International Journal of Women's Health

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REVIEW

Current perspectives on fetal and neonatal alloimmune thrombocytopenia – increasing clinical concerns and new treatment opportunities

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This article was published in the following Dove Press journal:
International Journal of Women's Health
19 April 2017
Number of times this article has been viewed

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Abstract: Differences in platelet type between the fetus and the mother can lead to maternal immunization and destruction of the fetal platelets, a condition named fetal and neonatal alloimmune thrombocytopenia (FNAIT). FNAIT is reported to occur in ~1 per 1,000 live born neonates. The major risk is intracranial hemorrhage in the fetus or newborn, which is associated with severe neurological complications or death. Since no countries have yet implemented a screening program to detect pregnancies at risk, the diagnosis is typically established after the birth of a child with symptoms. Reports on broader clinical impact have increased clinical concern and awareness. Along with new treatment options for FNAIT, the debate around antenatal screening to detect pregnancies at risk of FNAIT has been revitalized.

Keywords: antibodies, screening, alloimmunization, platelets, newborn, pregnancy

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is not a common pregnancy complication but carries a significant risk of severe fetal and/or neonatal complications and has been recognized as the major cause of primary hemorrhagic morbidity and mortality in fetuses and newborns.[1] In neonatal intensive care units, severe thrombocytopenia (platelet count $<50\times10^9$/L) is reported in 5%–22% of children.[2,3] Most of these cases have underlying causes such as prematurity, congenital infections, maternal immune thrombocytopenic purpura, or chronic fetal hypoxia.[3,4] However, in otherwise healthy term newborns with isolated severe thrombocytopenia, the most frequent cause is FNAIT.[5–7] The condition occurs in ~1 per 1,000 births in Caucasian populations.[7]

The aim of this review was to give an overview of FNAIT, with a focus on recent developments in its clinical aspects and treatment options.

Pathogenesis

The fetus is semiallogeneic by nature, but generally well tolerated by the maternal immune system. However, some polymorphisms can cause maternal alloimmunization in incompatible pregnancies – resulting in maternal antibodies that target fetal cells for destruction. The clinical manifestations of the conditions depend on the target for the maternal alloantibodies. The most classic immune response in incompatible pregnancies is immune response to RhD antigens on fetal red cells. Red cell alloimmunization can cause hemolytic disease of the fetus or newborn (HDFN). Fetomaternal incompatibility for human neutrophil antigens may induce antibodies targeting neutrophils causing neonatal neutropenia making the newborn

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Dovepress
http://dx.doi.org/10.2147/IJWH.S90753

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susceptible for infections. Incompatibility for human platelet antigens (HPAs) can induce antibodies against fetal platelets, which may lead to FNAIT and hemorrhagic complications. FNAIT is defined as fetal or neonatal thrombocytopenia caused by antibodies targeting alloantigens on fetal platelets (from now on referred to as alloantibodies) because of incompatibility between fetal and maternal platelet antigens.

Maternal antiplatelet immunoglobulins (IgG) are transported across the placenta (mostly IgG_1 and IgG_3) to the fetal blood system, primarily by the major histocompatibility complex (MHC)-class I-related neonatal Fc receptor.[8] These antibodies will bind to the fetal platelets, and the platelets will subsequently be removed from the fetal circulation by phagocytosis.

The HPAs are located on platelet membrane glycoprotein receptors. These glycoproteins play fundamental roles in platelet functions, such as adhesion and aggregation. Most HPAs are based on single-nucleotide polymorphisms resulting in amino acid substitutions localized on the main platelet receptors: integrin αIIbβ3 (GPIIb/IIIa, CD41/CD61: the fibrinogen receptor), the GPIb-IX-V complex (CD42, von Willebrand factor receptor), and the GPIa/IIa complex (α2β1, CD29, the collagen receptor).[9,10] HPA-15 is the only exception; this biallelic system is carried by the platelet membrane protein CD109,[11] which is a part of the transforming growth factor-β receptor system.[12] For a more comprehensive presentation of platelet membrane glycoproteins, the recent review by Zdravic et al[13] is suggested.

Platelet-specific antigens were first described in the late 1950s and early 1960s.[14,15] To date, 35 different platelet-specific alloantigens have been described as targets for antibodies in FNAIT, of which 12 are grouped in six biallelic systems (HPA-1, -2, -3, -4, -5, and -15; http://www.ebi.ac.uk/ipd/hpa/table1 [accessed September 2016]).

Antigen incompatibility in HPA-1 is found to cause 80%–90% of FNAIT cases in the Caucasian population.[16–18] The HPA-1 antigen is located on the integrin β3, defined by a Leu33Pro polymorphism in the PSI domain. Carriers of the Leu33 allelic variant are defined as HPA-1a positive, whereas those who carry homozygous Pro33 alleles are termed HPA-1a negative or HPA-1bb. The classic HPA-1a antigen is a part of the integrin αIIbβ3 complex, also known as the fibrinogen receptor, which is restricted to platelets and megakaryocytes. However, the integrin β3 subunit of the fibrinogen receptor is also part of the integrin αVβ3 complex (vitronectin receptor), which is expressed on other fetal cells, including angiogenic endothelial cells and invasive trophoblasts.[19,20]

Fetal megakaryocytes – the precursors of platelets – are found in lung and liver as early as in the 12th gestational week. Platelet counts in the healthy fetus are within normal adult range no later than 18th gestational weeks.[21,22] Fetal platelet antigens are expressed in normal amounts as early as week 16.[20] Maternal IgG alloantibodies from previous pregnancies are detectable in fetal blood from gestational week 6[23] and start to increase from early in the second trimester.[23,24] Fetal thrombocytopenia caused by maternal alloantibodies may therefore occur very early during pregnancy.

The immune response against HPA-1a is strongly associated with the human MHC class II allele *HLA-DRB3*01:01*.[25–29] In the Norwegian screening study, 90% of HPA-1a immunized women were *DRB3*01:01* positive.[25] In comparison, 28% of a random population were *DRB3*01:01* positive.[26] This strong association suggests that CD4 T-cell activation by the DRA/DRB3*01:01 molecule is a determining event in the immune response against HPA-1a. In support of this notion, it has been shown that integrin β3-derived peptides with Leu33 (HPA-1a peptide), but not with Pro33, bind well to the DRA/DRB3*01:01 molecule and thus can be presented by antigen-presenting cells.[30,31] Also, HPA-1a-specific DRA/DRB3*01:01-restricted CD4 T cells have been isolated from women who have had a child affected by FNAIT.[32,33] Predictably, DRA/DRB3*01:01-restricted HPA-1a-specific CD4 T cells provide essential help to HPA-1a-specific B cells to differentiate to anti-HPA-1a antibody producing plasma cells. Leu 33 has been shown to serve as an anchor residue for stable binding of HPA-1a peptide to the DRA/DRB3*01:01 molecule[31] and is not solvent exposed. T-cell recognition of the allogeneic leu33 residue is therefore indirect.[34]

Despite large efforts, we still do not completely understand what makes some HPA-1bb women prone to alloimmunization; most are not immunized in connection with an HPA-1 incompatible pregnancy. A recent observation by Li et al[35] that infection status in the mother may play a role is interesting and implies that a proinflammatory event trigger the alloimmune response. However, we should also focus on understanding the mechanisms that induce immune tolerance, which could have an important role in preventing most women from becoming alloimmunized.

The clinical relevance of different anti-HPA antibodies varies among different ethnic groups. In a Caucasian population, anti-HPA-1a antibodies are by far the most common and clinically relevant cause of FNAIT.[17,18,36] Approximately

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2% of Caucasian women are HPA-1a negative and at risk of being immunized in connection with an HPA-1 incompatible pregnancy.[25,37] The frequency of FNAIT due to anti-HPA-1a antibodies is reported to be 1:1,100 live births.[18,25,38] An overview of the pathophysiology of maternal HPA-1 alloimmunization is shown in Figure 1.

In addition, anti-HPA-5b antibodies cause FNAIT in 7%–16% and anti-HPA-15b in 2%–4% of the cases.[16,17,36,39] The African–American population seems to have a lower incidence of anti-HPA-1a-induced FNAIT but have higher risk of alloimmunization to HPA-2 and HPA-5 antigens.[40] Among Japanese, HPA-4 and HPA-5 alloimmunizations are most frequent.[41,42]

The human leukocyte antigen class I (HLA class I) is present on all nucleated cells and platelets in the human body. The genes that encode HLA class I are the most polymorphic in the human genome. Exposure to non-self-HLA can activate the host immune system and lead to the production of alloantibodies. It is well known that anti-HLA class I antibodies can have severe clinical consequences, such as rejection of allografts[43,44] or destruction of transfused platelets.[45] Maternal anti-HLA class I antibodies are detected during pregnancy in at least 30% of multigravida.[46–49] Although these antibodies have been reported in association with various pregnancy complications, the possible harmful effects on pregnancy are still not clear.[50] Numerous reports describe suspected cases of FNAIT with maternal anti-HLA class I antibodies as the only finding and possible explanation of neonatal thrombocytopenia.[51–55] It has therefore been suggested that maternal anti-HLA class I antibodies may cause FNAIT, but this is still controversial.[46,56]

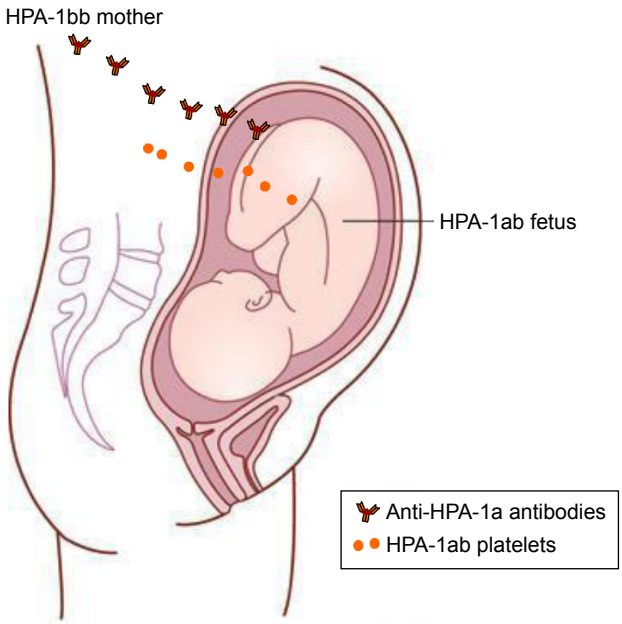

Figure 1 Pathophysiology of maternal HPA-1 alloimmunization.
Notes: In an HPA-1bb mother who is pregnant with an HPA-1ab fetus, fetal platelets/fetal platelet antigen may enter the maternal circulation and lead to the production of anti-HPA-1a antibodies in the mother. Copyright © 2003. The Norwegian Medical Association. Reproduced from Heier HE, Berge LN, Hervig T, et al. Immunisering i svangerskapet. [Immunization during pregnancy]. *Tidsskr Nor Laegeforen*. 2009;129(19):2016–2018.[137]
Abbreviation: HPA, human platelet antigen.

Diagnosis

The diagnosis of FNAIT requires that the fetus/neonate carries a platelet alloantigen that the mother lacks, and to which she has made detectable antibodies.[57] The current gold standard for the detection of platelet-specific antibodies is the monoclonal antibody-specific immobilization of platelet antigen (MAIPA) assay,[58] a sensitive and specific[59,60] capture immunoassay. Quantitation of anti-HPA-1a antibodies is done using a modified MAIPA assay.[61] Other HPA alloantibody specificities are normally not quantified. Other techniques are also possible to use. For instance, different Luminex bead-based assays for the detection of anti-HPA-1a antibodies have been tested and are used by some.[62] Furthermore, low-avidity anti-HPA-1a antibodies may be detected using surface plasmon resonance technology.[63]

Cordocentesis has been used in order to identify thrombocytopenic fetuses requiring intrauterine platelet transfusions and also to help decide on antenatal maternal treatment. Because of high risk of procedure-related complications,[64] avoidance of invasive procedures is currently recommended.[4,65–67]

Assays for noninvasive prenatal testing to detect fetal HPA-1a DNA in maternal plasma have been developed and are in use in many research laboratories, but are not yet implemented in routine clinical practice in most countries.[68–72] Determination of paternal zygosity may be relevant. If the father is typed and found to be HPA-1aa, the pregnancy will always be HPA-1 incompatible and fetal HPA-1 genotyping is not necessary. Whereas if the father is HPA-1ab, there is a 50% chance of the fetus being HPA-1bb and compatible with the mother, and in this situation knowing the fetal HPA-1 genotype would be clinically helpful.

Clinical presentation and outcome

Neonatal thrombocytopenia

The suspicion of FNAIT is typically raised when a newborn develops widespread skin petechiae shortly after birth and blood tests show severe thrombocytopenia. Most FNAIT cases present with platelet counts well below 50×10^9/L.[25,39,73] Clinical symptoms range from no symptoms to limited or widespread skin petechiae or purpura to symptoms of

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extra- or intracranial hemorrhage (ICH). Baseline characteristics of HPA-1-induced FNAIT are shown in Figure 2.

Intracranial hemorrhage

ICH is the major reason for clinical concern in FNAIT. ICH due to FNAIT is reported to occur in 1 of 10,000 births.[7] A recent review of prospective screening and intervention studies reported ICH in 7% of severe FNAIT cases (neonatal platelet count $<50\times10^9$/L).[37] Retrospective studies report a frequency of ICH due to FNAIT in 13%–21% of severe cases.[17,39,74] The clinical outcome of ICH due to FNAIT is reported to be worse compared to neonatal ICH from other causes[75,76] and may be connected to the typical locations of the bleedings in the brain. Severe neurological complications are found in 36%–68% of ICH cases[24,26,77,78] and fetal or neonatal death due to ICH is reported in the range of 9%–46%[24,57,68,79] when evaluated retrospectively. A large cohort study from the international No Intracranial Hemorrhage (NOICH) registry described 43 cases of ICH caused by FNAIT in depth and found that the majority of bleedings (54%) happened before the third trimester and 67% before 34 gestational weeks.[77] Similar results were recently published for a French cohort of ICH cases caused by FNAIT,[79] and a recent systematic review on clinical consequences of neonatal alloimmune thrombocytopenia also describes this tendency.[7] Results from the NOICH registry further indicated that boys may be more prone to bleeding compared with girls.[77]

The majority of ICH cases are reported to occur in the first-born child.[77] Thus, in most of the reported cases of ICH, antenatal treatment was not given since the risk of FNAIT typically was not known. The recurrence rate of ICH in subsequent pregnancies is reported to be 79%.[64] If the index FNAIT child did not have ICH, the risk of ICH in the next pregnancy has been estimated at 7%.[64]

Intrauterine fetal death (IUFD) is sometimes reported as an FNAIT complication separate from ICH, but there are no data to indicate that the cause of FNAIT-related IUFD should be something else than ICH. Therefore, IUFD will not be discussed separately.

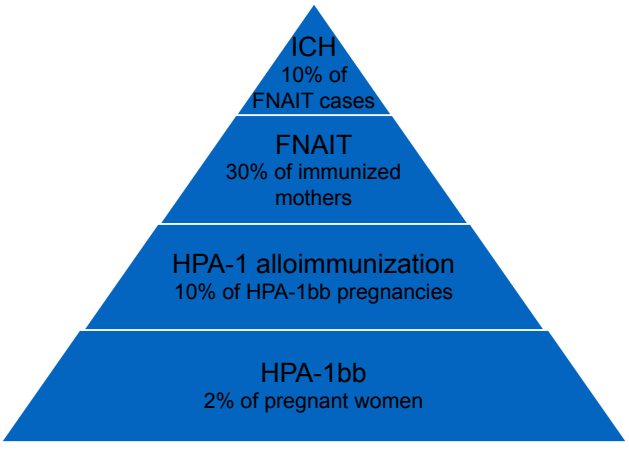

Figure 2 Baseline characteristics of HPA-1-induced fetal and neonatal alloimmune thrombocytopenia.
Abbreviations: ICH, intracranial hemorrhage; FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen.

Extracranial hemorrhage

FNAIT may lead to severe bleeding other than ICH in neonates with FNAIT. In the recent overview of extracranial FNAIT hemorrhage by Winkelhorst et al,[80] a wide variety of bleeding complications were reported in the 21 cases identified. Gastrointestinal bleedings constituted the majority of cases, followed by pulmonary hemorrhage. Some of these bleedings were life-threatening, and therefore, it is important for clinicians to be aware of possible extracranial bleedings in the fetus or neonate when managing an HPA-alloimmunized pregnancy or caring for a neonate with severe FNAIT.

Miscarriage

Mothers of FNAIT-affected children often report a history of miscarriages, including second trimester miscarriages, suggesting that the risk of miscarriage may be increased.[81] In a murine model of FNAIT, it was found that maternal anti-integrin β3 antibodies promoted fetal miscarriage,[82,83] and recent data from the same group suggest that anti-integrin β3 antibodies may activate placental natural killer cells leading to placenta damage and miscarriage through antibody dependent cellular cytotoxicity.[84]

Yet, no human study has specifically addressed whether there is an association between maternal HPA alloimmunization and miscarriage. Given the high prevalence of miscarriage in general and lack of understanding and treatment options for recurrent miscarriage, it is rather surprising that this area of pregnancy outcome for HPA alloimmunization has not received more attention.

Placental function and birth weight

Normal placental function is vital for a successful and uncomplicated pregnancy. Placental development and function are primarily established during the first half of pregnancy, although its growth and maturation continues throughout the pregnancy. Defect placentation is a common denominator for the "great obstetric syndromes" – preeclampsia, intrauterine death, and fetal growth restriction. Growth restricted fetuses/low birth weight newborns have increased risk of disease and death in the

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newborn period, as well as in adulthood.[85–87] How mother and fetus co-exist and "negotiate" to achieve normal placentation is complex and not yet fully understood.

We previously found a strong association between the presence of maternal anti-HPA-1a antibodies and reduced birth weight in boys.[88] A similar observation was made in an international multicenter study, showing that 23% of neonates with ICH were below the 10th percentile for birth weight and defined as small for gestational age.[77] Recently, we also found a similar association between the presence of maternal anti-HLA class I antibodies and reduced birth weight in cases where the child was thrombocytopenic at birth, and in this work, we also observed concurrently lower placental weight.[89]

HPA-1 antigens are expressed on the surface of fetal invading trophoblasts as part of the vitronectin receptor, and we know that anti-HPA-1a antibodies can bind the HPA-1a antigen when present on the vitronectin receptor.[90,91] The vitronectin receptor promotes cell adhesion and migration of primary cytotrophoblasts.[92,93] Recently, it was found that anti-HPA-1a antibody affected adhesion, migration, and invasive capacity of extravillous throphoblasts using a first trimester trophoblast-derived cell line (HTR-8/SVneo), indicating that maternal anti-HPA-1a antibodies could lead to defect placentation, in turn leading to poor fetal growth (Eksteen et al, personal communication, January, 2017). Together with our previous observation that mothers with anti-HPA-1a antibodies give birth to children with lower birth weight, the findings of the present study indicate that anti-HPA-1a antibodies can interfere with placental development. The mechanisms linking FNAIT to placenta/birth weight are currently being explored.

Predictors of clinical outcome

Several studies have demonstrated an association between anti-HPA-1a antibody levels in pregnancy and the severity of neonatal thrombocytopenia.[94–96] In a former large prospective screening study in Norway, maternal anti-HPA-1a antibody levels ≥3 IU/mL during pregnancy was found to be highly sensitive (>90%) in predicting severe neonatal thrombocytopenia,[96] and this level is currently used as cut-off in the national clinical guidelines to decide on delivery mode and place (www.legeforeningen.no). Some retrospective studies did not find such a relationship.[97,98] These discrepant results have been discussed, and it was suggested that quantitation of maternal anti-HPA-1a antibody level by MAIPA can be useful in a screening setting but maybe not in cases where FNAIT was already diagnosed in a previous pregnancy.[99] This explanation makes sense; when monitoring a risk pregnancy where a previous child had severe FNAIT, the obstetric history alone has strong predictive value. Furthermore, the anti-HPA-1a antibody level range is typically limited to very high levels in many such cases and statistical models aiming to study antibody level as a continuous variable will therefore fail to demonstrate significant associations.

A retrospective study reported that maternal anti-HPA-1a antibody levels may be used as a prognostic factor of intravenous immunoglobulin (IVIg) therapy success or failure.[100] This study was criticized for several weaknesses,[101] but the possibility of using anti-HPA-1a antibody levels to decide on antenatal management and delivery is important and deserves more attention. The ongoing Polish FNAIT screening study Prevention of FNAIT in Polish Newborns (PREVFNAIT; http://www.konfliktplytkowy.ihit.waw.pl/en/) will therefore give us valuable data on 1) the effect of antenatal IVIg in a screening setting and 2) whether maternal anti-HPA-1a antibody levels during pregnancy is useful to evaluate a possible IVIg effect.

For decades, the "FNAIT paradigm" has been that maternal anti-HPA-1a antibodies cause destruction of fetal platelets and that it is the low number of platelets in the fetus/newborn that trigger bleeding. Questioning this paradigm, we recently learned that anti-HPA-1a antibodies can bind cerebral endothelium carrying the vitronectin receptor and exert a direct negative effect that may cause ICH, bypassing the role of low platelet number alone as the main trigger for ICH.[102] This strengthens the importance of using antibody levels instead of fetal platelet counts as tools in management planning. Following up on this, the most recent FNAIT research reported that in children with ICH caused by FNAIT, anti-HPA-1a antibodies in the mother targeted the vitronectin receptor ($\alpha v\beta 3$), whereas maternal sera from FNAIT cases where the fetus/neonate did not have ICH had mainly antibodies binding the fibrinogen receptor ($\alpha IIb\beta 3$).[103] Therefore, it will be important for future FNAIT research to differentiate between anti-HPA-1a antibodies binding to the fibrinogen receptor on platelets and antibodies binding to both the fibrinogen and the vitronectin receptors. These results need to be confirmed and explored further, but fit well with the current understanding of a direct antibody-mediated effect on vessel wall integrity and trophoblast functions.

Maternal anti-HPA-1a antibody levels in pregnancies where the fetus/neonate has ICH are reported to be very high compared with severe FNAIT cases without detectable ICH.[77,79] However, we do not yet have good prospective data

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to determine whether maternal anti-HPA-1a antibody levels during pregnancy may be useful as an additional predictive factor for the risk of ICH.

The composition and heterogeneity of the terminal sugars of the Fc portion of IgG antibodies can affect the effector functions of the antibody, and certain glycosylation patterns are known to play a role as disease biomarker. Two research groups recently described decreased fucosylation of anti-HPA-1a antibodies causing FNAIT, and that fucosylation may be useful to predict disease severity.[104,105]

Management

Intravenous immunoglobulin

Previous severe FNAIT, with or without bleeding complications, is currently used clinically to determine the risk of severe FNAIT in subsequent pregnancies, and as such serves as the major basis in antenatal management planning. Weekly IVIg treatment to the mother starting from the second trimester is the first-line therapy of choice in most of the Western countries and is administered when the risk of FNAIT is considered to be high.[4,67,106,107] The treatment is considered effective when the neonatal platelet count is increased or ICH avoided in a subsequent pregnancy compared with the previous FNAIT pregnancy, with the underlying assumption that FNAIT gets worse in younger siblings. In a recent Norwegian prospective study, the natural course of FNAIT in several subsequent pregnancies was reported for the first time.[108] Our data showed that younger siblings of FNAIT-affected children had unchanged or higher neonatal platelet counts *without* antenatal treatment in the majority of subsequent pregnancies. Therefore, this study did not support the common opinion that the outcome after HPA-1a alloimmunization is generally worse in the next pregnancy. Thus, increased neonatal platelet count in a subsequent FNAIT pregnancy may not always reflect an antenatal treatment effect. Delbos et al reported that efficacy of IVIg treatment may be dependent on maternal HLA-DRB4*0101 haplotype,[79] also suggesting the possible use of several HLA-DR haplotypes as predictive markers of clinical outcome.

In a review of maternal IVIg response, it was commented that despite controversy whether IVIg increases fetal platelet counts, all IVIg studies report identical low frequency of ICH,[109] indicating that the possible effect of IVIg may be different from increased platelet count. Results from the NOICH study found that IVIg treatment during the subsequent pregnancy seemed to be protective with regard to ICH in most cases, reducing the ICH recurrence risk from 79% as previously reported to 11%.[77] In a murine model of FNAIT, it was demonstrated that treatment with IVIg to immunized mice prevented ICH in the pups,[83] and the same group later published data suggesting that IVIg prevented ICH by restoring angiogenesis in the fetal brain.[102]

Corticosteroids

Some clinicians use systemic corticosteroids alongside IVIg as a means of supporting the action of IVIg. Dexamethasone is not recommended due to risk of oligohydramnios at higher doses[110] and lack of effect at lower doses.[111] Prednisone is therefore the recommended choice; however, the potential benefits versus risks deserves further evaluation.[112]

Cordocentesis

Repeat cordocentesis to measure fetal platelet count followed by intrauterine platelet transfusions in case of severe fetal thrombocytopenia was commonly performed previously, but is nowadays abandoned by many countries due to high risk of procedure-related complications.[113,114] Some countries still combine diagnostic fetal blood sampling (FBS) with maternal IVIgs, with or without a second FBS to decide on treatment effect and mode of delivery. However, a complete non-invasive management strategy is advocated by most.[65,67,115]

Pre-implantation genetic diagnosis

When the mother is HPA-1bb and the father is HPA-1ab, there is a 50% chance that the fetus will be HPA-1a positive. In cases of a previously FNAIT-affected sibling, some women are not eligible for antenatal IVIg treatment due to hypersensitivity. The possibility of performing pre-implantation genetic diagnosis for HPA-1 incompatibility in order to select an HPA-1bb embryo for in vitro fertilization (IVF) has been described in a case report.[116] This may be a desirable option for couples facing a similar situation.

In vitro fertilization

When the mother is HPA-1bb and the father is HPA-1aa, pre-implantation genetic diagnosis is not helpful, as the fetus will always be HPA-1ab. The use of HPA-1-matched sperm donor is a new procedure. The first woman in Norway to conceive after using an HPA-1-matched sperm donor delivered a healthy boy with normal platelet count in 2014.[117] In Spring 2016, the second child was delivered using this treatment strategy, and this pregnancy also underwent without complications and a healthy newborn with normal platelet count was born by caesarean section (Dr Peter Fedorscak, Oslo University Hospital, personal communication, May 2016). Needless to

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say, more experience with this treatment option is needed before introducing this as part of a general management program. Because of the ethical challenges, we would generally recommend to consider the use of HPA-1-matched sperm donor only for the minority of HPA-1bb women with a history of recurrent severe FNAIT-related complications, where the alternative would be to refrain from further pregnancies.

HPA-1 typing is not routinely performed in connection with the use of IVF. IVF was reported to be involved in four severe cases of anti-HPA-1a-induced FNAIT.[118] In three out of the four cases, the fetuses were HPA-1aa homozygous, which could not occur in naturally conceived HPA-1 incompatible pregnancy. In these cases, either the surrogate or mother was HPA-1bb homozygous. The authors speculate that a homozygous HPA-1a fetus express twice as much incompatible antigen on their platelets, inducing a stronger maternal immune response. Alternatively, the severity could be due to antibody binding to *all* fibrinogen receptors on fetal platelets; only half of the receptors can be bound on platelets in HPA-1ab individuals, leaving platelets partially functional. Anti-HPA-1a antibodies affect HPA-1aa platelet function more than HPA-1ab.[90] This finding needs to be confirmed or disproved by others. However, their conclusion that all women should be HPA-1 genotyped before serving as a surrogate mother seems feasible and deserves attention in view of the rapidly increased use of surrogacy.

Mode of delivery

Whether delivery by caesarean section prevents ICH in FNAIT affected neonates is not really known.[37,119] Vaginal delivery is advised by some as an option when fetal platelet count is $>50\times10^9$/L.[111] However, this approach requires FBS in order to know the fetal platelet count around the time of delivery. A Dutch pilot study of 32 pregnancies where an older sibling had FNAIT *without* ICH found that vaginal delivery was not associated with an increased risk of ICH.[120] The current policy in the Netherlands is to induce vaginal delivery at 37–38 weeks without FBS first. If the woman has a previous caesarean section, they may sometimes do a FBS before inducing delivery. If the previous child had ICH, delivery is performed by elective caesarean section at 36 weeks (prof Dick Oepkes, Director of the Dutch National Centre for Fetal Therapy, Leiden University Medical Centre in the Netherlands, personal communication, March, 2016). The intervention part of the Norwegian screening study consisted of delivering all HPA-1a alloimmunized women by caesarean section at 36–38 weeks followed by immediate transfusion of HPA-1 compatible platelets if the newborn was severely thrombocytopenic.[25] Delivery by caesarean section was one of several interventions in this study, and the isolated effect of delivery mode is therefore difficult to assess. Still, mortality and morbidity were significantly reduced in the screening and intervention population compared with historical controls.[29] The current management guideline in Norway recommends delivery by elective caesarean section around 38 weeks if the maternal anti-HPA-1a antibody level is ≥3 IU/mL, irrelevant of previous obstetric history.

Since the vast majority of ICH caused by FNAIT is found to occur before delivery, and little data support the idea that ICH due to FNAIT tend to occur in connection with delivery, it is difficult to argue that the risk of ICH is affected by mode of delivery. The risk of ICH when older siblings did not suffer from ICH is reported to be 7%.[57] A larger study sample is therefore needed before we can conclude whether vaginal delivery for this patient group is safe or not. In many places, HPA-1bb platelets are not available in the blood banks on a daily basis. A planned delivery – whether vaginally or by surgery – is therefore important in order to have appropriate platelets available in case of a severely thrombocytopenic newborn.

Postnatal management of the newborn

The majority of FNAIT-affected newborns will not have suffered ICH before delivery. Preventing ICH by increasing platelet count above a certain threshold is therefore considered a neonatal emergency, and prompt correction by platelet transfusion should be done based on clinical suspicion without awaiting laboratory confirmation of the diagnosis.[4] However, it is not clear what threshold should be used to trigger platelet transfusion.[121,122] Previous reports also suggest that neonates with HPA-5b incompatibility may be at risk of bleeding at higher platelet counts compared with HPA-1 incompatibility.[39] It is recommended to give compatible platelet concentrates instead of random donor platelets, due to both larger platelet increment and longer half-life of the transfused platelets.[123,124] Random donor platelets may be used when compatible platelets are not available.[123] The use of IVIg as treatment to increase neonatal platelet count varies, but is often recommended as supplemental therapy for 1–3 days depending on platelet increment response of transfusions.[106,107,122,124] Other management options include corticosteroid therapy, but documentation of effect is poor.[125] It is also recommended that all babies with severe FNAIT should have a cranial ultrasound for the detection of ICH.[122]

In summary, there is consensus on postnatal correction of severe thrombocytopenia, but antenatal treatment management

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protocols vary. Knowledge gaps on the natural history of FNAIT, together with lack of randomized controlled trials evaluating the effects of different treatment options, are probably a major reason for the struggle to have common management protocols. Still, nobody questions the severity of this disorder. Therefore, there is no doubt that a preventive approach hindering the mother from becoming HPA-1a alloimmunized in the first place would be welcomed by all.

A prophylactic approach to FNAIT

FNAIT is often referred to as the platelet counterpart of HDFN, but traditionally presented with one important exception – time of immunization. Alloimmunization against the RhD antigen mainly occurs in connection with delivery as a result of fetomaternal hemorrhage.[126,127] Until recently, it was believed that most immunizations to HPA-1a occurred during the first incompatible pregnancy and not so often in connection with delivery. This assumption was based on retrospective observations. Now, data from several prospective investigations have challenged this belief. In the Norwegian screening study, it was found that >75% of HPA-1a alloimmunizations occurred after delivery, suggesting that delivery may be the immunizing stimulus.[96] Similar prospective data were also presented by Turner et al[73] and Williamson et al,[18] reporting a low frequency of immunizations during first pregnancies (4% and 24%, respectively). Thus, the pathophysiology of FNAIT seems to be more similar to HDFN than previously thought. This recognition has opened the possibility to prevent anti-HPA-1a-induced FNAIT by postnatal administration of HPA-1a antibodies to HPA-1a-negative women delivering an HPA-1a-positive child. This is actually the same strategy that has been used to prevent HDFN with great success during the past 50 years. In order to test this hypothesis, a proof-of-principle study using glycoprotein integrin β3 (GPIIIa)-deficient mice was conducted. Administration of human polyclonal anti-HPA-1a or murine monoclonal anti-HPA-1a (clone SZ21) were both able to suppress the antibody response to transfused human HPA-1a-positive platelets. The induction of antibody-mediated immune suppression was also carried out using murine wild-type platelets transfused to GPIIIa-deficient mice. The antibody response to platelets was significantly reduced in mice receiving anti-GPIIIa in conjunction with platelet transfusion. Breeding experiments further demonstrated that the platelet count in the pups born by the mice that had received prophylaxis after the platelet transfusion was significantly higher compared to controls where the mother did not receive prophylactic treatment. The number of pregnancies with miscarriages and dead pups was also significantly lower when the platelet transfusion was followed by prophylaxis.[128] Altogether, these results support the hypothesis that administration of anti-HPA-1a to HPA-1a-negative women after delivery of an HPA-1a-positive child may prevent immunization to HPA-1a, thereby preventing the development of FNAIT in a subsequent pregnancy. The hypothesis to prevent immunization to HPA-1a will be tested in pregnant women in an EU-supported clinical trial (www.profnait.eu).

Another potential strategy to prevent HPA-1a immunization could be to target the antigen-specific T-cell responses in these women. Little is known about how the T-cell response shapes the quality of the subsequent anti-HPA-1a antibody response and whether it could be possible to induce immune tolerance to HPA-1a by oral administration of peptides in an efficient tolerogenic formulation. Such tolerance may depend on induction of tolerogenic regulatory T cells or on clonal deletion or induction of clonal anergy.[129]

Screening

No country has yet started screening of all pregnant women to detect HPA-1a-negative pregnancies, in order to identify women at risk of alloimmunization. The implementation of such a national screening program for FNAIT has been debated in several countries.[25,37,107] So far, all countries have turned down the idea because of the lack of prophylaxis or effective treatment modalities. In comparison, RhD typing was introduced in pregnancy screening programs 20 years before prophylaxis was started. Identification and follow-up of RhD-negative pregnancies at risk for anti-D alloimmunization have greatly reduced the risk of morbidity in newborns being exposed. Results from the Norwegian screening study showed that implementation of a screening program for HPA-1a-negative pregnancies could improve clinical outcome[25] and be cost-effective.[130] Several other studies have also concluded that a screening and intervention program for maternal HPA-1 alloimmunization is likely to be cost-effective.[37,73,131,132] Without antenatal screening, we only detect a minority of cases.[133] In a recent assessment of prospective studies on screening for HPA-1a alloimmunization including 176,000 low-risk pregnancies, it was concluded that screening of all pregnancies combined with antenatal treatment may reduce mortality and morbidity associated with FNAIT but that large-scale screening studies are needed to evaluate the effect of currently used interventions.[37] Introduction of antenatal screening for FNAIT was considered in relation to the revised World Health Organization screening criteria,[134] and it was concluded that the screening criteria were fulfilled.[135] The ongoing Polish PREVFNAIT screening study is primarily undertaken to demonstrate the feasibility of implementing antenatal HPA-1

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screening as a national routine later. In the Netherlands, the planned HPA screening In Pregnancy study aim to pave the way for the implementation of screening.

Opponents to introducing an antenatal screening program for FNAIT point out that no randomized controlled trials have been conducted to assess the possible clinical and economic benefits of screening and also that there is no consensus on how to treat pregnancies at risk of FNAIT once these pregnancies are identified.[4,106] Those in favor of screening state that randomized controlled trials would be unethical to perform and that we will never gain this knowledge without first introducing screening.[135,136]

In the absence of antenatal screening for the detection of pregnancies at risk, previous obstetric history serves as the main basis for antenatal management protocols.[64,119] ICH or severe thrombocytopenia in the previous neonate is considered useful to predict an increased risk of severe FNAIT in subsequent pregnancies. This strategy a priory excludes any management of the first FNAIT-affected pregnancy before the child is born, and it is well documented that severe FNAIT may occur in the first-born child.[17,39]

Conclusion

Despite large efforts, there are still considerable knowledge gaps on the pathophysiology of FNAIT. This is probably the major reason for the lack of consensus on how to manage pregnancies at risk of FNAIT. New knowledge indicating placenta as a target of maternal anti-HPA-1a antibodies in addition to fetal platelets increases clinical concern. The broader clinical impact of FNAIT together with new treatment opportunities for FNAIT strengthens the need for antenatal screening to detect pregnancies at risk of FNAIT. Without a screening program for the detection of HPA-1a-negative pregnancies, the FNAIT diagnosis is almost always established after birth of a symptomatic child. With the current non-screening policy, we only detect a minority of FNAIT cases. An antibody-mediated prophylaxis to prevent HPA-1 is currently being developed and has the potential to prevent severe mortality and morbidity in newborns from FNAIT. However, it is impossible to offer an antenatal prophylaxis to HPA-1bb pregnant women without knowing who they are. Introduction of antenatal screening programs should therefore be considered.

Disclosure

BS and AH have financial relationships with Prophylix Pharma AS, a small medical company aiming to develop a FNAIT prophylaxis. HT, MTA, and TBS report no conflicts of interest in this work.

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