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IMMUNE HEMATOLOGIC DISEASE

TRANSFUSION

A combined effect of anti-HPA-1a and anti-HLA Class I in pregnancy?

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Abstract

Background: Maternal anti–human leukocyte antigen (HLA) Class I is commonly detected alongside anti–human platelet antigen (HPA)-1a in fetal and neonatal alloimmune thrombocytopenia (FNAIT). Little is known regarding whether the presence of anti-HLA Class I may exert an additive effect on the risk and severity of FNAIT.

Methods and Materials: We reanalyzed samples originally collected as part of a large Norwegian screening study on FNAIT during 1995-2004. This study identified and managed 170 pregnancies where the mother was HPA-1a negative and had detectable anti-HPA-1a during pregnancy. Maternal samples from 166 of these pregnancies were rescreened for anti-HLA Class I, revealing 111 (67%) that were antibody positive. Various regression models were used to assess if and how maternal anti-HLA Class I influenced the neonatal platelet count.

Results and Conclusions: Unadjusted neonatal platelet counts and the frequency of neonatal thrombocytopenia was not significantly affected by the presence of anti-HLA Class I alongside anti–HPA-1a, but results from regression analyses revealed a possible increased risk when the mother was nulliparous. These results warrant further investigation.

The causative role of maternal human platelet antigen (HPA) antibodies in fetal and neonatal alloimmune thrombocytopenia (FNAIT) is well established, but it is still not clear what role anti-HLA Class I may play in FNAIT.[1-7] Interestingly, a combination of anti-HLA Class I and anti-HPA antibodies is detected in as many as 37% to 45% of mothers giving birth to a neonate with FNAIT.[8-12]

Our group recently demonstrated that in neonates with suspected FNAIT, where maternal anti-HLA Class I was detected but no HPA antibodies, these antibodies specifically targeted paternally inherited epitopes.[13] Further, our data showed a possible association between anti-HLA Class I level in the mother and perinatal outcome in relation to neonatal thrombocytopenia.[13,14] Anti-HLA Class I

Abbreviations: FNAIT, fetal and neonatal alloimmune thrombocytopenia; HLA, human leukocyte antigen; HPA, human platelet antigen; ICH, intracranial hemorrhage; MAIPA, monoclonal antibody immobilization of platelet antigen; MFI, median fluorescence intensity

is a well-known cause of platelet refractoriness following transfusion.[15,16] These antibodies are also commonly detected during pregnancy in general, although their potential impact remains unclear.[17]

Despite being a common occurrence, the possible additive effect on anti-HLA Class I on HPA-1a–induced FNAIT has not been studied in a prospective setting. We hypothesized that the presence of maternal anti-HLA Class I, in addition to anti–HPA-1a, influence the severity of FNAIT. To investigate this hypothesis, we analyzed data from the previous large Norwegian screening study[18] and compared neonatal platelet counts in newborns of HPA-1a–immunized mothers with and without anti-HLA Class I.

1 | METHODS

1.1 | Study population

The samples were originally collected as part of a prospective screening and intervention study aiming to reduce morbidity and mortality of neonatal alloimmune thrombocytopenia.[18] A total of 100 448 pregnant women were recruited consecutively with no applied inclusion criteria from December 1995 until March 2004 from North Norway, and during September 2001 until March 2004 in the southern part of Norway. All included women were HPA-1a antigen typed, and all HPA-1a–negative women were screened for anti–HPA-1a and genotyped for *HLA-DRB3*01:01*. For the current study, all HPA-1a–negative women with anti–HPA-1a detected during pregnancy were included. Pregnancies without detectable maternal anti-HPA-1a and cases in which antibodies were detected only in the postpartum sample were not included in this study. All included neonates had a cranial ultrasound examination after delivery to check for intracranial hemorrhage.

1.2 | Laboratory analysis

Maternal blood samples were collected every fourth week during pregnancy and screened for anti–HPA-1a using flow cytometry or by monoclonal antibody immobilization of platelet antigen (MAIPA).[19] Quantification of anti–HPA-1a levels was done using a modified MAIPA test.[20,21] If anti–HPA-1a was detected, delivery was performed by cesarean section 2 to 4 weeks before term. Compatible HPA-1a–negative platelets were transfused to the neonate if the platelet count was less than 35×10^9/L and/or if petechiae were seen. The original study is described in further detail by Kjeldsen-Kragh et al..[18]

For the purposes of the current study, maternal anti-HLA Class I was later detected by a screening test (FlowPRA 1, One Lambda) in the maternal samples originally collected during the screening study. The samples were stored at −70°C. The last available sample before delivery was used for analysis, with a median sample time of 35 weeks of gestation (standard deviation, 3 weeks). The median fluorescence intensity (MFI) of all measured events for each sample was used as an approximation of anti-HLA Class I level.

1.3 | Definitions

Thrombocytopenia was defined as a platelet count below 150×10^9/L. Severe thrombocytopenia was defined as a platelet count below 50×10^9/L.

1.4 | Ethics

The study was approved by the Regional Committee for Medical Research Ethics, North Norway (REK 13/1995). Informed written consent was obtained from all women included in the study.

1.5 | Statistical Analysis

We used multivariable linear and logistic regression models to evaluate the potential impact of maternal anti-HLA Class I on neonatal platelet count. The linear models had platelet count ($\times 10^9$/L, continuous) as the dependent variable, while the logistic models had thrombocytopenia ($<150 \times 10^9$/L, yes/no) as the dependent variable. Maternal anti–HPA-1a level (log-transformed IU/mL, continuous) and parity (continuous) were included as covariates in all models due to their potential confounding effect, alongside anti-HLA Class I status (positive or negative).

All models were repeated with maternal anti-HLA Class I level (log-transformed MFI, continuous) as an independent variable, substituted for maternal anti-HLA Class I status (positive or negative).

Due to a significant interaction effect between parity and anti-HLA Class I status/level in all models, an interaction term parity × anti-HLA Class I status/level was included in all models.

There was no significant interaction between anti–HPA-1a levels and anti-HLA Class I status/levels in any of the described regression models.

The hypothesis of normally distributed data was tested using the Kolmogorov–Smirnov test. Differences in means for continuous variables with normally distributed data

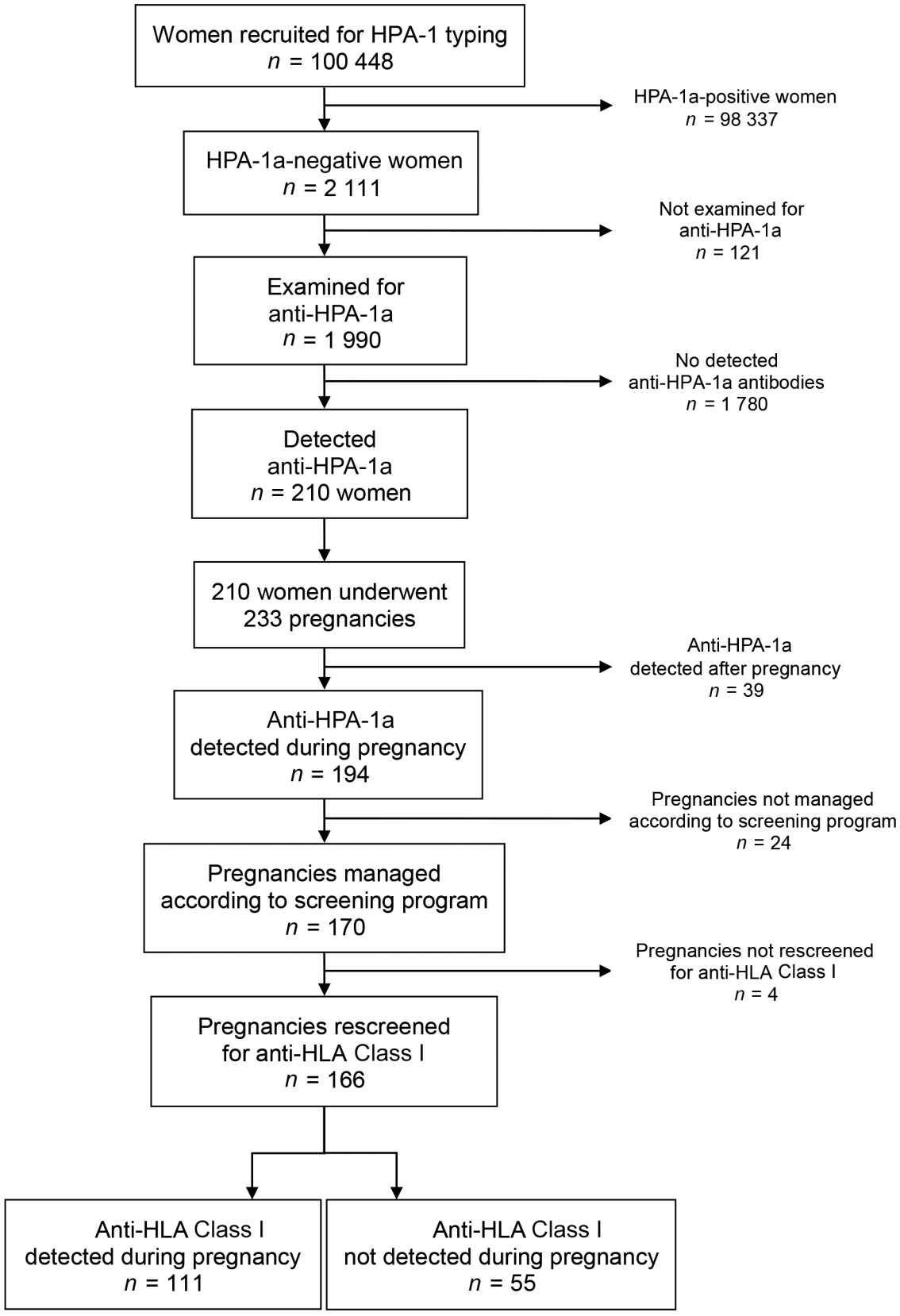

FIGURE 1 Study populations

were tested using an independent samples t test, while a Mann–Whitney U test was used for continuous variables that were not normally distributed. Fisher's exact test was used for comparing categorical variables between groups. A P value of <.05 was considered significant, and 95% confidence intervals (CIs) are reported where appropriate.

1.6 | Software

Statistical analysis was performed using computer software (Stata for Windows version 15.0, Stata Corporation). Figures and tables were also produced using computer software (Microsoft Office, Microsoft Corporation; and SPSS version 24.0, SPSS Inc.).

2 | RESULTS

Of the 100 448 pregnant women who were recruited, 2111 were typed as HPA-1a negative. A total of 1990 of these HPA-1a–negative women were examined for anti–HPA-1a, with a positive detection in 210 (10.6%). These 210 women underwent 233 pregnancies. Of these cases, anti–HPA-1a was detected during pregnancy in 194 women. Of these 194 pregnancies, 170 were managed according to the described program. Further details are described by Kjeldsen-Kragh et al..[18] Selection of study population is described in Figure 1.

For the current study, samples from 166 of the 170 HPA-1a–alloimmunized pregnancies were rescreened for anti-HLA Class I (samples missing for four pregnancies). The majority of these HPA-1a alloimmunized women (N = 111; 67%) tested positive for anti-HLA Class I (from here on referred to as anti-HLA positive). Further maternal and neonatal characteristics are described in Table 1.

Of the 166 samples 146 were typed for maternal *HLA-DRB3*01:01*, and of these, 135 (92%) were *HLA-DRB3*01:01* positive. Of nulliparous mothers, 33 of 38 (87%) were *HLA-DRB3*01:01* positive, while 102 of 108 (94%) of multiparous mothers were *HLA-DRB3*01:01* positive. This difference was not statistically significant (Fisher's exact test, P = .155). Among anti-HLA Class I–negative mothers, 45 of 48 (94%) were *HLA- DRB3*01:01* positive, while 90 of 98 (92%) of anti-HLA Class I–positive mothers were *HLA-DRB3*01:01* positive. This difference was not statistically significant (Fisher's exact test, $P = 1.000$).

Anti–HPA-1a levels and anti-HLA Class I levels were not significantly correlated (log-transformed antibody levels, Pearson's $r = 0.096$, p = 0.219). Anti–HPA-1a levels were significantly correlated with neonatal platelet count (log-transformed antibody levels, Pearson's $r = -0.574$, $P < .001$).

Unadjusted neonatal platelet counts, as well as the frequency of neonatal thrombocytopenia, were not significantly influenced by whether the mother had anti-HLA Class I (Table 1). Two neonates were found to have intracranial hemorrhage (ICH), and both had anti-HLA Class

TABLE 1 Maternal and neonatal characteristics for HPA-1a alloimmunized pregnancies

	All pregnancies (n = 166)	Anti-HLA antibody positive pregnancies (n = 111)	Anti-HLA antibody negative pregnancies (n = 55)	P value[a]
Nulliparous, n (%)	40 (24)	24 (22)	16 (29)	0.336
Primiparous, n (%)	89 (54)	59 (53)	30 (55)	0.999
Secundiparous, n (%)	30 (18)	21 (19)	9 (16)	0.831
Gestational age at delivery, mean wk[d] (SD)	37^1 (1^2)	37^1 (1^2)	37^0 (1^2)	0.521
Anti–HPA-1a positive at birth, n (%)	126 (76)	84 (76)	42 (76)	0.999
Anti–HPA-1a level at birth, median IU/mL (IQR)	1.4 (0.1-12.1)	2.7 (0.1-15.8)	0.6 (0.1-5.4)	0.196
Neonatal platelet count at birth, median (IQR)	151 (34-251)	131 (31-260)	166 (46-251)	0.519
	135 (28-246)[b]	76 (30-205)[b]	224 (26-266)[b]	0.176[b]
Thrombocytopenic newborns, n (%)	83 (50)	57 (51)	26 (47)	0.742
	20 (50)[b]	15 (63)[b]	5 (31)[b]	0.105[b]

Note: There were no missing data for the described variables.

Abbreviations: HLA, human leukocyte antigen; HPA, human platelet antigen; IQR, interquartile range; SD, standard deviation.

[a]Comparing anti-HLA–positive vs –negative pregnancies.

[b]Only pregnancies from nulliparous mothers.

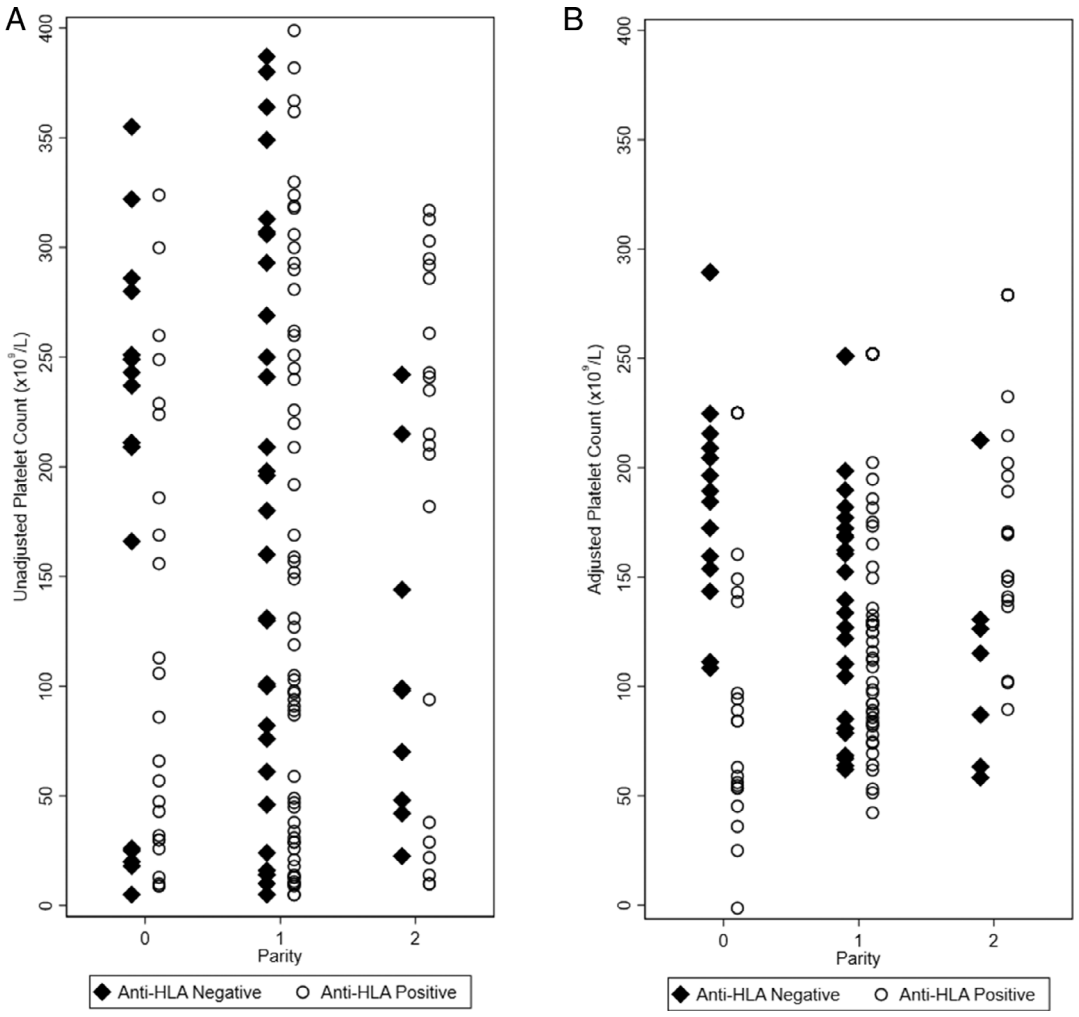

FIGURE 2 A, Unadjusted neonatal platelet counts. Unadjusted neonatal platelet counts sorted by maternal parity and antibody status. Parity >2 not shown (N = 7). B, Adjusted neonatal platelet counts.* Predicted neonatal platelet counts sorted by maternal parity and antibody status. Parity >2 not shown (N = 7). *Adjusted for anti–HPA-1a level, parity, anti-HLA Class I antibody presence and interaction between parity and anti-HLA Class I presence using a linear regression model described under Methods

I–positive mothers. Unadjusted neonatal platelet counts are presented in Figure 2A.

Adjusted platelet counts (using the linear regression model described in Statistical Analysis) were significantly influenced by anti-HLA Class I status in pregnancies in which the mother was nulliparous (ie, expecting the first child) or secundiparous (ie, expecting the third child). In pregnancies in which the mother was nulliparous, there was a significantly reduced neonatal platelet count if the mother was anti-HLA positive ($\beta = -64 \times 10^9$/L, 95% CI, −116 to −12). There was no significant difference in platelet count between children born of women with and without HLA antibodies if the mother was primiparous (ie, expecting the second child). In contrast to the nulliparous mothers, there was a significantly increased neonatal platelet count if the mother was secundiparous and anti-HLA positive ($\beta = 67 \times 10^9$/L, 95% CI, 10-123). Results from the linear regression model are presented in Table 2. Adjusted neonatal platelet counts from the linear regression model, in relation to parity and maternal anti-HLA status, are presented in Figure 2. The figure demonstrates the difference in neonatal platelet count between the anti-HLA–positive versus –negative group for different levels of parity.

In line with the results from the linear regression model, which used a continuous platelet count as the dependent variable, there was also an increased risk of neonatal thrombocytopenia among the anti-HLA–positive group if the mother was nulliparous in the logistic model (OR, 6.99; 95% CI, 1.70-28.72), and a decreased risk if the mother was secundiparous (OR, 0.09; 95% CI, 0.02-0.45). There was no significant difference in risk of thrombocytopenia between children born of primiparous women with or without HLA antibodies (data not

shown). Results from the logistic regression model are presented in Table 3.

Self-reported gravida status was available for all included women (N = 166). There were 13 women who reported to be primigravida, of which 5 (38%) were anti-HLA positive. To assess whether the effect on platelet count was due to the mother being primigravida rather than nulliparous, we repeated the regression analyses with these 13 primigravida pregnancies excluded. The effect estimates without the primigravida included were similar to those from the main models. Anti-HLA–positive pregnancies were associated with a reduced neonatal platelet count (β, -93×10^9/L; 95% CI, −156 to −30) and increased risk of neonatal thrombocytopenia (OR, 26.67; 95% CI, 3.50-203.01) if the mother was nulliparous, and an increased neonatal platelet count (β, 77×10^9/L; 95% CI, 18-136) and reduced risk of neonatal thrombocytopenia (OR, 0.05; 95% CI, 0.01-0.31) if the mother was secundiparous. There was still no significant difference in neonatal platelet count or risk of thrombocytopenia between anti-HLA–positive and –negative pregnancies if the mother was primiparous (data not shown).

Self-reported information on paternity was available in 133 pregnancies (80%). The majority (N = 105; 63%) reported that all births had been with the same father. Repeating the aforementioned regression analyses with this information included as a dichotomous variable (yes/no) produced similar estimates: Anti-HLA–positive pregnancies were associated with a reduced neonatal platelet count (β = -85×10^9/L; 95% CI, −150 to −19) and increased risk of neonatal thrombocytopenia (OR, 18.72; 95% CI, 2.35-149.02) if the mother was nulliparous, and increased neonatal platelet count (β = 77×10^9/L; 95% CI, 11-142) and reduced risk of neonatal thrombocytopenia (OR, 0.06; 95% CI, 0.01-0.42) if the mother was secundiparous.

We further repeated the analyses using a semiquantitative measure of anti-HLA level. MFI levels of maternal anti-HLA Class I (continuous) were not significantly correlated with neonatal platelet count for the study population as a whole (log-transformed antibody level, Pearson's $r = -0.057$; p = 0.465). However, we did see an effect of these antibody levels on neonatal platelet counts in the regression models. Increasing MFI levels of maternal anti-HLA Class I were significantly associated with a reduced neonatal platelet count (β = −18.7; 95% CI, −36.6 to −0.9) as well as an increased frequency of neonatal thrombocytopenia (logistic regression, OR, 1.88; 95% CI, 1.09-3.25) when the mother was nulliparous. Likewise, among pregnancies where the mother was

TABLE 2 Linear regression coefficients for neonatal platelet counts by levels of parity[a]

Variable	β	SE	95% CI
Anti-HLA class I antibodies (positive/negative)			
Parity = 0	−64.2	26.2	−116.0 to −12.5
Parity = 1	1.2	16.1	−30.6 to 32.9
Parity = 2	66.5	28.8	9.7 to 123.4
Parity (0-4)	−38.4	19.5	−76.9 to 0.1
Anti–HPA-1a level (IU/mL, log-transformed)	−23.9	2.7	−29.1 to −18.6
Interaction term (Anti-HLA Class I × parity)	65.4	22.3	21.2 to 109.5

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; HPA, human platelet antigen; SE, standard error.
[a]Beta coefficients for parity >2 (N = 7) are not presented, since none of these were anti-HLA Class I negative.

TABLE 3 Odds ratios for neonatal thrombocytopenia by levels of parity[a]

Variable	Odds ratio	SE	95% CI
Anti-HLA Class I (positive/negative)			
Parity = 0	6.99	5.04	1.70-28.72
Parity = 1	0.80	0.35	0.34-1.87
Parity = 2	0.09	0.07	0.02-0.45
Parity (0-4)	4.27	2.29	1.49-12.23
Anti–HPA-1a level (IU/mL, log-transformed)	1.76	0.16	1.48-2.09
Interaction term (Anti-HLA Class I × parity)	0.11	0.07	0.03-0.39

[a]Beta coefficients for parity >2 (N = 7) are not presented, since none of these were anti-HLA Class I negative.

secundiparous an increasing MFI level was associated with an increased neonatal platelet count (β = 20.5; 95% CI, 0.6-40.4) and reduced risk of neonatal thrombocytopenia (OR, 0.43; 95% CI, 0.22-0.83).

Mean maternal anti–HPA-1a levels around time of delivery were not significantly different when comparing HPA-1a–alloimmunized pregnancies with or without anti-HLA Class I (non–log-transformed median difference, 2.0 IU/mL; $P = .196$). Some of these women (N = 40) had detectable anti–HPA-1a earlier during pregnancy, but at the time of delivery the anti–HPA-1a was no longer detectable, and the antibody level included in the analysis was zero. If we exclude these 40 pregnancies and look only at the subpopulation where anti–HPA-1a antibodies were detectable also around time of delivery (N = 126 pregnancies; 76% of study population), the anti–HPA-1a antibody levels were higher in the anti-HLA–positive group (non–log-transformed median difference, 3.3 IU/mL; $P = .041$). The potential confounding effect of anti–HPA-1a level was accounted for by including it as a covariate in all regression models.

3 | DISCUSSION

Using data from a large prospective screening study, we have explored whether the presence of maternal anti-HLA Class I in addition to anti–HPA-1a are associated with an increase in both the risk and severity of FNAIT. The results from unadjusted analyses do not suggest that anti-HLA Class I increases these risks. This is in accordance with the results in a recent retrospective study from Germany.[22] However, regression analyses indicate that there may be an increased risk of FNAIT in nulliparous pregnancies. More surprisingly, our data also indicate that these antibodies may have a possible *protective* effect among secundiparous pregnancies. Overall, these results illustrate the complexity of this issue, and that we still cannot exclude the possibility that maternal anti-HLA Class I may play a role in FNAIT. These results also illustrate the importance of assessing several variables together when analyzing single factors that may impact neonatal thrombocytopenia and that important findings may be lost when not performing multivariate statistical analyses.

ICH in a previous child is a known risk factor for severe FNAIT.[23] Also, expression of the *HLA-DRB3*01:01* allele has been shown to be strongly associated with not only the risk of HPA-1a alloimmunization[24] but also neonatal outcome.[25] Whether maternal anti-HPA-1a levels influence the severity of neonatal alloimmune thrombocytopenia has been disputed by some.[26,27] However, a recent systematic review of the available literature concluded that there is an association between maternal anti–HPA-1a level and neonatal platelet count.[28] Importantly, our multivariate regression analyses indicate that the anti-HLA class I in nulliparous cases had an independent and additive effect on neonatal platelet counts, irrelevant of anti–HPA-1a level.

Due to the common occurrence of maternal anti-HLA class I during pregnancy,[29,30] it is surprising that no previous study has looked systematically at the possible additive effect of anti-HLA Class I on FNAIT severity in HPA-1 alloimmunization. However, a recent report identified HLA sensitization as a strong and independent predictor for anti-HPA formation.[31] These findings are in accordance with the high frequency of anti-HLA Class I in our study population (67%). These results may point to an underlying immune stimulation, resulting in alloimmunization toward several alloantigens. We did not examine for the presence of other anti-HPAs. However, given the rarity of such antibodies in comparison to anti–HPA-1a, it is unlikely that any other platelet-specific antibodies would have altered the results significantly.

Detection of maternal anti-HLA Class I is generally reported to be closely linked with increasing parity.[29,30] However, we found that the potential harmful effect of anti-HLA Class I on neonatal platelet count was predicated on observations in nulliparous women. This is in line with a recent observational studies of suspected cases of FNAIT due to anti-HLA Class I, where the frequency of nulliparous women was unexpectedly high for a population of pregnancies that was selected based on the presence of maternal anti-HLA Class I.[14,32] Nulliparity is known to be a significant risk factor for many adverse neonatal outcomes.[33] The maternal immune system may react more strongly to a maternal-paternal antigen mismatch in a first pregnancy, before a potential tolerance is achieved.[34] Or perhaps more likely, the anti-HLA Class I detected in multiparous women could be directed toward paternal antigens expressed in a previous pregnancy and therefore not relevant to the pregnancy in question. This is, of course, also possible for the nulliparous pregnancies where the mother was not primigravida. We were puzzled to find evidence of a possible protective effect of maternal anti-HLA Class I for women expecting their third, but not their second, child. This result is not easily explained biologically and must be interpreted with caution. Due to the small sample sizes, we cannot rule out the possibility of a false-positive result. How maternal HLA class I alloimmunization alongside anti–HPA-1a in multiparous women is associated with neonatal platelet count should be more closely addressed in future studies where HLA Class I genotyping of the mother and child is included. Our findings do not rule out the possibility that anti-HLA Class I may have similar harmful effects even in multiparous women if the anti-HLA Class I is paternal specific.

Due to the lack of fetal and maternal DNA, we were not able to confirm whether the anti-HLA Class I in question was child specific. However, in an observational study on anti-HLA Class I and neonatal thrombocytopenia, we recently demonstrated that the majority of maternal anti-HLA Class I in suspected cases of FNAIT (even in some multiparous pregnancies) were specific toward paternally inherited fetal epitopes.[13] We recommend that future studies include HLA Class I genotyping of the mother and child as part of their investigations.

It remains unclear why we repeatedly observe isolated thrombocytopenia in relation to anti-HLA Class I and not pancytopenia. There are multiple theories as to why this is, such as the abundance of platelets versus white blood cells present in circulation, but this question would have to be addressed in a study that includes repeated sampling of multiple cell counts.

There are many possible causes of neonatal thrombocytopenia, such as infection, fetal growth restriction, asphyxia, and many more.[35] In this study, we did not extensively rule out other possible causes of thrombocytopenia. However, since this was a prospective study where we compared neonatal platelet counts from HPA-1a–immunized women based on whether they had anti-HLA class I in addition, it is unlikely that the distribution of other underlying factors contributing to neonatal thrombocytopenia would be differently distributed between these two groups, as long as these factors are not closely tied to the development of anti-HLA Class I.

The data presented in this study originate from a large prospective study conducted in Norway, with very few missing data, and should therefore be representative of a North European population of pregnancies where the mother is HPA-1a negative.

The MFI used to describe anti-HLA Class I level in this study is an approximation, since the FlowPRA 1 Screening Test is not validated as a quantitative measure of antibody level by the producer. Any findings related to anti-HLA Class I level should therefore be interpreted with some caution. We recommend that future studies implement assays validated for quantification of anti-HLA Class I levels to further investigate these hypotheses.

We did not have data on neonatal platelet count in pregnancies from HPA-1bb women without detectable anti–HPA-1a. Whether maternal anti-HLA Class I may also influence the risk of neonatal thrombocytopenia for this much larger population could therefore not be assessed but deserves to be considered in future studies.

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CONFLICT OF INTEREST

JD and HT have disclosed no conflicts of interest. JK-K, AH, BS, and MK belong to the group of founders and owners of Prophylix AS, a Norwegian biotech company, which has been developing a hyperimmune anti–HPA-1a IgG for the prevention of fetal and neonatal alloimmune thrombocytopenia. The assets of Prophylix AS was recently acquired by Rallybio IPA, LLC.

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