Received: 19 December 2021 | Accepted: 18 March 2022

DOI: 10.1111/bjh.18173

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

REVIEW

Anti-human platelet antigen-5b antibodies and fetal and neonatal alloimmune thrombocytopenia; incidental association or cause and effect?

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Summary

Most cases of fetal and neonatal thrombocytopenia (FNAIT) are caused by maternal anti-human platelet antigen-1a antibodies (anti-HPA-1a). Anti-HPA-5b antibodies are the second most common antibodies in suspected FNAIT cases. Given the high prevalence of anti-HPA-5b antibodies in pregnant women delivering healthy newborns, the association with FNAIT may be coincidental. This review of the literature related to FNAIT using the MEDLINE database was conducted according to PRISMA guidelines. A retrospective analysis of a single-centre cohort of 817 suspected FNAIT cases was conducted. The pooled prevalence of anti-HPA-5b antibodies in unselected pregnant women of European descent was 1.96% (n = 3113), compared with 3.4% (n = 5003) in women with suspected FNAIT. We found weak evidence that a small proportion of pregnant women presenting with anti-HPA-5b antibodies will give birth to a newborn with mild thrombocytopenia. The neonatal platelet counts were not different between suspected FNAIT cases (n = 817) with and without maternal anti-HPA-5b antibodies. The prevalence of maternal anti-HPA-5b antibodies was not different between neonates with intracranial haemorrhage and healthy controls. The current experimental and epidemiological evidence does not support the hypothesis that anti-HPA-5b antibodies cause severe thrombocytopenia or bleeding complications in the fetus or newborn.

KEYWORDS
anti-HPA-5b, fetal medicine, fetal and neonatal alloimmune thrombocytopenia

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal antibodies directed against fetal platelet antigens inherited from the father. Placental transport of maternal immunoglobulin G class antiplatelet antibodies to the fetal circulation may lead to thrombocytopenia and bleeding complications in the fetus or newborn.[1] The estimated incidence of FNAIT is 1 in 1000 live births, and its most severe complication, intracranial haemorrhage (ICH), occurs

Abbreviations: CI, confidence interval; FNAIT, fetal and neonatal alloimmune thrombocytopenia; GP, glycoprotein; HPA, human platelet antigen; ICH, intracranial haemorrhage; IVIG, intravenous immune globulin; MAIPA, monoclonal antibody-specific immobilization of platelet antigens; NR, not reported.

in 1 of 10 000 pregnancies, in the majority of cases before 28 gestational weeks, often affecting the first-born child.[2,3] In Caucasians, most of the FNAIT cases are caused by maternal antibodies against human platelet antigen (HPA)-1a.[4] Second most common are maternal anti-HPA-5b antibodies that are implicated in approximately 15% of diagnosed FNAIT cases.[5–7] The platelet antigen HPA-5b (previously called Br[a]) was discovered in 1988 by Kiefel et al.[8] following detection of antibodies in the sera of four mothers of newborns with thrombocytopenia. They utilized a glycoprotein-specific enzyme immunoassay using monoclonal antibodies for antigen immobilization [monoclonal antibody-specific immobilization of platelet antigens (MAIPA)[9]]. The HPA-5 antigen system was the first polymorphism located on platelet glycoprotein (GP) Ia/IIa (α2β1 integrin, CD49b, VLA-2), and antibodies can be best detected by glycoprotein-specific assays since GPIa/IIa is expressed at a low copy number on platelets (1000 HPA-5b binding sites on heterozygous platelets).[10] The HPA-5a/b-associated single nucleotide polymorphism (ITGA2 c.1600G > A) is located on the GPIa subunit, leading to a glutamine (HPA-5a)-to-lysine (HPA-5b) amino acid exchange at residue 505 of the mature protein.[11]

After the discovery of the HPA-5 system, suspected FNAIT cases were retrospectively screened, and anti-HPA-5b antibodies were detected in the sera of mothers who had given birth to neonates with thrombocytopenia with or without haemorrhagic symptoms.[12,13] In cases where anti-HPA-5b antibodies were implicated, a less severe bleeding tendency was observed, compared with FNAIT caused by anti-HPA-1a antibodies.[13,14]

However, these retrospective studies did not include appropriate control groups. A prospective study screening healthy pregnant women demonstrated a high prevalence of anti-HPA-5b antibodies at delivery (17/916 cases; 1.82%); none of their neonates were thrombocytopenic (platelet count $<150\times10^9$/l).[15] Therefore, the detection of anti-HPA-5b antibodies in suspected FNAIT cases could be coincidental and not causal.

This systematic review aimed to assess the predictive value of anti-HPA-5b antibody detection in pregnant women to determine if the fetus or newborn is at risk for thrombocytopenia and/or bleeding complications. A retrospective analysis of a single-centre cohort of 817 suspected FNAIT cases[16] was performed along with a meta-analysis of published cohorts. To the best of our knowledge, this is the first systematic review on the possible role of anti-HPA-5b antibodies in FNAIT.

MATERIALS AND METHODS

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] A comprehensive electronic search via the PubMed interface was performed in the MEDLINE database from 1988 to 5 October 2020. The search strategy is presented in Table S1. All identified studies were uploaded in a web-based Citavi database (Citavi, Swiss Academic Software, Wädenswil, Switzerland). Two investigators (J.A. and G.B.) independently screened the titles and abstracts. Reference lists were cross-checked for relevant citations.

Study selection

To assess the possible association of anti-HPA-5b antibodies with outcomes, we developed the following questions according to the standardized population/intervention (risk factor)/comparison/outcome (PICO) format.[18]

- PICO question 1: Anti-HPA-5b is a possible risk factor in pregnant women

In pregnant women (population) is the detection of anti-HPA-5b (intervention/risk factor) a risk for adverse fetal or neonatal outcomes (outcome) compared with pregnancies without any anti-HPA antibody (comparison)?

- PICO question 2: Anti-HPA-5b is a possible risk factor in suspected FNAIT cases

In women with suspected FNAIT (population), is the detection of anti-HPA-5b (intervention/risk factor) a risk for adverse fetal or neonatal outcomes (outcome) compared with women with suspected FNAIT without any anti-HPA antibody (comparison)?

To calculate the prevalence of anti-HPA-5b antibodies in both populations, all studies reporting the presence of the possible risk factor, i.e., anti-HPA-5b, in the respective population were included regardless of reporting fetal or neonatal outcomes. Studies reporting fewer than 10 subjects were excluded. Cases with additional anti-HPA antibodies (e.g. anti-HPA-5b and anti-HPA-1a) as well as mothers with immune thrombocytopenia were also excluded.

Fetal or neonatal outcomes were stratified as follows: thrombocytopenia (platelet count $<150\times10^9$/l), severe thrombocytopenia (platelet count $<50\times10^9$/l), bleeding grade I (cutaneous); bleeding grade II (mucosal) and bleeding grade III (ICH).

Retrospective analysis of 817 families with suspected FNAIT

We analysed the possible association of anti-HPA-5b antibodies with fetal and neonatal outcomes in 817 families (mother, father and neonate) with suspected FNAIT referred to our Centre for Fetomaternal Incompatibility. Case definitions, work-up of suspected FNAIT families and outcome assessment were described elsewhere.[16] This case series included 25 cases with maternal anti-HPA-5b antibodies. Due to a missing platelet count in one case, 24 cases were analysed for the possible association between neonatal platelet count and absence or presence of maternal anti-HPA-5b antibodies.

Study approval

The retrospective analysis of FNAIT cases was approved by the Ethics Committee of the Medical Faculty, Justus-Liebig University (Giessen, Germany) (File no. 82/09).

Statistical analysis

Statistical analyses were performed using GraphPad Prism software version 9.1.2 (GraphPad, San Diego, CA, USA). The possible difference of neonatal platelet counts in cases with and without maternal anti-HPA antibodies was analysed with the Mann–Whitney test. A p-value <0.05 was considered significant.

RESULTS

Study selection

The systematic MEDLINE search revealed a total of 1231 citations (Table S1). The cross-check process for relevant citations in reference lists identified an additional five publications or conference abstracts, demonstrating the validity of the search strategy. Of all citations, nine addressed PICO question 1 (Table 1), and 11 addressed PICO question 2 (Table 2). Anti-HPA-5b-associated case reports and case series without denominator/comparison for the calculation of anti-HPA-5b antibody prevalence were not included in this systematic review. A recent relevant article[33] was included after the systematic literature search was finalised.

Anti-HPA-5b antibodies are prevalent in unselected pregnant women

We identified nine population-based screening studies investigating the prevalence of anti-HPA-5b antibodies in unselected pregnant women or women with a history of pregnancy (Table 1). The allele frequency of HPA-5b has a large range across populations, reaching values of up to 0.4 in Central Africa, 0.07–0.12 in Europe and 0.01 in Asia.[35] HPA-5b genotyping of subjects, screened for the presence of antibodies, was not performed in most studies. Thus, we could not correct the prevalence of anti-HPA-5b antibodies in pregnant women according to allele frequencies of the investigated population. For this meta-analysis, we combined data from five European studies.[15,19–22] The pooled prevalence of anti-HPA-5b antibodies in unselected pregnant women or women with a history of pregnancy was 1.96% [95% confidence interval (CI) 1.11%–2.84%; n = 3113 (Table 1)].

Two European studies have reported neonatal outcomes. Ribera et al.[19] did not diagnose clinically apparent FNAIT at delivery in 12 of 800 pregnant women who were immunized to HPA-5b. The platelet count of neonates was not reported. Panzer et al.[15] reported the presence of anti-HPA-5b antibodies in 17 of 933 (1.82%) pregnant women with uncomplicated pregnancy at delivery; none of their neonates were thrombocytopenic (platelet count $<150 \times 10^9$/l).

One Japanese study presented neonatal outcomes. Ohto et al. screened 24 630 pregnant women in the first trimester and identified anti-HPA-5b antibodies in 168 (0.68%) women.[23] The authors compared the occurrence of thrombocytopenia (platelet count $<150 \times 10^9$/l) in 48 incompatible pregnancies (maternal anti-HPA-5b antibody was detected, and the neonate had HPA-5b) with the occurrence of thrombocytopenia in 161 controls. The proportion of newborns with thrombocytopenia was significantly different (17%, 8/48 incompatible pregnancies vs 2.42%, 4/161 controls). However, in mothers with anti-HPA-5b, the rate of thrombocytopenia in infants who were incompatible for HPA-5b (17%, 8/48) was not significantly different from that in infants without HPA-5b (8%, 4/53).[23] However, this conclusion should be interpreted cautiously due to the small number of observations.

Anti-HPA-5b antibodies are not associated with neonatal bleeding complications in unselected pregnant women

Three of the population-based screening studies have reported data on possible fetal or neonatal bleeding complications in a total of 197 pregnant women with anti-HPA-5b (pooled data from two European studies and one Japanese study) (Table 1).[15,19,23] Fetal and neonatal bleeding complications were not reported.

We tabulated the likelihood for HPA-5b-incompatible pregnancies, presence of anti-HPA-5b antibodies in pregnant women, severe thrombocytopenia, and ICH in comparison with HPA-1a-incompatible pregnancies (Table 3). Approximately 2% of all pregnancies in European populations are incompatible for HPA-1a, and approximately 7% of all pregnancies are incompatible for HPA-5b. Furthermore, the immunogenicity of HPA-5b is higher, resulting in a 10-fold higher prevalence of HPA-5b antibodies (approximately 2%) compared with anti-HPA-1a antibodies (approximately 0.2%) in unselected pregnancies. In approximately 20% of women immunized to anti-HPA-1a, the fetus suffered from severe thrombocytopenia (platelet count $<50 \times 10^9$/l).[2] By contrast, in unselected pregnant women immunized to anti-HPA-5b (n = 65[15,23]), severe thrombocytopenia was not observed. The risk of ICH in women immunized to anti-HPA-1a is approximately 5% of all women immunized (1:10 000 pregnancies). ICH was not reported in 197 women immunized to anti-HPA-5b that were diagnosed by screening unselected pregnant women.[15,19,23]

TABLE 1 PICO question 1: Studies investigating the prevalence of anti-HPA-5b antibodies in pregnant women or women with a history of pregnancy. Events: Neonatal thrombocytopenia (PLT < 150×10^9/l)

Authors	Population	Anti-HPA-5b-positive		Anti-HPA-5b-negative		% anti-HPA-5b-positive	Morbidity of anti-HPA-5b+cases	Additional information
		Events	Total	Events	Total			
European populations								
Ribera et al.[19]	Pregnant women at delivery ($n = 800$)	0[a]	12	NR	788	1.50	No	
Panzer et al. [15]	Pregnant women with uncomplicated pregnancy at delivery ($n = 933$)	0	17	35[b]	916	1.82[c]	No	Caucasian mothers
Schnaidt and Wernet[20]	Female blood donors with a history of pregnancy >6 months after delivery ($n = 500$)	NR	16	NR	484	3.20	NR	
Boehlen et al.[21]	Female blood donors (HPA-5aa) with a history of pregnancy ($n = 98$)	NR	2	NR	123[d]	1.63	NR	Caucasian mothers (>99%)
Twilfert et al.[22]	Female blood donors with a history of pregnancy ($n = 816$)	NR	14	NR	802	1.72	NR	
Sum			61		3113	1.96%		
						95% CI 1.11–2.84		
Japanese and African populations								
Ohto et al.[23]	Pregnant women at first trimester ($n = 24\,630$)		168	NR	24 462	0.68	No	
	Incompatible pregnancies versus controls[e]	NR 8	48	4	161		No	Japanese pregnant women, $p < 0.05$
Skouri et al.[24]	Women (HPA-5aa) with a history of ≥3 pregnancies ($n = 186$)	NR	8	NR	281[f]	2.86	NR	Tunesian mothers
Jeremiah et al.[25]	Women with a history of ≥2 pregnancies >1 year after delivery ($n = 100$)	NR	30	NR	70	30.00	NR	Nigerian and West African mothers
Husebekk et al.[26]	Random pregnant women ($n = 200$) and pregnant women with maternal phenotype HPA-1bb ($n = 167$)	NR	16	NR	351	4.36	NR	Egyptian mothers

Abbreviations: FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; NR, not reported; PICO, population/intervention (risk factor)/comparison/outcome; PLT, platelets.

[a]No case with clinically apparent FNAIT was reported; the platelet count of neonates was not reported.

[b]The platelet count was not determined in 73 of 916 neonates.

[c]The prevalence of anti-HPA-5b antibodies may have been underestimated. The authors exclusively examined HPA-5aa homozygous mothers who delivered a heterozygous offspring for the presence of anti-HPA-5b antibodies.

[d]The authors included 98 female HPA-5aa blood donors. We extrapolated the number representing an unselected population including all HPA-5 genotypes according to the reported phenotype frequency of HPA-5aa (79.6%).

[e]Incompatible pregnancies, maternal anti-HPA-5b antibody was detected, neonate HPA-5b-positive; controls, 161 healthy neonates born to mothers negative for antibody against platelets ($p < 0.05$). In mothers having anti-HPA-5b, the rate of thrombocytopenia in HPA-5b-incompatible infants (17%, 8/48) was not significantly different from that in HPA-5b-negative infants (8%, 4/53). For details see text.

[f]The authors included 186 HPA-5aa women with a history of ≥3 pregnancies. We extrapolated the number representing an unselected population including all HPA-5 genotypes according to the reported phenotype frequency of HPA-5aa (66.2%).

TABLE 2 PICO question 2: Studies investigating the prevalence of anti-HPA-5b antibodies in suspected FNAIT cases (cases with additional anti-HPA-antibodies, e.g. anti-HPA-1a excluded). Events: Severity of haemorrhage (I, cutaneous; II, mucosal and III intracranial haemorrhage)

			Anti-HPA-5b-positive			
Authors	**Population**	***n***	**Total (*n*)**	**Neonatal platelet count (10^9/l)**	**Events (*n*)**	**% anti-HPA-5b-positive**
European populations						
Mueller-Eckhardt et al.[4], Kroll et al.[13]	FNAIT-suspected HPA-1a-positive	219	9	2–88	I (1)	4.11
Taaning et al.[27]	FNAIT suspected[a]	59	5	NR	NR	8.47
Uhrynowska et al.[28]	FNAIT suspected[b]	160[c]	2	NR	NR	1.25
de Moerloose et al.[29]	FNAIT suspected	31	2	39, 75	No	3.23
Berry et al.[30]	FNAIT suspected	305	9	NR	NR	2.95
Uhrynowska et al.[31]	FNAIT suspected; mothers with normal platelet count	91	1	96	No	1.10
Mandelbaum et al.[32]	FNAIT suspected	309	26	NR	NR	8.41
Ghevaert et al.[6]	FNAIT suspected	1148	31[d]	NR	I (1), III (4)[e]	2.70
de Vos et al.[33]	FNAIT suspected	1864	60	Median 48 (IQR 18–81)[f]	I, II (8/40), III (4/40)	3.22
This study	FNAIT suspected	817	25	7–143	no ICH	3.68
Sum		5003	170			3.40 95% CI 2.07–5.75
American populations						
Davoren et al.[5]	FNAIT suspected; American mothers	3743	137	NR	NR	3.66
Castro et al.[34]	Thrombocytopenic newborns (platelet count $<100\times10^9$/l); Brasil Indigenous, African and Caucasian mothers	105	6	34–98	No	5.71[g]

Abbreviations: FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; ICH, intracranial haemorrhage; IQR, interquartile range; MAIPA, monoclonal antibody-specific immobilization of platelet antigens; NR, not reported; PICO, population/intervention (risk factor)/comparison/outcome.

[a]Exclusion of neonates with infections, extreme prematurity or other severe illnesses.

[b]Exclusion of neonates with maternal immune thrombocytopenic purpura.

[c]Only cases that were investigated by MAIPA were included in this analysis.

[d]One mother had a chronic and profound thrombocytopenia.

[e]In two of the four cases with ICH, the neonatal platelet count was in the normal range (169 and 179×10^9/l), and in the two others, the platelet count was at a level which was perceived safe (61 and 55×10^9/l). It remains unclear why the two cases with neonatal platelet counts of 169 and 179×10^9/l respectively, were categorised as FNAIT.

[f]Cases without antenatal treatment.

[g]The prevalence of anti-HPA-5b antibodies may have been underestimated. The authors exclusively examined HPA-5aa homozygous mothers who delivered a heterozygous offspring for the presence of anti-HPA-5b antibodies.

In suspected FNAIT cases, the prevalence of anti-HPA-5b antibodies is marginally increased compared with unselected pregnancies

Ten European studies have reported the prevalence of anti-HPA-5b antibodies in clinically suspected FNAIT cases, i.e. case series that were analysed by reference laboratories retrospectively (Table 2). The pooled prevalence of anti-HPA-5b antibodies in suspected FNAIT cases was 3.40% (95% CI 2.07–5.75, n = 5003). Thus, the prevalence of anti-HPA-5b antibodies in suspected FNAIT cases was 1.73-fold enriched compared with unselected pregnancies (1.96%, Table 1). In comparison, the prevalence of anti-HPA-1a antibodies in suspected FNAIT cases was approximately 50-fold enriched compared with the prevalence in unselected pregnancies (0.2%, Table 3; considering a prevalence of approximately 10% anti-HPA-1a antibodies in suspected FNAIT cases)[6,33]

Neonatal platelet counts in suspected FNAIT cases with and without detection of maternal anti-HPA-5b antibodies were not different

Published studies have not compared neonatal platelet counts in suspected FNAIT cases with and without anti-HPA-5b. We analysed a cohort of 817 suspected FNAIT cases that were recently published within another context[16] and excluded families with missing neonatal platelet counts. A comparison of median platelet counts was performed between cases without maternal anti-HPA antibodies (n = 605), with maternal anti-HPA-1a antibodies (n = 132)

TABLE 3 Probabilities for HPA-5b-incompatible pregnancies, presence of anti-HPA-5b antibodies in pregnant women, severe thrombocytopenia and intracranial haemorrhage in comparison to HPA-1a-incompatible pregnancies (prospective screening of unselected European populations)

Definition of population	HPA-1a incompatibility (*n*/10 000 pregnant women)	HPA-5b incompatibility (*n*/10 000 pregnant women)
Mother at risk for immunization (antigen-negative; genotype HPA-1bb or HPA-5aa)[a]	225 (2.25% of all pregnancies)	8464 (84.64% of all pregnancies)
Probability of incompatible pregnancy (genotype of the foetus HPA-1ab or HPA-5ab)	191 (1.91% of all pregnancies)	677 (6.77% of all pregnancies)
Anti-HPA antibody detected[b]	20 (~10% of incompatible pregnancies ~0.2% of all pregnancies)	196 (28.95% of incompatible pregnancies, 1.96% of all pregnancies)
Severe thrombocytopaenia[b] (platelet count $<50\times10^9$/l)	~4 ~20% of immunized pregnancies	NR
Intracranial haemorrhage[b]	~1	NR

Note: Number screened for HPA-1a incompatibility: >200 000[2]; number screened for HPA-5b incompatibility: 26 363.[15,19,23]

Abbreviations: HPA, human platelet antigen; NR, not reported.

[a]The following allele frequencies were used for calculation of probabilities: HPA-1a, *f* 0.85; HPA-5b *f* 0.08.

[b]The figures for HPA-1a-incompatible pregnancies were taken from a recent meta-analysis.[2] The figures for HPA-5b-incompatible pregnancies were taken from Table 1.

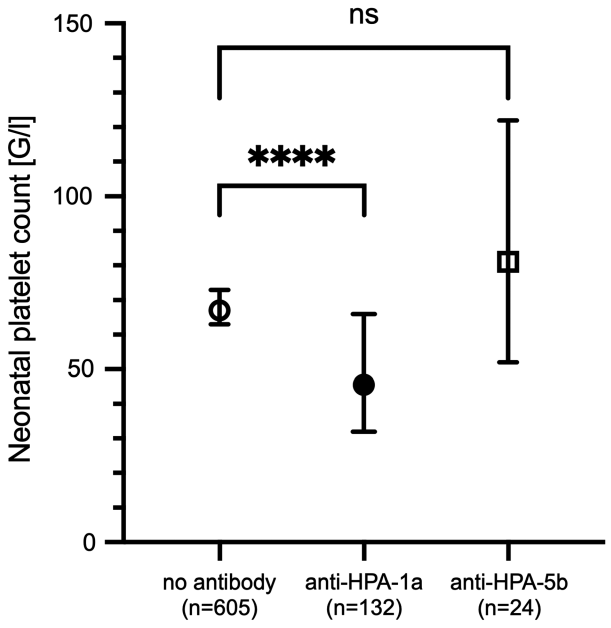

FIGURE 1 Neonatal platelet count (median and 95% CI of median) in suspected FNAIT cases without and with detection of anti-HPA-1a or anti-HPA-5b antibodies (cases with additional anti-HPA antibodies or cases without neonatal platelet count excluded). The neonatal platelet count between controls (median 67.00; 95% CI 63.00–73.00) and cases with maternal anti-HPA-1a antibodies (median 45.50; 95% CI 32.00–66.00) differed significantly (****, $p<0.0001$, Mann–Whitney test, two-tailed). No difference was found in the neonatal platelet counts between controls and cases with maternal anti-HPA-5b antibodies (median 81.00; 95% CI 52.00–122.00; ns, not significant, Mann–Whitney test, two-tailed). CI, confidence interval; FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen

and with maternal anti-HPA-5b antibodies ($n = 24$; multiple HPA antibodies excluded) (Figure 1). The platelet counts of newborns were not different between cases with and without maternal anti-HPA-5b antibodies. By contrast, the platelet count in newborns of mothers with anti-HPA-1a antibodies was significantly lower than that in newborns of mothers without anti-HPA antibodies.

Anti-HPA-5b-associated ICH cases that were diagnosed in retrospective cohort studies of suspected FNAIT demonstrate high neonatal platelet counts

No published studies have compared the incidence and characteristics of ICH in suspected FNAIT cases with and without anti-HPA-5b. In our case series of 25 mothers with anti-HPA-5b with suspected FNAIT, ICH was not reported. ICH cases that were associated with maternal anti-HPA-5b antibodies in retrospective cohort studies of suspected FNAIT (Table 2) demonstrated normal or moderately decreased neonatal platelet counts. The initial neonatal platelet counts of four anti-HPA-5b-associated ICH cases in the cohort study of Gheveart et al.[6] were 61, 169, 55 and 179×10^9/l respectively. Three cases were newly diagnosed, one case (initial platelet count 179×10^9/l) was from the intra-uterine transfusion programme. It remains unclear why the two cases with neonatal platelet counts of 169 and 179 respectively, were categorised as FNAIT. Three of these four newborns did not present with skin bleeding, which is common in anti-HPA-1a-associated ICH cases. de Vos et al.[33] reported outcomes of 40 suspected FNAIT cases with maternal anti-HPA-5b antibodies and neonates incompatible for HPA-5b. Of 40 neonates with incompatible status, four (10%) suffered from ICH. However, in a control group of 10 additional cases with maternal anti-HPA-5b antibodies but compatible neonates (genotype HPA-5aa), the incidence of ICH was the same (1/10, 10%). In this study, the neonatal platelet count nadir of three cases with ICH in anti-HPA-5b incompatible pregnancies was 75, 133, and 240×10^9/l. The latter two cases were antenatally treated with intravenous immune globulin (IVIG) after detection of cerebral abnormalities that had been observed with routine ultrasound investigations during pregnancy. In a fourth case, the platelet count was not

tested due to intra-uterine fetal demise[33]—Thijs de Vos, personal communication). These findings are contrary to the neonatal platelet counts observed in anti-HPA-1a-associated ICH cases that were almost always $<30\times10^9$/l.[6,33]

The prevalence of maternal anti-HPA-5b antibodies between neonates with ICH and healthy controls was not different

Refsum et al.[36] identified 286 neonates with ICH born from 32 weeks of gestation based on a Swedish neonatal quality registry. The retrospective analysis of 105 maternal sera revealed two mothers (1.9%) with anti-HPA-5b antibodies. Thus, the prevalence of maternal anti-HPA-5b antibodies was not different between neonates with ICH and healthy controls (1.96%, Table 1).

DISCUSSION

In European studies, anti-HPA-5b antibodies are detected in 1.96% (95% CI 1.11–2.84) of healthy unselected pregnant women. Two European studies[15,19] reported data on neonatal outcomes. Absence of bleeding was documented in 29/29 anti-HPA-5b-immunized pregnancies,[15,19] and normal platelet counts in 17/17 cases.[15] In a large cohort, one Japanese study[23] reported an association of anti-HPA-5b antibodies with mild neonatal thrombocytopenia in a subset of cases in which neonatal platelet counts were analysed. This study reported an unusually high rate of thrombocytopenia (2.42% and 8%) in two different control groups. This contrasts to the general finding that, overall, thrombocytopenia occurs in <1% of all newborns.[37] The same group[38] reported that a high titre (≥64) of anti-HPA-5b antibodies was associated with mild neonatal thrombocytopenia (platelet count $<150\times10^9$/l) at day 3 after birth in 5/10 (50%) of cases. An antibody titre of less than 64 was not associated with thrombocytopenia at day 3 after birth (n = 14). Interestingly, the platelet count at birth was independent of the anti-HPA-5b antibody titre [antibody titre, <64: mean platelet count, 267 (SD 81; n = 20); antibody titre ≥64: mean platelet count, 205 (SD 62; n = 18)]. In conclusion, the association of anti-HPA-5b antibodies in unselected pregnancies with mild neonatal thrombocytopenia was only reported in a single study. Thus, the replication of this finding in an independent prospective cohort study is needed.

The pooled analysis of all published screening studies in healthy pregnant women, reporting neonatal outcomes, revealed 197 anti-HPA-5b-positive cases. None of 65 neonates with neonatal platelet counts reported[15,23] suffered from severe thrombocytopenia (platelet count $<50\times10^9$/l). Fetal or neonatal bleeding complications were not reported in 197/197 cases.

Ten European studies have reported the prevalence of anti-HPA-5b antibodies in retrospective cohort studies of suspected FNAIT cases. We calculated a pooled prevalence of 3.4% (95% CI 2.07–5.75). This represents a marginal enrichment of 1.73-fold compared with healthy controls. From the available studies, it cannot be excluded that this enrichment is due to an observer bias: in a diagnostic setting, the observer may interpret borderline results as positive if there is a clinical suspicion of FNAIT, the mother was negative for HPA-5b, and the fetus or newborn had HPA-5b. Other possible confounding factors may include pregnancy-related factors that caused neonatal thrombocytopenia as well as alloimmune response to HPA-5b. Suspected FNAIT cases may include a higher proportion of multi-gravida. Conversely, anti-HPA-5b antibodies may be causal in inducing thrombocytopenia in the highly selected group of suspected FNAIT cases. If the marginal enrichment of anti-HPA-5b antibody prevalence in a case series of suspected FNAIT was true, this finding would reflect an association of a small subset of anti-HPA-5b antibodies with mild fetal or neonatal thrombocytopenia.

The retrospective analysis of our cohort of 817 suspected FNAIT cases did not reveal any difference in the neonatal platelet count between cases (maternal anti-HPA-5b was detected; neonates were HPA-5b-positive) and controls (no maternal anti-HPA antibody detected) (Figure 1).

Interestingly, nearly all anti-HPA-5b-associated ICH cases reported in retrospective cohort studies of suspected FNAIT cases[6,33] presented with normal or moderately decreased neonatal platelet counts (platelet count $>50\times10^9$/l). Again, this may indicate an incidental association rather than causation. Refsum et al.,[36] investigating ICH in neonates born from 32 weeks of gestation, demonstrated a prevalence of anti-HPA-5b antibodies (1.9%) that did not differ from that in controls (1.96%, this study). In conclusion, the epidemiological findings do not support the hypothesis that anti-HPA-5b antibodies cause severe fetal or neonatal thrombocytopenia or bleeding complications.

Vos et al.[33] analysed retrospectively suspected FNAIT cases and concluded that anti-HPA-5b antibodies can (causally) be associated with neonatal bleeding symptoms. In our view, the presented data only partly support this conclusion. First, in multi-gravida with a FNAIT-suspected child, 79% (38/48) of anti-HPA-5b cases were HPA-5b incompatible (child HPA-5b-positive), whereas 52% were expected. The authors argued that this enrichment of incompatible pregnancies would favour a causal relationship between anti-HPA-5b and FNAIT. If we assume causality between maternal anti-HPA-5b antibody and FNAIT, we expect that 100% of pregnancies are incompatible. This was true for anti-HPA-1a-associated cases in the same study. The finding that 21% of women with anti-HPA-5b carried an HPA-5b-negative fetus favours the hypothesis that anti-HPA-5b is—in many cases—not causally associated with fetal or neonatal thrombocytopenia. Second, ICH occurred in 10% of HPA-5b-incompatible (4/40) as well as in 10% of HPA-5b-compatible (1/10) pregnancies; thus, in this cohort, anti-HPA-5b was not associated with severe bleeding.

Furthermore, additional *in vivo* studies, both in mice and humans, may support our view that anti-HPA-5b

antibodies are not causing bleeding complications. The α2β1 integrin, carrying the HPA-5a/b polymorphism, is expressed on various cell types, including epithelial cells, endothelial cells, fibroblasts, subpopulations of neutrophils, monocytes, mast cells, NK cells, activated T cells, platelets/megakaryocytes and trophoblasts.[39] Accordingly, the HPA-5a/b polymorphism was also demonstrated on endothelial cells[40] and activated T cells.[41] The expression level varies up to 10-fold in association with a silent genetic polymorphism (807C>T).[42] Further studies showed a linkage between HPA-5b and C807 (low expresser); the T807 allele (high expresser) is linked to the HPA-5a allele. HPA-5ab platelets only express around 1000 copies of HPA-5b[10] and since the α2 integrin is expressed on a variety of other cell types in addition to platelets, it is likely that only a rather low number of maternal anti-HPA-5b antibodies binds to each fetal platelet making it less likely to be phagocytosed by macrophages.

Mice lacking α2 integrin (*ITGA2*$^{-/-}$)[43,44] are viable, develop normally, and can reproduce. The bleeding times in *ITGA2*$^{-/-}$ mice are normal.[44]

The role of α2β1 integrin in leukocyte activation and migration within the extracellular matrix environment prompted several investigators to test anti-α2β1 integrin-blocking antibodies for the treatment of inflammatory conditions in several *in vivo* models.[45–47] The injection of therapeutic doses of unmodified anti-α2 integrin antibody (clone Ha1/29) into mice did not lead to thrombocytopenia or bleeding complications.

Vatelizumab, a humanized and silenced (lacking complement and Fc receptor activation) anti-human α2 integrin-blocking antibody, was evaluated for its safety and efficacy in phase II trials (NCT02222948/NCT02306811) in patients with relapsing/remitting multiple sclerosis. These trials were terminated because they lacked efficacy. Bleeding complications were not reported.[48]

Passive transfer of platelet alloantibodies by transfusion of therapeutic plasma is a rare cause of thrombocytopenia in the recipient, that is, in almost all cases, caused by anti-HPA-1a antibodies originating from plasma units of female blood donors with a history of pregnancy.[49] To our knowledge, only one single case report of passive alloimmune thrombocytopenia due to anti-HPA-5b antibodies was published.[50] Given the thousands of anti-HPA-5b-containing plasma units that were transfused annually worldwide before the implementation of the male-only plasma policy, this case report may represent a coincidence rather than a causative role of anti-HPA-5b antibody and thrombocytopenia in this patient.

Anti-HPA-5a antibodies,[51] as well as antibodies to rare antigens residing on the α2 integrin chain (HPA-13b,[52] HPA-18b,[53] HPA-25b[54]), were detected in suspected FNAIT cases. Furthermore, anti-HPA-5b antibodies were described in association with post-transfusion purpura[55–57] and humoral graft-versus-host reaction[58] following allogeneic haematopoietic stem cell transplantation. Given the observational nature of these rare case reports, any conclusion on the causation of thrombocytopenia by the implicated antibodies cannot be drawn.

Anti-HPA-5b antibodies are frequently detected in patients with earlier transfusions[59] and platelet transfusion refractoriness. Immunization against human leukocyte antigen (HLA) class I antigens is the primary cause of immune-mediated refractoriness to platelet transfusions.[60] The detection of anti-HPA-5b antibodies in patients who had transfusion is usually confounded by concurrent anti-HLA class I antibodies.[59,60] Thus, the putative causative role of anti-HPA-5b antibodies in platelet transfusion refractoriness remains unclear.

In conclusion, weak evidence from one study[23] confirmed a small proportion of healthy pregnant women presenting with anti-HPA-5b antibodies will give birth to a newborn with mild thrombocytopenia. This study should be independently replicated and future studies must report complete data on fetal/neonatal outcome in all cases and in an unbiased control group.[61] Retrospective cohort studies of suspected FNAIT cases have demonstrated a marginal anti-HPA-5b antibody prevalence enrichment compared with healthy controls.

Current experimental and epidemiological evidence does not support the hypothesis that anti-HPA-5b antibodies cause severe thrombocytopenia. To prove or reject this hypothesis, a large prospective screening study that focuses on the natural course of anti-HPA-5b-associated pregnancies is needed.[33] Severe bleeding complications (e.g. ICH) in rare cases could be the result of coincidence or may be caused by other anti-HPA-5b-associated mechanisms not related to thrombocytopenia. So, the possible pathogenesis of ICH in cases with maternal HPA-5b is unclear. Therefore, in pregnant women without earlier pregnancies complicated by thrombocytopenia and/or bleeding complications and with incidental finding of anti-HPA-5b, prophylactic therapy with intravenous immune globulin (IVIG) does not seem to be justified. IVIG is used off-label for this indication and has significant side effects.

During the last two decades, the prospective screening of pregnant women for anti-HPA-1a associated FNAIT[62] has been discussed. The results of the present study show that prospective screening of pregnant women for anti-HPA-5b alongside with screening for anti-HPA-1a-associated FNAIT is not supported by current evidence.

ACKNOWLEDGEMENTS

We are indebted to Thijs de Vos who provided additional information concerning a recent publication.[33]

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Gregor Bein and Sentot Santoso designed the study. Yalin Duong, Sandra Wienzek-Lischka, and Nina Cooper retrieved data from the in-house laboratory information system and performed retrospective analysis of clinical

data. Julia Alm and Gregor Bein designed the search strategy for meta-analysis. Julia Alm and Gregor Bein screened and extracted data from the literature. Gregor Bein and Julia Alm contributed to the first draft of the manuscript. Ulrich J. Sachs and Volker Kiefel interpreted the data and critically revised the manuscript. Gregor Bein assumed the final responsibility to submit the manuscript for publication. All authors had full access to all data, carefully reviewed the manuscript and approved the final version.

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How to cite this article: Alm J, Duong Y, Wienzek-Lischka S, Cooper N, Santoso S, Sachs UJ, et al. Anti-human platelet antigen-5b antibodies and fetal and neonatal alloimmune thrombocytopenia; incidental association or cause and effect?. Br J Haematol. 2022;198:14–23. https://doi.org/10.1111/bjh.18173