0,65-4,0)
Other bleeding complications	0	0		

IVIG immunoglobulins
Continuous variables are reported as mean (CI), and categorical variables as number (%).
*adjusted for gestational age at start of IVIG

DISCUSSION

Our findings show no difference in neonatal PLT count at birth or degree of thrombocytopenia between the two different dosages of IVIG treatment in pregnancies complicated by FNAIT with an affected sibling with no ICH. These results confirm earlier findings from our uncompleted RCT comparing the lower 0.5 dose with the standard 1.0 dose of IVIG.[13]

Until 1984, the traditional management of subsequent pregnancies in women with a previous history of FNAIT consisted of an early elective cesarean section and transfusion of PLTs after birth. Since the publication of Daffos and colleagues (1984), one of the pioneers of fetal blood sampling (FBS), several centers throughout the world started treating fetal thrombocytopenia in a similar fashion to anemia due to RBC alloimmunization, by serial intrauterine PLT transfusions.[14-17] In 1988, Bussel and coworkers reported on seven cases of FNAIT successfully treated by maternal administration of IVIG, using 1 g/kg per week.[4] This dosage was based on their experience with idiopathic thrombocytopenic purpura. A few subsequent studies confirmed effectiveness of this treatment.[10,11,18] Until recently however, the need to give such a high dose was never challenged.

Previous in vitro studies have shown a limitation, likely by saturation, of Fc-receptor-mediated transplacental transport of IgG, which leads to the suggestion that increasing the dose of IVIG does not result in a higher concentration of IgG in the fetal circulation.[12,19] This was supported clinically by the findings of our RCT.[13]

Until now there is no consensus about the gestational age of starting IVIG treatment and recommendations differ about using a particular dose, (varying from 0.5 to 2.0 g/kg per week). The treatment of FNAIT is usually only stratified according to the presence or absence of ICH in the previous child and the timing of its occurrence.[20] Generally a history with an affected child with ICH leads to a higher dose of IVIG and an earlier onset of IVIG treatment.

Besides our RCT, three small randomized trials have been published comparing different regimens for treatment of FNAIT in pregnant women with a previous child without ICH without any difference in bleeding complications or PLT count.[21-23] In one of these studies randomization was done between different dosages IVIG (2.0g/kg per week vs. 1.0g/kg per week plus 0.5mg/kg per day prednisone), in the other two the comparison was between IVIG and either prednisone or dexamethasone. All studies confirm effectiveness of noninvasive IVIG treatment in preventing thrombocytopenia-related ICH, and although views on the optimal dose may differ, it appears clear that there is no place left for invasive treatment using PLT transfusions.[10]

The number of women included in our study is still limited. However with a cohort of 109 women treated with IVIG for FNAIT, it is still one of the largest studies evaluating treatment modalities in such a rare disease as FNAIT. Unless trials are done using screening of populations as a means of subject selection, it seems unlikely that prospective studies will ever be significantly larger.

Analysis of our patient characteristics showed a significant difference in gestational age at start of IVIG treatment between the two treatment groups. It is conceivable that starting IVIG in an earlier stage of pregnancy leads to better neonatal outcome. However this association was not found with regression analysis and no significant difference in outcome was seen. Explanation for the difference in gestational age at start IVIG treatment is a change in treatment protocol for FNAIT over the years, starting at 28 instead of 32 weeks, implemented to have a uniform policy in several European centers.

8

The cases in this study were collected from different countries and therefore may reflect several institutions policies. Since most countries only stratify antenatal treatment according to the presence or absence of ICH in a previous child we consider the two study groups comparable. Therefore it is not likely that this had led to any selection bias.

The use of any medication in pregnancy, especially substances that cross the placenta, should be carefully considered, balancing perceived benefit against potential harm for mother and fetus. Since most effects, both beneficial and harmful, are often dose-dependent, reducing the dose to the minimum effective level is an important principal.

As IVIG is known for its immunomodulating characteristics, care should be taken using it in pregnancy. However, apart from one study suggesting an increase of IgE, no clinically apparent adverse effects in early childhood could be demonstrated.[24,25] Serious maternal side effects such as aseptic meningitis, renal and cardiovascular dysfunction, are uncommon. Mild discomfort such as headache is often reported, and appears dose-dependent. All these issues underline the importance of using IVIG in pregnancies with FNAIT in the lowest possible effective dose.

IVIG is produced from blood of thousands of human blood donors, and it is expensive. The working mechanism is not clear. Most likely, it acts on various levels, in maternal serum, at the level of placental transfer if IgG and in the fetal blood, blocking Fc-receptors on macrophages.[26]

Recent research by Yougbare and colleagues supports the hypothesis that IVIG may aid in protection against bleeding, instead of merely causing a rise in PLTs.[27] They showed that impairment of angiogenesis rather than thrombocytopenia is the critical cause of the ICH in FNAIT. In their murine-model study, ICH only occurred in fetuses and neonates with anti–β3 integrin–mediated, but not anti-GPIbα–mediated FNAIT, despite similar thrombocytopenia in both groups. Only anti–β3integrin–mediated FNAIT reduced brain and retina vessel density, impaired angiogenic signaling, and increased endothelial cell apoptosis.

This might be an explanation for the phenomenon of 'nonresponders', that is, fetuses not responding to IVIG with PLT counts remaining less than 50×10^9/L, reported to be approximately 20%.[10,28] Also in our study neonates were born with severe thrombocytopenia ($< 30\times10^9$/L) despite IVIG treatment (respectively 15% in the 0.5 g of IVIG group and 11% in the 1 g of IVIG group). For PLT counts $< 50 \times 10^9$/L the figures were 30% and 19% respectively. None of the differences between both groups were significant. The persistent occurrence of (severe) thrombocytopenia under antenatal treatment seems worrying but the most important finding is that neither in our study nor in several other studies did ICHs occur, suggesting other protective effects of IVIG.[10]

Without routine screening for FNAIT in all pregnancies, most women nowadays can only be treated in the pregnancy after the birth of an affected child. We would support implementation of routine HPA type and antibody screening in the near future.[2] Reducing overall costs of a screening and intervention program, by lowering the dose of IVIG for immunized women, may help to accelerate its introduction.

In conclusion, our study shows no difference in neonatal PLT count or degree of thrombocytopenia when two different dosages of IVG are compared in the treatment of pregnancies complicated by FNAIT with an affected sibling with no ICH.

This suggests that a lower dose of IVIG might be as effective as the more standard higher dose of IVIG in preventing severe thrombocytopenia. Further prospective studies are needed to confirm this.

8

REFERENCES

1. Williamson LM, Hackett G, Rennie J, et al. The natural history of fetomaternal alloimmuniza-tion to the platelet specific antigen HPA-1a (PIAI, Zwa) as determined by antenatal screening. Blood 1998;92:2280–7.

2. Kamphuis MM, Paridaans N, Porcelijn L, et al. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. BJOG 2010;117:1335-43.

3. Knight M, Pierce M, Allen D, et al. The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: a UK national study using three data sources. Br J Haematol 2011;152:460-8.

4. Bussel JB, Berkowitz RL, McFarland JG et al. Antenatal treatment of -neonatal alloimmune thrombocytopenia. N Engl J Med 1988;319:1374–1378.

5. Hara T, Miyazaki S, Yoshida N, et al. High doses of gamma globulin and methylprednisolone therapy for idiopathic thrombocytopenic purpura in children. Eur J Pediatr 1985;144:40-2.

6. Newland AC, Boots MA, Patterson KG. Intravenous IgG for autoimmune thrombocytopenia in pregnancy. N Engl J Med 1984;26:261-2.

7. Derycke M, Dreyfus M, Ropert JC, et al. Intravenous immunoglobulin for neonatal isoimmune thrombocytopenia. Arch Dis Child 1985;60:667-9.

8. Sidiropoulos D, Straume B. The treatment of neonatal isoimmune thrombocytopenia with in-travenous immunoglobin (IgG i.v.). Blut 1984;48:383-6.

9. Radder CM, Brand A, Kanhai HH. A less invasive treatment strategy to prevent intracranial hemorrhage in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2001;185:683-8.

10. Van den Akker ESA, Oepkes D, Lopriore E, et al. Noninvasive antenatal management of fetal and neonatal alloimmune thrombocytopenia: safe and effective. BJOG 2007;14:469–73.

11. Yinon Y, Spira M, Solomon O, et al. Antenatal noninvasive treatment of patients at risk for alloimmune thrombocytopenia without a history of intracranial hemorrhage. Am J Obstet Gynecol 2006;195:1153–1157.

12. Radder CM, Kanhai HH, Brand A. On the mechanism of high dose maternal intravenous im-munoglobulin (IVIG) in alloimmune thrombocytopenia. In: Radder CM (thesis). Management of Fetal Alloimmune Thrombocytopenia. Amsterdam, Print Partners Ipskamp, 2004, pp 69–81.

13. Paridaans NP, Kamphuis MM, Taune Wikman A, et al. Low-Dose versus Standard-Dose Intrave-nous Immunoglobulin to Prevent Fetal Intracranial Hemorrhage in Fetal and Neonatal Alloim-mune Thrombocytopenia: A Randomized Trial. Fetal Diagn Ther 2015;38:147-53.

14. Daffos F, Forestier F, Muller JY, et al. Prenatal treatment of alloimmune thrombocytopenia. Lancet 1984;2:632.

15. Kaplan C, Daffos F, Forestier F, et al. Management of alloimmune thrombocytopenia: antena-tal diagnosis and in utero transfusion of maternal platelets. Blood 1988;72:340-3.

16. Lynch L, Bussel J, Goldberg JD, et al. The in utero diagnosis and management of alloimmune thrombocytopenia. Prenat Diagn 1988;8:329-31.

17. Nicolini U, Rodeck CH, Kochenour NK, et al. In-utero platelet transfusion for alloimmune thrombocytopenia. Lancet 1988;2:506.

18. Lynch L, Bussel JB, McFarland JG. Antenatal treatment of alloimmune thrombocytopenia. Obstet Gynecol 1992;80:67-71.

19. Urbaniak SJ, Duncan JI, Armstrong-Fisher SS, et al. Variable inhibition of placental IgG transfer in vitro with commercial IVgG preparations. Br J Haematol 1999;107:815–817.

20. Pacheco LD, Berkowitz RL, Moise KJ et al. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. Obstet Gynecol. 2011;1185:1157-63.

21. Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol 1996;174:1414-23.

22. Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol 2006;107:91-6.

23. Berkowitz RL, Lesser ML, McFarland JG, et al. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomized controlled trial. Obstet Gynecol 2007;110:249-55.

24. Gelfand EW. Intravenous Immune Globulin in Autoimmune and Inflammatory Diseases. N Engl J Med 2012;367:2015-25.

25. Radder CM, de Haan MJ, Brand A, et al. Follow up of children after antenatal treatment for alloimmune thrombocytopenia. Early Hum Dev 2004;80:65-76.

26. Ni H, Chen P, Spring CM, ayeh E, et al. A novel murine model of fetal and neonatal alloimmune thrombocytopenia: response to intravenous IgG therapy. Blood 2006;107:2976–2983.

27. Yougbaré I, Lang S, Yang H, et al. Maternal anti-platelet β3 integrins impair angiogenesis and cause intracranial hemorrhage. J Clin Invest 2015 ;125:1545-56.

28. Tiller H, Husebekk A, Skogen B, et al. True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: a prospective observational follow-up study. BJOG.2015; 91471-0528.

8