UK National Screening Committee

Screening for fetomaternal alloimmune thrombocytopenia

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: Final

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Solutions for Public Health

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies and the policy review process can be found at

https://www.gov.uk/guidance/evidence-and-recommendations-nhs-population-screening#evidence-review-process

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Abbreviations List

AUC	Area under the curve
HPA	Human Platelet Antigen
ICH	Intracranial haemorrhage
IUFD	Intrauterine foetal death
IVIG	Intravenous Immunoglobulins
FMAIT	Fetomaternal alloimmune thrombocytopenia
FNAIT	Feto-neonatal alloimmune thrombocytopenia
NAIT	Neonatal alloimmune thrombocytopenia
NHS	National Health Service
RCT	Randomised controlled trial
UK	United Kingdom
UK NSC	UK National Screening Committee

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from Public Health England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Plain English Summary

Feto-maternal alloimmune thrombocytopenia (FMAIT) is a rare condition that causes the destruction of the smallest of cells that circulate in the bloodstream (platelets) of a fetus or newborn. The fetus inherits surface proteins on the platelets from both its parents. If the fetus inherits a platelet protein from the father which is not present in the mother, she may produce antibodies against the protein because her body recognises it as foreign to her. Antibodies may cross from the mother's blood to the fetus and they may destroy fetal platelets. Platelets are important in preventing and stopping bleeding and if they are reduced to a very low level the fetus or newborn is at high risk of spontaneous bleeding into the brain (intracranial haemorrhage), under the skin or into other major organs. The effect of FMAIT on the fetus or newborn ranges from no symptoms at all, to severe lifelong disability or death.

The condition is relatively uncommon and latest figures suggest that in the general population in the UK, 0.04% of newborns (40 per 100,000 births) will develop severe FMAIT with a low platelet count of $<50x10^9$/L.

This document reviews evidence published between January 2011 and March 2016 that relates to the question of population screening for FMAIT. The aim of screening for FMAIT would be to identify pregnant women at risk of developing a severe form of the condition in order to manage the pregnancy and period after the birth to reduce the likelihood of severe disability or death of the baby.

This document updates the previous review for the UK National Screening Committee (UK NSC) completed in 2012 which recommended that a population screening programme for FMAIT should not be introduced in the UK. The focus of this update is the evaluation of the latest research to answer four questions which link to areas of uncertainty about a population based screening programme for FMAIT.

Question 1: What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?

- From the latest evidence this update concludes that there remains some uncertainty about the proportion of FMAIT that results in serious adverse outcomes for the fetus/baby. It remains unclear as to what extent the major differences between the numbers of babies with severe FMAIT from screening studies and the numbers that are clinically diagnosed are because of over-diagnosis through screening, or under-diagnosis by doctors in the absence of screening.

Question 2: Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?

- There is no evidence of a reliable predictor that can routinely identify first pregnancies of women at high risk of the baby developing severe FMAIT leading to disability or death of the baby before or after birth.

Question 3: What it the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?

- The additional studies identified since 2011 do not provide evidence for a single optimal management strategy to prevent serious adverse outcomes in the newborn from FMAIT.

Question 4: What are the most effective screening strategies to identify pregnancies at high risk of serious adverse outcomes due to FMAIT?

- From the literature search for this review no population based screening programmes or high quality studies for an FMAIT screening programme were identified. There is therefore no evidence for the most effective screening strategy to identify first pregnancies at high risk of adverse outcomes from the development of FMAIT.

Because of these uncertainties the review concludes that a population screening programme should not be introduced in the UK.

Executive Summary

This document reviews evidence published between January 2011 and March 2016 on screening for fetomaternal alloimmune thrombocytopenia (FMAIT).

Background

Thrombocytopenia is a generic term for a reduction of platelets in the blood. FMAIT refers to a type of thrombocytopenia affecting a fetus or neonate due to maternal antibody production against a human platelet antigen (HPA) that a fetus has inherited from his/her father. These antibodies can cross the placenta from mother to baby and reduce the number of platelets in the fetal blood which is a risk factor for bleeding. The effect of FMAIT on the fetus or neonate ranges from no symptoms at all to intracranial haemorrhage resulting in severe neurological disability or death.

The condition can appear in a first (index) pregnancy but FMAIT is currently usually only diagnosed after the birth of a baby with thrombocytopenia. Therefore only subsequent pregnancies where there is a known risk are actively managed to avoid the development of FMAIT. Pregnancies are likely to be at known risk if it occurs between the same mother and father where FMAIT developed and was diagnosed during or soon after delivery of an earlier pregnancy.

FMAIT is also known as FNAIT or NAIT (Fetal/neonatal alloimmune thrombocytopenia). When drawing on evidence from particular studies this report will use the term used by the authors.

Previous findings

The current UK NSC policy is that systematic population screening for FMAIT is not recommended. The previous UK NSC external review of screening for FMAIT was published in 2012. The key points made were:

- There is no robust evidence that the level or other characteristics of maternal anti-HPA-1a antibodies can reliably predict which cases of FMAIT will be more severe and therefore more likely to benefit from medical intervention.
- Without a reliable predictive test for the severity of FMAIT, there is substantial potential for over-diagnosis and unnecessary intervention. If the estimates derived from screening studies are applied to a UK birth cohort of 700,000 births one would expect to find approximately 1400 women with maternal anti-platelet antibodies each year, in 420 (30%) of which the fetus would have severe thrombocytopenia. However the number of babies with clinically-detected FMAIT appear to be only about 85 per year and the majority of these will not have long-term sequelae due to bleeding. These figures indicate that the babies of most women who would be identified as screen-positive if an antenatal screening programme were started are born healthy, without receiving any medical intervention.
- There is not yet any convincing evidence that medical intervention improves the outcomes of pregnancies that are identified through antenatal screening. No randomised controlled trials (RCTs) of screening have been conducted. A non-randomised controlled trial planned across Norway, Denmark and the Netherlands may generate further evidence regarding the

effectiveness of intravenous immunoglobulins (IVIG) or preterm Caesarean section (CS), compared with no treatment.
- Neither IVIG nor preterm CS is recommended by any UK guidelines as treatment for screen-detected FMAIT.

The current review

The current review explores the volume, quality and direction of the literature published since 2012 and focuses on key questions relating to the conclusions of the previous review. The aim of the review is to inform discussion on whether the recent evidence provides a sufficient basis on which to recommend the introduction of an NHS population based antenatal screening programme for FMAIT in the UK. The focus of this update is the evaluation of the latest research to answer four questions which link to areas of uncertainty about a population based screening programme for FMAIT.

Question 1: What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?

- There remains some uncertainty about the proportion of FMAIT that results in serious adverse outcomes for the fetus/baby. From the latest evidence this update concludes that it remains unclear as to what extent the major differences between the numbers of babies with severe FMAIT from screening studies and the numbers that are clinically diagnosed are because of over-diagnosis through screening, or under-diagnosis by doctors in the absence of screening.

Question 2: Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?

- This review concludes that there is no evidence that the level or other characteristics of maternal anti-HPA-1a can routinely indicate which women in their first pregnancy will have a fetus/newborn that will develop severe FMAIT and suffer disability or death and may benefit from medical intervention.
- The relationship between possible predictors such as blood typing, HLA genotyping and FMAIT is still not fully understood in first pregnancies although correlations between these factors and severe FMAIT have been reported. There may be potential to use HLA genotyping to reduce the size of the population of women who need to be followed up†. However currently the evidence is not clear that these predictors could be clinically useful in identifying women at high risk of having a fetus/newborn with severe FMAIT in their first pregnancy.

Question 3: What is the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?

- This review concludes that the additional studies identified since 2011 do not provide consistent evidence for a single optimal management strategy to prevent serious adverse outcomes in the newborn from FMAIT that has developed in a first pregnancy.

Question 4: What are the most effective screening strategies to identify pregnancies at high risk of serious adverse outcomes due to FMAIT?

- From the literature search for this review no population based screening programmes or RCTs for an FMAIT screening programme were identified. There is therefore no new evidence for the most effective screening strategy to identify first pregnancies at high risk of adverse outcomes from the development of FMAIT.

Recommendations

At present, the evidence base is insufficient to recommend a UK systematic population screening programme for FMAIT.

Researchers involved in the PREVNAIT[1] and PROFNAIT (http://www.profnait.eu/profnait-project/) projects are collecting further data about biomarkers and the possibility of prophylaxis for HPA-1a and this will add to the understanding of how to predict severe FMAIT and whether use of anti-HPA-1a prophylaxis would reduce the risk of severe FMAIT.

Introduction

Thrombocytopenia is a reduction of platelets. Feto-maternal alloimmune thrombocytopenia (FMAIT) is thrombocytopenia in the fetus or neonate due to maternal antibodies developing against human platelet antigens (HPAs) that a fetus has inherited from his/her father and that the mother lacks. FMAIT occurs when the maternal antibodies cross the placenta from mother to baby, destroying platelets, causing thrombocytopenia that ranges from a mild to severe condition and in some cases can cause foetal or neonatal death[1].

The most serious potential consequences of FMAIT are intracranial haemorrhage (ICH) and intrauterine fetal death (IUFD). Other complications include bleeding into other organs such as the gut, the scalp, and the eyes[2]. FMAIT-related ICH and IUFD occur only among babies with severe thrombocytopenia. However, only a minority of babies with severe thrombocytopenia suffer from bleeding complications[3]. The 2012 UK NSC review included an earlier systematic review of studies of women screened antenatally with severe NAIT[3] and reported a rate of 0.04% (40 per 100,000). Knight et al (2011)[4] estimated the incidence of clinically-detected FMAIT in the UK as 12.4 (95% CI 10.7 – 14.3) per 100,000 births, equivalent to approximately 85 babies per year. Of those 85 babies 8 will die or be severely disabled by 1 year of age.

Over 80% of FMAIT cases result from a mother and fetus incompatibility to the human platelet antigen- 1a (HPA-1a) with the remaining cases due to antibodies produced against HPA-5b (15%) and other HPAs (5%)[1].

The condition can appear in a first (index) pregnancy, but FMAIT is currently only usually diagnosed after the birth of a baby with thrombocytopenia so only subsequent pregnancies with the same biological father where there is a known risk are actively managed to avoid the development of FMAIT.

It is unclear exactly how pregnant women are alloimmunised against fetal HPAs although a number of mechanisms have been explored. Antibody production by women is initiated when fetal platelet antigens reach the mothers lymph nodes and spleen. This could occur during fetal-maternal haemorrhage during delivery or miscarriage of the first (index) pregnancy and possibly early in pregnancy when trophoblasts or trophoblast microparticles are thought to have a role.

At birth FMAIT is usually suspected because of haemorrhage presenting as petechia, haematomas, melena, retinal bleeding, haematuria or haemoptysis. Platelet counts may sometimes fall after delivery[1]. In around 50% of babies where the mothers have been alloimmunised platelet counts are normal.

FMAIT is also known as FNAIT or NAIT (Fetal/neonatal alloimmune thrombocytopenia). When drawing on evidence from particular studies this report will use the term used by the authors.

Basis for current recommendation

The current UK NSC policy is that the systematic population screening of adults for FMAIT is not recommended. The previous UK NSC external review of screening for FMAIT was produced in 2012[5]. The key points made were:

1. There is not yet consistent evidence that the level of maternal anti-HPA-1a antibodies can reliably predict which cases of FMAIT will be more severe, and therefore more likely to benefit from medical intervention
2. Without such a test there is substantial potential for over-diagnosis and unnecessary intervention. If the estimates derived from screening studies are applied to a UK birth cohort of 700,000 births one would expect to find approximately 1400 women with maternal anti-platelet antibodies each year, in 420 (30%) of which the fetus would have severe thrombocytopenia.
3. However the number of babies with clinically-detected FMAIT appears to be only about 85 per year. These figures indicate that the babies of most women who would be identified as screen-positive if a programme were started are born healthy, without receiving any medical intervention.
4. There is not yet any convincing evidence that medical intervention improves the outcomes of pregnancies that are identified through antenatal screening. The non-randomised controlled trial that is planned across Norway, Denmark and the Netherlands may generate further evidence regarding the effectiveness of IVIG or preterm CS, compared with no treatment.
5. Neither IVIG nor preterm CS is recommended by any UK guidelines as treatment for screen-detected FMAIT.
6. No RCTs of screening have been conducted.

Current update review and approach taken

The current review considers screening for FMAIT and was prepared by Solutions for Public Health, in discussion with the UK National Screening Committee (UK NSC).

The key questions addressed in the current review were developed by the UK NSC and are based on the key areas where FMAIT did not meet the criteria for a screening programme in the last 2012 UK NSC review. The aim of the current review is to update the evidence in key areas including;

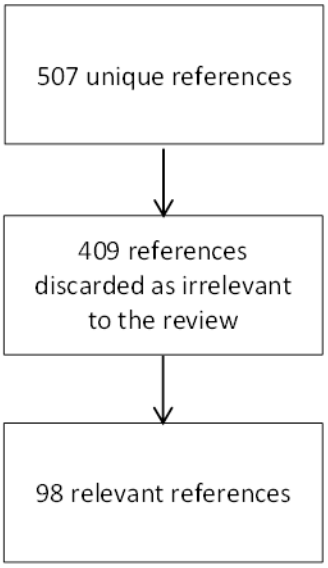
- The incidence of severe FMAIT outcomes
- The identification of a reliable predictor of the severity of FMAIT
- The agreed effective clinical management of a pregnancy once FMAIT is identified.

The key questions addressed in this review and the UK NSC criteria that they relate to are presented in Table 1.

A systematic literature search of four databases was conducted by the UK NSC in February 2016 for evidence published since January 2011. The search was structured around the issues previously raised in the last 2012 UK NSC external review. A total of 507 unique references were identified and sifted by title and abstract by the UK NSC for potential relevance to the review. Details of the databases searched, search terms and inclusion and exclusion criteria used for the initial screening of results are presented in the Search Strategy section at the end of this report.

Ninety-eight references were passed to Solutions for Public Health for further appraisal and possible inclusion in the final review after initial check for relevance to the review questions (Figure 1).

Figure 1: Flow diagram of studies identified and sifted prior to appraisal by SPH



Selection and appraisal of studies by SPH was undertaken by one reviewer, and the decisions made about the inclusion and exclusion of studies was discussed with a second reviewer.

Of the 98 references, 32 studies were identified as directly relevant to the review based on title and abstract sifting. Reasons for exclusion at the abstract stage include, the full text of the paper being in a language other than English, papers describing the prevalence of antibodies in different populations, conference abstracts, papers included in the previous review and opinion pieces (including letters) without any primary data. The full texts of the 32 studies were further assessed. Two additional studies, suggested for inclusion by an external expert, were evaluated by the reviewers. Such studies were not retrieved by the systematic literature search because at the time of the search the studies were not yet been indexed in Medline.

Of the 32 studies assessed at full text, 11 were included in the final analysis with further information drawn from 3 review papers summarising current advances in the field. All primary research studies included are tabulated in the appendices.

Exclusions include papers describing:

- Laboratory quality of a particular test (rather than as part of a screening programme) (5 studies)
- Retrospective case series thrombocytopenia (mixed aetiology not just FMAIT) (1 study)
- Proposed management algorithm for FNAIT by a clinician (1 study)
- Reviews older than the 3 included (2 studies)
- Studies included in the previous review (2 studies)
- An RCT protocol not directly related to FMAIT (1 study)
- Commentaries about:
    - Test (4 studies)
    - Treatment (5 studies)

The review was quality assured by a second senior reviewer who was not involved with the writing of the review in accordance with Solutions for Public Health's quality assurance process.

Table 1: Key questions for current review of screening for FMAIT

Criterion*	Key Questions	# Studies Included
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.	1) What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?	3
	2) Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?	5
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	3) What it the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?	3
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	4) What are the most effective screening strategies to identify pregnancies at high risk of serious adverse outcomes due to FMAIT?	0

* These criterion are available online at: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme (January 2016)

Appraisal against UK NSC Criteria*

Each of the four key questions and their associated criteria are considered in turn below. Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in the light of the volume, quality and applicability of the body of evidence. Several factors were considered in determining the quality of the identified evidence, including study design, methodology and risk of bias of the evidence.

Criterion 1: The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.

Key Question 1: What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?

Population screening studies differ in the incidence of severe FMAIT detected compared to studies where FMAIT is typically clinically diagnosed. Screen detected FMAIT is determined by a newborn platelet count of $<50x10^9$/L whereas clinically diagnosed FMAIT requires some evidence of a bleed or incidental findings of low platelet count. The previous review reported that it is not yet clear if screening detects FMAIT in fetuses who would not have significant bleeding and would be healthy or whether clinicians are underdiagnosing clinically significant cases[5].

Description of the evidence

Three papers published between 2011 and 2016 were identified that focus on determining the proportion of FMAIT that results in serious adverse outcomes for the baby. A systematic review of studies of the incidence of NAIT and two observational studies are included. Details of the studies are tabulated in appendices 1–3.

Kamphuis et al (2014)[6] carried out a systematic review of the incidence and consequences of NAIT with the following research questions:

- What is the incidence of HPA-1A associated with thrombocytopenia?
- How severely are the neonates affected?

Six studies, all prospective cohort studies, met the inclusion criteria of:

- A screened low risk unselected population
- A record of severe thrombocytopenia with a platelet count$<50x10^9$/L identified through screening
- A record of the number of cases of severe thrombocytopenia due to HPA-1a alloimmunisation clearly stated.
- A record of all clinical signs of bleeding

The 6 studies included in Kampuis et al (2014) were published between 1993 and 2000. As such the individual studies were not separately identified in the search for the current UK NSC review (which covers studies published between January 2011 and March 2016), or in the search for the previous 2012 UKNSC review (which covered studies published between 2002 and 2011). Whilst the 2014 systematic review does not provide evidence from new studies it has been included as a useful overview of published studies on the incidence and consequences of NAIT.

In total 59,425 newborns were tested postnatally for NAIT (range from 933 to 24,010). Twenty four (0.04%) or 40 per 100,000 newborns were diagnosed with severe NAIT (platelet count <50 $x10^9$/L) of which 6 (25%) or 10 per 100,000 had ICH, likely to be of antenatal origin. It is important to note that the studies included in the systematic review did not exclude pregnancies managed for NAIT as a result of a previously affected sibling. It might be expected that this would lead to an underestimate of severe NAIT.

Tiller et al (2015)[7] carried out a prospective observational follow up study of all 210 HPA-1a alloimmunized women, identified during the Norwegian antenatal screening and intervention study, who gave birth to one or more children between 2004 and 2012. During the study 50 HPA-1a alloimmunised women were identified with at least one subsequent pregnancy after the index pregnancy (50 index pregnancies and 45 subsequent HPA-1a incompatible pregnancies were included) (Table 2). There was one case of ICH identified in the index pregnancies and no ICH recorded for subsequent pregnancies.

Table 2: Proportion of FMAIT, ICH and severe FMAIT in first and subsequent pregnancies -follow up observation from the Norwegian screening and intervention study[7].

	Index pregnancy (n=50)	Subsequent pregnancies (n=45)
FMAIT present	31/50 (62%)	32/45 (71%)
ICH	1/50 (2%)	0/45 (0%)
Severe thrombocytopenia	14/50 (28%)	10/45 (22%)

Of the 50 index pregnancies 19 (38%) neonates did not develop FMAIT and had normal neonatal platelet counts as did 13/45 (29%) of the babies from subsequent pregnancies. Where the index baby had FMAIT, two thirds of younger siblings had higher or unchanged platelet counts and one third had lower platelet counts (without antenatal treatment) compared to the index baby. Out of the index pregnancies 28% had severe thrombocytopenia and 2% had an ICH. The authors found a significant association between maternal anti-HPA-1a antibody level and neonatal platelet counts after adjusting for confounding factors of maternal age, parity, gestational age at time of delivery, sex of fetus) in a linear mixed model including index and subsequent pregnancies ($p<0.001$). However, sample sizes are small and the study underpowered to detect statistical differences.

Tiller et al (2013)[8] undertook a retrospective cohort study to characterize pregnancies where FMAIT developed and ICH was diagnosed. A total of 43 neonates (37 mothers), from a mix of first and subsequent pregnancies, were identified from the No Intra-Cranial Hemorrhage

(NOICH) registry; a sub-set of a total of 592 FMAIT cases in the database. Of the 43 neonates, ICH occurred before 28 weeks in 23 (54%) of cases. Male babies accounted for 28 (65%) of the cases. Antenatal treatment was not given in 39 (91%) cases. Of the 37 mothers, this was their first born child for 26 (70%) although of those only 10/26 (38%) had had no previous pregnancy with the remaining 16/26 (62%) having experienced a previous miscarriage.

Discussion

Quantity and quality of evidence

Three papers from between 2011 and 2016 were relevant to the first question in this review.

The systematic review[6] comprising 6 studies is the latest published pooled estimate of the incidence of FMAIT and a valuable addition to the understanding of the condition. However one confounding factor was that the studies included did not exclude pregnancies managed for NAIT as a result of a previously affected sibling so severe NAIT may well be under-reported. The studies within the systematic review[6] were scored for risk of bias, but none of the 6 studies achieved the highest possible score and the authors noted that their estimates of incidence were likely to be an underestimate.

The prospective cohort study[7] was a follow up to the Norwegian screening and intervention study and so can be considered representative of the possible outcomes of screening an unselected population. However, FMAIT is uncommon so it is difficult to identify a cohort with sample sizes large enough to result in adequately powered statistical differences between groups.

The retrospective cohort study[8] is likely to be subject to confounding and information bias and these types of studies are usually considered low grade evidence.

Applicability of the evidence to a potential NHS screening programme

It is difficult to determine the natural incidence of severe FMAIT as all pregnancies identified as at risk, either as a first (e g; the Norway Screening and Intervention Programme) or subsequent pregnancy, were managed to avoid adverse outcomes for the baby. The retrospective cohort study [8] did identify pregnancies where there had been no clinical management interventions but only 10/37 (27%) were primagravide. The evidence suggests that a significant proportion of women may miscarry during their first pregnancy before being identified as having a high risk of developing FMAIT adding to the difficulty in determining the natural incidence of severe FMAIT.

Systematic reviews by Kamphuis et al in 2010[3] (appraised in the UKNSC 2012 review) alongside their 2014[6] review (appraised here) focused on NAIT detected antenatally and postnatally respectively. These reviews both selected studies testing for NAIT in unselected populations to determine incidence of severe NAIT. Both systematic reviews reported a rate of severe NAIT of 0.04% or 40 per 100,000 newborns. This is somewhat higher than the rates clinically detected in the UK (0.012%)[4] or 12 per 100,000 newborns. Rates of ICH in the antenatal[3] review is 0.003-0.004% (3-4 per 100,000 births), in the postnatal review[6] it is 0.010% (10 per 100,000 births) and in the clinically detected cases in the UK 0.0015% (1.5 per 100,000)[4]. It remains uncertain as to what extent these differences between the numbers of newborns with severe NAIT predicted from unselected population studies and the numbers that are clinically diagnosed represents over-diagnosis through routine testing, or under-diagnosis by paediatricians in the absence of

screening. The consensus of the International Collaboration for Transfusion Medicine Guidelines (ICTMG) group who are developing clinical practice guidelines for the management of FNAIT is that the systematic reviews by Kamphus[3,6] are likely to best reflect the rate of FNAIT and severe FNAIT in the population[†].

Key Question 2: Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?

One of the key issues raised in the previous 2012 UK NSC review concerned the lack of an accurate predictor of severe FMAIT and as such there is substantial potential for over-diagnosis and unnecessary intervention. The 2012 review concluded that if the estimates derived from screening studies are applied to a UK birth cohort of 700,000 births one would expect to find approximately 1400 women with maternal anti-platelet antibodies each year, in 420 (30%) of which the fetus would have severe thrombocytopenia[5]. However, the number of babies with clinically-detected FMAIT appears to be lower, at about 85 per year[4]. These figures indicated that the babies of most women who would be identified as screen-positive, if a programme were started, are born healthy without receiving any medical intervention[5].

Description of the evidence

There were an additional 5 studies published since 2011 included in this review that focussed on determining an accurate predictor of severe FMAIT. Studies are tabulated in the appendices 4 to 9. The predictors included maternal HPA alloantibody level, blood group typing and HPA antigen typing.

Maternal anti-HPA alloantibody level

Bertrand et al (2011)[9] carried out a retrospective survey of cases (between 1980 and 2009) reporting laboratory and clinical information from 75 women and 155 pregnancies selected on the basis of:

- Group A: Index pregnancy unmanaged in 62 women (plus 4 subsequent unmanaged pregnancies)
- Group B: A subsequent managed pregnancy following an index pregnancy
- Group C: Complete obstetric and sibling history
- Group D: Data on fetal and neonatal status

The women and pregnancies were categorised by their antenatal management. The control population group A had no antenatal management and contained 62 index cases of NAIT and 4 subsequent unmanaged pregnancies. Group B included 11 pregnancies where corticosteroids were used as antenatal management, group C included 27 pregnancies where IVIG was used and group D comprised 54 pregnancies where a combination of IVIG plus steroids was used. Groups B, C and D were all subsequent pregnancies to the index pregnancies in group A.

[†] ICTMG (FNAIT) group December 19th 2016 Personal communication.

The study reported that severe thrombocytopenia in the control group (66 pregnancies) was not correlated with either maternal genetic background (ABO or HLA) or maternal alloantibody concentration at delivery.

With subsequent pregnancies (groups, B, C and D) the maternal alloantibody concentration during pregnancy prior to treatment and before 28 weeks gestation was correlated with severe FMAIT (p=0.0016). The authors determined an antibody concentration threshold of 28IU/mL resulted in a sensitivity of 81.2% a specificity of 83.3 % and positive and negative predictive values of 86.7% and 76.9% respectively to detect severe FMAIT.

Bertrand et al (2014)[10] provided additional data to their study published in 2011. The new data suggest that the predictive values of maternal HPA-1a antibody concentrations (analysed as area under the curve AUC) and newborn platelet count are correlated. The authors suggest that an AUC threshold of 23 IU/mL ($p<0.0001$) leads to a sensitivity of 76.19%, a specificity of 78.95%, and a negative predictive value of 85.71% and a positive predictive value of 66.67%.

Sanio et al (2013)[11] aimed to study the clinical usefulness of maternal antibody levels in predicting severe FMAIT. The authors reanalysed all the cases of confirmed HPA-1a referred to the Finnish Red Cross Blood Service Platelet Immunology Laboratory from 1986 to 2010. Index pregnancies were identified where HPA-1a alloimmunisation was apparent for the first time of which complete data was available for 72 women. Following the index pregnancy 28 women had 45 subsequent pregnancies with a total of 129 pregnancies included in the study. For the index pregnancies there was poor correlation between the postpartum maternal anti-HPA-1a antibody level, neonatal platelet count and severe FMAIT (p=0.074). For subsequent pregnancies complete data were available for 16 cases and there was a weak correlation between second trimester maternal anti HPA-1a antibody levels and neonatal platelet count (p=0.047). The positive predictive value of maternal HPA-1a antibody level for foetal platelet count ($<20 \times 10^9$L) in the index pregnancy was 80% and for subsequent pregnancies it was 90%. The corresponding negative predictive values were 17% and 31%. Cut off levels with sufficient sensitivity and specificity could not be determined from these cases. The authors concluded that in clinical practice previous obstetric history still remains the most useful predictive parameter of severe FMAIT.

Blood groups A, B &O

Ahlen et al (2012)[12] examined the maternal ABO blood groups and frequency of HPA-1a immunisation of women identified in a large prospective screening and intervention study carried out in Norway from 1995 to 2004. A total of 100,448 pregnant women were typed for the platelet antigen HPA-1a negative. Of the 2,111 (2.1%) women who were HPA-1a negative, 1990 were further tested and anti-HPA antibodies were detected in 154 women during pregnancy.

The ABO phenotype distribution among the 154 women was similar to the distribution in the general Norwegian population indicating that the maternal ABO type does not influence the risk of HPA-1a immunisation.

The maternal ABO phenotype did show some linkage with severity of NAIT. Women with a blood group A had higher frequencies of NAIT and severe NAIT compared to women with blood group O (p=0.005). Only 20% of pregnancies among immunised women with blood group O resulted in

severe NAIT compared to 47% with blood group A. When the ABO genotype was analysed the mean platelet counts are significantly different (p<0.019) between the types. With maternal blood group A the frequency of newborns with severe NAIT was 42% where the mother carried one A allele (A101, A102) compared to 69% where mothers carry two A alleles. With maternal blood group O frequencies of severe NAIT was 9% where the mother did not carry the O02 allele compared to 27% if the mother carried one or two O02 alleles although this was not significant (p=0.33).

HPA typing

Loewenthal et al (2013)[13] tested if certain allele variants are involved in the immune process leading to severe FMAIT. The case control study recruited 23 women who had previously given birth to newborns with FMAIT due to HPA-1a incompatibility with their partners. The control group comprised 24 women who delivered at term newborns with thrombocytopenia with a suspicion of NAIT which was subsequently ruled out. The frequency of women carrying HLA DRB3*01:01 in the study group was very high (91%) as was the allele HLA DRB4*01:01 (61%). The compound heterozygosity of the two alleles was 57% in the study group compared to none in the control group and the odds ratio for carriers of both alleles compared to carriers of neither allele is larger than 700 suggesting a strong correlation with FMAIT. This combination of alleles appears to increase the risk of FMAIT over and above the already elevated risk of carrying HLA-DRB3*0101 alone.

Characteristics of pregnancies with severe adverse outcome

Delbos et al (2016)[14] studied the gynaecologic and immunogenic variables of cases of anti HPA-1a FNAIT within three groups:

- Group I; Severe FNAIT no ICH (n=52)
- Group II; Severe FNAIT with ICH (n=27)
- Group III; Suspected severe FNAIT (no ICH) without detectable maternal anti HPA-1a antibodies (n=19)

Multigravida were more common in Group II (81%) than Group I (48%; p=0.007 OR 4.66; 95%CI 1.43-18.22) or Group III (42%; p=0.002; OR 5.82; 95% CI 1.09-35.9).

Median newborn fetal platelet count was significantly lower (p<0.001) in infants born to anti HPA alloimmunised women (Groups I and II) compared to non-alloimmunised women (Group III). Fetal platelet counts were lowest in Group II compared to Group I (p=0.004). HPA-1a alloantibody concentrations were higher in the ICH group (II) than Group I (p=0.002). The frequency of allele HLA-DRB3*01:01 was significantly lower in Group III (21.1%) and the control group (33%) than Groups I and II (84.4% p<0.001). There was no difference in frequency of this allele between Groups I and II. The allele HLA-DRB4*01:01P was more frequent in Group III (63.2%) than Groups I and II (40%). This allele was also more common in Group III than the control group (35%; p=0.04). HLA-DQB1*02:01P was more frequent in Groups I and II than Group III (p=0.003).

Discussion

Quantity and quality of evidence

The evidence of a correlation between ABO typing or HLA genotyping and severe FMAIT is limited to a small number of observational studies with relatively small numbers of women included due to the rarity of the condition.

The studies published since 2011 and included in this review focus on women undergoing second or subsequent pregnancies although the control group in Bertrand et al (2011) comprised women with a first born child (of which 51% where primigravidae). In this group there was no correlation between maternal alloantibody concentration, blood type or HLA genotype and severity of FMAIT. There was a correlation between maternal antibody level and severity of FMAIT in groups B, C and D that comprised women with subsequent pregnancies. This paper was critiqued by two other groups of researchers (Kjeldsen-Kragh et al 2011[15] and Sachs et al 2011[16]) who commented that:

- Cases had been highly selected and were unlikely to be a representative sample of FMAIT so results should not be generalised.
- The authors should have reported the statistical uncertainty considering their sensitivity and specificity calculations were based on 28 and 37 cases.
- It was not valid to conclude that maternal alloantibody concentration at delivery was not correlated with maternal genetic background (HLA-DRB3) as the frequency of this allele has been shown to be as high as 98% in mothers and children with FMAIT.

Applicability of the evidence to a potential NHS screening programme

Overall the studies published since 2011 and included in this review are not testing for predictors in the cohort of women that would be the focus of an NHS screening programme (those undergoing a first pregnancy). The one study comprising a group of primigravidae found no correlation of severity of FMAIT with maternal alloantibody concentration, blood type or HLA genotype. This may be because alloimmunisation has been shown to occur after delivery in many first pregnancies. The Norwegian Screening and Intervention Programme[17] reported that with first born children 75% of mothers where alloimmunised in the six weeks following delivery.

Summary Criterion 1: Not met

There is not yet reliable evidence that the level of maternal anti-HPA-1a alloantibodies can consistently predict which cases of FMAIT will be more severe, and therefore, more likely to benefit from medical intervention in a first pregnancy. Differences between incidence estimates from screened populations and rates of clinically diagnosed cases of FMAIT and a lack of evidence of the reliability of a minimally invasive predictor of high risk pregnancies has not changed substantially since the last review.

There is as yet no evidence that AOB typing would be potential predictor severity of FMAIT. There is evidence that HLA genotyping has some future clinical potential in predicting severe FMAIT .

Criterion 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

Key Question 3: What it the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?

The 2012 UK NSC review identified a Cochrane review (Rayment et al 2011)[18] focused on trials comprising treatment of pregnant women at high risk of FMAIT (second or subsequent pregnancies) but found there were no RCTs which demonstrate that IVIG is an effective treatment for FMAIT in screen-detected pregnancies. IVIG has been shown to suppress maternal antibody production and reduce placental transfer of pathological antibodies. Corticosteroids in the form of prednisone are used to support the action of IVIG. The Cochrane review states;

"there is conflicting evidence on its [IVIGs] efficacy in preventing ICH, with some reports documenting good results and others reporting failure of IVIG to prevent haemorrhage, particularly in severely affected fetuses".

However there is the suggestion that some treatment is better than none although an optimal treatment regime has not been determined.

"IVIG in combination with prednisone is more effective in raising the fetal platelet count than IVIG alone in high-risk pregnancies, where the pre-treatment fetal platelet count < 20 x10*9/l or the affected sibling sustained a peripartum ICH. The optimal timing of administration and the dose of prednisone and IVIG is unclear, but studies demonstrating efficacy initiated treatment at 20-26 weeks….From these trials it appears that stratification of patients according to the sibling history, and tailoring of treatment accordingly is safe, allowing a less intensive approach to treatment and monitoring where the sibling platelet count was > 20 x 10*9/l and there was no ICH. Where the sibling platelet counts were lower, or there was a history of ICH more intensive treatment is still associated with significant failure but the combination of IVIG and prednisone is superior to IVIG alone."

Description of the evidence

The latest literature search identified 3 studies that were subsequently included in this review that focussed on the efficacy of different antenatal management strategies to prevent serious adverse outcomes of FMAIT in the newborn. The studies are tabulated in appendices 9 to 11.

Antenatal IVIG

Paridaans et al (2015)[19] undertook a multi-centre randomised controlled trial across Sweden, the Netherlands and Australia. Pregnant women with platelet antigen antibodies and an affected previous child without ICH were included. Participants (n=23) were randomised to IVIG at 0.5 or 1 g/kg per week. No side effects were seen in either of the treatment groups. Perinatal survival was 100% and no ICH was observed in either treatment group. There was no statistical difference between platelet counts at birth (p=0.644) observed in each group. Overall the trial lacked sufficient power to prove equivalence to the standard dose of 1 g/kg with a lower IVIG dose of 0.5 g/kg although the results suggest that the lower dose is safe and effective for pregnancies complicated by FNAIT in women with an affected sibling without ICH.

Van der Lugt et al (2015)[20] carried out a retrospective review of FNAIT cases treated with antenatal IVIG from 2006 to 2012 at a centre in the Netherlands. All cases were known due to a

previously affected pregnancy. Twenty two neonates with FNAIT treated with IVIG were included. Severe FNAIT was detected in 12 (55%) of neonates with one experiencing an ICH. Most neonates received a platelet transfusion after birth (8/12; 67%). None of the neonates required postnatal treatment with IVIG. The authors concluded that the study suggested that IVIG was effective and safe. The retrospective design, low sample size and variation in cut offs for antenatal and neonatal management limit the applicability of the results.

IVIG treated pregnancies and Caesarean section

Bertrand et al (2014)[10] have suggested that the predictive values of maternal HPA-1a antibody concentrations (analysed as area under the curve AUC) and newborn platelet count are correlated and can help clinicians predict a fetal response to maternal therapy. Therapy failure was more likely to happen in women with >2 pregnancies than those with ≤2 pregnancies indicating that multigravida is a risk factor for therapy failure. The authors suggest that an AUC below 23 UI/mL could be considered low risk for FMAIT and vaginal delivery would be appropriate whereas an AUC of >23 UI/mL indicates a higher risk of severe thrombocytopenia and planned CS.

Discussion

Quality and quantity of evidence

Due to the rarity of the condition studies tend to be small and observational. The one RCT reported here stopped early due to poor recruitment and so was underpowered (Paridaans et al 2015)[19].

Applicability of evidence to an NHS Screening programme

These studies add to the evidence about the management of subsequent pregnancies identified following an index pregnancy but it is unclear if the results would be applicable to a first high risk pregnancy identified through a screening programme where it is possible that a significant proportion of women will not be alloimmunised until after delivery[17].

Summary Criterion 9: Not met

The additional studies identified since 2011 do not provide sufficient robust additional evidence for an optimal management strategy for anti-HPA-1a women identified as part of a screening programme to prevent serious adverse outcomes to their child in their first pregnancy.

Criterion 11: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

Key Question 4: What are the most effective screening strategies to identify pregnancies at high risk of serious adverse outcomes due to FMAIT?

The 2012 UK NSC review reported that there had been no RCTs of a screening programme focused on the effectiveness of reducing morbidity and mortality from FMAIT.

Description of the evidence

There were no randomised controlled trials or other studies identified in the literature search for this update assessing a full screening strategy for an FMAIT screening programme. Different researchers have focused on different elements of the screening pathway such as identifying a reliable predictor of severe FMAIT with suitable thresholds and an agreed management strategy in addition to the longer term development of prophylaxis. Currently only second and subsequent pregnancies are identified as at high risk as a consequence of an adverse outcome and diagnosis of FMAIT in a first pregnancy.

Discussion

Quantity and quality of the evidence

There is no additional high grade evidence identified since the last UK NSC review to indicate the most effective screening strategy to identify first pregnancies at high risk of adverse outcomes from the development of FMAIT.

Summary Criterion 11: Not met

There is no additional high grade evidence identified since the last review to indicate the most effective screening strategy to identify first pregnancies at high risk of adverse outcomes from the development of FMAIT and in the absence of evidence this criterion is not met.

Conclusions and implications for policy

This report assesses screening for FMAIT against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if evidence published since 2011 suggests that the current recommendation not to screen for FMAIT in the UK should be retained or if it requires further consideration.

The volume, quality, applicability and consistency of evidence published since January 2011 does not indicate that screening for FMAIT should be recommended in the UK. None of the questions posed in this review could be answered reliably with high grade evidence over and above evidence available to the previous review;

- There remains some uncertainty about the proportion of FMAIT that results in serious adverse outcomes for the fetus/baby.
- It remains unclear why there are differences between the numbers of babies with severe FMAIT determined through screening in unselected populations compared to clinically detected cases identified in the UK. This could be due to the over-diagnosis through screening or under diagnosis by clinicians in the absence of screening or a combination of the two factors.
- There is no evidence of a reliable predictor that can routinely identify first pregnancies of women at high risk of the baby developing severe FMAIT leading to disability or death of the baby before or after birth.
- The additional studies identified since 2011 do not provide high grade evidence of an effective treatment strategy to prevent serious adverse outcomes from FMAIT in the newborn.

- From the literature search for this review no population based screening programmes or high quality studies for an FMAIT screening programme were identified. There is therefore no evidence for the most effective screening strategy to identify first pregnancies at high risk of adverse outcomes from the development of FMAIT.

On the basis of the evidence identified through this review it is recommended that the current recommendation not to introduce a population screening programme for FMAIT should be retained.

Future developments

Researchers from the Norwegian group that conducted the largest studies of population screening for FMAIT are exploring the possibility of prophylaxis for HPA-1a immunisation and have set up a large scale project (PROFNAIT) (Kjeldsen-Kragh et al 2012)[21]. It is possible that FMAIT can be prevented in a similar way to the model for preventing haemolytic disease of the fetus and newborn (HDFN) where maternal alloimmunisation against fetal red blood cell antigens inherited from the father results in fetal anaemia

Anti-HPA-1a for clinical usage has now been approved by the European Medicines Agency as an orphan drug for FNAIT. Prophylix Pharma AS is collaborating with a large pharmaceutical company for production of this drug which will be tested in a randomized controlled clinical trial after completion of phase I/II studies.

Brojer et al (2015)[1] outlined the PREVFNAIT project in Poland that is aiming to test around 30,000 pregnant women for HPA-1a. Those women at risk of alloimmunisation will be tested for anti-HPA-1a antibodies at 16,20,24,32 and 40 weeks of gestation and at 6 weeks postnatally. All alloimmunised women resulting from a previous pregnancy will be treated with 1 g/Kg IVIG weekly from 24 to 28 weeks of pregnancy. Appropriate therapy for those women alloimmunised in their first pregnancies will be made based on individual foetal platelet count. The second project aim is to find biomarkers for predicting the risk of antibody development and FMAIT.

Evidence from the PREVNAIT and PROFNAIT projects will further elucidate possible biomarkers of severe FMAIT and indicate whether the use of anti-HPA-1a prophylaxis would reduce the risk of severe FMAIT.

Search strategy

A literature search on fetomaternal alloimmune thrombocytopenia (FMAIT) screening in pregnancy was performed by Elaine Garrett, UK NSC Librarian.

SOURCES SEARCHED: Medline, Embase, Cochrane Library and Maternity and Infant Care

DATES OF SEARCH: Medline 2011-February Week 3 2016 and Medline in Process 2011-Feb 26, 2016; Embase 2011-Feb 26, 2016, Cochrane Library 2011-2016; Maternity and Infant Care 2011-January 2016.

SEARCH STRATEGY
Medline (OVID interface). Similar searches were carried out in other databases.

1 Thrombocytopenia, Neonatal Alloimmune/(238)
2 Alloimmune thrombocytopenia.tw. (725)
3 fnait.tw. (63)
4 fmait.tw. (35)
5 naitp.tw. (33)
6 nait.tw. (151)
7 or/1-6 (828)
8 (2011* or 2012* or 2013* or 2014* or 2015* or 2016*).dc. (3743093)
9 7 and 8 (166)

Results

Database	No. citations retrieved	Exclusive
Medline	166	28
Medline in Process	28	9
Embase	470	459
Cochrane Library	15	9
Maternity and Infant Care	21	2
Total	**700**	**507**

After automatic and manual de-duplication, 507 unique references were sifted by title and abstract, and where necessary and available the full text, for potential relevance to the review. Ninety-eight papers remained and were passed to the SPH reviewer for further consideration.

These 98 references were classified as follows:

Category	No. of citations
Systematic reviews	2
Non-systematic reviews	22
The condition	9

Incidence/prevalence of condition*:* UK (1) Europe (1) Australia (2)	
Predictors of severe outcomes	7
HPA allele frequencies Africa (3) Asia (5) Europe (1) Pacific Islands (1) South America (2) Rare types (1)	14
The test Reviews (2) HPA-typing (7) Antibody detection (10)	19
Treatment Reviews (9) Antenatal (3) Neonatal (8) Outcomes (3)	24
Screening programme	1
Total	**98**

Appendices

Question 1

Appendix number	1
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	1) What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?
Publication details	Kamphuis M.M., Paridaans N.P., Porcelijn L., Lopriore E., Oepkes D. **Incidence and consequences of neonatal alloimmune thrombocytopenia: A systematic review.** *Pediatrics. 133 (4) (pp 715-721), 2014.*
Study details	Systematic review
Study objectives	To estimate the population incidence and consequences of NAIT.
Inclusions	Studies were included if they reporting on all of the following criteria;

	• Low risk newborns with severe FMAIT (platelets <50x10^9/L) identified via screening • Number of cases of severe FMAIT were clearly stated • Clinical signs of bleeding
Exclusions	• All non-prospective studies • All studies where method other than cord blood platelet count was used • Screening was in low risk unselected population
Population	Pregnant women and neonates
Intervention/ test	N/A
Comparator	N/A
Results	• Six studies included in the review. • A total of 59,425 neonates were screened (range 933–24,101) when studies were combined. • At post-natal screening 24 (0.04%) had severe FNAIT. • Of those 24 with severe FNAIT 6 (25%) had an ICH
Comments	None of the studies excluded pregnant women already known to have the complication of FMAIT and who were already undergoing treatment.

Appendix number	2
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	1) What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?
Publication details	Tiller H., Husebekk A., Skogen B., et al. **True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: a prospective observational follow-up study.** *BJOG: An International Journal of Obstetrics and Gynaecology. 9 March 2015. Online version ahead of print.*
Study details	Prospective observational follow up study
Study objectives	To assess neonatal platelet counts by comparing alloimmunised pregnancies from a Norwegian screening and intervention study with subsequent pregnancies from the same women.
Inclusions	All HPA-1a immunised women from the Norwegian screening study who gave birth to

	more than one child from 2004 to 2012.
Exclusions	Non-immunised (no detectable anti-HPA-1a antibodies) HPA-1bb women were excluded. If neonatal platelet type was missing the pregnancy was also excluded from the study.
Population	HPA-1a immunised women from a large Norwegian screening study that gave birth to one or more children after the screening study ended (2004–2012).
Intervention/ test	N/A
Comparator	N/A
Results	45 women identified as having HPA-1a incompatible pregnancies subsequent to their index pregnancy • 13/45 (29%) of neonates had normal platelet counts(i.e. no FMAIT) • The neonatal platelet count in children from subsequent pregnancies was not significantly different compared to neonatal platelet count in the older sibling • Paired data (29 index and first subsequent pregnancy pairs) showed 18% of subsequent neonates had an increase in platelet count, 52% had similar counts and 30% had decreased platelet counts. • Using index neonates with FMAIT as a denominator two thirds of younger siblings had higher or unchanged counts and one third had lower platelet counts. • Where the index neonate had severe thrombocytopenia 14 (71%) of subsequent neonates also had severe FMAIT, and 4 cases improved to moderate (3) or no (1) FMAIT • Using index neonates (15) with no FMAIT (but known incompatibility) then subsequent neonates showed 67% (10/15) with normal platelet count, 2/15 had moderate and 3/15 had severe thrombocytopenia. • All index pregnancies classified as low risk due to low anti-HPA-1a antibody levels resulted in low risk subsequent pregnancies. There was a similar pattern with high risk pregnancies. • The data do not support the opinion that generally FNAIT gets worse in younger siblings. • Need to be cautious in interpreting increased neonatal platelet count in a subsequent FNAIT pregnancy as an antenatal treatment effect.
Comments	

Appendix number	3
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.

Relevant Key question	1) What proportion of FMAIT results in serious adverse outcomes for the fetus/baby?
Publication details	Tiller H., Kamphuis M.M., Flodmark O., Papadogiannakis N., David A.L., Sainio S., Koskinen S., Javela K., Wikman A.T., Kekomaki R., Kanhai H.H.H., Oepkes D., Husebekk A., Westgren M. **Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: An observational cohort study of 43 cases from an international multicentre registry.** *BMJ Open. 3 (3) (no pagination), 2013. Article Number: 002490. Date of Publication: 2013.*
Study details	Case series of all recorded ICH caused by FMAIT from the NOICH registry 2001–2010
Study objectives	To characterise pregnancies where FNAIT with ICH has occurred with a focus on bleeding onset.
Inclusions	1) Incompatibility between maternal and paternal/fetal HPA type confirmed. 2) Incompatibility confirmed and neonate suffered ICH 3) Anti HPA antibodies detected in the mother
Exclusions	1) All cases on NOICH registry where ICH not confirmed.
Population	All neonates/mothers registered on NOICH registry
Intervention/ test	N/A
Comparator	N/A
Results	43 fetuses and neonates (37 mothers) out of a total of 592 FNAIT cases on the NOICH registry had confirmed ICH. • HPA-1a allo-immunisation accounted for 39/43 (91%) cases • HPA 5b allo-immunisation accounted for 3/43 (7%) cases • gpIa/IIa incompatibility accounted for 1/43 (2.3%) cases • This was the first born child for 26/37 mothers but of these 16/26(62%) had had a previous miscarriage.
Comments	

Question 2

Appendix number	4
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	**2)** Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?
Publication	Ahlen M.T., Husebekk A., Killie M.K., Kjeldsen-Kragh J., Olsson M.L., Skogen B. **The development of severe neonatal alloimmune thrombocytopenia due to anti-HPA-1a**

details	**antibodies is correlated to maternal ABO genotypes.** *Clinical and Developmental Immunology. 2012 (no pagination), 2012. Article Number: 156867. Date of Publication: 2012.*
Study details	Prospective observational study
Study objectives	Assess possible correlation between maternal ABO blood group phenotype or underlying genotype and severe thrombocytopenia in the newborn.
Inclusions	All pregnant women approached in 3 three districts in Norway between 1995 and 2004 who agreed to be typed for HPA-1.
Exclusions	Pregnant women not agreeing to HPA-1 allotyping between 1995 and 2004
Population	Pregnant women in Norway recruited for HPA-1 allotyping from 1995 to 2004.
Intervention/ test	N/A
Comparator	N/A
Results	100,448 pregnant women were typed HPA-1 of which 2,111(2.1%) were HPA-1 negative. Of those, 146 women underwent 158 HPA-1a incompatible pregnancies. • Distribution of ABO phenotype among immunised mothers was similar to the general Norwegian population • Of the 158 pregnancies there were 83 (52%) cases of NAIT and 53 (33.5%)cases of severe NAIT • 46.6% maternal blood type A had babies with severe FMAIT • 20% maternal blood type O had babies with severe FMAIT • Frequency of moderate NAIT was not lower among blood group O mothers compared to those blood group A
Comments	Authors postulated possible reasons for differences but they could not pinpoint a mechanism for this difference.

Appendix number	5
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	2) Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?
Publication details	Bertrand G., Drame M., Martageix C., Kaplan C. **Prediction of the fetal status in non-invasive management of alloimmune thrombocytopenia.** *Blood. 117 (11) (pp 3209-3213), 2011. Date of Publication: 17 Mar 2011.* Comments in: Blood. 118 (9) (pp 2637-2640), 2011. http://www.bloodjournal.org/content/117/11/3209

Study details	Case series
Study objectives	Assess possible correlation between severe thrombocytopenia in newborns and: • Maternal and paternal A or O blood group • Maternal allele HLA-DRB3 • Maternal alloantibody concentration
Inclusions	Selected FNAIT cases referred to one laboratory between 1981 and 2009
Exclusions	Non-FNAIT cases
Population	Pregnant women
Intervention/ test	N/A
Comparator	N/A
Results	• High HPA-1 maternal alloantibody count measured before 28 weeks gestation is correlated with low platelet count and severe thrombocytopenia (sensitivity 81.2%, specificity 86.7%) • Maternal and paternal blood group and maternal allele HLA-DRB3 is not correlated with severity of thrombocytopenia
Comments	1. The findings by Bertrand et al are disputed by Kjeldsen-Kragh et al[15] in an editorial letter outlining methodological weaknesses with the study methodology. These include: • Lack of statistical clarity • Confounding issues due to different management and technological methods used over three decades of laboratory testing • Lack of justification and definition of cut off values of tests. 2. Bertrand et al subsequently published additional detail and data about their methodology in 2014 that addressed these concerns (see appendix 9)

Appendix number	6
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	2) Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?
Publication details	Delbos F., Bertrand G., Croisille L., Ansart-Pirenne H., Bierling P., Kaplan C. **Fetal and neonatal alloimmune thrombocytopenia: Predictive factors of intracranial haemorrhage.** *Transfusion. 56 (1) (pp 59-66), 2016. Date of Publication: 01 Jan 2016.*
Study details	Case series between 1987 and 2012

Study objectives	Identification of risk factors of ICH and of response to maternal therapy following gynaelogic and immonogenetic analysis of variables in patients.
Inclusions	Cases selected according to PLT genotype of the mother (HPA-1bb) and the infant (HPA- 1ab)
Exclusions	All cases not meeting inclusion criteria.
Population	Pregnant women
Intervention/ test	N/A
Comparator	N/A
Results	3 groups Group I – Antibodies detected no ICH present, *n*=52 Group II – Newborns with ICH, HLA-A and HLA-B antibodies present, *n*=27 Group III – Newborns with severe thrombocytopenia at birth, no ICH, no HLA-1a antibodies detected, *n*=19 • Multigravida more common Grp II than Grp I (p=0.007) and Grp III (p=0.02) • Pregnancies reaching delivery: Grp 1 = 100%, Grp II =52%, Grp III =89% • Median concentration of maternal alloantibodies higher in Grp II compared to Grp 1 (p=0.002) • Frequency of HLA DRB3*01:01 significantly lower in Grp III (21.05%) and in the control Grp (33%) than in Grp I and Grp II (84.44%; p<0.001) • HLA DQB1*02:01P more frequent in Grp I and Grp II than Grp III (p=0.03) • HLADRB4*01:01P was higher in those who did not develop antibodies against HPA-1A in Grp III (63.16%) compared to Grp I and Grp II (40%; p=0.11) • ICH occurred in the 3rd trimester (16/17) and 2nd trimester (1/17) • In Grp I 25 women had subsequent IVIG managed pregnancies (32 newborns) and no ICH recorded although 40% were severely thrombocytopenic at birth
Comments	

Appendix number	7
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious treatable disease.
Relevant Key question	2) Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?
Publication details	Loewenthal R., Rosenberg N., Kalt R., Dardik R., Landau M., Yahalom V., Avishai O., Frenkel O., Gazit E., Steinberg D.M, Lipitz S., Salomon O. **Compound heterozygosity of HLA-DRB3 * 01:01 and HLA-DRB4 * 01:01 as a potential predictor of fetal neonatal**

	alloimmune thrombocytopenia. *Transfusion. 53 (2) (pp 344-352), 2013. Date of Publication: February 2013.*
Study details	Case control study
Study objectives	To study whether certain allele variants are involved in the immune process leading to FNAIT and to analyse whether the response to IVIG treatment correlates to a particular genotype and to determine if the combination of anti GPA-1a and anti HLA class 1 antibodies specific against the fathers antigens leads to more severe thrombocytopenia
Inclusions	Pregnant women who had previously given birth to newborns with FNAIT due to HPA-1a incompatibility with their partners and were found to have antibodies directed to their partners HPA-1a antigen. A control group consisted of 24 women who delivered at term newborns with thrombocytopenia and/or suspicion of FNAIT but FNAIT was subsequently ruled out.
Exclusions	Pregnant women not fulfilling the inclusion criteria
Population	Pregnant women delivering newborns with thrombocytopenia
Intervention/ test	N/A
Comparator	N/A
Results	• Ninety one per cent of women in the study group carried HLA DRB3*01:01compared to 21% in the control group. • HLA DRB4*01:01 allele was more frequent in the FNAIT cases than controls both with and without the presence of the other allele HLA DRB3*01:01. • 13/23 (57%) women had both HLA allele's in the study group compared to none in the control group. • HLA DQB1*02 genotype was carried by 12/23 women in the study group and 8/24 in the control group (p=0.013) • Crystal structure of HLA DRB3*01:01and HLA DRB4*01:01suggests that separately they could be involved with binding HPA-1a epitope leading to an immune response. • It is suggested that the presence of both alleles may contribute more to the development of FNAIT compared to the presence of only one allele.
Comments	

Appendix number	8
Relevant criteria	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including the development from latent to declared disease and/or there should be robust evidence about the association between the

	risk or disease marker and serious treatable disease.
Relevant Key question	2) Has a reliable predictor of severe neonatal outcome been identified in studies of FMAIT?
Publication details	Sainio S., Javela K., Tuimala J., Koskinen S. **Usefulness of maternal anti-HPA-1a antibody quantitation in predicting severity of foetal-maternal alloimmune thrombocytopenia.** *Transfusion Medicine. 23 (2) (pp 114-120), 2013. Date of Publication: April 2013.*
Study details	Antibody levels collected from 84 women and 129 pregnancies were obtained at delivery (from1986 to 2010). Antibody levels were compared with the severity of neonatal disease in the index and in the subsequent pregnancies.
Study objectives	Understand the correlation between maternal antibody levels and neonatal thrombocytopenia
Inclusions	Anti HPA-1a antibodies levels from women and neonates with FMAIT (from 1986 to 2010) on the National MAIT register held by the Finish Red Cross Blood Service were collected.
Exclusions	Anyone not meeting the above criteria on the FMAIT register held by Finish Red Cross Blood Service
Population	FMAIT register
Intervention/ test	N/A
Comparator	N/A
Results	• Overall there was no strong correlation between the maternal HPA-1a level and neonatal platelet count (p=0.074). • Platelet counts and antibody levels in cases of cutaneous or intracranial haemorrhage were significantly different from cases where there was no ICH. • The positive predictive value of maternal antibody level for a fetal platelet count was 90% but the negative predictive value was only 31%. • In the absence of a reliable laboratory assay that can predict FMAIT or even recurrent ICH previous obstetric history remains the most useful predictive tool in clinical practice. • Barely detectable levels were also observed in severely affected pregnancies. Cut off values with sufficient sensitivity and specificity could not be found.
Comments	

Question 3

Appendix number	9
Relevant criteria	9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider

	benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.
Relevant Key question	3) What it the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?
Publication details	Bertrand G., Petermann R., Kaplan C. **Prediction of IVIG treatment efficiency in fetal/neonatal alloimmune thrombocytopenia.** *Blood. 124 (4) (pp 654-655), 2014. Date of Publication: 24 Jul 2014.* http://www.bloodjournal.org/content/124/4/654
Study details	Letter – update on case series reported in Bertrand G., Drame M., Martageix C., Kaplan C. **Prediction of the fetal status in non-invasive management of alloimmune thrombocytopenia.** *Blood. 117 (11) (pp 3209-3213), 2011. Date of Publication: 17 Mar 2011.* Comments in: Blood. 118 (9) (pp 2637-2640), 2011. http://www.bloodjournal.org/content/117/11/3209
Study objectives	Assess possible correlation between fetal therapy response (newborn platelet count) and maternal alloantibody concentration in second gestation women.
Inclusions	Selected FNAIT cases referred to one laboratory between 1981 and 2009
Exclusions	Non-FNAIT cases
Population	Pregnant women
Intervention/ test	N/A
Comparator	N/A
Results	• Antibody concentrations analysed by calculation of area under the curve (AUC) which correlated with newborn platelet count. • An AUC threshold of 23IU/mL was established — below this value there was considered to be a low risk of severe thrombocytopenia post-partum and a high risk if AUC is above this level — ($p<0.0001$; sensitivity 76.2%; specificity 78.9%, negative predictive value 85.7% and positive predictive value of 66.7%)
Comments	This is an update of the data with additional detail of the study methodology outlined in Bertrand et al 2011 (appendix 5).

Appendix number	10
Relevant criteria	9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.
Relevant Key	3) What it the optimal management strategy for anti-HPA-1a women to prevent

question	serious adverse outcomes in the newborn?
Publication details	Paridaans N.P., Kamphuis M.M., Wikman A.T., Tiblad E., Van Den Akker E.S., Lopriore E., Challis D., Westgren M., Oepkes D. **Low-Dose versus Standard-Dose Intravenous Immunoglobulin to Prevent Fetal Intracranial Haemorrhage in Fetal and Neonatal Alloimmune Thrombocytopenia: A Randomized Trial.** *Fetal Diagnosis and Therapy. 38 (pp 147-153), 2015. Date of Publication: 25 Aug 2015*
Study details	Randomised controlled multi-centre trial conducted in Sweden, Netherlands and Australia
Study objectives	To compare low does vs standard dose IVIG to prevent ICH in FMAIT.
Inclusions	Pregnant women with singleton pregnancy with HPA alloantibodies at gestational age 12–28 weeks who had given birth to an affected sibling but without ICH were included
Exclusions	Women with autoimmune thrombocytopenia, multiple pregnancies, fetuses and neonates with major congenital anomalies and chromosomal abnormalities, and those whose affected sibling had ICH were excluded.
Population	Pregnant women
Intervention/ test	IVIG administered weekly from 28 weeks gestation until delivery with standard dose (1 gm/kg)
Comparator	IVIG administered weekly from 28 weeks gestation until delivery with low dose (0.5 gm/kg
Results	23 women were randomised into two groups. Outcomes: • Perinatal survival was 100% • No ICH observed in ether group. • No difference between platelet count at birth (<30x109/l p=0.493, <50x109/l p=0.563 and <150x109/l p=0.563) • No serious side effects were reported in either treatment group.
Comments	The trial was underpowered due to lack of recruitment of women and a larger RCT is required to prove equivalence of a lower dose of IVIG compared to standard dose.

Appendix number	11
Relevant criteria	9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.
Relevant Key	3) What it the optimal management strategy for anti-HPA-1a women to prevent serious adverse outcomes in the newborn?

question	
Publication details	Van Der Lugt N.M.., Kamphuis M.M., Paridaans N.P.M., Figee A., Oepkes D., Walther F.J., Lopriore E. **Neonatal outcome in alloimmune thrombocytopenia after maternal treatment with intravenous immunoglobulin.** *Blood Transfusion. 13 (1) (pp 66-71), 2015. Date of Publication: 2015.*
Study details	Retrospective case series
Study objectives	To collate outcomes of pregnancies where IVIG had been given to women at standard and high risk of NAIT due to a previous affected pregnancy.
Inclusions	All infants with NAIT treated with antenatal maternal IVIG from 2006 to 2012 identified due to a previous affected pregnancy.
Exclusions	Infants without NAIT
Population	Infants with NAIT
Intervention/ test	IVIG
Comparator	None
Results	12 (55%) of neonates were born with severe NAIT, including one with ICH. Most neonates received a platelet transfusion after birth (8/12; 67%). None of the neonates required postnatal treatment with IVIG.
Comments	

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