Transfusion and Apheresis Science xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Fetal and neonatal alloimmune thrombocytopenia – The Norwegian management model

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ARTICLE INFO

Keywords:
Thrombocytopenia
Newborn
HPA
Alloimmunization
Antenatal
Neonatal

ABSTRACT

In Norway, the management strategy for fetal and neonatal alloimmune thrombocytopenia (FNAIT) has for more than two decades differed from most other countries. The focus of this paper is to describe and discuss the Norwegian FNAIT management program. We recommend antenatal IVIg to women who previously have had a child with FNAIT-induced ICH, and usually not to HPA-1a alloimmunized pregnant women where a previous child had FNAIT, but not ICH. When deciding management strategy, we use not only the obstetric history but also the antenatal anti-HPA-1a antibody level as a tool for risk stratification. The Norwegian National Unit for Platelet Immunology (NNUPI) at the University Hospital of North Norway in Tromsø provides diagnostic and consulting service for the clinicians and the blood banks all over the country, and serves as a national reference laboratory for FNAIT investigations.

1. Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is typically suspected in a term-born neonate where widespread petechiae or other signs of bleeding develop shortly after birth, in the absence of any other condition known to be associated with neonatal thrombocytopenia. Thrombocytopenia in FNAIT is mainly due to maternal antibodies against human platelet antigen (HPA)-1a. Occasionally, FNAIT is suspected during fetal life due to ultrasound findings such as intrauterine fetal death, intracranial haemorrhage (ICH), isolated ventriculomegaly or extracranial haemorrhage in the fetus. The main clinical concern with FNAIT is ICH. A growing number of reports also describe links between maternal HPA-1a alloimmunization and reduced birth weight, and intrauterine growth restriction risk has been suggested to be another effect of HPA-1a alloimmunization [1,2]. The frequency of ICH due to FNAIT is reported in 1:10,000 newborns [3], a number which may be an underestimate of the true incidence, since it is well documented that FNAIT is an underdiagnosed condition [4,5] and diagnostics of FNAIT is only available in few places.

The high recurrence risk of severe FNAIT in subsequent pregnancies [6] has urged several preventive strategies. As there is currently no screening program introduced to identify the 2 % HPA-1a negative pregnant Caucasian women at risk of having a child with FNAIT, primary prevention has not been an option. Secondary prevention is only possible when the risk of FNAIT is known before the child is born. There is no international consensus regarding the antenatal management for these high-risk pregnancies. Clinical guidelines vary between countries and even between different hospitals. Most women known to be HPA-1a-immunized are treated off-label with weekly high-dose intravenous immunoglobulin (IVIg) during pregnancy. Gestational age for starting this treatment as well as the dose varies, but generally the treatment starts during the second trimester and 1 g/kg/week is a commonly used dose [7]. Some centres stratify the treatment according to the presence or absence of ICH in the previous child and when ICH occurred, i.e., early or late in pregnancy or perinatally. Recently a systematic review compared different antenatal treatment strategies [8]. This review proposed that first line antenatal management in FNAIT is weekly IVIg administration, with or without the addition of corticosteroids. Despite the widespread use of this treatment modality, solid evidence for the efficacy of IVIg in preventing severe FNAIT is lacking [8,9].

In Norway, the FNAIT management strategy has for more than two decades differed from most other countries, since IVIg is only rarely used in the management of HPA-1a-immunized women. The "Norwegian FNAIT model" has puzzled many colleagues in other countries, and some have even mentioned concern regarding the safety

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https://doi.org/10.1016/j.transci.2019.102711

of our antenatal management strategy. Norway, being a small Nordic country, maintains the Nordic welfare model with universal health care and a comprehensive social security system. Norway has had the highest Human Development Index ranking in the world since 2009. Understanding why we do not offer antenatal IVIg as a standard therapy in the context of HPA-1a alloimmunization is perhaps not easy and deserves to be explained. The focus of this paper is therefore to describe the Norwegian FNAIT management program, followed by a discussion of the strategy.

2. The Norwegian FNAIT management model

2.1. Clinical follow-up

In HPA-1a-immunized pregnant women where a previous child had FNAIT, but not ICH, IVIg is usually not given. Instead, immunized women are closely monitored throughout the pregnancy. Maternal anti-HPA-1a antibody levels are measured using a quantitative Monoclonal Antibody-specific Immobilization of Platelet Antigens (MAIPA) assay [10] every 4th week starting from 28 gestational weeks until delivery. If anti-HPA-1a antibody levels reach 3 IU/mL or higher at any time point, we recommend repetitive ultrasonographic examinations to look for signs of fetal intra- or extracranial haemorrhage as well as fetal growth assessments.

Since 2014 the National clinical guidelines for obstetricians in Norway changed to recommending antenatal IVIg to women who previously have had a child with FNAIT-induced ICH. This change was based on some evidence of reduced risk of fetal/neonatal ICH in subsequent pregnancies by administration of IVIg when an older sibling suffered from ICH [2]. The current recommendation is to start IVIg treatment around 20 weeks of gestation at 1 g/kg/week until delivery.

Women with high anti-HPA-1a antibody levels during pregnancy ($\geq$ 3 IU/mL) are delivered by elective caesarean section (CS) at around gestational week 38–39 in hospitals with a neonatal intensive care unit as well as HPA-1a negative platelets available for the newborn in need. If the woman previously had a child with ICH and has very high anti-HPA-1a antibody levels during the subsequent pregnancy, a slightly earlier delivery, around 37 weeks is considered.

Platelet count is measured from cord blood immediately after delivery, and prompt transfusion is given, typically starting within 30 min after birth. The current threshold to offer neonatal platelet transfusion is platelet count is $< 35 \times 10^9$/L. We also recommend to scan the baby's head by ultrasonography to rule out ICH in all cases of severe FNAIT (i.e. platelet count $\leq 50 \times 10^9$/L), even if the neonate shows no clinical signs of haemorrhage. See Fig. 1 for an overview of the clinical follow-up algorithm.

In pregnancies where the father is heterozygous (HPA-1ab) or not typed, determination of fetal HPA-1 type can preclude unnecessary follow-ups and interventions. Non-Invasive Prenatal Testing (NIPT) for HPA-1 can be performed using cell-free fetal DNA in maternal circulation [11–13]. A NIPT test for fetal HPA-1 typing is currently under validation at the Norwegian National Unit for Platelet Immunology (NNUPI) but will require approval from the Norwegian Health Authorities prior to clinical use.

2.2. The Norwegian National Unit for Platelet Immunology (NNUPI)

Since 1995, the NNUPI at the University Hospital of North Norway in Tromsø has provided national diagnostic and consulting service for the clinicians and the blood banks when FNAIT or other platelet antibody-mediated conditions have been suspected, serving as a national reference laboratory for FNAIT investigations. Furthermore, NNUPI also provides compatible antigen-negative platelet concentrates to patients. The Immunology Research Group at UiT The Arctic University of Norway in Tromsø has had a close collaboration with NNUPI for many years on FNAIT research.

NNUPI performs around 50 FNAIT-related investigations per year, including thrombocytopenia in the newborn, follow-up of HPA-alloimmunized women during subsequent pregnancies, follow-up of non-immunized HPA-1bb pregnant women, as well as referrals after suspected ICH detected during fetal ultrasound examinations. It is well known that FNAIT is severely under-diagnosed in Norway in the non-screening setting [4].

2.3. Laboratory FNAIT assessments

A set of laboratory analyses is required to support FNAIT diagnosis in a newborn with thrombocytopenia, with two central aims: confirmation of incompatibility in a platelet antigen between mother and newborn and detection of maternal antibodies against antigen expressed on neonatal platelets. The algorithm for investigations has been modified in line with availability of tests and recommendations, and the current strategy is outlined in Fig. 2.

To do full FNAIT investigation analyses, we request 10 mL of peripheral blood (EDTA) from both the mother and the father, in addition to 2 − 3 mL peripheral blood or cord blood, depending on availability from the newborn, taken at the time of delivery or as soon as FNAIT is suspected. The initial tests aim to quickly assess if FNAIT is the diagnosis, and to provide compatible platelet transfusions when necessary. A flow cytometric cross-match of maternal plasma with neonatal/paternal and HPA-defined panel platelets by indirect Platelet Immuno Fluorescence Test (PIFT) is performed [14], as well as direct PIFT to detect any *in vivo*-bound antibodies on neonatal platelets and exclude autoantibodies on maternal/paternal platelets that would interfere with test results. In addition, HPA-1a phenotyping of maternal platelets by flow cytometry [15] is performed immediately, since anti-HPA-1a alloantibodies is the by far most common cause of FNAIT in Norway. All these tests can be performed within hours to rapidly guide selection of blood components. HPA-1bb blood components can be provided on short notice; mainly platelet concentrates for the newborn but also red

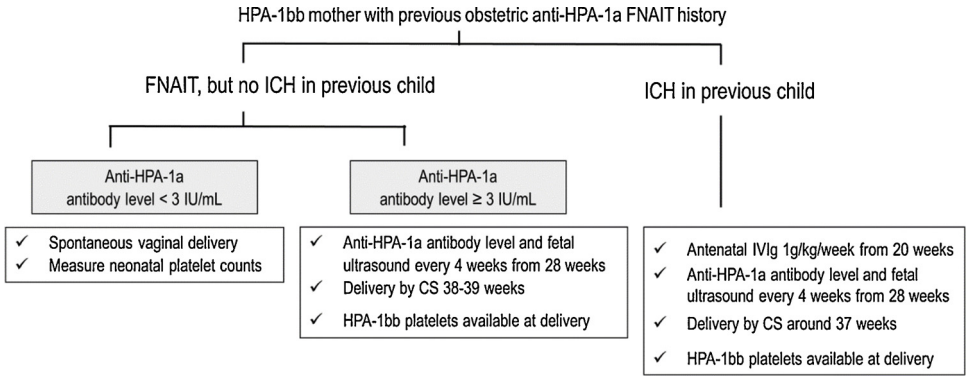

Fig. 1. Algorithm for clinical follow-up during pregnancy of HPA-1a alloimmunized women with a prior obstetric history of FNAIT.

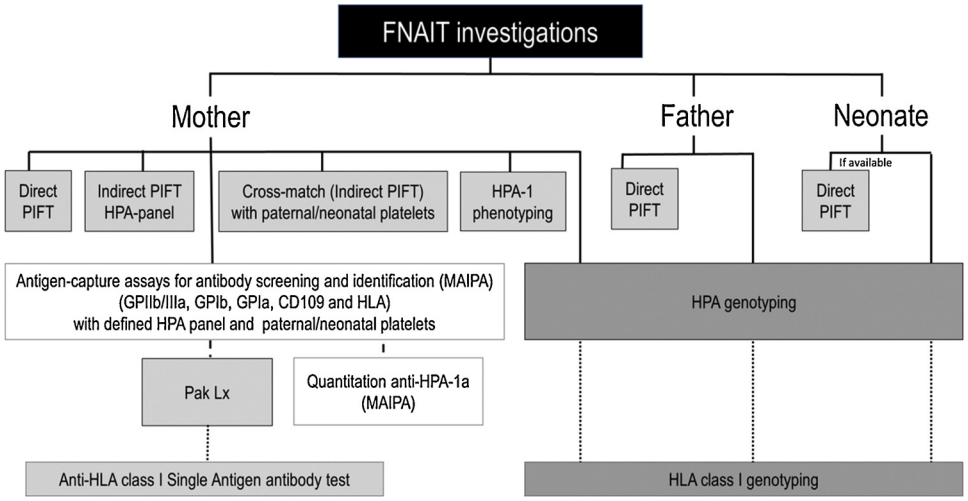

Fig. 2. Algorithm for laboratory analysis in FNAIT investigations.
At least two serological tests, including solid-phase assays for antibody analysis of maternal plasma. PIFT, Platelet Immune-Fluorescence test, MAIPA; Monoclonal Antibody-specific Immobilization of Platelet Antigens. Pak Lx is a commercial bead-based test for anti-platelet antibodies.

cell concentrates, if necessary, for the mother. HPA-1bb platelet concentrates are also available as shelf-product at the Norwegian National Advisory Unit of Immunohematology at Oslo University Hospital.

HPA genotyping in HPA-1, -2, -3.-5 and -15 systems is also routinely performed as part of the investigations, with the possibility of extended typing for HPA-4, HPA-6 and -9 in case of non-conclusive reactivity patterns or non-Caucasian individuals.

For a complete and conclusive FNAIT investigation, maternal plasma is tested for glycoprotein-specific antibodies in a MAIPA screening assay with neonatal and/or paternal platelets and platelet from blood donors with defined reactivity against gpIIb/IIIa, gpIb/IX, gpIa/IIa, CD109 and HLA class I [16]. HPA-specificity in most cases is determined by MAIPA, while quantitative MAIPA [17,18] is used to determine the levels of anti-HPA-1a when detected.

If the MAIPA assay is negative, a commercial bead-based test for anti-platelet antibodies Pak Lx (Immucor, Georgia, USA) is used as an additional test before excluding the presence of anti-HPA antibodies. If no anti-HPA antibodies are detected in Pak Lx either, we conclude that there is no HPA-alloimmunization.

Other platelet-reactive antibodies (anti-HLA, anti-A/ anti-B or anti-CD36 or private antigens) can also give a positive cross-match. Although there is still no clear understanding whether anti-HLA class I antibodies may cause severe thrombocytopenia in the newborn [19–23], we perform a more detailed analysis of the HLA antibodies, when maternal anti-HLA class I antibodies are the sole reactive antibodies. It is then essential to show whether the neonate express the cognate HLA class I antigens. Maternal anti-HLA antibody specificity is determined by LIFECODES Single Antigen LSA Class I assay (Immucor) and HLA class I genotyping of the neonate is performed by LIFECODES HLA SSO RAPID assays for HLA-A, -B and –C (Immucor).

Some HPA-1bb pregnant women without obstetric history of FNAIT are previously HPA typed in connection to blood and/or platelet donation or during the previous HPA-1 screening program [24] These women are tested for *HLA-DRB3*01:01* and for those found to be positive, we strongly recommend testing for anti-HPA-1a antibodies in gestational weeks 20 and 34 in line with the Norwegian national guidelines. If anti-HPA antibodies are detected, we recommend follow-up by MAIPA every 4th week from gestational week 28. Anti-HPA-1a antibodies are quantified if present, while other specificities are re-tested in subsequent samples. For women found to be *HLA-DRB3*01:01*-negative we inform that the risk of HPA-1a alloimmunization and FNAIT is low, but we still offer antibody testing if the clinician judge this is necessary. In addition, we recommend measuring the platelet count of the newborn in order to be able to transfuse the child immediately in those rare case where the platelet count is low despite the mother being *HLA-DRB3*01:01* negative.

In emergencies the results are communicated immediately to the clinicians, followed by a written report from all laboratory analyses and interpretational comments. This includes recommendations for follow-up in subsequent pregnancies as well as recommendations of suitable future blood components for the alloimmunized woman, if necessary. An information letter is also sent to the mother.

3. Discussion

Our current FNAIT management strategy has been tested out in a large prospective screening and intervention study, where the management strategy was found to be clearly beneficial in terms of reducing risk of ICH and intrauterine fetal death as compared to historic prospective controls [24]. Our strategy is therefore evidence-based, at least in a screening setting. However, there may be a selection bias for more severe FNAIT cases in the current non-screening setting.

Compared to how most Western countries manage pregnancies where the risk of FNAIT is known before birth, Norway differs in two important ways: first, we rarely use antenatal IVIg. Second, instead of purely using obstetric history as risk predictor, we add the antenatal anti-HPA-1a antibody level as a predictor when deciding management strategy. Whether or not maternal anti-HPA-1a antibody levels influence the severity of neonatal alloimmune thrombocytopenia has been disputed by some [25,26]. However, a recent systematic review of the available literature concluded that there is an association between maternal anti-HPA-1a antibody level and neonatal platelet count, both when assessed prospectively and retrospectively, but with some acknowledged limitations [27]. The cut-off antibody level of 3 IU/mL that we currently use to stratify risk and intervention in these pregnancies is based on prospective data [28], and we practice the same cut-off in a non-screening setting. Improvements in antibody analysis and increasing knowledge about different properties and subtypes of anti-HPA-1a antibodies [29,30] may have potential for a more targeted and individualized management strategy.

Our reluctance towards off-label use of IVIg to all HPA-1a alloimmunized pregnant women is not mainly due to high-cost or the fact that IVIg has side-effects [31–33]. We are more concerned of the lack of evidence of a clinically relevant preventive effect when used in *all* HPA-1a alloimmunized women. The Norwegian cohort of HPA-1a alloimmunized pregnancies where the mother did not receive antenatal IVIg may reflect the natural history of FNAIT regarding the neonatal outcome. If high-dose IVIg treatment is effective in preventing ICH, one would expect a poorer neonatal outcome in Norway as compared to other Western countries. For this reason, we have initiated a study where we evaluate all Norwegian non-IVIg-treated HPA-1a alloimmunized pregnancies during the last 20 years assessing neonatal outcome.

The efficacy of antenatal IVIg treatment has not yet been evaluated in a randomized placebo-controlled clinical trial. Whether it is ethically acceptable to conduct a placebo-controlled clinical trial of IVIg for this condition is also questionable [9]. The Norwegian cohort of non-selected non-IVIg treated HPA-1a alloimmunized pregnancies may hence serve as an important control group when evaluating the effect of IVIg.

The Norwegian management strategy includes delivery by elective cesarean section (CS) 1–2 weeks prior to term, in pregnancies where the risk of FNAIT is considered high. This risk assessment is mainly based on anti-HPA-1a antibody levels. Whether or not CS prevents FNAIT-associated ICH is still unsettled, but we cannot disregard that the mode of delivery may have contributed to the good neonatal outcome of the previous screening- and intervention study [24]. Data from the NOICH study showed that most ICH cases happened before delivery [2], thus questioning the need of CS to prevent ICH. However, the NOICH ICH data were based on retrospective cases, and thus prone to selection bias. Clearly more data are needed to settle this issue. In Norway we have decided to continue this delivery strategy until more data concerning the safety of vaginal birth for these pregnancies are available. There are clear benefits of having a planned day-time delivery for the multi-disciplinary team around the patient, as well as having compatible platelet concentrates ready for the newborn, if needed.

Several Western countries are currently considering implementation of a screening program to identify pregnancies at risk of FNAIT. It is an open question what antenatal management regimen should be applied to all HPA-1a negative pregnant women where anti-HPA-1a antibodies are detected during pregnancy – especially when a previous obstetric history of FNAIT is missing to guide risk assessment. The Norwegian FNAIT experience should therefore be part of management considerations in a screening setting.

The current Norwegian FNAIT guidelines are continuation of the management principals with positive experience from the previous large screening study. Differences in health culture between Norway and other Western countries may also explain different management strategies, for instance regarding risk assessment and management. Norwegian obstetricians being more prone to having natural vaginal birth compared to American obstetricians is an interesting example of cultural differences [34]. Litigation practice in obstetrics in Norway is still relatively «sober», although there is an increasing pressure toward minimizing all risks associated with pregnancy and delivery.

In conclusion, we will still practice a restrictive use of antenatal IVIg as long as solid evidence of effect is lacking regarding use in all HPA-1a alloimmunized pregnancies. We will also continue to monitor closely the clinical outcomes of FNAIT while working toward implementation of antenatal HPA-1a screening that will certainly reduce the burden of FNAIT.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship contributions

HT planned the manuscript. HT and MTA drafted the manuscript. All authors revised and approved the final version of the manuscript.

Declaration of Competing Interest

AH belong to the group of founders and owners of Prophylix AS, a Norwegian biotech company, which has been developing a hyper-immune anti-HPA-1a IgG for the prevention of fetal and neonatal alloimmune thrombocytopenia. The assets of Prophylix AS were recently acquired by Rallybio IPA, LLC. The remaining authors declare no competing financial interests.

Acknowledgments

We thank medical student Tina Coucheron at UiT The Arctic University of Norway for valuable comments and revision of the manuscript.

References

[1] Tiller H, Killie MK, Husebekk A, Skogen B, Ni H, Kjeldsen-Kragh J, et al. Platelet antibodies and fetal growth: maternal antibodies against fetal platelet antigen 1a are strongly associated with reduced birthweight in boys. Acta Obstet Gynecol Scand 2012;91(1):79–86.
[2] Tiller H, Kamphuis MM, Flodmark O, Papadogiannakis N, David AL, Sainio S, et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. BMJ Open 2013;3(3):e002490.
[3] Kamphuis MM, Paridaans NP, Porcelijn L, Lopriore E, Oepkes D. Incidence and consequences of neonatal alloimmune thrombocytopenia: a systematic review. Pediatrics 2014;133(4):715–21.
[4] Tiller H, Killie M, Skogen B, Øian P, Husebekk A. Neonatal alloimmune thrombocytopenia in Norway: poor detection rate with nonscreening versus a general screening programme. BJOG Int J Obstet Gynaecol 2009;116(4):594–8.
[5] Davoren A, McParland P, Barnes CA, Murphy WG. Neonatal alloimmune thrombocytopenia in the Irish population: a discrepancy between observed and expected cases. J Clin Pathol 2002;55(4):289–92.
[6] Radder C, Brand A, Kanhai H. Will it ever be possible to balance the risk of intracranial haemorrhage in fetal or neonatal alloimmune thrombocytopenia against the risk of treatment strategies to prevent it? Vox Sang 2003;84(4):318–25.
[7] Kamphuis MM, Oepkes D. Fetal and neonatal alloimmune thrombocytopenia: prenatal interventions. Prenat Diagn 2011;31(7):712–9.
[8] Winkelhorst D, Murphy MF, Greinacher A, Shehata N, Bakchoul T, Massey E, et al. Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review. Blood 2017;129(11):1538–47.
[9] Rayment R, Brunskill SJ, Soothill PW, Roberts DJ, Bussel JB, Murphy MF. Antenatal interventions for fetomaternal alloimmune thrombocytopenia. Cochrane Database Syst Rev 2011(5).
[10] Killie MK, Salma W, Bertelsen E, Skogen B, Husebekk A. Quantitative MAIPA: comparison of different MAIPA protocols. Transfus Apher Sci 2010;43(2):149–54.
[11] Scheffer P, Ait Soussan A, Verhagen O, Page-Christiaens G, et al. Noninvasive fetal genotyping of human platelet antigen-1a. BJOG Int J Obstet Gynaecol 2011;118(11):1392–5.
[12] Ferro M, Macher HC, Fornés G, Martín-Sánchez J, Jimenez-Arriscado P, Molinero P, et al. Noninvasive prenatal diagnosis by cell-free DNA screening for fetomaternal HPA-1a platelet incompatibility. Transfusion 2018;58(10):2272–9.
[13] Wienzek-Lischka S, Krautwurst A, Fröhner V, Hackstein H, Gattenlöhner S, Bräuninger A, et al. Noninvasive fetal genotyping of human platelet antigen-1a using targeted massively parallel sequencing. Transfusion 2015;55(6pt2):1538–44.
[14] Skogen B, Christiansen D, Husebekk A. Flow cytometric analysis in platelet cross-matching using a platelet suspension immunofluorescence test. Transfusion 1995;35(10):832–6.
[15] Killie MK, Kjeldsen-Kragh J, Randen I, Skogen B, Husebekk A. Evaluation of a new flow cytometric HPA 1a screening method: a rapid and reliable tool for HPA 1a screening of blood donors and pregnant women. Transfus Apher Sci 2004;30(2):89–92.
[16] Kiefel V, Santoso S, Weisheit M, Mueller-Eckhardt C. Monoclonal antibody–specific immobilization of platelet antigens (MAIPA): a new tool for the identification of platelet-reactive antibodies. Blood 1987;70(6):1722–6.
[17] Bertrand G, Jallu V, Gouet M, Kjaer KM, Lambin P, Husebekk A, et al. Quantification of human platelet antigen-1a antibodies with the monoclonal antibody immobilization of platelet antigens procedure. Transfusion 2005;45(8):1319–23.
[18] Jaegtvik S, Husebekk A, Aune B, Øian P, Dahl L, Skogen B. Neonatal alloimmune thrombocytopenia due to anti-HPA 1a antibodies; the level of maternal antibodies predicts the severity of thrombocytopenia in the newborn. BJOG Int J Obstet Gynaecol 2000;107(5):691–4.
[19] Dahl J, Refsum E, Ahlen MT, Egeland T, Jensen T, Viken MK, et al. Unraveling the role of maternal anti-HLA class I antibodies in fetal and neonatal thrombocytopenia—antibody specificity analysis using epitope data. J Reprod Immunol 2017;122:1–9.
[20] Lashley EE, Meuleman T, Claas FH. Beneficial or harmful effect of antipaternal human leukocyte antibodies on pregnancy outcome? A systematic review and meta-analysis. Am J Reprod Immunol 2013;70(2):87–103.
[21] King KE, Kao K, Bray P, Casella JF, Blakemore K, Callan N, et al. The role of HLA antibodies in neonatal thrombocytopenia: a prospective study. Tissue Antigens 1996;47(3):206–11.
[22] Koyama N, Ohama Y, Kaneko K, Itakura Y, Nakamura T, Takasaki J, et al. Association of neonatal thrombocytopenia and maternal anti-HLA antibodies. Pediatr Int 1991;33(1):71–6.
[23] Panzer S, Auerbach L, Cechova E, Fischer G, Holensteiner A, KITTL EM, et al. Maternal alloimmunization against fetal platelet antigens: a prospective study. Br J Haematol 1995;90(3):655–60.
[24] Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R, et al. A screening and intervention program aimed to reduce mortality and serious

morbidity associated with severe neonatal alloimmune thrombocytopenia. Blood 2007;110(3):833–9.
[25] Turner ML, Bessos H, Fagge T, Harkness M, Rentoul F, Seymour J, et al. Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. Transfusion 2005;45(12):1945–56.
[26] Ghevaert C, Campbell K, Stafford P, Metcalfe P, Casbard A, Smith GA, et al. HPA-1a antibody potency and bioactivity do not predict severity of fetomaternal alloimmune thrombocytopenia. Transfusion 2007;47(7):1296–305.
[27] Kjær M, Bertrand G, Bakchoul T, Massey E, Baker JM, Lieberman L, et al. Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal Alloimmune Thrombocytopenia: a systematic review. Vox Sang 2019;114(1):79–94.
[28] Killie MK, Husebekk A, Kjeldsen-Kragh J, Skogen B. A prospective study of maternal anti-HPA 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. Haematologica 2008;93(6):870–7.
[29] Santoso S, Wihadmadyatami H, Bakchoul T, Werth S, Al-Fakhri N, Bein G, et al. Antiendothelial αvβ3 antibodies are a major cause of intracranial bleeding in fetal/neonatal alloimmune thrombocytopenia. Arterioscler Thromb Vasc Biol 2016;36(8):1517–24.
[30] Sonneveld ME, Natunen S, Sainio S, Koeleman CA, Holst S, Dekkers G, et al. Glycosylation pattern of anti-platelet IgG is stable during pregnancy and predicts clinical outcome in alloimmune thrombocytopenia. Br J Haematol 2016;174(2):310–20.
[31] Rossi KQ, Lehman KJ, O'Shaughnessy RW. Effects of antepartum therapy for fetal alloimmune thrombocytopenia on maternal lifestyle. J Matern Neonatal Med 2016;29(11):1783–8.
[32] Berkowitz RL, Bussel JB, McFarland JG. Alloimmune thrombocytopenia: state of the art 2006. Am J Obstet Gynecol 2006;195(4):907–13.
[33] Birchall JE, Murphy Kaplan MF, Cecile Kroll H, Group EFATS. European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. Br J Haematol 2003;122(2):275–88.
[34] Backe B, Salvesen KÅ, Sviggum O. Norwegian obstetricians prefer vaginal route of delivery. Lancet 2002;359(9306):629.