Fetal and neonatal alloimmune thrombocytopenia: the proof of the pudding is in the eating

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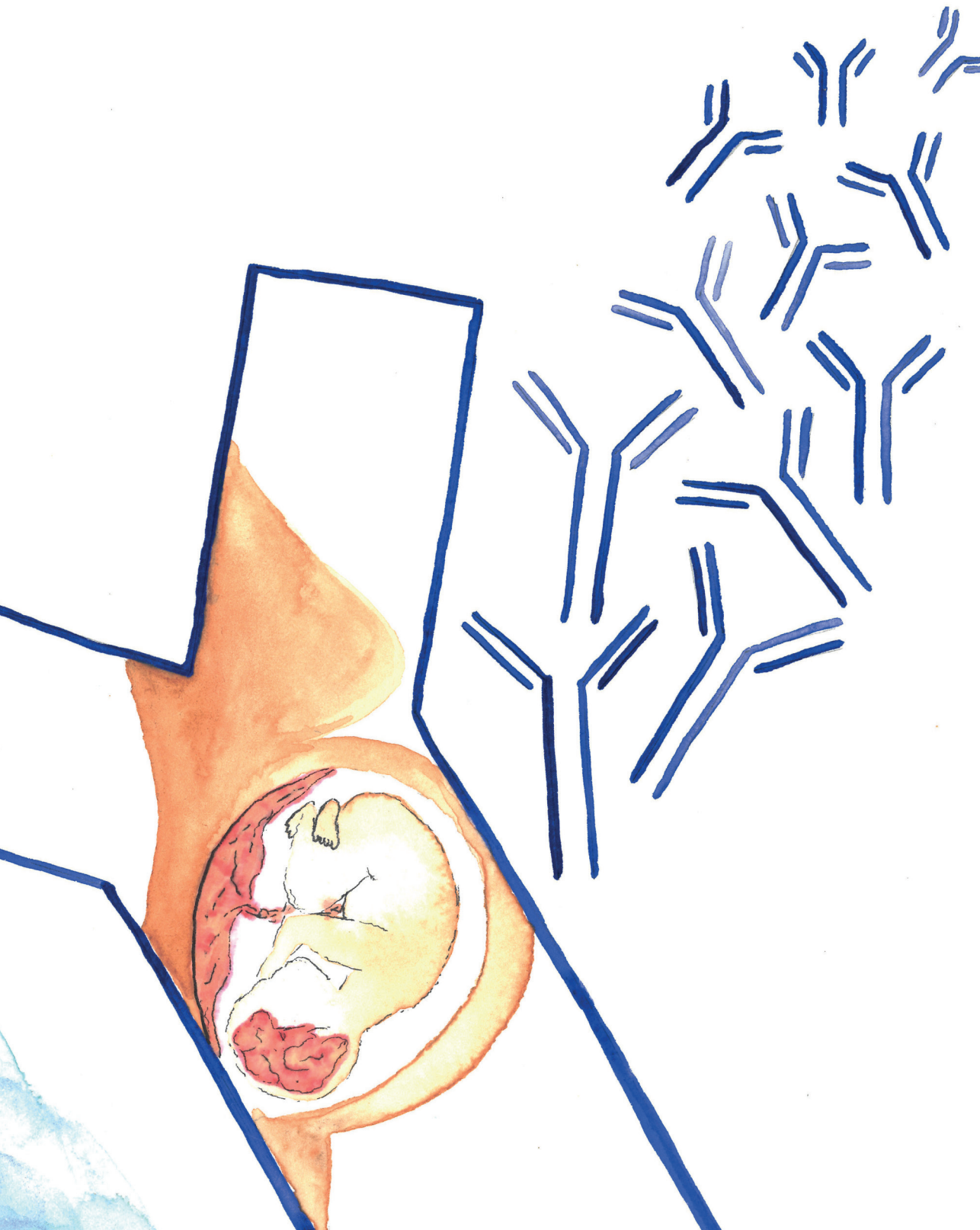

CHAPTER 1

Epidemiology and management of fetal and neonatal alloimmune thrombocytopenia

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ABSTRACT

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a disease in pregnancy characterized by maternal alloantibodies directed against the human platelet antigen (HPA). These antibodies can cause intracranial hemorrhage (ICH) or other major bleeding resulting in lifelong handicaps or death. Optimal fetal care can be provided by timely identification of pregnancies at risk. However, this can only be done by routinely antenatal screening. Whether nationwide screening is cost-effective is still being debated. HPA-1a alloantibodies are estimated to be found in 1 in 400 pregnancies resulting in severe burden and fetal ICH in 1 in 10.000 pregnancies. Antenatal treatment is focused on the prevention of fetal ICH and consists of weekly maternal IVIg administration. In high-risk FNAIT treatment should be initiated at 12-18 weeks gestational age using high dosage and in standard-risk FNAIT at 20-28 weeks gestational age using a lower dosage. Postnatal prophylactic platelet transfusions are often given in case of severe thrombocytopenia to prevent bleedings. The optimal threshold and product for postnatal transfusion is not known and international consensus is lacking. In this review practical guidelines for antenatal and postnatal management are offered to clinicians that face the challenge of reducing the risk of bleeding in fetuses and infants affected by FNAIT.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare but severe disease in pregnancy. FNAIT develops in pregnancy due to maternal alloimmunization and results in thrombocytopenia and a risk of bleeding in the fetus and neonate. Clinical presentation may vary from an asymptomatic thrombocytopenia as a finding by chance to skin bleeding or severe organ bleeding.[1] The most severe complication being intracranial hemorrhage (ICH), that can lead to perinatal death or lifelong neurologic sequelae.[2] FNAIT is the most frequent cause of thrombocytopenia in otherwise healthy born neonates with an incidence of approximately 1 in 1,500 pregnancies.[3] As FNAIT is a rare condition and often not recognized by clinicians, this entails difficulties to determine the burden of this disease on population level.[4] In addition, strong evidence for the optimal antenatal and postnatal treatment is lacking due to the limited number and size of randomized trials or observational studies.[5, 6] In this review we aim to summarize the current knowledge about the epidemiology of FNAIT and provide an overview on antenatal and postnatal management strategies based on the most recent literature.

PATHOGENESIS

In FNAIT, maternal exposure to incompatible, paternally derived, fetal HPA can lead to immunization and formation of alloantibodies. During pregnancy, active transport of IgG takes place form the mother to the unborn child over the placenta by binding to the neonatal Fc-receptor (FcRn).[7, 8] Hence, IgG class HPA-alloantibodies bind to fetal platelets, leading to phagocytosis of the fetal platelets causing thrombocytopenia and a risk of bleeding in these infants.[9, 10] Thrombocytopenia in FNAIT does not only result from the destruction of platelets, but may also worsen due to the suppression of platelet production by megakaryocytes. Suppression of megakaryocytopoesis has recently been shown in *in vitro* experiments in the presence of HPA-1a alloantibodies.[11]

HUMAN PLATELET ANTIGENS

Maternal alloantibody formation is triggered by exposure to incompatible HPA. Nowadays 41 HPAs are known and described. HPAs are epitopes present on five cell surface platelet glycoproteins (GP).[12, 13] These glycoproteins play an important role in platelet function for instance adhesion, aggregation and hemostatic plug formation.[14] Approximately 80% of the FNAIT cases in the white population are caused by alloantibodies directed the HPA-1a epitope. Therefore, we will focus on anti-HPA-1a-mediated FNAIT in this review unless stated otherwise. The HPA-1a is carried by the β3 integrin, which is part of the fibrinogen receptor.[15] The β3 integrin is also expressed in complex with the αV integrin as the vitronectin receptor, by endothelial cells, the placenta syncytiotrophoblast and by other tissue during

development of the human embryo.[16-18] This finding has led to interesting ideas about early immunization and functional effects of alloantibodies in FNAIT.

IMMUNIZATION

Immunization in FNAIT can occur early in pregnancy and lead to clinically relevant disease already in first affected pregnancies. The relevance of these immunizations was questioned by Skogen *et al.*[19] mentioning that the rate of immunization in primigravidae was 8-24%. However, in two case series describing intracranial hemorrhages (ICH) due to FNAIT, ICH occurred in first pregnancies in 24-27% of the cases, underlining that immunization and clinically relevant disease can occur already in early stages of first pregnancies.[2, 20] Previous research highlighted the contribution of several risk factors that play a role in HPA immunization during pregnancy. For some HPA antigens, such as HPA-1a, the exposure of the HPA-1a epitope on the placenta may play an important a role.[21] Furthermore, if HPA-1a negative women carry the MHC class II allele HLA-DRB3*01:01, this may promote the anti-HPA-1a immune response, due to optimal HPA-1a peptide presentation.[22, 23]

FUNCTIONAL EFFECTS OF ANTIBODIES

Approximately 10-25% of children with a severe thrombocytopenia caused by FNAIT develop an ICH.[4] However, the relationship between ICH and thrombocytopenia is not linear and the majority of FNAIT children do not develop an ICH. It may very well be that cranial bleedings are not solely caused by thrombocytopenia. The observation in a murine model with thrombocytopenic fetuses that were born without ICH supports this idea.[24] The expression of the β3 chain on both platelets and endothelial cells lead to the idea that bleedings in FNAIT can occur by the binding of antibodies to endothelial cells. Animal studies and *ex vivo* studies with human cord blood derived endothelial cells showed that HPA-antibodies directed against the β3-chain reduced endothelial cell proliferation, angiogenesis and endothelial integrity.[25, 26] Santoso *et al.*[27] recently found a larger proportion of vitronectin-receptor specific antibodies in maternal sera of FNAIT cases with ICH, compared to the sera from pregnancies without the occurrence of an ICH in the infant. The occurrence of ICH in fetuses and neonates with FNAIT may result from the combination of severe thrombocytopenia and endothelial damage, leading respectively to insufficiency of the hemostatic system and vessel wall injury.

TABLE 1. Prospective cohort studies assessing the incidence of FNAIT

Author, year	HPA-1a negative	Antenatal anti-HPA-1a	PLT < 50 × 10^9/L	Mild bleeding	Severe bleeding	Intervention
Mueller-Eckhardt, 1985 [28]	26/1,211 (2.1)	2/26 (7.7)	0	0	0	None
Reznikoff-Etievant, 1988 [29]	27/860 (3.1)	0/27 (0)	0	0	0	None
Blanchette 1990 [30]	81/5,000 (1.6)	3/50 (6.0)	1	0	1	NTCS, PP
Doughty, 1995 [31]	74/3,473 (3.2)	1/71 (1.4)	0*	0*	0	FBS/IUPT, IVIg, PP
Durand-Zaleski, 1996 [32]	52/2,066 (2.5)	4/45 (8.9)	1	0	0	FBS, IVIg, CTS
Williamson, 1998 [33]	618/24,417 (2.5)	37/385 (9.6)**	8	7	1	PP
Davoren, 2003 [31]	54/4,090 (1.3)	2/34 (5.9)	1	1	0	FBS, IUPT, PP
Maslanka, 2003 [34]	144/8,013 (1.8)	12/122 (9.8)	3	1	0	IUPT, IVIg
Turner, 2005 [35]	546/26,506 (2.1)	25/318 (7.9)	5	3	0	PP
Kjeldsen-Kragh, 2007 [36]	2,111/100,448 (2.1)	144/1,990 (7.2)	48	NR	2	NTSC, PP
Debska, 2018 [37]	373/15,204 (2.5)	22/373 (5.9)	3	NR	NR	IUPT, IVIg

*One HPA-1a negative women delivered two severely affected twin children, anti-HPA-1a antibodies detected after birth, not detected by prenatal screening.

** Two pregnancies ended in loss of the baby, one at 15 weeks, another as neonatal death from immaturity after CS at 25 weeks for severe pre-eclampsia.

Numbers are n/N (%)

Abbreviations: CST, antenatal corticosteroids; FBS, fetal blood sampling; FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; IUPT, intrauterine platelet transfusion; IVIg, antenatal intravenous immunoglobulins; NR, not reported; NT, not tested; NTCS, near-term cesarean section; PLT, platelet count; PP, postnatal platelets available for transfusion. Severe FNAIT is defined as neonatal platelet count at birth <50 x 10^9/L. Mild bleeding is defined as only skin or mucosal bleeding. Severe bleeding is defined as internal organ hemorrhage or ICH.

EPIDEMIOLOGY

Knowledge about the epidemiology of FNAIT is obtained from retrospective data of cases sent to reference laboratories and prospective screening studies. Studies with a retrospective study design are often prone for bias. Not the least because FNAIT cases are often missed and underdiagnosed in the absence of a nationwide screening programme.[38, 39] FNAIT as a cause of intrauterine fetal demise (IUFD) is often not considered and the burden of FNAIT might be even larger when miscarriages and IUFD are taken into account. Large prospective screening studies that address the incidence of FNAIT have been performed in several countries (Table 1). In general, studies with a prospective study design are less prone for bias. However, interventions in these studies might influence the outcome of the disease, which makes it difficult to assess the natural course of the disease. In addition, it should be noted that two types of screening studies have been performed; postnatal screening studies that screen for alloantibodies in thrombocytopenic neonates[40-45] and antenatal screening studies that assess neonatal outcome after screening for antibodies, mainly performed in HPA-1a-negative women.[28-37, 46]

INCIDENCE OF HPA-ALLOANTIBODIES

Incidence of HPA-alloantibodies varies due to genetic variation between populations.[13] In 2004 Davoren *et al.*[47], described the HPA specificity of 1162 different FNAIT cases in a white population.

Based on this study, around 80% of the FNAIT cases are caused by HPA-1a alloantibodies. HPA-5b alloantibodies are responsible for ~10% of the FNAIT cases. When cases with HPA-2, -3 and -15 alloantibodies are added to this list approximately 95% of the FNAIT cases are covered.[47] In the Asian population most FNAIT cases are caused by antibodies directed against HPA-5b, followed by anti-HPA-4b; the HPA-4 antigens are present on the β3-integrin like HPA-1.[48] Since most studies are based on patient series that were collected retrospectively it is difficult to estimate natural occurrence and pathogenicity of these alloantibodies. Based on the available studies, antibodies against low frequent antigens are rare, and their contribution to the morbidity of FNAIT in the white population is negligible.[49]

Kamphuis *et al.*[3] performed a systematic review on the incidence of FNAIT in 2010. In total 176,084 antenatal screened pregnancies were included. Based on these studies the authors estimated that 2.1% of the pregnant women are HPA-1a negative in the white population and therefore at risk for FNAIT. The risk of antibody formation in HPA-1a negative women during reproductive age was calculated to be 9.7% (294 of the 3,028 cases). In 2018 Dębska *et al.*[37] found that the risk of antibody formation was 8.6% in the study population of Polish screening program. In a recent Norwegian study, the risk of postpartum immunization for an HLA-DRB3*01:01 positive women delivering an HPA-1a positive child was calculated to 12.7%.[50]

INCIDENCE OF SEVERE THROMBOCYTOPENIA

Clinical symptoms in FNAIT vary from asymptomatic thrombocytopenia to severe (intracranial) hemorrhages. In literature, FNAIT is often defined as neonates with alloantibodies and a platelet count < 50×10^9/L with or without ICH. Differences in definitions on severe FNAIT makes it difficult to compare different studies and assess the natural history of FNAIT. Kamphuis *et al.*[4] assessed the incidence of severe FNAIT in a review in 2014 and compared antenatal and postnatal screening studies. The incidence of severe FNAIT, defined as platelet count < 50×10^9/L, was estimated to be 0.04% in both antenatal and postnatal screening studies.[4]

INCIDENCE OF INTRACRANIAL HEMORRHAGES (ICH)

The development of ICH is not directly associated with the severity of thrombocytopenia, given that only a small proportion of severely thrombocytopenic infants suffer from bleeding complications.[4] In addition to this, severe bleedings have been described in cases with moderate thrombocytopenia.[51] Shortage of platelets is therefore unlikely to be the only factor that causes ICH. Over the last years more evidence emerged showing that the maternal alloantibodies can also cause damage to the endothelium that might result in ICH.[26, 27] It is not known at which moment in pregnancy the developing brain is most vulnerable for damage induced by these kinds of alloantibodies. It may also be that these types of alloantibodies do not only lead to ICH but also to other type of cerebral damage or small bleedings. These lesions

can remain subclinical directly after birth but lead to developmental delay on the long term.

Two cohort studies by Tiller *et al.*[20] and Winkelhorst *et al*[2] described the localization and extensiveness of FNAIT-related ICH. In these studies, 43 and 21 cases, respectively were described. Approximately 90% of these cases were caused by HPA-1a alloantibodies. Tiller *et al.*[20] described that most of the bleedings were intraparenchymal. This finding was confirmed by Winkelhorst *et al.*[2] showing that 19 bleedings were intraparenchymal complicated by hydrocephalus in 11 cases. The survival rate of children with ICH due to FNAIT varied from 65% to 52%. The risk on neurological sequelae in survivors was high, ranging from 70% to 53%.

The incidence of ICH varies from 9.9% to 25% of the severe FNAIT cases based on antenatal and postnatal screening studies, respectively (Figure 1).[4] Antenatal screening studies may underestimate the incidence of ICH as imaging was not performed routinely in all screening studies. However, Refsum *et al.*[52] performed a retrospective cohort study and assessed the presence of HPA alloantibodies in a cohort of neonates born with an ICH. In this study, HPA alloantibodies were only found in 3 of the 105 maternal serum samples. The authors acknowledge that this study might be affected by bias, although the study implicates that the true incidence on FNAIT-related ICH might be less than previously thought.

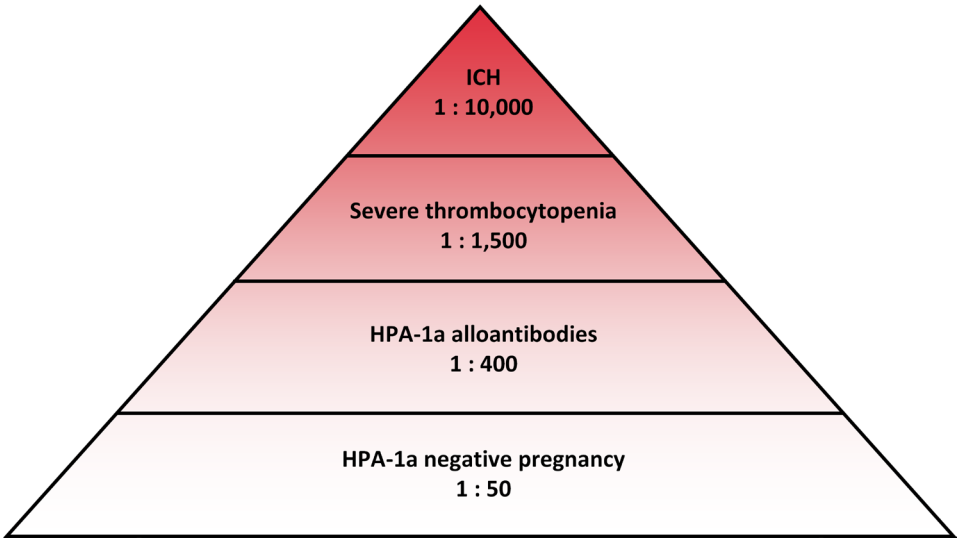

FIGURE 1. Epidemiology of anti-HPA-1a induced FNAIT
Severe thrombocytopenia is defined as a platelet count below 50×10^9/L.
Abbreviations: HPA, Human platelet antigen; FNAIT, fetal and neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage; L, liter.

The recurrence rate of ICH in FNAIT is difficult to assess since studies are retrospective and biased by different treatment interventions. In addition, as severe cases might be more likely to be published, studies on this subject are also more prone for publication bias. In 2003 Radder *et al.*[53] performed a retrospective cohort study to assess the recurrence risk of ICH after a pregnancy complicated by an ICH due to FNAIT. The recurrence rate of an ICH due to FNAIT in subsequent pregnancies was estimated on 79%. Besides ICH, other life-threatening organ bleedings, like pulmonary, ocular and gastrointestinal bleedings, are described in FNAIT.[54, 55] Since these bleedings are less well known and probably underreported, it is impossible to estimate the incidence of these bleedings.[1]

ANTENATAL MANAGEMENT

The majority of ICH in FNAIT develop during pregnancy.[20] These hemorrhages have an important contribution to the burden of FNAIT. To prevent these ICH, treatment during pregnancy must be initiated early enough in pregnancy. Alloantibodies develop without clinical symptoms during pregnancy. Details about diagnostics of these antibodies are published by Porcelijn *et al.*[56]. The only way to prevent severe complications in first pregnancies is by screening and timely antenatal treatment. In the absence of routine screening, antenatal treatment is mostly started in subsequent pregnancies after the first affected child was born. When FNAIT is suspected, diagnostic tests should confirm or rule out FNAIT, in this way clinical management can be adapted adequately in the future. Clinicians are challenged to reduce the risk of bleedings in FNAIT, this can be done by treatment during pregnancy. In the past, the mainstay of treatment was based on invasive intrauterine platelet transfusions, similar to blood transfusions in red cell immunization. Nowadays, non-invasive approaches using maternal IVIg administration have been shown to be equally or even more effective, and preferable due to a reduced risk of complications.

RISK STRATIFICATION

If FNAIT is confirmed antenatally, pregnancies should be closely monitored by a specialized obstetrician. Currently we use the clinical outcome of a previous FNAIT pregnancies for risk stratification. Some studies show that alloantibody levels could predict disease severity[57] an approach which has been used in Norway for two decades.[58] However severe FNAIT cases have been described with low antibody levels implicating that sensitivity is low.[59] It may be that pregnancies with HPA-5b or HPA-15b antibodies could be considered as low risk pregnancies and alloantibodies against HPA-1a and HPA-3a as high risk, however, the risk for the individual pregnancy on an HPA-alloantibody mediated bleeding in the infant can yet not be predicted. Data set from large prospective studies comparing clinical outcome of different

HPA antibodies will be the first step to adjust clinical management for different HPA types. Despite efforts to find a reliable prognostic marker until know, no single marker has been found to predict disease severity accurately. Maternal HLA DRB3*01:01 status is suggested as a prognostic marker for immunization and formation of potent HPA-1a antibodies during pregnancy. More research is needed to confirm these findings.

INTRAUTERINE TRANSFUSIONS

Fetal blood sampling (FBS) and intrauterine platelet transfusions (IUPTs) were traditionally the only treatment options to reduce the risk of ICH and severe thrombocytopenia. Intrauterine intravascular, ultrasound-guided red blood cell transfusions to treat fetal anemia were introduced in the 1980s. Daffos and colleagues[60] were the first that applied this technique on FNAIT. After their successful first intra-uterine platelet transfusion others followed. However, there are important differences between intra-uterine red blood cell transfusions for fetal anemia compared to platelet transfusions for fetal thrombocytopenia. Since the fetus is at risk for bleeding due to FNAIT, puncture of the umbilical cord is a dangerous procedure. In addition, the half-life of the transfused platelets is short, making it necessary to perform weekly transfusions. The high risk of complications related to fetal blood sampling or intra uterine transfusions was confirmed in a recent systematic review by Winkelhorst *et al*. [5]. In total, 26 studies were included, of which 4 were randomized controlled trails, 5 prospective studies and 17 retrospective studies. The most frequently reported complication due to FBS or IUPT was an emergency cesarean section. The authors describe that complications occurred in 11% of the pregnancies treated with invasive therapy (54 of 497 treated pregnancies in 24 studies). Complications resulted in fetal death or neonatal loss in 26% of cases. The overall mortality rate was 4%, with more than half of the mortality related to FBS/IUTP.[5]

MATERNAL INTRAVENOUS IMMUNOGLOBULINS (IVIG) ADMINISTRATION

In the past, IVIg administration was successfully used in pregnancies complicated by maternal idiopathic thrombocytopenic purpura (ITP). Later, in 1988, Bussel and colleagues[61] were the first to report a positive effect of antenatal maternal IVIg treatment in pregnancies with FNAIT. IVIg are made from human IgG antibodies extracted from pooled human donor blood. The exact therapeutic mechanism of maternal IVIg treatment is unknown. The various proposed mechanism that could be responsible for the effect are discussed by Wabnitza *et al.*[62]. Evidence about optimal treatment options is obtained mostly from cases series and was recently summarized in a systematic review as part of an international guideline on FNAIT.[5, 63] In the absence of a reliable clinical or biochemical marker to predict platelet count or clinical outcome on FNAIT, treatment is based on the obstetric medical history. FNAIT pregnancies are usually classified as 'high-risk' in case of a previous pregnancy with a severely affected child with ICH or severe hemorrhage, while all other pregnancies with sibling with FNAIT without ICH are considered as 'standard risk'. First line treatment in high-risk pregnancies is weekly maternal IVIg administration from 12-16 weeks of gestational age with a standard

dosage regime of 1 g/kg/week. In some centers, dosage is increased to 2 g/kg/week around 20 weeks gestational age and/or corticosteroids are added. Since side effects of IVIg treatment are dose-dependent and the beneficial effect of increment in dosage is based on low evidence, therapy is not intensified in high-risk pregnancies in the Netherlands. In a randomized trial to assess the optimal dosage in FNAIT the risk on adverse outcomes was not different between low-dose (0.5 g/kg/week) or high dose (1.0 g/kg/week).[64] As this trial was stopped early due to poor recruitment a definitive conclusion regarding dose could not be drawn from this trial. Yet the standard dosage regimen in standard risk pregnancies at our center has been lowered to 0.5 g/kg/week. Treatment in standard risk pregnancies is usually started from 20 to 28 weeks gestational age, antenatal management strategies in the Netherlands are summarized in figure 2.

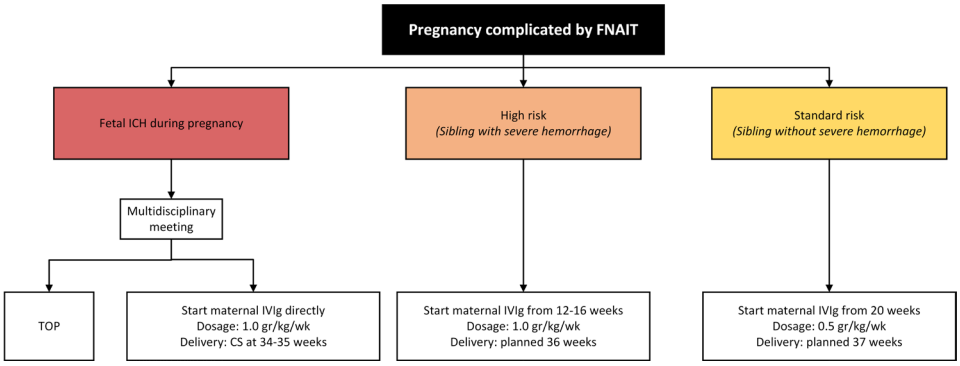

FIGURE 2. Flowchart antenatal treatment
Abbreviations: FNAIT, Fetal and neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage; TOP, termination of pregnancy; IVIg, Intravenous immune globulins; gr/kg/week: grams per kilogram (bodyweight) per week.

IVIg administration is performed blindly, without FBS or IUPT, and this makes it impossible for clinicians to monitor the therapeutic effect of this treatment. Side effects can be classified in maternal and fetal side effects. The most important maternal side effects are headache and flu-like symptoms. One case of maternal pancytopenia was reported, in this case full blood count was normalized spontaneously 6 weeks after pregnancy.[65, 66] Possible long-term effects on the development the immune system of children are not well known. In one study, complete blood count and leukocyte differentiation were assessed in 20 cord blood samples, and in this study no abnormal maturation of the immune system was seen in children with FNAIT who received antenatal IVIg treatment or IUPT.[67] In the same cohort, a questionnaire study was performed and showed no increase of pediatric infections in IVIg treated cases. However, treatment regime in this cohort was heterogeneous and groups were small.[68] Since side effects of maternal IVIg treatment during pregnancies on the development of the fetus were not assessed adequately and no randomized placebo-controlled trial was performed

to show clinical efficacy, IVIg treatment for this indication is still 'off label'. This, even though IVIg treatment is recommended in virtually all guidelines. Additional studies on maternal and neonatal effects of IVIg are required, including the effects on long-term neurodevelopment outcome and immune system should be performed.

In conclusion, invasive antenatal management are equally effective but invasive interventions have a higher risk of complications. Therefore, maternal IVIg administration is first line treatment as antenatal management in FNAIT. This recommendation was integrated in the most recent international guideline on clinical management strategies of FNAIT.[63]

CORTICOSTEROIDS

In addition to maternal IVIg treatment, corticosteroids are sometimes added as antenatal treatment in some centers and mentioned in guidelines. However, the evidence for the use of corticosteroids is very weak, and the fetal and maternal side effects should not be underestimated.[63] Winkelhorst *et al.* [5] assessed 11 studies that compared IVIg treatment with and without the addition of corticosteroids. Only one study showed an increase in platelet count,[69] while all other studies failed to report beneficial effects. Given the important side effects and the lack of evidence for a beneficial effect, we think that this treatment should not be applied as first line treatment in FNAIT.

MODE AND TIMING OF DELIVERY

Peripartum management should be focused on reduction of the risk of bleeding by minimizing the factors contributing to bleeding complications. Strong evidence for best peripartum strategies is lacking. There is consensus about reticence in the use scalp electrodes, scalp blood samplings or assisted vaginal delivery. Elective cesarean delivery is the preferred mode of delivery in some centers. This is based on the assumption that delivery could trigger ICH in FNAIT cases, based on a retrospective cohort study. In this study, 200 FNAIT cases were described, all 17 FNAIT related ICH occurred before or within 24 hours after birth.[51] However, in this study no routine ultrasound prior to and after delivery was performed. Time-point of development of ICH is therefore not certain or by definition induced by delivery. Van den Akker *et al.*[70] performed a cohort study on standard risk FNAIT pregnancies. In this study 23 vaginal deliveries and 9 cesarean sections (CS) were included, and they showed that vaginal delivery was not associated with an increased risk on ICH. Another argument to reconsider routine near term elective cesareans is the risk on neonatal complications. Neonatal complications related to pulmonary maladaptation or prematurity were observed in 37 (21.5%) of the neonates in the large prospective Norwegian screening study that performed near team CS to prevent ICH. [36] In our opinion, given the lack of evidence and the potential increased risks of neonatal morbidity, CS should not routinely be performed in FNAIT pregnancies.

FUTURE TREATMENT OPTIONS

In analogy to the prevention of RhD using immunoprophylaxis, prevention of immunization and development of FNAIT has been shown to be effective in a murine model.[71] However, no clinical trials have yet confirmed this effect in humans. Kjær and Skogen[72] discuss the challenges of developing a hyperimmune anti-HPA-1a IgG for the prevention of HPA-1a-immunization. Another future therapeutic option might be an FcRn receptor blocker that can inhibit the transportation of alloantibodies over the placenta. Preclinical studies showed promising results,[73] and a study in red cell alloimmunized pregnancies is currently ongoing.[74]

POSTNATAL MANAGEMENT: OPTIMAL TRANSFUSION THRESHOLDS AND PLATELET PRODUCT

TRANSFUSION THRESHOLD

The optimal postnatal management strategy for neonates with FNAIT is unknown and is currently mostly based on expert opinions and single center observational data. Due to the rarity of disease and its heterogeneity, randomized trials will need a high number of inclusions and a large consortium contributing to the study. A recent systematic review on the postnatal treatment concludes that there is no sufficient evidence on the optimal postnatal treatment to prevent bleeding in infants that suffer from FNAIT.[6] After birth, prophylactic platelet transfusions are advised in case of severe thrombocytopenia in virtually all guidelines, but transfusion thresholds vary. Prophylactic platelet transfusions are given to prevent bleedings, but the evidence for the preventive effect of platelet transfusions is controversial and has recently been questioned[75-77] In a recent systematic review, the opposite was found to be more plausible, as transfusions in thrombocytopenic preterm neonates were associated with increased risk of bleeding.[78] A recently published randomized trial on prophylactic platelet transfusions thresholds in preterm infants confirmed the results of the systematic review.[79] This study showed that a higher platelet transfusion threshold (50×10^9/L) was associated with a higher mortality rate and bleeding than a more restrictive transfusion threshold (25×10^9/L). Although this study included only preterm neonates and excluded neonates with FNAIT, one could argue that prophylactic transfusions in FNAIT neonates, with potentially fragile vessel walls due to endothelial damage, could be harmful too. A randomized trial in FNAIT neonates would be required to determine the optimal transfusion threshold. Until then, we suggest to follow national guidelines and transfer knowledge obtained from randomized trails performed in preterm infants. Figure 3 provides an overview of a Dutch transfusion guideline in FNAIT. A transfusion threshold of 50×10^9/L in neonates suffering from FNAIT with active bleeding is suggested and a threshold of 25×10^9/L in neonates without active bleeding.

PLATELET PRODUCT

HPA-typed platelets, negative for the implicated HPA antigen, have traditionally been regarded as the optimal platelet product in FNAIT neonates, as these products would not be susceptible to the pathogenic antibodies present in these children. In a recent study in a national cohort in 102 firstly diagnosed FNAIT cases, we found a similar platelet increment in both HPA-matched and random platelet transfusions.[80] In our opinion, random platelet transfusions could be viewed as first-line treatment in case acute bleeding or severe thrombocytopenia. In most countries, HPA-matched platelets are not readily available and reducing delay by using random platelets may be preferable. No large benefits of neonatal IVIg treatment were observed in our small cohort.[80] Also the beneficial effect of IVIg treatment postnatal is questioned in a recent systematic review on postnatal treatment in FNAIT.[6] Pragmatically we advise to perform a platelet transfusion without delay using random platelets, at a platelet count < 25 × 10^9/L or in case of a severe bleeding, unless an HPA-matched product is readily available. IVIg treatment is not advised as first line postnatal treatment.

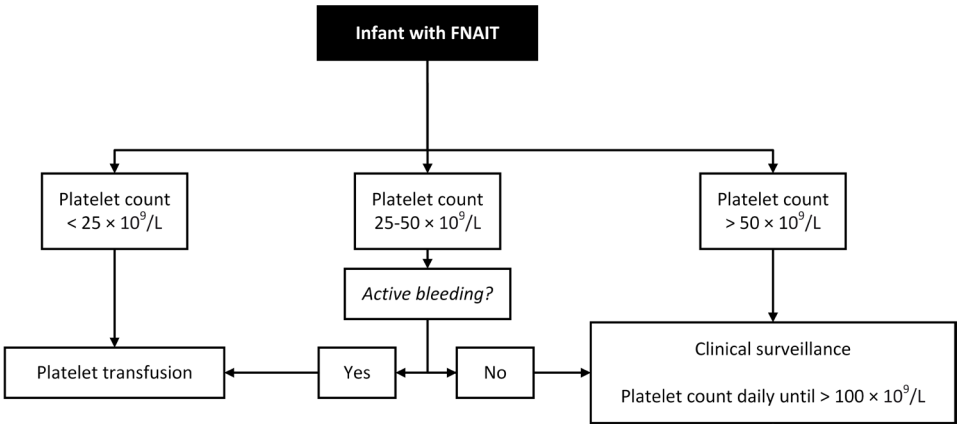

FIGURE 3. Flowchart postnatal treatment
This flowchart is based on the Dutch transfusion guideline for infants.
Abbreviation: L, liter.

LONG-TERM OUTCOME

Literature about the long-term outcome on FNAIT without ICH is scarce.[2,20] The first follow-up study on FNAIT cases was performed by Ward *et al.*[81] and published in 2006. They concluded that development of children treated for FNAIT was better compared to their non-treated siblings. Their conclusions were based on questionnaires taken by telephone, assessing the behavioral outcome of the children and were limited by a 40% lost-to-follow-up rate. A second follow-up study including 39 children was published by a research group from our center in 2004. This study showed that the outcome in children with FNAIT and exposed to maternal IVIg treatment was similar to the normal population.[68] However, this study included a heterogenic group of children with different treatment strategies including IUT, hampering definitive conclusions. More research is needed to provide insight in the long-term development of children that suffered from FNAIT.

FUTURE PERSPECTIVES

The introduction of an antenatal screening on FNAIT has been a topic of scientific debate in the past decades and has been discussed by the health authorities in several countries, for instance Norway, Denmark, the United Kingdom and the Netherlands. The World Health Organization stimulated the use of the criteria from Wilson and Jungner to decide whether a population screening program is of benefit to a population and the overall health care system. These criteria can be used to guide the debate on antenatal screening on FNAIT.[82] Two of these criteria should be priority in research on FNAIT. First, the natural course and incidence on FNAIT should be addressed. Second, attention should be paid to the development of diagnostic tools to identify the pregnancies at risk for severe neonatal outcome. As discussed earlier, most studies that address the incidence of FNAIT are either performed retrospectively or performed prospectively in combination with interventions. Therefore, results on the natural course of the disease could be biased. Importantly, most studies used platelet count as a primary outcome marker instead of clinically more relevant outcomes such as major bleeding and/or perinatal death.[4] Conducting a study that addresses these outcomes will be extremely challenging since the incidence of these major bleeding is estimated on 1 in 10.000 pregnancies and thousands of pregnancies would have to be screened. An important research priority on this subject is the development of diagnostic tools to predict clinical outcome, hence, to identify the cases who need antenatal therapy and interventions. Future international collaboration involving both clinicians and scientists might lead to this diagnostic assay to identify pregnancies at risk and prevent burden of FNAIT in future.

TOWARDS ROUTINE HPA-SCREENING IN PREGNANCY TO PREVENT FNAIT – THE HIP STUDY

In 2017, a large prospective screening study started in the Netherlands to assess the incidence on clinically relevant FNAIT cases.[83, 84] Maternal serum samples of HPA-1a negative and HPA-1a positive controls and clinical data are collected. We expect to end our study in spring 2020. In contrast to other screening studies, this study is completely observational without any perinatal management applied, which allows the assessment of the natural history of this disease. More importantly, this study will provide a uniform serum sample collection (alloimmunized pregnancies without clinical disease) that can be used to develop and test diagnostic assays to identify pregnancies at risk. In this way the HIP study will contribute important knowledge and provide arguments in the debate on antenatal screening on FNAIT.

CONCLUSION

FNAIT causes severe burden and fetal ICH in 1 in 10.000 pregnancies. Antenatal, non-invasive treatment strategies are nowadays viewed as preferred management since they bear a lower risk of intrauterine complications. In high-risk FNAIT, antenatal IVIg treatment should be initiated at 12-18 weeks gestational age, using a high dosage. In standard-risk FNAIT antenatal IVIg should be started between 20-28 weeks gestational age using a lower dosage. Postnatal treatment strategies consist of platelet transfusions in case of severe thrombocytopenia, using either HPA-selected or unselected, depending on which one is more readily available. The optimal threshold for prophylactic transfusion is not known and varies between countries. A more restrictive transfusion strategy using a lower platelet threshold was recently shown to be superior to a liberal strategy using a higher threshold in preterm neonates. Whether this may also apply to term neonates with FNAIT is not known. Further studies are needed to evaluate the natural history and long-term neurodevelopmental outcome in FNAIT to optimize risk assessment and identify pregnancies at risk for ICH. Prevention of FNAIT is key and can be achieved by antenatal screening. Implementation of national screening programs will probably strongly reduce the burden of this severe disease.

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