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Fetal and neonatal alloimmune thrombocytopenia : towards implementation of screening in pregnancy

Kamphuis, M.M.

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Author: Kamphuis, Marije

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CHAPTER 3

INCIDENCE AND CONSEQUENCES OF NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: A SYSTEMATIC REVIEW

**MM Kamphuis
NP Paridaans
L Porcelijn
E Lopriore
D Oepkes**

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ABSTRACT

Background

Neonatal alloimmune thrombocytopenia (NAIT) is a potentially devastating disease, which may lead to intracranial hemorrhage in the fetus or neonate, often with death or major neurological damage as consequences. There are no routine screening programs for NAIT. Preventive measures are only taken in a subsequent pregnancy. To estimate the population incidence of NAIT and its consequences we conducted a review of the literature. Our result may aid in the design of a screening program.

Methods

An electronic literature search using MEDLINE, EMBASE and Cochrane database, and references of retrieved articles. Eligible for inclusion were all prospective studies aimed at diagnosing NAIT in a general, nonselected newborn population, with sufficient information on platelet count at birth, bleeding complications and treatment. Titles and abstracts were reviewed followed by review of full text publications. Studies were independently assessed by 2 reviewers for methodological quality. Disagreements were resolved by consensus including a third reviewer.

Results

From the initial 768 studies identified, 21 remained for full text analysis, 6 of which met the inclusion criteria. In total, 59 425 newborns were screened, with severe thrombocytopenia in 89 cases (0.15%). NAIT was diagnosed in 24 of these 89 newborns (27%). In 6 (25%) of these cases an intracranial hemorrhage was found, all likely of antenatal origin.

Conclusions

NAIT is one of the most important causes of neonatal thrombocytopenia. Intracranial hemorrhage due to NAIT occurs in 10 per 100 000 neonates, commonly before birth. Screening for NAIT might be effective, but should be done antenatally.

INTRODUCTION

Low platelet count is a risk factor for bleeding complications. In newborns, the most feared bleeding is intracranial hemorrhage (ICH), which may lead to death or severe lifelong neurological handicap. Severe thrombocytopenia (platelet count $< 50 \times 10^9/L$) is estimated to be present in 1:700 unselected newborns.^{1,2} A major cause of isolated severe thrombocytopenia in term neonates is neonatal alloimmune thrombocytopenia (NAIT)³, with an incidence of 1 in 1000 live births.⁴ In NAIT, platelet destruction is caused by maternal immunoglobulin G allo-antibodies formed during pregnancy because of incompatibility of maternal and fetal (thus paternal) antigens on the platelet's surface. In Caucasians, 85% of immunizations are caused by alloantibodies against Human Platelet Antigens (HPA) 1a, commonly acquired during pregnancy.⁵

NAIT can be diagnosed either after clinical bleeding symptoms in the neonate, or after detection of a fetal intracranial bleeding on ultrasound examination. Thrombocytopenia may also be detected unexpectedly when blood is tested for other purposes. In the absence of skin bleeding, the diagnosis may be delayed or not be made at all, leaving the child at risk for ICH until spontaneous increase in platelet count occurs.

One option for early detection and therefore reduced time-to-treatment of NAIT would be to screen all neonates for this disease. Given the high disease burden for the affected child and the family, and high costs for health care and society in case of ICH with brain damage, prevention of even a few cases may make screening cost-effective. Alternatively, as has been advocated recently by several investigators, pregnant women could be screened for HPA-type and tested for allo-antibodies.^{5,6,7}

The debate on screening for NAIT is complicated by the lack of a good population data on incidence of severe thrombocytopenia and bleeding complications.

Before considering a screening program, a reliable estimate of incidence and severity of NAIT in the general population is required. Several screening studies have been performed by using HPA-typing of pregnant women. We recently reviewed these studies, and found that in most, antenatal or intrapartum interventions were offered. Therefore, the true natural history, with unbiased outcomes in neonates, could not be derived from these studies.⁵ We therefore performed a systematic review of studies on screening low risk, untreated newborns for thrombocytopenia. The aim of this study was to systematically assess the reported prevalence of severe thrombocytopenia in newborns secondary to NAIT with sub-analysis of ICH due to NAIT. The outcomes of this analysis can provide an essential element in preparation for a screening project, aimed at timely identification of fetuses or neonates at risk for NAIT to prevent the burden of this hazardous disease in the future.

METHODS

Data sources and study selection

We searched the following databases for studies on severe neonatal thrombocytopenia due to NAIT and intracranial hemorrhage: PubMed, Embase, and Cochrane. We used the following keywords: "Thrombocytopenia"[Majr:NoExp] OR "Thrombocytopenia, Neonatal Alloimmune"[Majr] OR "alloimmune thrombocytopenia"[ti] OR "NAIT"[ti] OR "NAITP"[ti] OR "FNAIT"[ti] OR "FNAITP"[ti] OR "neonatal thrombocytopenia"[ti] OR "HPA 1a"[ti] OR "HPA-1a"[ti] AND ("Mass Screening"[Mesh] OR "screening"[all fields] OR "SCREEN"[all fields] OR "Incidence"[Mesh] OR "incidence"[all fields]). We accepted original articles, short communications and letters to the editor. In addition a search was performed from the reference list of all identified articles. When needed, we contacted authors for additional, unpublished information. There were no language restrictions.

The specific research questions were: what is the incidence of HPA-1a associated thrombocytopenia? and How severely are the neonates affected?

Studies were eligible for inclusion in this review if they fulfilled the following criteria: First, the study reported on low-risk newborns with severe thrombocytopenia, defined as a platelet count $<50 \times 10^9/L$, identified through screening. Second, the number of cases of severe thrombocytopenia caused by HPA-1a alloimmunization was clearly stated. Third the study reported on clinical signs of bleeding.

We subsequently excluded all nonprospective studies. Furthermore, studies were excluded when the method of screening was a method other than measuring platelet count in cord blood or when screening was not done in a low-risk unselected population. Because we wanted to identify the incidence of HPA-1a immunization in the Caucasian population, screenings studies in a non-Caucasian population, where HPA-1bb is rare, were excluded.

Data review and analysis

Two of the authors (MK and NP) initially screened all the titles and abstracts of articles, identified by the review search strategy, for relevance. Only studies clearly irrelevant were excluded at this stage. All other studies were assessed on the basis of their full text for inclusion versus exclusion by 2 reviewers independently using the criteria indicated earlier. Discrepancies were to be resolved by discussion with a third reviewer but this was proven unnecessary.

Statistical analysis

The main outcome of this systematic review was the pooled incidence of NAIT. We also wanted to assess the burden of this disease in a general population of newborns. We extracted the following primary outcome data from the selected studies: number of severe thrombocytopenic newborns (defined as a platelet count $<50 \times 10^9/L$) detected by the screening, the incidence of NAIT in that group and the number of neonatal bleed-

ding signs, ICH, and combined adverse outcome defined as perinatal mortality and morbidity associated with severe thrombocytopenia.

From the selected articles, we only used the information of pregnancies and newborns from which all relevant data on primary outcomes were available. Descriptive analysis of the outcome parameters was performed by dividing the total number of newborns with the outcome parameter by the total number of newborns screened. Numbers are given in rate per 100 000, with 95% confidence intervals (CIs).

Methodological Quality

An additional evaluation to decrease the risk of bias was performed by searching for components that could hamper accurate estimation of the true natural incidence of NAIT and the associated bleeding complications. The following study characteristics were evaluated: adequacy of inclusion and of outcome determination. For the evaluation of inclusion of patients, 1 point was given if (consecutive) nonselected patients were included; therefore details of the selection criteria for newborns included and excluded were studied. For outcome determination, 1 point was given if all patients included in the study were tested for thrombocytopenia, and 1 point was given if the laboratory tests to detect NAIT were clearly described. In addition, 1 point was given if no interventions, either antenatally and postnatally, were offered to prevent bleeding complications and 1 point was given if methods to detect bleeding complications were clearly shown.

Consequently each study could attain a maximum of 5 points. Studies that scored 0 or 1 point were considered to have a high risk of bias, studies with 2 or 3 points as intermediate risk, and studies with 4 to 5 points as studies with low risk of bias.

RESULTS

Systematic literature search

The initial search revealed 768 studies. During the first screening, 747 studies were excluded, and 21 studies were assessed on the basis of their full text for inclusion or exclusion using the criteria described. After critical appraisal of the full text of the remaining 21 articles independently by two authors (MK and NP) 6 studies were included in the review.^{1,2,8-11} The main reason for exclusion was that screening was not performed in a low-risk population but in newborns selected by the history of siblings, who suffered from (F)NAIT during pregnancy or at birth. Another important reason for exclusion was the use of case finding through maternal HPA-1a typing in unselected pregnant women, with further analysis in those women who were typed negative for HPA-1a.

One prospective screening study was excluded because it was conducted in Brazil where, probably related to ethnicity, no cases of HPA-1a immunization were found.¹²

The process of literature searching and study selection is illustrated in figure 3.1.

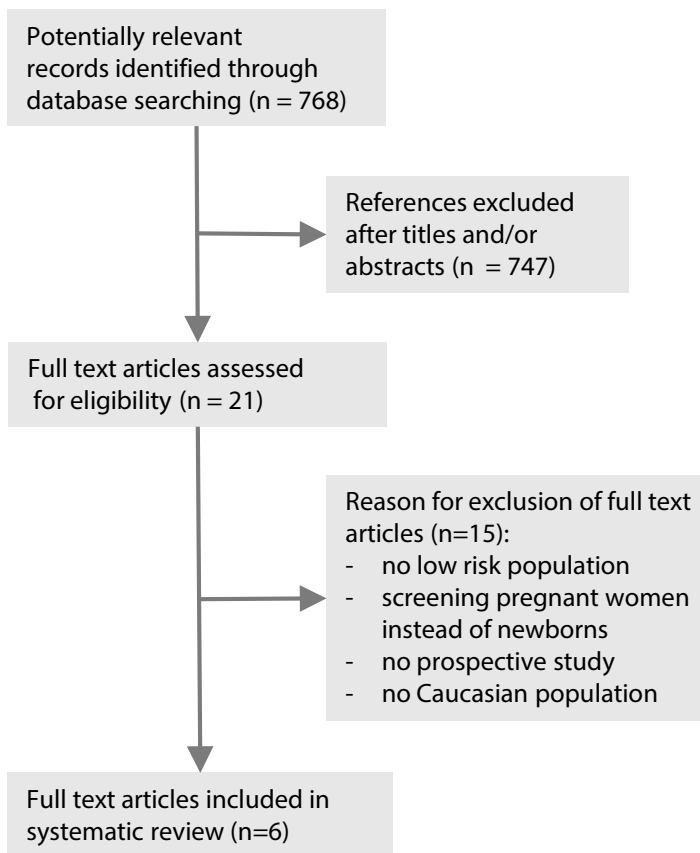


Figure 3.1
Process from initial search to final inclusion

Study characteristics

No randomized controlled trials were found. All included studies were prospective cohort studies, comparable in study design and information provided. The studies were published between 1993 and 2000. In the 6 selected studies, a total of 59 425 neonates were screened with a range from 933 to 24 101. Table 3.1 lists the primary outcome data obtained from these 6 studies.

Uhrynowska et al studied the incidence of thrombocytopenia in both unselected mothers and newborns.¹¹ De Moerlose et al and Burrows et al⁸ measured platelet count in all mothers of the newborns screened. The other 3 studies focused on neonatal thrombocytopenia.^{1,8,10}

One study analyzed 2 control groups to identify the incidence of alloimmunization in respectively thrombocytopenic mothers of non-thrombocytopenic newborns and non-thrombocytopenic mothers of non-thrombocytopenic newborn.² The difference

was statistically significant between the group of mothers with thrombocytopenic newborns and the control groups but not between the 2 control groups.

Only 1 paper reported a sample size calculation¹; all the others chose a fixed time period, varying from 1 to 7 years.

Methodological quality and heterogeneity

Known HPA-alloimmunization

All study authors stated that they aimed to determine the true incidence of NAIT in an unselected population of newborns. In all series however, ≥ 1 babies were born to mothers already known to have antiplatelet alloantibodies, often with previously affected siblings. Dreyfus et al specifically mentioned that children born to women with previously affected children due to NAIT were not excluded.¹ Panzer et al included only those deliveries with an uncomplicated history of pregnancy and delivery, without further specification.⁹ Only Burrows et al provided information about the history of the mothers with affected offspring.⁸ In their study of 18 mothers found to have HPA-1a alloimmunization, 15 had a previous affected child, and 3 alloimmunized women were sisters of women with known NAIT.

Parity

Only in the study of Panzer et al⁹ and Saino et al¹⁰, was parity of the mothers mentioned.^{9,10} In the study of Panzer et al, only the parity of the HPA-1a negative mothers ($n = 11$) was mentioned: 10 were primiparae, 2 had previous abortions and 1 had a third delivery with 4 previous abortions. None of these mothers were found to have HPA alloantibodies. In the study of Saino et al, ($n = 4489$) half of all included mothers were nulliparous, 33% had 1 previous child and 17% had ≥ 2 previous deliveries.

Gestational age

Saino et al included only full-term infants.¹⁰ Uhrynowska et al included 6.8% preterm neonates.¹¹ In the study of de Moerloose et al, 19 neonates (0.23%) were premature.² Panzer et al stated that they only included deliveries with an uncomplicated history of pregnancy and delivery.⁹ This suggests that premature deliveries were excluded. In the other 2 studies premature deliveries were not excluded, without specific numbers given.^{1,8}

Laboratory testing details

The blood tests in all studies were clearly described, and references to the appropriate literature were provided. The number of total children born and the percentage of included newborns during the study period are mentioned in table 3.1. Cord blood samples were not taken from all included neonates. This percentage varied between 88 % and 99%. Main reasons for drop out were refusal of mothers, inability of caregivers

Table 3.1 Outcome of postnatal screening studies for NAIT included in the analysis

Author Year	Included/ Total newborns ^a	Newborns tested ^b	Severe thrombocytopenia (PC < 50 x10 ⁹ /L)	Bias Assessment	Severe NAIT (PC < 50 x10 ⁹ /L + HPA-antibodies)	ICH Antenatal origin	ICH Postnatal origin
Burrows 1993 ⁸	16068/16124	15932 (99%)	19 (0.12%)	4	10 (0.06%)	3 (0.02%)	0
Panzer 1995 ⁹	NA	933	4	2	0	0	0
Dreyfus 1997 ¹	6081/8836	5632 (93%)	9 (0.16%)	2	4 (0.07%)	1 (0.02%)	0
De Moerloose 1998 ²	9485	8388 (88%)	10 (0.12%)	3	3 (0.04%)	1 (0.01%)	0
Sainio 2000 ¹⁰	4588/5285	4489 (98%)	11 (0.24%)	4	2 ^c (0.04%)	0	0
Uhrynowska 2000 ¹¹	26275	24101 (90%)	36 (0.15%)	3	5 ^d (0.02%)	1 (0.004%)	0
Total		59475	89 (0.15%)		24 (0.04%)	6 (0.01%)	0

PC, platelet count; NA, not available; ICH intracranial hemorrhage

^a actual included cases versus total newborns in the study period

^b Actual amount of newborns tested for thrombocytopenia

^c 1 case PC 37 x10⁹/L HPA-1a incompatibility, no anti HPA-1a antibodies detected

^d 1 case PC 31 x10⁹/L HPA-1a incompatibility, no anti HPA-1a antibodies detected

to draw blood (workload), or technical problems (clotting of the blood sample). Only Dreyfus et al compared 100 of these nonsampled babies with 100 babies of the sampled cohort to examine a possible bias.¹ Comparison (screened versus non-screened) showed no significant difference in gender, ethnic origin, gestational age at delivery, parity, mode of delivery, Apgar score and resuscitation of the neonate. There was a significant difference found for birth weight (lower) and maternal age (higher) in the screened population. The difference in birth weight might bias the incidence of NAIT in the screened group. It has been reported that HPA-1a alloimmunization is associated with reduced birth weight,¹² and neonates with low birth weight are more prone to have thrombocytopenia and therefore are maybe more likely to be tested for thrombocytopenia. This may have biased to a higher incidence of NAIT.

In all studies, platelet count was measured in cord blood at birth, with confirmation from neonatal capillary or venous blood. The definition of neonatal thrombocytopenia varied among the studies ranging from 50×10⁹/L⁵, to 100×10⁹/L⁸, to 150×10⁹/L^{1,2,8,9}. In our review we included only those cases with platelets < 50×10⁹/L:

The diagnosis of NAIT was confirmed by the detection of anti HPA-1a antibodies in the mother of an HPA-1a incompatible infant. In the studies of Uhrynowska et al and Panzer et al, HPA-typing was done in all maternal plasma, followed by evaluation for HPA-1a antibodies in case of HPA-1a incompatibility.^{9,11} In the other studies this was only done in case of confirmed neonatal thrombocytopenia.^{1,2,8,9}

In the study of Burrows et al the percentage of alloimmunization (formation of anti HPA-1a antibodies) in case of severe thrombocytopenia was not described.⁸ In 19 of the 15 932 pregnancies, parental mismatch for HPA-1a was noted after detecting a low platelet count in the newborn.

Antenatal and postnatal interventions

None of the studies excluded pregnancies already known to be complicated by NAIT. In these cases, various antenatal preventive interventions were described. Saino et al described 1 pregnancy with known HPA-1a alloimmunization treated antenatally with maternal intravenous immunoglobulins (IVIG) and a single intrauterine platelet transfusion.¹⁰

De Moerloose et al described 1 case in which fetal blood sampling was performed at 32 weeks' gestation for Rh-D alloimmunization.² Severe thrombocytopenia was incidentally discovered. Bleeding and persistent bradycardia occurred during the procedure, followed by emergency cesarean section. The neonate was found to have a severe intracranial hemorrhage and died after 3 days.

Burrows et al used antenatal IVIG therapy successfully in 16 pregnancies with known risk for NAIT.⁸ The 3 neonates with severe ICH in their series were not born from mothers with a known history of NAIT.

Dreyfus et al described intrauterine fetal blood sampling in a pregnancy with known NAIT, which resulted in excessive bleeding and emergency cesarean delivery.¹ A severely thrombocytopenic child was born who suffered from ICH. The neonate was treated immediately with matched platelets and IVIG. A left subependymal hemorrhage resolved without sequelae.

Saino et al used IVIG and platelet transfusions in 2 neonates with unexpected thrombocytopenia.¹⁰ Dreyfus et al treated 2 thrombocytopenic neonates from pregnancies without a history of NAIT with IVIG.¹

The other 4 studies did not provide data on postnatal treatment.^{2,8,9,11}

Evaluation of bleeding complications

Routine ultrasound on the screened neonates was not performed in any study to detect signs of intracranial bleeding. Only 2 articles noted that ultrasonography was done in all neonates with severe thrombocytopenia to exclude ICH.^{8,9} Because ultrasound is not always routinely performed in the absence of clinical ICH symptoms, this may have led to underdiagnosing, and lower incidence, of ICH. Only Saino et al described all full-term intrauterine deaths and performed autopsies on all. None had signs of serious hemorrhage.¹⁰

Risk of bias assessment

Four studies (Dreyfus et al¹, de Moerloose et al², Panzer et al⁹, and Uhrynowska et al¹¹) were classified as intermediate risk (received 2 or 3 points) and 2 studies (Burrows et al⁸, Saino et al¹⁰) as low risk (received 4 points). No study received the maximum of 5 points.

Perinatal mortality and neonatal morbidity

In the cumulative cohort of the 6 included studies, with a total of almost 60 000 newborns tested, the pooled prevalence of severe thrombocytopenia (platelet count $<50 \times 10^9/L$) in neonates was 150 per 100 000 (0.15%; 95% CI, 0.0012-0.0018). In 24 cases (27%) NAIT was the cause of thrombocytopenia. In 6 of 24 neonates, ICH was detected, with an incidence of 39 per 100 000 neonates, most likely all 6 of antenatal origin. All neonates with low platelets and ICH in these series were diagnosed with NAIT. Details of this group are listed in table 3.2. The study of Panzer et al was not included in this table because no cases of NAIT were found.

A sensitivity analysis was performed with 2 studies with the lowest estimates risk of bias. The pooled prevalence of severe thrombocytopenia was then calculated as 0.0015 (95% CI, 0.0013-0.0017), which is similar with the pooled data of all the studies.

Table 3.2 Characteristics of neonates affected by HPA-1a alloimmunization

Author Year	NAIT Cases	PC ($\times 10^9/L$)	Bleeding Signs	Neonatal illness	Intervention
Burrows 1993 ⁸	1-9	6-40	ICH (n=2)	--	Antenatal IVIG (n=7); 2 ICH Cases, no antenatal intervention
	10	unknown	ICH	IUFD at 35 wks	-
Dreyfus 1997 ¹	1	46	-	IUGR	Postnatal IVIG
	2	50	-	-	-
	3	2	Petechiae	-	Postnatal IVIG
	4	20	bleeding after FBS	ICH/Porencephaly	Antenatal IUPT Postnatal IVIG
De Moerloose 1998 ²	1	48	Petechiae	-	unknown
	2	20	Petechiae	-	unknown
Sainio 2000 ¹⁰	1	18	Petechiae	-	Postnatal IVIG
	2	33	-	-	Antenatal IVIG + IUPT
	3	40	-	-	Postnatal IVIG
Uhrynowska, 2000 ¹¹	1	47	-	-	Unknown
	2	41	ICH	Infection, prematurity	Unknown
	3	18	Petechiae	-	Unknown
	4	27	None	-	Unknown
	5	25	Petechiae	-	Unknown

FBS fetal blood sampling; IUFD intrauterine fetal death; IUGR intrauterine growth restriction; IUPT intrauterine platelet transfusion; IVIG intravenous immunoglobulin; — none.

DISCUSSION

Neonatal thrombocytopenia is a serious condition, requiring rapid diagnostic and therapeutic action to prevent bleeding complications. A major cause in otherwise healthy term newborns is NAIT.

Although this systematic review of screening studies in general populations produces the best possible estimate of the incidences of NAIT and NAIT-related ICH, underestimation remains likely. Older studies on risks for ICH in HPA-immunized pregnancies cited an incidence ranging from 7 to 26%, or 3 to 10 per 100 000 pregnancies.^{13,14} However, true natural history information is lacking. Our previous review on screening studies performed in pregnant women at risk for FNAIT⁵ showed that screen-positive cases and those already known to have alloantibodies against fetal platelets received, understandably, various types of interventions. The results of the current review showed a pooled incidence of severe NAIT of 63 per 100 000, with 6 cases of ICH per 100 000 (table 3.3). All cases of ICH reported in these 2 reviews were (likely) of antenatal origin. The difference in the incidence of ICH, 9.9% vs 25% (Fisher's Exact test $P = .087$) does not reach statistical significance because of limited numbers. However, the difference in our view is most likely explained by the use of interventions, which is only possible in the antenatally screened group.

Without routine screening in low-risk, general populations of pregnant women or newborns, the diagnosis of FNAIT is often missed. Tiller et al calculated that testing for FNAIT only in the presence of clinical symptoms would miss the diagnosis in 86% of cases.¹⁵ Other study data showed that even in neonates born with severe thrombocytopenia, timely diagnostic testing for NAIT was not performed in 15% of the cases, with severe consequences for the subsequent pregnancies resulting in the occurrence of ICH.¹⁶ Missing the diagnosis is obviously potentially hazardous for the neonate. In addition, the mother is unaware that in a subsequent pregnancy, the risks for fetal or neonatal bleeding complications are high. This is particularly important given the highly effective preventive measures that are currently available.¹⁷

Our review confirms previous reports suggesting that the majority of cases of ICH develop in utero.^{5,18} A recent study of Tiller et al showed that most cases of ICH seem to occur before the 28th week of gestation.¹⁹ Therefore, screening neonates with the

Table 3.3 Comparison of Incidences of FNAIT and ICH in Antenatal versus Postnatal screening studies

Studies	Number of subjects screened	Severe FNAIT ^a	ICH
Antenatal screening ^b	176 084	71 (0.04%)	7 (9.9%)
Postnatal screening ^c	59 425	24 (0.04%)	6 (25%)

^a Thrombocytopenia < 50 × 10⁹/L

^b Kamphuis et al

^c Current study

aim to timely detect and treat severe thrombocytopenia will have limited effectiveness. Neonatal screening may have some benefit particularly in the asymptomatic thrombocytopenic child, although the studies we analyzed were not designed to investigate this. An expected benefit would be to provide the mother with knowledge that FNAIT may occur in future pregnancies, and she should consult a fetal medicine specialist to help prevent complications.

3

Significantly more benefit can be expected from general screening of pregnant women for HPA type and anti-HPA alloantibodies. Intervention options for screen-positive pregnancies suggested by investigators are weekly IVIG infusions to the mother, timed near-term delivery by induction of labor or cesarean delivery, birth in a perinatal center with immediate availability of matched platelets and combinations of these measures. Several groups have published calculations of costs and potential benefits of screening and intervention, all coming to the same conclusion that such programs are likely cost-effective.^{5-7,20-22} The main reason for cost-effectiveness, despite large-scale testing and, in the case of IVIG, expensive treatment, is the fact that the disease burden and costs for a child with lifelong severe neurological damage from ICH is excessive.

CONCLUSION

This review shows that NAIT is among the most important causes of severe thrombocytopenia in newborns, with ICH in at least 10 per 100 000 newborns. Given the antenatal origin of most intracranial bleedings, the best option to reduce the associated mortality and morbidity seems to be screening all pregnant women for HPA alloimmunization, followed by effective interventions.

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