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ABSTRACT

Affecting 1 per 1000 to 2000 pregnancies, Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) is the leading cause for (severe) thrombocytopenia in term neonates. Due to an incompatibility between fetal and maternal platelets, maternal alloantibodies are formed against paternally derived human platelet antigens (HPAs). The alloantibodies can cross the placenta into the fetal circulation, where they can destruct the fetal platelets. As a result, severe thrombocytopenia may occur, potentially leading to intracranial hemorrhage (ICH) or severe organ bleeding during pregnancy or shortly after birth. In the absence of a universal prenatal screening program focussed on HPA-1a, FNAIT is often diagnosed too late, typically after the onset of severe fetal or neonatal bleeding complications. A screening program could be very effective in identifying the first pregnancy complicated with FNAIT, allowing timely intervention and prevent severe ICH and its associated long-term permanent sequelae. The aim of this review is to provide a comprehensive overview of the existing evidence regarding a possible future screening program for FNAIT. Additionally, challenges will be explored that need to be addressed for successful implementation of a screening program.

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Table 1
Results of screening studies and cost-effectiveness studies on FNAIT.

Study	Year/ Country	Number screened	FNAIT cases identified	Outcome
Screening primiparous women and newborns for fetal/neonatal alloimmune thrombocytopenia: a prospective comparison of effectiveness and costs. Immune Thrombocytopenia Working Group. Durand-Zaleski et al. [19].	1996 France	2066 first pregnancies; 6081 newborns	4 HPA-1a negative women with antibodies 2 fetuses with thrombocytopenia due to alloimmunization 5 newborns with thrombocytopenia due to alloimmunization	Prevalence anti-HPA-1a was 2/1000. The prevalence FNAIT 1/1000 (2 fetuses antenatally confirmed with fetal blood sampling, 2 women delivered infants without FNAIT). Screening newborns for FNAIT ($18,000) is more cost-effective than screening primiparous ($45,000).
The natural history of fetomaternal alloimmunization to the platelet-specific antigen HPA-1a (PlA1, Zwa) as determined by antenatal screening. Williamson et al. [3].	1998 United Kingdom	24,417 pregnant women	In 46/387 pregnancies anti-HPA-1a was detected; One fetus died in utero, 9 infants were severely thrombocytopenic and 10 were mildly thrombocytopenic.	HPA-1a and HLA-DRB3*01:01 typing in combination with anti-HPA-1a quantification enables identification of pregnancies at risk for severe thrombocytopenia.
Antenatal screening for human platelet antigen-1a: results of a prospective study at a large maternity hospital in Ireland. Davoren et al. [26].	2003 Ireland	4090 pregnant women	34 women with antibodies were followed and 3 infants had clinically significant thrombocytopenia at birth	The study demonstrated the feasibility of implementing routine antenatal HPA-1a screening.
Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. Turner et al. [27].	2005 Scotland	26,506 pregnant women	28 women with anti-HPA-1a antibodies; 4 neonates received HPA-1a negative platelet transfusions and 3 neonates had signs of mild bleeding	Severe NAIT due to HPA-1a is underdiagnosed without a prenatal screening program.
A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. Kjeldsen-Kragh et al. [20].	2007 Norway	100,448 pregnant women	In 210 women anti-HPA-1a antibodies were detected; 55 neonates had severe thrombocytopenia and 30 suffered from mild to moderate thrombocytopenia; 2 children developed ICH	Implementation of a prenatal screening program, in combination with timely intervention is able to reduce mortality and morbidity. Only the use of obstetric history is not sufficient enough for predicting the risk of severe thrombocytopenia in the following pregnancy.
Sub-study: Cost-effectiveness of antenatal screening for neonatal alloimmune thrombocytopenia. Killie et al. [28].	2007 Norway	100,448 pregnant women		Screening and intervention for 100,000 pregnant women could reduce healthcare costs by approximately 2.2 million USD/1.7 million euros and save between 210 and 230 quality-adjusted life years.
Sub-study: Neonatal alloimmune thrombocytopenia in Norway: poor detection rate with non-screening versus a general screening programme. Tiller et al. [16].	2009 Norway	HPA-1a typing of 100,448 pregnancies	85 cases of FNAIT out of 94.421 births	The detection rate of FNAIT in Norway without screening was 14 % of the expected rate.
Sub-study: Screening for fetal and neonatal alloimmune thrombocytopenia - lessons learned from a Norwegian screening program. Kjaer et al. [25].	2018 Norway			HLA-DRB3*01:01 typing, quantification of antibodies against HPA-1a and non-invasive fetal-HPA-1a typing are thought to eventually decrease the number of high-risk women who need follow-up during their pregnancy.
A prospective study of maternal anti-HPA 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. Killie et al. [22].	2008 Norway	1990 pregnant women	Anti-HPA-1a antibodies were detected in 172 pregnancies; a platelet count below 50 * 10^9/L was observed in 52 children.	Measuring anti-HPA-1a levels could be valuable in a prenatal screening program to identify high-risk pregnancies that might benefit from IVIg treatment.
Sub-study: Neonatal alloimmune thrombocytopenia is not what it was: a lesson learned from a large prospective screening and intervention program. Skogen et al. [21].	2009 Norway			Anti-HPA-1a levels are inversely correlated with the platelet count after birth.
Natural history of human platelet antigen 1a-alloimmunized pregnancies: a prospective observational cohort study. de Vos et al. [2].	2023 The Netherlands	153,106 pregnant women	Detection of anti-HPA-1a antibodies in 85 women; one fetus was diagnosed with ICH and 3 had mild bleedings.	Incidence of severe bleeding was 11 per 10,000 HPA-1a-negative pregnancies and could be prevented by a prenatal screening program for alloimmunization against HPA-1a. An association was found of the presence of FNAIT and preterm

(*continued on next page*)

Table 1 (*continued*)

Study	Year/ Country	Number screened	FNAIT cases identified	Outcome
				delivery, reduced birthweight and hypertensive disorders.
Sub-study: Screening of pregnant women for foetal neonatal alloimmune thrombocytopenia: A cost–utility analysis. de Vos et al. [29].	2024 The Netherlands			Screening for anti-HPA-1a antibodies will cost €4.7 million per year and result in a gain of 226 quality-adjusted life years (QALYs) per year. A prenatal screening program might be cost-effective, but a pilot screening is necessary.

1. Introduction

Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) is a condition caused by the formation of alloantibodies by the pregnant women against paternally derived human platelet antigens (HPAs) expressed by fetal cells. Alloantibodies of immunoglobulin (Ig)G type are transported by the placenta into the fetal circulation, where they may induce destruction of the fetal platelets and may also suppress their production. This can result in severe thrombocytopenia in the fetus, potentially leading to intracranial hemorrhage (ICH) or severe organ bleedings during pregnancy or shortly after birth. To date, 41 different HPAs have been identified, with anti-HPA-1a being the most common cause of FNAIT, accounting for approximately 80 % of the cases in Europeans. Approximately 2 percent of Caucasian women are HPA-1a-negative, whereas HPA-1a negativity is more rare in other ethnicities [1–3]. In these women, the risk of antibody formation during pregnancy lies between 8 and 10 % [1,4]. HPA -1a negative women who carry the HLA-DRB3*01:01 class II molecule are at higher risk of pregnancies complicated by severe FNAIT and are capable of mounting a strong alloimmune response resulting in higher antibody titers [5–8]. The risk of HPA-1a-alloimmunization in these women is estimated to be around 12.7 %, compared to 0.5 % in women who do not carry the HLA-DRB3*01:01 class II molecule, hence about 20-times higher [9]. Similarly, in a Dutch cohort it was observed that the risk to immunize in HPA-1a negative/HLA-DRB3*01:01 positive women was 28.1 % compared to 1.6 % in HPA-1a negative/HLA-DRB3*01:01 negative women [2].

In 10–15 % of FNAIT cases, alloantibodies against HPA-5b are discovered. However, although HPA-5b antibodies may lead to thrombocytopenia in the child, it is unclear if these will lead to severe bleeding symptoms or are rather an incidental finding upon laboratory investigation in thrombocytopenic newborns [8,10,11].

At present, no universal prenatal screening program exists, although it could be very effective in identifying women at risk for alloimmunization against HPA-1a. Without a screening program, FNAIT is often diagnosed too late, typically after the onset of severe fetal or neonatal bleeding complications. Most often, the diagnosis is made postnatally, either when newborns have clinically visible bleeding symptoms such as petechiae, hematomas or ICH, combined with severe thrombocytopenia or incidentally when a low platelet count is detected during a complete blood count performed for unrelated reasons. While rare, FNAIT is sometimes identified prenatally through additional testing following the detection of fetal ICH on ultrasound.

Approximately 60 % of the FNAIT cases occur already in the first pregnancy [12]. With a prenatal screening program these cases will be identified and, if necessary, treated at an early stage. Furthermore, a policy on timing and mode of delivery may be beneficial to have all preventive measures taken to prevent bleeding in the baby. Women will be closely followed up during their subsequent pregnancies to timely start treatment. With this approach, severe fetal and neonatal bleeding consequences and lifelong impairment could be prevented.

Antenatal treatment approach for FNAIT varies between countries. IVIg has been used as an antenatal treatment for alloimmunized women since 1987 and demonstrated a success rate of 98.7 % in preventing ICH in a subsequent pregnancy [13,14]. If FNAIT can be diagnosed in time, it is hypothesized this treatment might also prevent ICH in first pregnancies, however this is never studied. Moreover, some countries use the addition of corticosteroids to IVIg, but the effectiveness of this approach has been debated [13]. It is hypothesized that corticosteroids support the efficiency of the treatment and are able to reduce adverse effects of IVIg, such as headache [13,15].

The current understanding on the pathophysiology and clinical management of FNAIT is primarily based on small retrospective studies. Subsequent pregnancies represent only a subset of cases, limiting a comprehensive understanding of this rare condition and whether disease may worsen or not in subsequent pregnancies. In populations without screening, the incidence is likely underestimated [1]. For example, a study in Norway calculated the FNAIT detection rate, comparing severe FNAIT cases as a result of anti-HPA-1a antibodies in a non-screened population versus the number of severe cases in the screening study, adjusted for the total birth population [16]. Without universal screening, only 16 % of the expected cases of severe FNAIT (in this study defined as thrombocytopenia $<50 \times 10^9$/L) caused by anti-HPA-1a antibodies were detected [16].

This review aims to present a comprehensive overview of the current evidence and knowledge on a possible future screening program for FNAIT. Furthermore, we will use the classic screening criteria proposed by Wilson and Jungner to review if sufficient data is currently available to start a screening program [17]. Importantly, some knowledge gaps can only be addressed by initiating a screening program: "the proof of the pudding is in the eating" [18]. Therefore, we discuss not only facilitators but also barriers that need to be addressed for successful implementation of a screening program.

2. Setting the stage: conditions for successfully implementing a screening program

2.1. Existing evidence on the outcomes of screening studies for FNAIT

The first FNAIT-screening study, published in 1996, screened 2066 women in their first pregnancy and 6081 newborns [19]. Women were screened only once during their first term of pregnancy for the HPA-1 allele and all newborns were systematically screened for thrombocytopenia (in this study defined as a platelet count $<150 \times 10^9$/L). This French study reported that screening newborns for FNAIT is more cost-effective ($18,000) than screening women in their first pregnancy ($45,000). However, a significant limitation of this approach is that screening newborns only, will not prevent fetal death or complications arising due to bleeding in the first pregnancy, which is the primary goal of a FNAIT prenatal screening program. Moreover, this study was not designed as a cost-effectiveness or cost-utility study, thus it is not possible to translate health benefits into monetary term.

More screening studies have been conducted in the following 20 years (Table 1). An earlier prospective and interventional study from 1998 in the United Kingdom highlighted that combining HPA-1a and HLA-DRB3*01:01 typing with anti-HPA-1a antibody quantification allows for the identification of pregnancies at risk for severe thrombocytopenia [3].

Furthermore, a prospective interventional study in Norway conducted between 1994 and 2004, suggested that a potential prenatal screening program incorporating HPA-1a typing, antibody screening against HPA-1a, close monitoring and antenatal management, could significantly reduce mortality and morbidity associated with FNAIT [20]. Antenatal management consisted of anti-HPA-1a antibody screening and elective caesarean section 2 to 4 weeks prior to term. No IVIg was administered to these women. While comparisons were made with historical controls, the screening program paired with timely intervention appeared to lower the incidence of severe FNAIT-cases from 10 out of 51 to 3 out of 57. Furthermore, this study demonstrated that relying solely on obstetric history is insufficient for predicting the risk of severe thrombocytopenia in subsequent pregnancies [20].

A recent prospective observational study conducted in a Dutch cohort, published in 2023, also demonstrated the potential benefits of a prenatal screening program for alloimmunization against HPA-1a in preventing severe thrombocytopenia and associated bleeding [2]. In this study 153,106 pregnant women were screened, resulting in one identified severe bleeding complication, which can be translated as a rate of severe bleeding in 11 per 10,000 HPA-1a-negative pregnancies. This study was unique in the fact that neither the pregnant women nor the health care providers had knowledge of the HPA-1a-negative type of the mother. Since HPA-1a antibodies were determined after delivery, alloimmunization was not known and also the researchers were not aware during data collection. Therefore, the major advantage of this study is that the true incidence of clinically detected FNAIT without any interference could be estimated. However, the observational design did not allow for routine examinations, possibly resulting in underreporting the bleeding risk. Additionally, anti-HPA-1a antibody levels were positively correlated with the severity of bleeding, consistent with findings from the Norwegian screening study. An inverse correlation between anti-HPA-1a levels and neonatal platelet counts was again demonstrated [16,21,22]. However, from previous work based on clinical cases diagnosed after birth, the correlation between HPA-1a antibody titers and thrombocytopenia was not strong; some cases were severely thrombocytopenic with low antibody titers in the maternal samples [23,24]. Still we think that, maternal HPA-1a typing combined with HLA-DRB3*01:01 determination identifies the majority of women at risk for clinically relevant anti-HPA-1a antibody formation; non-invasive fetal-HPA-1a-typing can be used to select pregnancies at risk. Quantification of anti-HPA-1a levels is expected to be used to refine risk assessments and potentially reduce the number of high-risk women requiring intensive follow-up, including IVIg treatment during pregnancy [22,25]. This is of great importance in preventing both overtreatment as well as undertreatment.

Looking at the cost-utility and cost-effectiveness of a potential screening program, there are four (sub)-studies to consider. A prospective screening study in Ireland published in 2003, demonstrated the feasibility of implementing routine antenatal HPA-1a screening. In addition, a cost-effectiveness study from 2005 screened 26,506 pregnant women and reported that severe FNAIT due to HPA-1a is underdiagnosed without a screening program [26,27]. Furthermore, the Norwegian screening study also evaluated the cost-effectiveness of a proposed screening program, showing that implementing screening and timely interventions could reduce healthcare costs while improving outcomes by saving quality-adjusted life years (QALYs) [28]. We recently published a sub-study, assessing the cost-utility of HPA-1a typing and anti-HPA-1a antibody screening as part of a possible prenatal screening program if conducted in the Netherlands [29]. This study showed that a prenatal screening program for anti-HPA-1a might be cost-effective, but that a pilot screening is essential to obtain more knowledge on the outcomes of screening.

2.2. Wilson and Jungner classic screening criteria

More than 50 years ago, Wilson and Jungner defined ten criteria for screening to guide the selection of conditions and diseases suitable for screening [17]. These criteria are primarily based on the ability to detect the condition at an early stage and the availability of effective treatment options. The ten criteria are demonstrated in the box below.

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed policy whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

In the following paragraphs, the Wilson and Jungner criteria will be shortly discussed and applied on a possible prenatal screening program for FNAIT. Policies and screening approaches vary by country due to differences in health care systems and culture differences. Therefore, the criteria are applied using a more international approach. The challenges arising from the criteria will be addressed in the subsequent section.

2.3. Criterium 1: the condition sought should be an important health problem

In western societies, HPA-1a mediated FNAIT affects 1 per 1000 to 2000 pregnancies and in cases of severe bleeding complications, it can lead to lifelong neurological impairment or death [30,31]. Of the children diagnosed with a severe thrombocytopenia due to FNAIT, approximately 10–25 % develops an ICH, potentially leading to lifelong handicaps or death of the child [32].

2.4. Criterium 2: there should be an accepted treatment for patients with recognized disease

HPA-alloimmunized women can be effectively treated during pregnancy with IVIg with or without the addition of corticosteroids [13,33,34]. One can argue that this treatment has only proven its effectiveness in subsequent pregnancies and may not yet be successful in first pregnancies.

Postnatally, neonates with a low platelet count are at risk for bleeding which can be managed with platelet transfusions. HPA-matched transfusions are considered an appropriate treatment for newborns with a platelet count between 25 and 50 * 10^9/L, depending on the presence of life threatening bleeding [33,35]. Without routine screening, HPA-matched platelets may not be available. Furthermore, the cause of thrombocytopenia may be identified late in the process, which increases the risk for undertreatment and acute bleeding.

2.5. Criterium 3: facilities for diagnosis and treatment should be available

Facilities to perform the laboratory testing for women at risk and their pregnancies at risk are available within platelet serology reference laboratories, academic institutes, or blood supply institutes. Determination of HPA-1a-antigen incompatibility between mother and fetus can be achieved through non-invasive HPA-1a-genotyping of the mother and HPA-1a-genotyping of the fetus with cell-free fetal DNA isolated from maternal plasma [36]. In most countries the alloantibody tests are performed in specialized laboratories. Women with HPA-alloimmunized pregnancies should receive ongoing care at a specialized center for appropriate management.

2.6. Criterium 4: there should be recognizable latent or early symptomatic stage

The first phase of the disease is the development of HPA-1a-alloantibodies by the pregnant woman. The most important aspect of the screening will be antibody detection prior to the occurrence of severe fetal bleeding, such as an ICH. These maternal anti-HPA-1a antibodies can be detected and quantified in blood samples taken from the mother, combined with HLA-typing for the HLA-DRB3*01:01 status to determine the risk of production of clinically significant levels of antibodies and therefore the risk for severe FNAIT [37,38]. If antibodies are detected, interventions for secondary prevention can be applied. The higher the antibody levels are, the higher the chance of ICH, although also at low levels ICHs can occur [23]. Furthermore, other factors such as endothelial damage in combination with severe thrombocytopenia have been proposed to contribute to the occurrence of ICH [5]. In addition, a correlation was found between a decrease in anti-HPA-1a fucosylation and severity of neonatal thrombocytopenia [39,40]. Unfortunately, there is no non-invasive method to determine fetal platelet counts. In some centers, platelet counts are determined from fetal blood samples at a gestational age of 28 weeks [41]. Other centers consider this as too high risk for extended bleeding in thrombocytopenic fetuses, which may cause emergency caesarean sections or may result in fetal demise [13]. In general, the presence of maternal HPA-1a antibodies with a certain level is regarded as a more acceptable approach for risk-stratification.

2.7. Criterium 5: there should be a suitable test or examination

For prenatal HPA-1a-induced FNAIT-screening, the following steps are recommended. The initial step involves testing the mother for HPA-1a negativity. Reagents to determine HPA-1a positivity or negativity are applicable and several in house developed methods have been published [3,20,22,26,42]. For women identified as HPA-1a negative, additional HLA-testing should be performed to determine HLA-DRB3*01:01 status. If a woman is both HPA-1a negative and HLA-DRB3*01:01 positive, fetal HPA-status should be assessed by either using HPA-1a paternal typing (at least 70 % of fathers will be homozygous HPA-1a positive) or fetal HPA-1a typing using cell-free fetal DNA (cffDNA) [43]. The presence of alloantibodies during pregnancy can be detected with commercially available assays, or in house developed tests such as platelet immune fluorescence tests using microscopy or flowcytometry or by the monoclonal antibody based immobilization of platelet antigen assay (MAIPA) [44]. The MAIPA can also be used for HPA-1a-antibody

quantification and is still the golden standard for antibody screening in clinically suspected FNAIT-cases [45]. Pregnancies at risk for FNAIT should be closely monitored through antibody quantification and ultrasounds should be conducted throughout the pregnancy. Timely initiation of IVIg, before the occurrence of bleeding complications, should follow the risk assessment.

2.8. Criterium 6: the test should be acceptable to the population

HPA-typing is performed with blood already taken for other population screening programmes to screen for red blood cell alloantibodies. It is a quick and efficient test that can be used to screen a large number of women simultaneously [46]. A questionnaire study on attitudes towards a prenatal screening program for FNAIT in the Netherlands found that 91 % of the women were in favour of such a screening, with 99 % expressing a willingness to participate [47].

2.9. Criterium 7: the natural history of the condition, including development from latent to declared disease, should be adequately understood

The incidence of severe bleeding complications, possibly resulting in neurodevelopmental impairment, is 11 in 10,000 HPA-1a negative pregnancies. Besides fetal bleeding and thrombocytopenia, signs of immunological damage in FNAIT placentas have been observed, which might explain the observed reduced birthweight and hypertensive disorders [2].

The natural history of FNAIT and especially its development in subsequent pregnancies may be better understood after the implementation of a screening program as most cases are currently identified at an advanced stage. However, a critical question remains: what factors drive the development of severe bleeding complications in some fetuses and neonates, while others are unaffected? Norway's more conservative approach to IVIg use has allowed for observation of the natural progression of FNAIT. Typically, the first pregnancy is affected [12], with a high recurrence rate in the subsequent pregnancies [48]. Gravidity seems not to be a risk factor for HPA-1a alloimmunization [2]. Unlike Hemolytic Disease of the Fetus and Newborn (HDFN), FNAIT does not necessarily worsen in subsequent pregnancies, and anti-HPA-1a levels often decline [22]. Norwegian researchers have shown that neonatal platelet counts in most subsequent pregnancies complicated with HPA-1a alloimmunization either remain stable or improve [49].

2.10. Criterium 8: theCre should be an agreed policy whom to treat as patients

Anti-HPA-1a accounts for approximately 80 % of the FNAIT-cases in the Caucasian population [8]. Therefore, any potential screening program should focus exclusively on HPA-1a. Introducing an antibody cut-off could help to minimize the risk of over-as well as undertreatment. However, a universal threshold for determining when to initiate treatment has yet to be established. There are varying opinions regarding the appropriate threshold for a possible antibody cut-off. An antibody cut-off that is too sensitive will likely result in overtreatment. However, if the cut-off is too high, there is a risk of not starting timely treatment leading to severe bleeding complications in the fetus. This boils down to the general challenge in every screening program: does the risk of missing cases, with a probability of morbidity and mortality as a result, outweigh the benefits of minimizing overtreatment?

2.11. Criterium 9: the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

In most western countries, a screening program for red blood cell alloantibodies is in place and HPA-typing programs will be an add on such programs. Therefore, the costs of a screening program for FNAIT may be limited to laboratory expenses for HPA-typing and antibody detection/quantification, since costs related to the screening infrastructure are already covered. FNAIT-screening will result in additional prenatal visits with detailed ultrasonography and the costs of antenatal and postnatal treatment if needed. Additional expenses may arise if an elective caesarean section is performed. The cost-effectiveness and cost-utility studies demonstrated that such a screening program can improve health outcomes by increasing quality-adjusted life years (QALYs) and reducing healthcare costs [20,28,29,50]. Timely intervention can prevent severe complications associated with FNAIT, avoiding disabilities that impact both the child's and the family's quality of life. Moreover, preventing fetal and neonatal ICH significantly reduces lifelong healthcare expenses, benefiting society. For example, screening and intervention in 100,000 pregnant women could save approximately 2.2 million USD/1.7 million euros and gain between 210 and 230 QALYs [28].

2.12. Criterium 10: case-finding should be a continuing process and not a 'once and for all' project

The possibility of an HPA-incompatible pregnancy will persist. Without screening, these women may remain undetected. In the future, prophylaxis to prevent HPA-alloimmunization might become possible, which will also make HPA-1a typing of the women and follow-up testing necessary [51].

Based on these arguments, we can conclude that a potential screening program aligns almost completely with the ten Wilson and Jungner criteria. Screening for FNAIT is not only useful and efficient but it is also cost-effective, especially if red blood cell alloantibody screening in pregnancy has already been implemented. Screening allows testing a large number of women simultaneously, and most importantly, identifying HPA-1a negative women results in better outcomes. If pregnancies at risk for FNAIT are identified upon antenatal screening, timely intervention could prevent the occurrence of fetal ICH.

Nevertheless, challenges are anticipated after implementation. The following paragraph will explore the potential difficulties

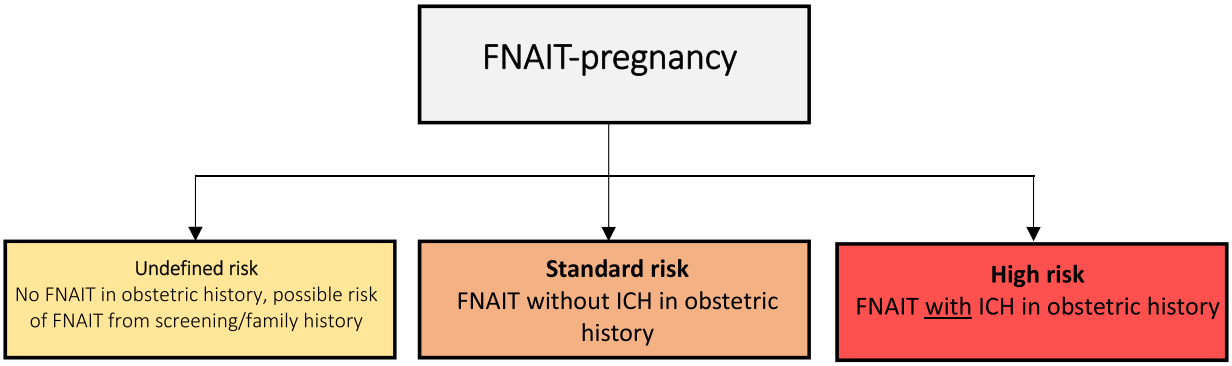

Fig. 1. Subdivision of FNAIT-pregnancies into risk groups.

caregivers may face during this process of implementation. The initial years of screening will help address knowledge gaps that remain unanswered as these can only be understood through the screening process itself: "*the proof of the pudding is in the eating*." Therefore, responsible implementation within a research setting is essential.

3. Challenges in designing and implementing a FNAIT screening program

In every large-scale screening program, the benefits should be carefully weighed against potential adverse outcomes. The implementation of such a program will highlight the current challenges on a larger scale and will also introduce new challenges and concerns that need to be addressed.

3.1. Challenge 1: timing of screening

Evidence on the exact timepoint for the development of ICH is limited and remains challenging to define. However, identifying this timepoint is of great importance for implementing a screening to identify HPA-1a negative women and subsequently antibody formation. The Norwegian research group demonstrated that more than 50 % of the ICH had developed before week 28 of the pregnancy and 67 % occurred before week 34 [31]. Most preferably, screening will take place after HPA-1a immunization but before any severe bleeding complications in the fetus have occurred. It is likely that multiple screening timepoints will be necessary, since it has been shown that immunization takes place throughout the whole pregnancy. To identify at-risk women promptly, it is important to recognize them early during their first-trimester routine prenatal visits. The first step in screening should be HPA-1a genotyping. HLA-DRB3*01:01 allele determination should be performed if the patient is HPA-1a-negative. In case of HLA-DRB3*01:01 positivity, the presence of antibodies should be determined. Our research group suggests to perform the first alloantibody-screening after the first trimester, but not later than 20 weeks [18]. This is because intracranial bleedings were detected from a gestational age of 20 weeks onwards [31]. However, some primigravida's will not have developed antibodies yet, making a second timepoint necessary, for example around week 27 of the pregnancy [18].

3.2. Challenge 2: whom to treat?

The foundation of a clear management policy lies in risk-stratification. Both literature and expert consensus have agreed on categorizing pregnancies based on the previous pregnancy and the presence of bleeding [13,33,48,52]. A high-risk pregnancy is defined as a subsequent pregnancy of a woman with anti-HPA-antibodies who had a child with ICH in her previous pregnancy, whereas a standard-risk pregnancy is defined as such a pregnancy without an ICH in the previous pregnancy (Pothof et al., a Delphi consensus study; manuscript submitted). However, once the screening is introduced, we aim that the group with an ICH in a previous pregnancy is hardly present, and in addition a third group of women with an undefined risk emerges (Fig. 1). These women may be pregnant with their first child, so there is no obstetric history available to guide management based on risk. This undefined risk also applies to women with a previous pregnancy but without alloantibodies. Another new group will also emerge, consisting of women who were antenatally treated based on high antibody thresholds in a previous pregnancy, which may have prevented bleeding, and who now may present in a subsequent pregnancy with alloantibodies.

One of the approaches proposed, is to use an antibody cut-off to identify pregnancies at higher risk of severe FNAIT complications. Additionally, a more precise cut-off could be implemented to provide more tailored treatment for women. For example, in a non-screening setting in the Netherlands, the high-risk group (women with a previous pregnancy complicated with ICH due to FNAIT) will always receive antenatal treatment with IVIg, regardless of antibody levels (publication in press) [53]. Starting IVIg in the undefined risk group and standard-risk group (women with a previous pregnancy complicated with FNAIT but without ICH) will follow a more deliberate approach in the current Dutch guideline, guided by an antibody cut-off of 2 IU/mL. This idea is supported by several studies that suggest maternal anti-HPA-1a antibody levels may effectively predict the severity of thrombocytopenia, the potential increased bleeding risk in the fetus, and the higher recurrence risk of ICH in the high-risk group [3,33,54]. However, the evidence

regarding the utility of antibody levels for FNAIT risk-stratification is limited and a definite cut-off with sufficient sensitivity and specificity has yet to be defined [3,55]. In a screening setting, it may be beneficial to implement a higher antibody cut-off for the undefined risk group, in order to prevent overtreatment. Management approaches in a screening setting will be further discussed in the following section.

3.3. Challenge 3: how to treat pregnancies identified through screening?

Treatment of FNAIT-pregnancies can be subdivided into antenatal- and postnatal management. In the absence of an universal antenatal approach, caregivers often follow local or national protocols or make decisions based on their own experience and/or literature. Clear national management policies should be established before implementing a nationwide screening. It is important to create policies that are tailored to the specific structure and framework of every country's healthcare system.

The clinical management for patients at risk still has ongoing challenges, especially after screening. In some cases, pregnant women identified through screening may lack an obstetric history to guide decisions regarding management. If antibodies are detected, the patient should be closely monitored. Based on alloantibody levels, it should be determined whether antenatal treatment with IVIg (with or without corticosteroids) is necessary and, if so, whether it should begin before 24 weeks or before 28 weeks.

Furthermore, in absence of large studies evaluating the safest mode of delivery (vaginal deliveries or caesarean sections), the optimal approach remains unclear. Given the concern that vaginal birth may trigger the development of ICH, along with practical considerations, many centers opt for an elective caesarean section. However, most cases of ICH in FNAIT occur before delivery, and there is insufficient evidence to establish a definitive link between the mode of delivery and the risk of ICH [6,14]. In absence of an obstetric history or for the group of women who will not be treated antenatally with IVIg, it is difficult to determine what the optimal mode of delivery should be.

Postnatally, HPA-matched platelet transfusions are recommended when a low platelet count is determined in the newborn [33,56]. However, perspectives on the use of HPA-matched platelets remain divided. A large multicentre study, including seven countries, reported a great variety in postnatal management [35]. While HPA-matched transfusion demonstrated a higher median platelet count compared with unmatched platelets, it remains unclear whether this is also associated with a reduced bleeding risk.

3.4. Challenge 4: overtreatment

Following challenge 1 and 2, one of the most critical subjects of debate is: how do we prevent overtreatment? There is no universally accepted antibody cut-off value on when to start antenatal treatment in alloimmunized women, nor is there agreement on the appropriate type of antenatal treatment or mode of delivery. While high maternal anti-HPA-1a levels are correlated with lower neonatal platelet count, a direct relation with an increased bleeding risk has not yet been established. The incidence of severe thrombocytopenia has been shown to be three to five times higher in clinically diagnosed cases with FNAIT, than in cases identified through prenatal screening [3,27,28,57]. These findings suggest that routine screening might identify milder or even asymptomatic cases. This uncertainty is particularly relevant for the group that will emerge following the implementation of a screening program.

For example, an HPA-1a negative women identified through screening will receive close monitoring for the development of alloantibodies. The cut-off for initiating IVIg treatment, as well as the dose regimen, varies between countries. Depending on national policies, the antibody cut-off levels may be set at 3, 10 or 50 IU/mL. A lower antibody threshold ensures that most women with detectable alloantibodies receive treatment, prioritizing a 'better safe than sorry' approach. However, the biggest concern with this approach will be overtreatment. The risks associated with overtreatment are side-effects from the IVIg treatment, increased anxiety during the current and subsequent pregnancy, higher health care costs and more follow-up visits. However, this largely depends on the specific country, its healthcare system, and infrastructure.

3.5. Future perspectives

3.5.1. Prevention of FNAIT

Primary prophylaxis for HPA-alloimmunization could prevent the development of HPA-alloantibodies and the severe bleeding complications as a consequence. The novel monoclonal anti-HPA-1a antibody (RLYB212) has been tested in HPA-1a negative participants and showed rapid elimination of HPA-1a positive platelets [51]. This suggests that the monoclonal could eradicate HPA-1a positive fetal platelets or other type of HPA-1a-positive material from the maternal circulation and thereby potentially prevent HPA-1a-alloimmunization in the mother. It is not known if fetal platelet or for example the HPA-1a-positive placenta itself elicits the immune response during pregnancy. In the next and currently ongoing phase of the development, the efficacy and safety of this prophylaxis for FNAIT is studied in pregnant women (clinical trial ID NCT06435845) [58].

3.5.2. Treatment of FNAIT

As previously discussed, women with high antibody levels are typically treated with IVIg during pregnancy. Additionally, clinical trials with a novel investigational drug, the monoclonal antibody Nipocalimab, aim to reduce the circulating IgG antibody level, including alloantibodies due to HPA-alloimmunization (clinical trial ID NCT06449651). Nipocalimab is an FcRn-inhibitor and has the potential to block the FcRn-receptor on the placenta [59]. It is thought that this would prevent transplacental transport of pathogenic alloantibodies into the fetal circulation and thereby reducing the risk of severe FNAIT. The FcRn-blockade could have the ability to totally block the transport of IgG into the fetal circulation in both HDFN and FNAIT and eliminate the use of IVIg and/or corticosteroids

Research agenda

- Certain knowledge gaps can only be addressed by initiating a screening program and therefore, responsible implementation within a research setting is essential.
- The natural history of FNAIT and its development in subsequent pregnancies may be better understood after the implementation of a screening program as most cases are identified at an advanced stage.

Practice points

- Prenatal screening will identify pregnancies at risk for FNAIT, resulting in timely intervention which could prevent the occurrence of fetal ICH.
- Certain knowledge gaps can only be addressed by initiating a screening program: "the proof of the pudding is in the eating".
- Patients at risk identified after screening brings new challenges in clinical management

[57]. Nipocalimab has already been tested in HDFN and will be proceeding in a phase 3 trial [59,60]. However, the results of the trial should substantiate these findings for FNAIT.

4. Conclusion

A universal consensus on the optimal diagnosis and management of FNAIT is currently lacking due to limited evidence, although it must be acknowledged that this depends on multiple factors. Moreover, the implementation of a FNAIT-screening program will not occur simultaneously across all countries, providing an opportunity to learn from each other's experiences. Therefore, it is crucial to implement screening in a research setting to fill the existing gaps. Continued speculation on potential outcomes will not answer critical research questions, without actually beginning the screening process. The strength of the evidence lies in taking action.

CRediT authorship contribution statement

R. Pothof: Writing – original draft, Methodology, Conceptualization. **T.W. de Vos:** Writing – review & editing. **E. Lopriore:** Writing – review & editing, Supervision, Methodology, Conceptualization. **D. Winkelhorst:** Writing – review & editing. **C.E. van der Schoot:** Writing – review & editing. **M. de Haas:** Writing – review & editing, Supervision, Methodology, Conceptualization. **E.J.T. Verweij:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Conflict of interest

none.

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