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Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: http://www.tandfonline.com/loi/ierr20

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To cite this article: Dian Winkelhorst , Dick Oepkes & Enrico Lopriore (2017) Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies, Expert Review of Hematology, 10:8, 729-737, DOI: 10.1080/17474086.2017.1346471

To link to this article: http://dx.doi.org/10.1080/17474086.2017.1346471

Accepted author version posted online: 23 Jun 2017.
Published online: 29 Jun 2017.

EXPERT REVIEW OF HEMATOLOGY, 2017
VOL. 10, NO. 8, 729–737
https://doi.org/10.1080/17474086.2017.1346471

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REVIEW

Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies

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ABSTRACT

Introduction: Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a relatively rare but potentially lethal disease, leading to severe bleeding complications in 1 in 11.000 newborns. It is the leading cause of thrombocytopenia in healthy term-born neonates.

Areas covered: This review summarizes the antenatal as well as postnatal treatment, thus creating a complete overview of all possible management strategies for FNAIT.

Expert commentary: The optimal antenatal therapy in order to prevent bleeding complications in pregnancies complicated by FNAIT is non-invasive treatment with weekly intravenous immunoglobulin (IVIG). Based on risk stratification, weekly doses of IVIG of 0.5 or 1.0g/kg should be administered started early in the second in high risk cases or at the end of the second trimester in low risk cases. The optimal postnatal treatment depends on the platelet count and the clinical condition of the newborn. Prompt administration of compatible platelet transfusion is the first treatment of choice in case of severe thrombocytopenia or active bleeding. In case matched platelets are not directly available, random platelets can also be administered initially to gain time until matched platelets are available. In case of persistent thrombocytopenia despite transfusions, IVIG 1.0–2.0g/kg can be administered.

ARTICLE HISTORY
Received 14 December 2016
Accepted 21 June 2017

KEYWORDS
FNAIT; alloimmune thrombocytopenia; IVIG; platelet transfusion; IUPT

1. Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is one of the leading causes of thrombocytopenia in otherwise healthy newborns [1,2]. FNAIT results from maternal alloantibody formation as a result of exposure to the incompatible, paternally derived human platelet antigen (HPA) on fetal platelets. When these HPA-alloantibodies enter the fetal circulation after passing the placenta through FcRn-mediated transport, they can destruct fetal platelets as well as damage endothelial cells, which may result in bleeding complications [3,4]. These bleedings can vary from minor skin manifestations to severe intracranial hemorrhages (ICHs) or even perinatal death [5,6]. In absence of population-based screening for FNAIT, cases are predominantly diagnosed in case of symptoms. Therefore, the clinical challenge lies in treating the thrombocytopenic neonate with newly diagnosed FNAIT and, in potential subsequent pregnancies, preventing the occurrence of such bleeding complications through antenatal therapy. Fortunately, these severe hemorrhages are rare complications of FNAIT, estimated to strike in 1 in 11,000 newborns [7]. Therefore, little evidence is available to support the choice for or the abandoning of specific treatment. In the absence of international guidelines and large trials comparing different strategies of treatment, most western countries and centers base their guidelines on low levels of evidence including clinical experience, small observational cohorts, and expert opinions. For the antenatal management, important progress was made over the last couple of years to generate more substantial evidence as ground for clinical recommendations. Next to an increase in observational cohort descriptions, both retrospective and prospective, attempts have also been made for randomized trials. These trials, however, are hampered by lack of an adequate control group (placebo or no treatment) [8–10]. In addition, most studies have a small sample size and therefore lack power for drawing firm conclusions on the occurrence of an ICH or perinatal death. Furthermore, without any international consensus, management strategies applied are highly heterogeneous, which makes it difficult to combine the data of primary studies. For neonatal management in FNAIT, evidence is even more scarce. No randomized studies have been performed and just a handful of observational studies have been executed, all retrospectively analyzing a small number of newborns treated at various centers with various management strategies. This review aims to provide an overview with all relevant literature and summarizes the evidence for both antenatal and postnatal management strategies in FNAIT.

2. Diagnosis

In the absence of population-based screening, suspicion of FNAIT predominantly arises in case of bleeding problems. Occasionally, these bleedings are detected or suspected during fetal life, in case of ultrasound abnormalities, especially in the

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fetal brain. More commonly suspicion of FNAIT emerges after birth and results from neonatal bleeding problems or a chance finding of an early-onset isolated severe thrombocytopenia. Additionally, FNAIT is sporadically diagnosed in case of a diagnostic work-up because of a sister or another family member with a pregnancy complicated by FNAIT. When FNAIT is suspected, or in case of a family member with FNAIT, diagnostic work-up should ideally include HPA genotyping of mother, father, and child to establish possible HPA incompatibilities, as well as serological testing (maternal–paternal serum crossmatch, and a maternal platelet antibody screening) [11–15]. A serological FNAIT diagnosis is confirmed in case of a maternal–neonatal or maternal–paternal incompatibility combined with the presence of specific anti-HPA in maternal serum. If, in case of suspicion due to an affected family member, after the HPA-typing, the pregnant women turns out to be HPA-1a negative, the HPA-1a type of father and, in case of paternal heterozygosity, consequently fetus can be determined as described below. In case of HPA-1a incompatibility between mother and fetus without anti-HPA-1a present, the alloantibody screening should be repeated every 2–4 weeks.

Adequate diagnosis does not only contribute to adequate management in the index cases, but is just as important for taking adequate measures in subsequent pregnancies to prevent bleeding complications.

3. Antenatal management

Antenatal management is usually applied in subsequent pregnancies after the birth of a first affected child. However, in case of diagnosis during pregnancy, the same management strategies are applied to index cases as well. The only exception is the gestational age to start treatment, which is at moment of diagnosis for index pregnancies. Antenatal management in subsequent pregnancies starts after conception with counseling, monitoring, and risk stratification. Also, depending on the HPA-alloimmunization that is involved, a prediction can be made on the severity of the disease. It is usually thought that, for example, HPA-15b or HPA-1b antibodies will cause less severe disease than, for example, HPA-3a or HPA-1a alloantibodies. However, in lack of sufficient evidence or literature to support these assumptions, no recommendations or guidelines exist to advice on different antenatal management strategies with different types of alloimmunizations.

3.1. Monitoring and risk stratification

First it has to be determined whether or not the pregnancy is incompatible and actually at risk for FNAIT, depending on paternal genotype for the causing antigen. When the father is homozygous, every consecutive pregnancy is incompatible and therefore the fetus is at risk. When the father is heterozygous, fetal genotyping has to be performed. In case of HPA-1a alloimmunization, this can be tested using the cell free fetal DNA in maternal plasma [16]. Additionally, using parallel sequencing, fetal HPA-3, HPA-5, HPA-15 might be determined, as suggested by Wienzek-Lischka et al. [17]. In other cases, an amniocentesis has to be performed to obtain fetal DNA.

When established that the pregnancy is incompatible for the HPA-alloantibody present in the maternal serum, the fetal brain should be closely monitored through serial ultrasound. At this stage, ideally a noninvasive diagnostic tool should be used to evaluate and monitor fetal disease severity and predict the occurrence of hemorrhages. For this purpose, some centers monitor alloantibody titers by titration and quantification, although mostly still in a research setting. While high anti-HPA-1a levels correlate with more severe disease, pregnancies with barely detectable antibody levels and a severely affected fetus or neonate have been described as well [18]. No reliable cut-off values to guide individual management have been established thus far. Therefore, its use in predicting the occurrence of fetal/neonatal bleeding is somewhat contradictory [18–20]. Several other mechanisms and markers are being studied extensively in order to enable us to predict the fetal and neonatal disease severity during pregnancy. For example, the glycosylation pattern of the Fc-part of the anti-HPA alloantibodies (e.g. fucosylation and galactosylation) is reported to correlate with neonatal platelet counts as well as disease severity [21,22]. Also, cord blood CRP levels are linked to disease severity as well [23]. Also, the HLA-DRB3*01:01 allele, which is associated with a higher risk of alloimmunization in case of a HPA-1a incompatible pregnancy, is thoroughly assessed for this reason and it has been shown that this allele and other HLA alleles have no additional value as a predictor of the disease severity or response to IVIG [24,25].

Another great new insight in understanding the occurrence of ICH in FNAIT is the interaction between anti-HPA-1a alloantibodies and endothelial cells. Since integrin β3 that carries the HPA-1a epitope is also present on endothelial cells (in complex with αV; αVβ3), it has been postulated that this leads to three different subtypes of anti-HPA-1a [26]. The first type is not complex-specific and will bind to β3, irrespective of its complex; the second subtype will bind to β3 only when in complex with α2 (principally platelets); the third type will bind solely to β3 when complexed to αV (principally endothelial cells). It has been suggested that this third type of antibody plays a key role in the development of bleeding complications. The first direct proof came from murine studies in both active and passive murine models [4]. They illuminated that ICHs occurred regardless of platelet counts and, more importantly, that HPA-1a antibodies inhibited angiogenic signaling, induced endothelial cell apoptosis, and decreased vessel density in affected brains as well as retinas. In addition, very recently a retrospective study assessing human FNAIT sera reported the occurrence of ICH to be related to the presence of endothelial-specific anti-HPA1a antibodies, the anti-αVβ3 subtype [26].

In light of the lacking parameters predicting the risk of bleeding complications in FNAIT, this yields a very promising focus point of future research. Therefore, in the absence of noninvasive reliable ultrasound or laboratory parameters during pregnancy to assess which incompatible and alloimmunized pregnancies are at greater risk for developing bleeding complications, the obstetric history is used. The most reliable predictor for the occurrence of severe bleeding complications so far is the occurrence of an ICH in siblings [27,28]. The recurrence rate, without the application of antenatal treatment, is estimated to be as high as 79% [29]. Therefore, the

history of a sibling that suffered from an ICH is usually used to adjust or intensify the antenatal treatment applied [27,30,31]. Kamphuis et al. [31] used a risk stratification based on a sibling with ICH (high risk) or no sibling with ICH (standard risk). Pacheco et al. [27] further divided this high risk group based on the timing of ICH, before or after 28 weeks' gestation. Bussel et al. [30] used the timing of ICH to intensify treatment as well and identified a high-risk group (ICH in perinatal period), a very high risk group (ICH between 28–36 weeks), and an extremely high risk group (ICH before 28 weeks). Formerly, fetal blood sampling (FBS) was used to assess fetal platelet counts and determine disease severity. However, due to high complication risks, this invasive (diagnostic) procedure is now almost completely abandoned as a first-line strategy.

3.2. Antenatal treatment

Before discussing possible antenatal treatment options, it is important to realize the true goal of antenatal treatment. In pregnancies complicated by FNAIT, the clinically relevant goal is to prevent bleeding complications, rather than preventing (severe) thrombocytopenia. Even extremely low platelet counts do not necessarily result in clinical bleeding, and there is increasing evidence for other pathological mechanisms playing a key role in the development of bleeding problems in FNAIT [4,5]. Therefore, the use of platelet counts as outcome parameter to assess the effectiveness of antenatal management is at least debatable. When comparing different management strategies, this should be taken into account. An overview of all antenatal treatment strategies can be found in Table 1 and a summary of our recommended management strategy is shown in Figure 1.

3.2.1. Platelet transfusion

The first prenatal management strategy in FNAIT was ultrasound-guided FBS, followed if needed by an intrauterine platelet transfusion (IUPT), was first performed by Daffos in 1983 [32].

Besides the advantage of assessing fetal status and being able to apply immediate treatment this invasive strategy has a lot of disadvantages and a high risk of complications. Not only is puncturing the umbilical cord of a potentially thrombocytopenic fetus in FNAIT extremely dangerous. The short life span of transfused platelets leads to the need of at least weekly IUPTs and therefore the accumulated complication risk per pregnancy, defined as a loss of pregnancy or emergency cesarean/delivery, is as high as 11% [33]. Nowadays, given the potential complications, only few specialized centers still use FBS with additional IUPT in their first-line management strategy.

3.2.2. Intravenous immunoglobulins (IVIG)

Trying to avoid applying the hazardous invasive management with FBS and IUPT, Bussel et al. [34] were the first to report the successful administration of IVIG in pregnancies complicated by FNAIT, which was directly adapted from the treatment of immune thrombocytopenia (ITP) during pregnancy. Immunoglobulin treatment has first been used in the treatment of primary immunodeficiency in 1952, but over the past decades the number of indications has been increasing rapidly [35,36]. IVIG is a multi-donor pooled blood product made of human IgG antibodies, which can theoretically result in the potential to transmit blood-born infections [37]. The most reported side effects of IVIG are dose-related and include headaches, dizziness, or skin rash. Rarely, renal failure, aseptic meningitis, and thrombotic complications occur [38]. The use of IVIG as an antenatal treatment in pregnancies complicated by FNAIT is still off-label and long-term follow-up data of children treated with IVIG during fetal life are currently lacking. However, a cohort study that examined neurodevelopmental outcome of 37 children exposed to IVIG concluded that in utero exposure to IVIG did not seem to have any clinically apparent adverse effects in early childhood [39]. In lack of studies comparing IVIG to an adequate control group (placebo or no treatment), no conclusions can be drawn on its effect. Instead, IVIG treatment is usually compared to invasive management strategies or treatment with IVIG and corticosteroids. In a recent systematic review, assessing a total of 27 studies, we reported a 98.7% success rate in preventing ICH in pregnancies treated with IVIG only [33]. This is in line with the 97.3% reported in the previous Cochrane analysis [40].

Due to the noninvasive nature and its effectiveness equal to FBS and IUPT, IVIG rapidly gained ground and is currently in most centers the first line of therapy in FNAIT. IVIG was first administered at 1.0g/kg maternal body weight per week,

Table 1. Overview antenatal and postnatal management strategies in FNAIT.

	Antenatal			Postnatal		
Treatment	Indication/Dose	Benefit	Risk	Indication/Dose	Benefit	Risk
Platelet transfusion	Various, from weekly to predelivery only	Treatment monitoring Prevents thrombocytopenia	High complication rate (fetal loss, emergency delivery)	First choice PLT < 20–30 prophylaxis PLT < 50–100 when bleeding	Direct effect on platelet count	Infections Allergic or febrile reactions
IVIG	First choice 0.5 g or 1 g/kg/wk	Noninvasive Prevents ICH	Blind administration Expensive	In addition to random PTx 1 g/kg/day for 2–5 days Not after antenatal IVIG	Prolongs and optimizes effect of random PTx	Delay in response
Corticosteroids	In addition to IVIG Prednisone 0.5 mg	Noninvasive, otherwise benefit unclear	Dose-related side effects Oligohydramnios	No indication Methylprednisone 1 mg iv every 8 h	Benefit unclear	No evidence

PLT: platelet count, $\times 10^9$/L; PTx: platelet transfusion; IVIG: intravenous immunoglobulins; ICH: intracranial hemorrhage.

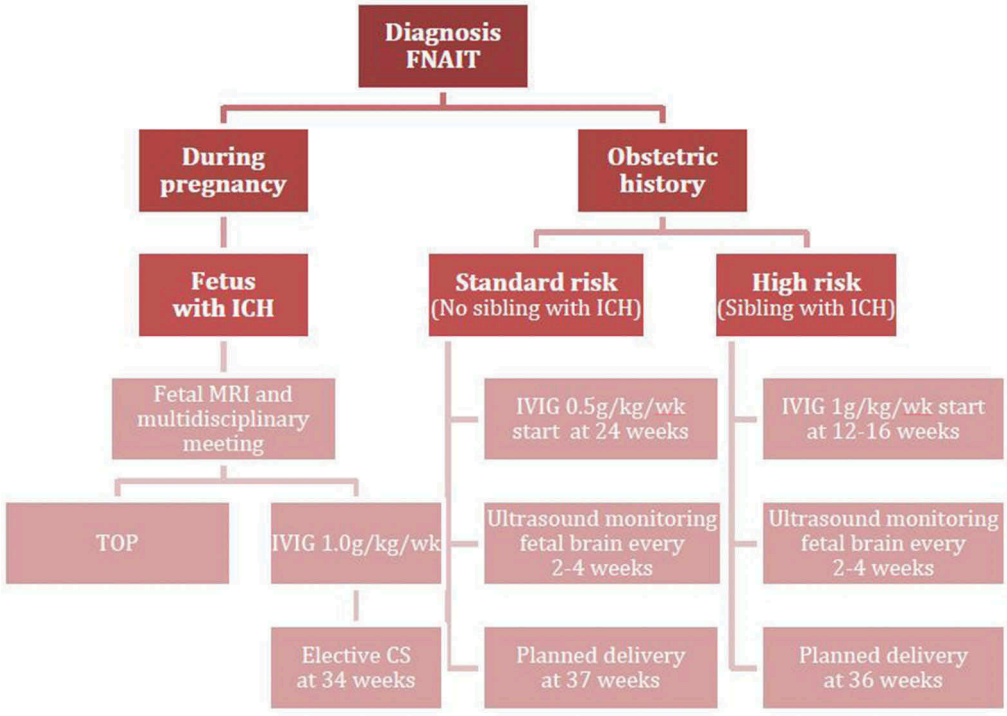

Figure 1. Recommendations for antenatal management in pregnancies complicated by FNAIT.

which was adapted from the treatment of ITP as well. Different strategies with regards to dose (0.5g/kg/wk or 2.0g/kg/wk) and start of treatment have been applied since [8,30,31]. Since, the only evident risk factor for developing an ICH thus far is the occurrence of an ICH in a sibling, it seems logical to stratify pregnancies into two groups with two different IVIG treatment strategies regarding dose and start.

The gestational age at start of treatment is mainly based on the estimated onset of ICHs. The largest study describing 43 cases of ICH, reported the gestational age of onset to be less than 28 weeks in 54% of the cases [41]. This supports starting IVIG earlier than the (in Europe) common 28 weeks' gestation, for example, 24 or even 20 weeks (which is common in the United States of America). More data are needed to make a firm recommendation. In women with a previous child with an ICH, IVIG is commonly started earlier, at 16 weeks' gestation or even earlier.

3.2.3. Corticosteroids

To reduce possible headache complaints and support its efficiency, corticosteroids can be added to the IVIG treatment. This strategy was first described by the group of Bussel et al. as well [34]. They started with the addition of 3–5 mg/kg dexamethasone to IVIG treatment, but due to limited effects as well as significant side effects such as oligohydramnios, this therapy was stopped soon as well as the appliance a lower dose of 1.5 mg dexamethasone because it had no additional effect compared to IVIG treatment alone [42,43]. Dexamethasone was then replaced by prednisone, which seems to have less side effects at a dose of 0.5 mg/kg/day. As singular treatment, it seems that prednisone (in a dose of 0.5 mg/kg/day) is inferior to IVIG treatment [44]. The benefit and efficacy of adding prednisone to IVIG is debated and not yet proven. The only study reporting a significant increase in platelet count when adding prednisone to IVIG used a self-defined and complex outcome measure (platelet count > 25 × 10^9 at second sampling, or an increase by >10 × 10^9 or a platelet count >40 × 10^9/L that was not decreased by >10 × 10^9/L) [9]. All other studies comparing IVIG treatment to a treatment with IVIG and steroids, including a randomized controlled trial, did not find any significant differences in platelet count, ICH or mortality [8,28,30,42,43,45].

3.3. Immunoprophylaxis

Adapted from the ability of preventing RhD-associated HDFN with the use of anti-D immunoprophylaxis during pregnancy and after delivery, another focus of antenatal treatment can be the prevention of alloimmunization, Studies using recombinant anti-HPA-1a antibody, B2GΔnab [46], have shown that this treatment effectively prolonged the survival of platelets up to three times, which suggests its in vivo therapeutic potential. However, no in vivo clinical studies assessing its efficacy and safety have been published thus far. Another approach is the use of human anti-HPA-1a antibodies, similar to the anti-D, that is extracted from the plasma of immunized women. This is currently being investigated in the PROFNAIT project [47]. No results of phase I/II or phase III clinical trials have been published.

3.4. Mode and timing delivery

Lastly, antenatal management includes the determination of the mode and timing of the delivery. In the largest prospective screening study on FNAIT performed thus far, 100,448 pregnant women were screened for their HPA-1a type and for anti-HPA-1a [48]. Anti-HPA-1a was found in 170 pregnancies and

instead of administration of antenatal treatment, a planned, near-term cesarean section was performed. Of these alloimmunized 170 pregnancies, 57 neonates with severe FNAIT were born, of which 3 suffered severe complications (ICH or intrauterine death). These numbers were compared to 15 previously published prospective studies combined (10 severe complications in 51 alloimmunized pregnancies). Based on this comparison they concluded that the applied strategy of a near-term cesarean resulted in a lower number of severe complications. It should be taken into consideration that this study did not describe whether or a routine ultrasound of the neonatal brain was performed to detect ICH that 21.5% of the neonates suffered adverse effects and were treated at the neonatal intensive care unit and that the design of the 15 studies was highly heterogenic. Furthermore, most studies with a high proportion of severe complications identified their cases postnatally, based diagnostic work-up in thrombocytopenic neonates instead of a antenatal.

Next to performing a cesarean as a treatment strategy, most centers perform a planned, near-term cesarean section, in order to reduce the risk of possible birth trauma. However, evidence for this rationale is lacking. First, specific intrapartum risk of bleeding has never been proven and, in a small cohort analysis, vaginal delivery was not associated with the occurrence of ICH [49]. Second, in the analysis of 43 cases of ICH, no intrapartum bleedings were detected and only 3 of 43 ICHs were thought to have occurred after delivery [41]. Also, most women receiving antenatal therapy are multiparous and a nontraumatic spontaneous delivery is usually expected. So, in women with a previous vaginal delivery, without a sibling who suffered from ICH, a planned induction of labor can be considered a safe strategy. Although no evidence exists to advise on a mode of delivery in case of an in utero ICH, the safest option possibly is a near-term CS. For all vaginal deliveries, it is recommended to avoid any potential traumatic events, such as scalp electrodes, scalp blood samplings, or assisted vaginal delivery. Directly after delivery, cord blood samples should be taken to rapidly assess platelet count.

4. Postnatal management

The goal of postnatal management in FNAIT is to prevent or stop neonatal thrombocytopenic hemorrhage. As part of the initial evaluation, newborns should be checked for skin bleeding and also a cranial ultrasound examination to exclude ICH should be performed. Laboratory evaluation should be performed immediately, preferably from cord blood, to assess the severity of the thrombocytopenia. Depending on both the clinical presentation and the severity of the thrombocytopenia, the optimal treatment will be determined.

4.1. Monitoring

During the first days of life, platelet counts should be evaluated daily. Because of a natural fall in neonatal platelet count in the first week of life, it is advised to monitor neonatal platelets at least until 5 days after birth or until there is a sustained rise in platelet count [50,51]. The nadir platelet count usually occurs at 36–48 h after birth. With or without treatment, the neonate should achieve normal platelet counts within 8–10 days.

Regardless of platelet count, all neonates with a confirmed diagnosis should undergo cerebral imaging by ultrasound, preferably within the first 24 h [5,52]. Most ICHs have already occurred in utero and are therefore mostly detected on the first days of life. However, ICH can occasionally be detected at or after the fourth or fifth day of life as well [41]. As low platelet counts in newborns have been proven to be associated with severe aggressive posterior retinopathy of prematurity, neonatal fundus examination can be considered, especially in neonates with severe thrombocytopenia [53].

4.2. Postnatal treatment

The best management of the neonate suffering from FNAIT depends on the clinical condition and the severity of the thrombocytopenia [54]. Despite the previously mentioned lack of evidence on postnatal management strategies, there is international consensus that the first choice of treatment should be a platelet transfusion, administered as quickly as possible. Other therapies that can be applied are IVIG or corticosteroids. Table 1 displays a summary of different postnatal management strategies. Also, an overview of observational studies describing neonatal treatment in FNAIT is given in Table 2.

4.2.1. Platelet transfusion

Platelet transfusions can be administered in case of neonatal thrombocytopenia in either a prophylactic (nonbleeding neonate) or a therapeutic setting (bleeding neonate). Of all thrombocytopenic neonates transfused, up to 98% were transfused as a prophylactic measure [55]. As with every therapy and especially prophylaxis, benefits have to outweigh the risks. In these cases the risks of the (potential) hemorrhage should be compared to the risks of platelet transfusions, which are the transmission of nonbacterial infections, immunization, febrile reactions, hemolytic reactions, allergic reactions, and transfusion-related lung injury [51,56,57].

Therefore thrombocytopenic neonates should only be transfused in case of (very) severe thrombocytopenia. Various thresholds for (prophylactic) platelet transfusions are currently being used, based on low level of evidence (mainly expert opinion). Over the last decades these thresholds have gradually been lowered due to lack of evidence of a protective effect [58]. For stable nonbleeding neonates, most centers have set a threshold for prophylactic transfusion at $30x10^9$/L. However, other centers, for example, the Dutch referral hospital for FNAIT, use a lower threshold of 20×10^9/L [59]. The threshold can be raised to 50×10^9/L in case of additional risk factors, such as a sibling that suffered from ICH, a planned operation, recovering from a large hemorrhage, severe prematurity (<32 weeks' gestation), low birth weight (<1000 g within the first week of age) or a clinically instable neonate. In the event of a bleeding neonate the threshold is usually heightened to 50×10^9/L, or even 100×10^9/L in case of large hemorrhages [60].

Ideally, the transfused product contains antigen-negative platelets. In case of a subsequent pregnancy or antenatal diagnosis of FNAIT, the responsible alloantibody is known and

Table 2. Observational cohort studies postnatal treatment.

			Treatment protocol			Outcome		Neonatal treatment[a]					Result treatment
Author, year	N	Index or subsequent	PTx Bleeding	PTx Nonbleeding	IVIG	Mean PLT at birth	PLT <30	PTx M	PTx R	PTx R + M	PTx + IVIG	Steroids added	Conclusions
Van der Lugt, 2015 Retrospective	22	Subsequent	PLT<50	PLT<20	PLT<20 after PTx	95	8	8	0	0	0	0	Safe platelet count at mean age 3 days
Bakchoul, 2013 Retrospective	17	Index PT<30 + PTx + 3day observation	Not reported, multicenter			11	17	2 (1.5)	7 (1.6)	0	8 (1.6)	0	PTx R is effective correcting PT<30 and should be first line of treatment in index FNAIT
Cook, 2012, Retrospective	20	Index (3)+ Subsequent (17)	Various, single center			92 (3–223)	2 (<20)	4 Unknown R/M/number			5	0	No conclusions on neonatal treatment
Te Pas, 2007, Retrospective	19	Index (6) + Subsequent (13)	PLT<50	PLT<50	Not reported	65	9	4 (1)	2 (1.5)	2 (4)	6 (3)	0	No effect of postnatal IVIG after antenatal IVIG when added to PTx
Ghevaert, 2007 Retrospective	120	Index	Various, multicenter			NR	NR	37	13	9	18	0	No conclusions on neonatal treatment
Fratellanza, 2006, Retrospective	12	Index	Not reported, single center			17	11	Unknown R/M/number	1		11	5	No conclusions on neonatal treatment
Kiefel, 2006, Retrospective	27	Index PTx R + 4day observation	Not reported, multicenter			NR	19	0	16 (1.3)	0	11 (2.1)	4 (2.8)	PLT increase >80 after 1–2 PTx R in 59%

[a]Data presented as number of cases with transfusions (mean number of transfusions)
PLT: platelet count, x10^9/l; PTx: platelet transfusion; R: random; M: matched; IVIG: intravenous immunoglobulins.

appropriate platelets can be ordered in time. However, in index cases, confirmation of the diagnosis can take a couple of days, so the responsible platelet alloantibody is still unknown. In view of poor outcome of major hemorrhages, platelet transfusions in these neonates should not be delayed [60–62]. In these cases ideally HPA-1bb/5aa platelets are transfused, which are antigen-negative for 90% of the FNAIT cases [63]. When unobtainable or not directly available, transfusion can contain either random platelets or washed maternal platelets. Although maternal platelets seem to be the superior option, because all alloantibodies in the fetal circulation are invariably unable to interact with maternal platelets, these need to be washed and irradiated, which can destroy the platelets and makes it a time-consuming strategy. In urgent situations, newborns can also be transfused with random platelets. As analyzed by Kiefel et al. [60], multiple random platelet transfusions are sufficient in increasing the platelet count in most of the FNAIT cases and are therefore an acceptable strategy when matched donor platelets are not available.

Despite consensus on platelet transfusion being the first line of therapy, there is no agreement on a 'safe' platelet count or an effective transfusion regime [64].

4.2.2. IVIG

In addition to being an effective antenatal treatment strategy in preventing bleeding complications, IVIG is also applied as a neonatal management strategy in FNAIT. Again its exact working mechanism is not quite revealed. Theories are that peripheral platelet destruction is inhibited through changes in Fc receptors on platelets and macrophages, as well as through Fc receptor-independent mechanisms [65,66]. For all indications, neonatal treatment of IVIG is used with a dose of 1–2 g/kg, during 2–5 consecutive days [67,68]. Based on a retrospective cohort analysis, we know that IVIG seems to have a response rate of approximately 65% in postnatally detected cases [67]. However, this effect takes longer than that of a platelet transfusion, and the rise in platelet count takes after IVIG treatment may take at least 24–48 h [68,69]. Therefore, IVIG should not be applied as first-line therapy alone in treatment of thrombocytopenic neonates with suspected FNAIT. Furthermore, when IVIG treatment is applied after antenatal maternal treatment with IVIG, the beneficial effect seems to be limited compared to the treatment with only platelet transfusions [68].

At our center, HPA-1bb/5aa platelet concentrates are available 24/7, therefore postnatal IVIG treatment is only administered in case of persistent very severe thrombocytopenia (<20 × 10^9/L) despite two previous matched platelet transfusions. In situations where there is no direct availability of matched platelets, IVIG can be added to a random transfusion in order to optimize and prolong the effect of the transfusion [70].

4.2.3. Other (corticosteroids, exchange transfusions)

Alternative management options include corticosteroid treatment and exchange transfusions. The administration of corticosteroids to treat thrombocytopenia, with a dose of 1 mg methylprednisone intravenous every 8 h, was previously suggested by the group of Bussel et al. [62]. However, considering the lack of evidence and possible side effects, the use of corticosteroids for this indication appears questionable [67,68,71].

In the previous century, exchange transfusion, which removes a part of the harmful circulating antibodies from the fetal circulation, was sometimes applied in very urgent situations where no platelets were available and treatment with IVIG would take too long [72]. This therapy is now completely abandoned due to the high risks of (bleeding) complications associated with exchange transfusions, particularly in thrombocytopenic neonates.

5. Expert commentary

FNAIT is an important health problem that may lead to potentially life-threatening disease. Evidence on management of FNAIT is limited, and with highly deviating designs in underpowered studies, it is hard to perceive a clear overview and develop international recommendations or clinical guidelines. However, we think that some conclusions can still be drawn from this little evidence. First, optimal antenatal management should be restricted to noninvasive treatment strategies. Because of the high complication rate per pregnancy, estimated to be as high as 11%, FBS or IUPT should be abandoned completely, whether applied as diagnostic or therapeutic procedure. Second, whereas no benefit of corticosteroid treatment is proven, noninvasive, antenatal treatment should consist of weekly IVIG infusions only. Taking into account the dose-related side effects, the off-label use, costs, and effectiveness as shown in small cohorts, IVIG should be dosed as low as possible. Though the level of evidence is weak, the effect of 0.5 g/kg/wk seems comparable to that of 1.0 g/kg/wk, when applied in standard risk pregnancies (without a sibling that suffered ICH) [31]. We think that in these standard-risk pregnancies the IVIG doses can be safely lowered to 0.5 g/kg/wk, starting at a gestational age of 24 weeks. Pregnancies after a first affected child that suffered an ICH should be considered as high-risk pregnancies and treatment should be started earlier, at 12–16 weeks, with the regular dose of 1.0 g/kg/wk. Decision on the mode of delivery should be primarily based on obstetric reasons, unless an in utero ICH occurred in the current pregnancy. Postnatal management guidelines are based on even weaker level of evidence, since no randomized controlled trials (RCTs) and only a few observational cohorts have been described. In case of confirmed or suspected FNAIT and a severe thrombocytopenia, the cornerstone and first choice of therapy is a platelet transfusion. Depending on the availability, a matched platelet transfusion should be used, potentially in combination with IVIG treatment. If matched platelets are unavailable, random platelets can be used but the increase in platelet count will be reduced. Threshold for transfusion can be lowered to 20×10^9/L in nonbleeding infants and should be raised to 50×10^9/L in case of bleeding neonates. There is need for either an RCT or a large observational cohort analysis to optimize recommendations on postnatal treatment of index and subsequent newborns with FNAIT. We think that, in order to make a truly meaningful improvement in the management of FNAIT, clinicians should be able to prevent the index cases from occurring, through population-based prenatal HPA-1a screening. This way it will be possible to identify the vast majority of the index cases of FNAIT, that is, the cases that are caused by anti-HPA-1a. Whereas HPA-1a is the predominant cause of FNAIT and of severe heamorrhage in specific, HPA-1a screening will lead to the most optimal prevention of severe bleeding complications. After detection of anti-HPA-1a cases, prevention can be achieved through timely pre-emptive antenatal therapy with IVIG or a possible immunoprophylaxis. Therefore, next to the need for increasing the level of evidence to optimize clinical guidelines and recommendations for FNAIT treatment, antenatal as well as postnatal, there is a lasting need for research assessing the efficacy of implementation of population-based FNAIT screening.

6. Five-year view

Given the rarity of the disease and therefore the difficulty in generating new evidence for determining optimal postnatal and antenatal treatment of FNAIT, more international collaboration is required to develop treatment guidelines and provide new evidence. Hopefully, in 5 years, invasive FBS and IUPT will be completely abandoned at all centers and replaced by antenatal IVIG treatment. In addition, we expect the debate about whether or not to implement prenatal screening for FNAIT will continue. With the results of our nationwide prospective screening study (HPA-screening In Pregnancy, HIP study), we hope to deliver the ultimate evidence to assess whether or not population based HPA-1a screening will be cost-effective and efficient, at least in the Netherlands. Next to tackling this unanswered problem, we are hoping that data from this study allows us to develop a risk-classification model. This will enable us to identify alloimmunized pregnancies at high risk for developing a bleeding complication and thus facilitate targeted antenatal management.

Key issues

- FNAIT is one of the leading causes of thrombocytopenia in otherwise healthy newborns
- Antenatal management used to include FBS and IUPT, but this management strategy has gradually been abandoned due to the potential complications and the valid alternative using IVIG.
- Antenatal management in FNAIT is nowadays mainly based on non-invasive treatment with weekly IVIG
- Neonatal treatment is determined by severity of thrombocytopenia and clinical condition
- First choice of neonatal therapy in FNAIT is a (matched) platelet transfusion
- Postnatal treatment can be complemented with IVIG treatment in case of no response to matched transfusions, or as an addition to random transfusions when no matched platelets are available.

Funding

The manuscript was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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