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

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# CHAPTER 7

## LOW-DOSE VERSUS STANDARD-DOSE INTRAVENOUS IMMUNOGLOBULIN TO PREVENT FETAL INTRACRANIAL HEMORRHAGE IN FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: A RANDOMIZED TRIAL

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# ABSTRACT

## Objective

Pregnancies at risk for fetal and neonatal alloimmune thrombocytopenia (FNAIT) are commonly treated using weekly intravenous immunoglobulins (IVIG), 1g/kg maternal weight. IVIG is an expensive multidonor human blood product with dose-related side effects. Our aim was to evaluate the effectiveness of IVIG at a lower dose, ie 0.5g/kg.

## Methods

This was a randomized controlled multicenter trial conducted in Sweden, the Netherlands and Australia. Pregnant women with human platelet antigen alloantibodies and an affected previous child without intracranial hemorrhage (ICH) were enrolled. The participants were randomized to IVIG at 0.5 or 1 g/kg per week. The analyses were per intention to treat. The primary outcome was fetal or neonatal ICH. Secondary outcomes were platelet count at birth, maternal and neonatal IgG levels, neonatal treatment and bleeding other than ICH.

## Results

A total of 23 women were randomized into two groups (low dose: n = 12; standard dose: n = 11). The trial was stopped early due to poor recruitment. No ICH occurred. The median newborn platelet count was $81 \times 10^9$/L (range 8–269) in the 0.5 g/kg group versus $110 \times 10^9$/L (range 11–279) in the 1 g/kg group (p = 0.644).

## Conclusion

The risk of adverse outcomes in FNAIT pregnancies treated with IVIG at 0.5 g/kg is very low, similar to that using 1 g/kg, although our uncompleted trial lacked the power to conclusively prove the noninferiority of using the low dose.

# INTRODUCTION

Fetal or neonatal alloimmune thrombocytopenia (FNAIT) is the result of platelet destruction in the fetus or neonate caused by maternal IgG 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, 1 in 50 Caucasian pregnant women is at risk to develop FNAIT. Actual sensitization occurs in 6-12% of HPA-1bb mothers, of whom 1 in 3 deliver a child with severe thrombocytopenia (<50x10$^9$/L).[2] The most devastating pathology associated with FNAIT is intracranial hemorrhage (ICH) in the fetus or newborn, often with death or severe, irreversible neurologic damage, which occurs in 10% of severely thrombocytopenic newborns.[2]

Until recently, repeated fetal blood sampling and intrauterine platelet transfusions was the only available treatment of fetuses with alloimmune thrombocytopenia. Bussel et al were the first, in 1988, to report beneficial effects of maternal administration of immunoglobulins (IVIG) in pregnancies with FNAIT. In all the 7 cases reported, the fetal platelet count increased substantially after treatment with IVIG 1 g/kg/wk.[3] This dosage was based on the dose used in the treatment of idiopathic thrombocytopenic purpura. No dose-finding studies for the treatment of FNAIT have ever been published.

In the past decade, several studies have been published supporting the safety and efficacy of noninvasive, IVIG-only treatment of FNAIT.[4-6] Currently, our standard treatment for pregnant women with FNAIT with a previous affected child without ICH is a weekly dose of 1 g/kg. Radder et al. reported that placental antibody transfer is not further increased with increasing IgG concentrations in the mother.[7] This suggests a limitation of the placental transfer via the Fc-receptor, likely due to saturation. We therefore hypothesized that a lower dose of IVIG might be equally effective in the treatment of FNAIT.

IVIG is an expensive multidonor human blood product, and although stringently tested, the risk of transmission of viral and other diseases remains. Dose-related maternal side effects have been described, including headache, fever, renal and cardiovascular dysfunction and aseptic meningitis. The aim of our study was to determine whether 0.5 g/kg per week of IVIG is as effective as 1 g/kg per week in the prevention of ICH in FNAIT.

# SUBJECTS AND METHODS

## Study design and participants

We performed an international, open-label randomized controlled trial in 4 tertiary care centers in 3 countries, to test the hypothesis that treating pregnant women with FNAIT, with an affected sib without ICH, with 0.5 gram IVIG/kg per week is just as effective as (non inferior to) the standard dose of 1 gram/kg per week.

Women with a singleton pregnancy with HPA allo-antibodies with a gestational age between 12 and 28 weeks, who had previously given birth to an affected sibling, with a platelet count < $150x10^9$ /L but without an ICH were included. HPA alloimmunization in the current pregnancy 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 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 antibodies. Each woman included in the study provided written informed consent accordance with institutional and national guidelines. The study was approved by the Leiden University Medical Center Medical Ethics Committee (MEC PP04.203), and by each centers' respective Institutional Review Board.

## Randomization

Randomization was performed between 26 and 28 weeks' gestation, after stratification for center and for HPA-1a and non HPA-1a, by the Web-based randomization service integrated in the central trial database, provided by the Karolinksa Institute, Stockholm, Sweden (www.medscinet.com). The patients were randomized to either the low dose (0.5 g/g/kg maternal weight per week) or the standard dosage, 1 g/kg per week of IVIG.



## Medication and management protocol

The brand of IVIG used was the IVIG with which the treating clinicians were accustomed to work in their centers. The medication was administered weekly, starting from 28 weeks' gestation until delivery over a period from 3 to 6 h according to the dose and tolerance.

The products utilized were Freeze-dried Immunoglobulin IV (CLB Sanquin, Amsterdam, The Netherlands) and Gammagard (Baxter International Inc., Deerfield, IL, USA). Side effects and complications were registered in the trial database.

Fetal ICH was ruled out by ultrasound before start of the treatment at 28 weeks. The ultrasound was repeated biweekly. The total IgG levels were measured before delivery in maternal serum and after delivery in neonatal cord blood. No fetal blood samplings were performed at any time. The choice of timing and mode of delivery was left to the discretion of the obstetrician. In case of a planned vaginal delivery, it was recommended not to use scalp electrodes, scalp blood sampling, or ventouse- or forceps-assisted delivery.

Directly after birth the platelet count in umbilical blood was tested automatically; in case of a count <$100x10^9$/L, a manual count was done. In all centers, HPA compatible platelets were available within 12 h after birth. A neonatologist examined the neonate 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. The course of the neonatal platelet count was recorded, as well as any form of treatment of thrombocytopenia.

The primary outcome was fetal or neonatal ICH. Secondary outcomes were fetal platelet count at birth, the total IgG levels in maternal serum and cord blood , type of neonatal treatment needed and signs of bleeding other than ICH.

### Statistical analysis

The study was set up as an equivalence trial. The null hypothesis was that the standard dose of 1 g/kg was superior. We wanted to test if the low dose of 0.5 g/kg was not inferior. We assumed that the probability of failure (prevalence of ICH) was 1%, if both groups were equal. Based on the assumption that the risk of failure in both groups was the same, we made a sample size calculation. We estimated a 5% specified maximal difference, meaning that the lower dose is inferior if the risk of failure is 5% higher than in the standard dose group. For a power of 80% and a one-sided 5% significance level, this means that 106 patients in each arm were needed to reject the null hypothesis. For the primary end point, the treatments are considered equivalent if the upper limit of the confidence interval of the difference was <5%.[8] The confidence interval for the difference in proportion was calculated using the quasi-exact method by Chen.[9]

Analysis was performed based on the intention-to-treat principle. For comparison of continuous data, the Kruskal-Wallis test was used; for categorical data we used the Fisher's exact test. Data are expressed as means (SD) or medians (ranges), and a p-value< 0.05 was considered significant. Calculations were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, Ill., USA)



## RESULTS

The trial started in January 2005. At this point 15 centers in 8 countries agreed to participate. We estimated an inclusion period of 3 years. Despite regular contact between the Trial Steering Committee and the responsible investigators in these centers, only 4 centers, in The Netherlands, Sweden and Australia, managed to recruit patients.

Due to the low number of patients included until September 2007 (n=23), the Trial Steering Committee decided to end the study. Reasons for the slow recruitment were inability to obtain institutional review board approval, the low number of eligible patients (leading to loss of interest for the study) and being too busy with projects of higher priority.

The study group consisted of 23 pregnancies, from which all but 1 received and completed the allocated treatment. One patient requested to switch from 0.5 to 1.0 g/kg in week 34. Twelve patients were allocated to 0.5g/kg per week, and 11 patients to the standard dose of 1.0g/kg per week. All patientes were analyzed. Figure 7.1 shows the flow diagram of the trial.

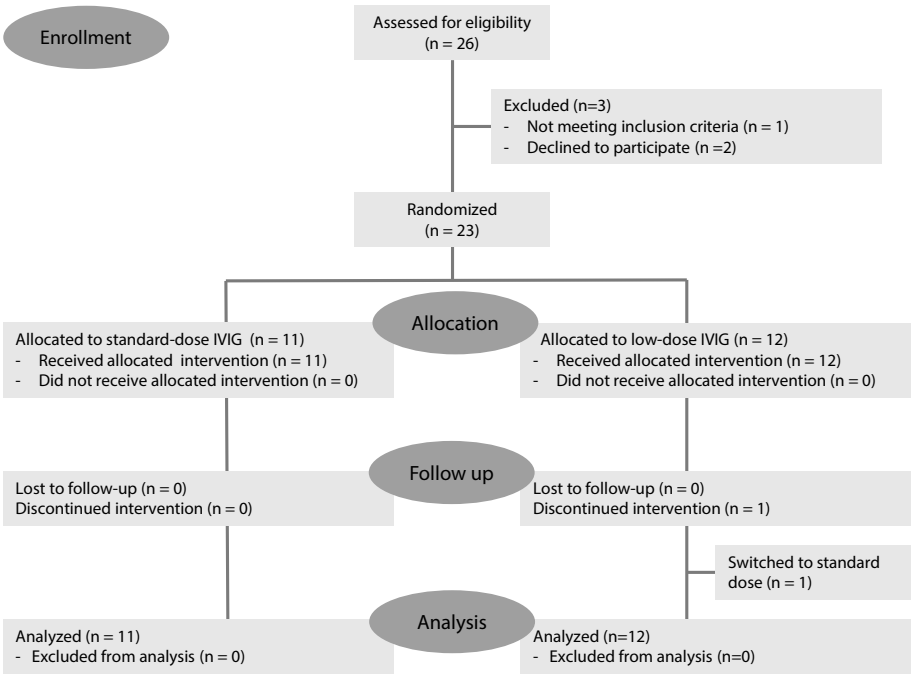


*Figure 7.1*
*Consolidated Standards of Reporting Trials (CONSORT) flow diagram*

*Table 7.1 Characteristics of pregnant women with FNAIT randomized to 0.5g/kg or 1g/kg IVIG*

| | IVIG 0.5 g/kg/wk N=12 | IVIG 1.0 g/kg/wk N=11 | P-value |
|---|---|---|---|
| Maternal age | 31 (29-39) | 32 (24-43) | 0.597 |
| Parity | 1 (1-2) | 1 (1-3) | 0.810 |
| Nr. of doses IVIG | 10 (7-11) | 11 (7-12) | 0.436 |
| Caucasian | 12 | 11 | 1.0 |
| HPA-1a | 11 | 11 | 0.338 |
| PC sibling ($x10^9$/L) | 17 (5-70) | 11 (2-49) | 0.532 |

*Data are shown as numbers or medians (ranges).*
*FNAIT fetal or neonatal alloimmune thrombocytopenia; IVIG Intravenous Immunoglobulin; HPA-1a Human Platelet Antigen 1a.*

The baseline characteristics of the included women are shown in table 7.1, showing both groups to be equal for all relevant parameters. Perinatal survival was 100%, and no ICH was observed. The difference in primary outcome is therefore 0%, with a 95% confidence interval of -25.2% to 23.6%. The platelet count at birth did not differ significantly (81 vs 110x$10^9$/L, p=0.644). The primary and secondary outcomes are given in table 7.2.

***Table 7.2*** *Outcome of pregnancies with FNAIT randomized to 0.5g/kg or 1g/kg IVIG*

| | IVIG 0.5 g/kg/wk | IVIG 1.0 g/kg/wk | P-value |
|---|---|---|---|
| Fetal ICH | 0 | 0 | 1.0 |
| Neonatal ICH | 0 | 0 | 1.0 |
| PC at birth | 81 (8-269) | 110 (11-279) | 0.644 |
| Nadir of platelet count | 71 (8-266) | 110 (9-202) | 0.943 |
| Bleeding (non ICH) | 0 | 0 | 1.0 |
| Perinatal survival | 12 (100%) | 11 (100%) | 1.0 |
| IVIG in neonatal period | 1 (8%) | 0 | 0.338 |
| Platelet transfusions in neonatal period | 2 (17%) | 3 (27%) | 0.547 |
| Maternal side effects | 0 | 0 | 1.0 |
| Fetal/neonatal adverse events | 0 | 0 | 1.0 |
| GA at birth | $38^{+0}$ ($34^{+3}$-$39^{+4}$) | $38^{+0}$ ($34^{+4}$-$38^{+5}$) | 0.665 |
| Vaginal birth | 7 (58%) | 10 (91%) | 0.037 |
| Planned CS | 4 (33%) | 1 (9%) | 0.168 |
| Emergency CS | 1 (8%) | 0 | 0.338 |
| Birth weight (gram) | 3087 (1940-3650) | 3420 (2605-3750) | 0.049 |
| *Platelet count:* | | | |
| $<30x\ 10^9$/L | 1 (8%) | 2 (18%) | 0.493 |
| $<50x\ 10^9$/L | 3 (25%) | 4 (36%) | 0.563 |
| $<150x\ 10^9$/L | 9 (75%) | 7 (64%) | 0.563 |

*Data shown as number (%) or median (range).*
*ICH Intracranial Hemorrhage; PC platelet count; IVIG intravenous immunoglobulins; GA Gestational Age, CS caesarean section*

***Table 7.3*** *IgG concentrations in maternal serum en neonatal cord blood samples of pregnancies complicated by FNAIT, treated with low dose or standard dose IVIG, compared to reference levels in normal pregnancies[10]*

| | Type of treatment | | |
|---|---|---|---|
| | 0.5 g/kg/wk | 1.0 g/kg/wk | Reference range |
| Cord blood IgG conc. | 16.0 (14.4-21.1) | 14.1 (12.9-18.4) | 11.6 (7.5-15.9) |
| Maternal serum IgG conc. | 19.4 (17.8-24.1) | 26.2 (17.4-36.3) | 8.0 (5.3-13.1) |
| Cordblood/serum ratio | 0.82 (0.63-1.08) | 0.61 (0.36-0.84) | 1.4 (0.9-2.0) |

*Data shown in g/L, and median (range)*

In table 7.3, the maternal serum and cord blood IgG levels are compared to the levels in the normal population, as expected[10] The maternal IgG serum levels were higher than in the normal population, as expected. The cord blood IgG levels were similar in the three groups. No serious side effects were reported in both treatment groups.

# DISCUSSION

Both the low IVIG dose of 0.5 g/kg and the standard dose of 1.0 g/kg IVIG were associated with the absence of ICH or death in all the studied pregnancies with FNAIT in women having given birth to an affected sibling without ICH. The platelet counts at birth, the need for neonatal treatment and the cord blood levels of IgG were also similar. For statistically significant evidence of equivalence, the number of recruited pregnant women was too small.

## Interpretation in light of other evidence

The results of our trial are consistent with the *in vitro* studies published by our group and others[7,11] showing a limitation, likely by saturation, of the Fc-receptor mediated transplacental transport of IgG. We confirmed in a clinical setting that a dose of 0.5 g/kg and a dose of 1 g/kg lead to similar IgG levels in the fetal circulation. In a recent review of the literature on the management of FNAIT, we found no studies using or evaluating a lower dose than 1 g/kg IVIG.[12] The dose of 1 g/kg used in most studies and protocols in the past decade is not based on dose-finding studies. Most users refer to Bussel et al[3], who first proposed treatment of FNAIT with IVIG and treated 7 women with a previously affected child (3 with ICH) with 1.0 g/kg per week after diagnostic fetal blood sampling showing a platelet count <100x10$^9$/L. All newborns appeared healthy, with platelet counts >30x10$^9$/L. Their choice for 1.0 g/kg was based on studies in patients with idiopathic thrombocytopenic purpura [13-15] and in neonates with alloimmune thrombocytopenia.[16,17] However, when analyzing these studies in detail, we found that the patients were actually treated with an IVIG dose of 0.4g/kg daily, for a period of several days. We assume that to permit administration once a week, this dose was recalculated to the 1 g/kg.

Three small randomized trials have been published comparing different regimens for the treatment of FNAIT in pregnant women with a previous child without ICH, all conducted by the same group from Cornell Medical College, New York, N.Y., USA. In the first study, IVIG at 1 g/kg only was compared with the same medication with added dexamethasone in 54 women, showing no benefit of dexamethasone. No case of ICH occurred.[18] In the second study, Berkowitz et al [19] studied 39 pregnant women, comparing 1 g/kg of IVIG with 0.5 mg/kg per day of prednisone. They used fetal blood sampling both before treatment and again during treatment to evaluate response, with addition of the medication given in the other arm in case of insufficient response. They found no difference in platelet counts at birth. Two fetal deaths of unknown cause (1 in each arm) occured 2 and 4 weeks after a fetal blood sampling, even though showing sufficient platelets. One fetal blood sampling was complicated by bradycardia and emergency caesarean section at 28 weeks' gestation. This neonate had a grade 3 ICH despite a platelet count of 68x10$^9$/L. One other neonate had a small grade 1 hemorrhage at term with a normal platelet count.

In the third study by this group[20], a total of 73 women were randomized to either IVIG 2.0g/kg per week (group A) or IVIG 1.0g/kg per week plus prednisone 0.5mg/kg per day (group B). At 32 weeks, fetal blood sampling was done, followed by either adding prednisone to group A or doubling the IVIG dose in group B. There was 1 small neonatal ICH in each group, apparently unrelated to FNAIT, since the platelet counts were normal. The platelet counts in both groups were similar. There were 4 complications of the fetal blood samplings: 2 emergency caesarean sections and 2 cases of preterm rupture of membranes within 24 h. Almost all women had moderate-to-severe side effects related to the treatments.

These small trials, just as underpowered as our own study, have limited meaning when trying to determine the optimal dose of IVIG. The most important conclusions from these studies in our view are that any IVIG treatment appears to effectively prevent thrombocytopenia-related ICH, and that fetal blood sampling in FNAIT is associated with more harm than good.[5]

The use of any medication in pregnancy, in particular substances that cross the placenta, should be carefully considered, balancing perceived benefit against potential harm to 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. IVIG has been used successfully in many immune-related diseases since the 1950s. For a number of indications, double-blind, placebo-controlled trials have shown its efficacy.[21] In addition, IVIG is used off-label for a number of rare diseases, including FNAIT, only based on observational studies or small underpowered controlled trials. The drug is produced using pooled plasma donated by thousands of paid or unpaid volunteers, with some concern remaining about the transmission of viral or other infections despite meticulous testing protocols. Its highly successful use in FNAIT has now almost completely and justly replaced the hazardous invasive management protocol based on fetal blood samplings and intrauterine transfusions utilized in the past.[5]

Many aspects of IVIG treatment however, are still unclear. The presumed mechanisms of action, described as 'immunomodulatory and anti-inflammatory', are manifold, and in part still to be unraveled.[21] The increasing use of IVIG in many autoimmune and inflammatory diseases could lead to shortages of this already expensive human blood donor product. Future research may result in using only a specific fraction of the IVIG product for specific diseases, or it may lead to bioengineering of a protein with IgG-like properties. As IVIG is known for its immunomodulating characteristics, there are some, at least theoretical, concerns with its use in pregnancy. One study showed a possible increase in IgE in children after maternal IVIG administration. However, no clinically apparent adverse effects in early childhood could be demonstrated.[22] Severe maternal side effects of IVIG, including aseptic meningitis as well as renal and cardiovascular dysfunction, are uncommon, while mild discomfort such as headache is often reported dose-dependently. All these issues underline the importance of using IVIG in pregnancies with FNAIT in the lowest possible effective dose.

An important limitation to our trial is the low number of recruited women. The lack of power to prove equivalence means that the data must be interpreted with care. We do agree, however, with Kahn and Hills[23], commenting on trials stopped early, that the results have to be taken as they stand and need to be shared with the medical community. In the absence of other comparative studies, and the lack of justification for the 1 g/kg dose, we suggest that our data at least do not show any benefit of a dose >0.5 g/kg dose in the treatment of FNAIT.

Our study concerned only those women with FNAIT whose previously affected child did not suffer from ICH. For the much smaller group of pregnant women who had a previous child with ICH, the optimal dose of IVIG still needs to be determined. An adequately powered trial for this group, however, will be very difficult to perform, as we discussed in a previous article.[24]

## CONCLUSION

We conclude that although our trial lacked sufficient power to prove equivalence to the standard dose of 1 g/ kg, administering an IVIG dose of 0.5 g/kg weekly appears safe and effective for pregnancies complicated by FNAIT in women with an affected sibling without ICH, reducing costs as well as long-term adverse events or side effects. We recommend using IVIG at a dose of 0.5 g/kg per week for the treatment of women with FNAIT without an affected sibling with ICH. A larger prospective study or randomized trial is needed to have sufficient power to prove the equivalence of a lower dose of IVIG compared to the standard dose of 1 g/kg. Adequately powered studies are also needed to find the optimal treatment protocol for pregnancies complicated by FNAIT for women with a previous child suffering from ICH.

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