DOI: 10.1111/1471-0528.13343
www.bjog.org

True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: a prospective observational follow-up study

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Accepted 17 January 2015. Published Online 9 March 2015.

Objectives To assess neonatal platelet counts by comparing alloimmunised pregnancies from a Norwegian screening and intervention study with subsequent pregnancies from the same women.

Design Prospective observational follow-up study.

Setting A university hospital.

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).

Methods Follow-up of maternal anti-HPA-1a antibody levels and neonatal platelet counts from the screening pregnancies were compared with subsequent pregnancies. None of the women received antenatal intravenous immunoglobulin (IVIG) treatment and neonatal platelet counts were therefore comparable.

Main outcome measures Change in neonatal platelet counts from one HPA-1a incompatible pregnancy to the next. Maternal anti-HPA-a1 antibody levels from one HPA-1a incompatible pregnancy to the next.

Results Forty-five incompatible subsequent pregnancies were identified. Overall, the neonatal platelet count in the subsequent pregnancy was improved (18%), unchanged (52%), or worse (30%), compared with the corresponding screening pregnancy. There was one case of fetal intracranial haemorrhage (ICH) identified in the screening (intrauterine fetal death detected at 30 weeks of gestation) and no ICH cases recorded for the subsequent pregnancies. In cases where the platelet count was lower in the subsequent pregnancy, the maternal anti-HPA-1a antibody level was higher compared with the screening pregnancy. In comparison, the maternal antibody level was lower in subsequent pregnancies where the platelet count improved.

Conclusions In contrast to what is often stated, we found that the neonatal platelet count was increased or unchanged in the majority of subsequent pregnancies of HPA-1a-immunised women.

Keywords Alloimmunisation, anti-HPA-1a, FNAIT, immune thrombocytopenia, natural course, neonatal thrombocytopenia.

Please cite this paper as: Tiller H, Husebekk A, Skogen B, Kjeldsen-Kragh J, Kjær M. True risk of fetal/neonatal alloimmune thrombocytopenia in subsequent pregnancies: a prospective observational follow-up study. BJOG 2015; DOI: 10.1111/1471-0528.13343.

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a result of fetal–maternal incompatibility in human platelet antigens (HPAs). FNAIT may cause severe fetal and/or neonatal thrombocytopenia, with intracranial haemorrhage (ICH) as the most feared complication. The vast majority of FNAIT cases are caused by maternal anti-HPA-1a antibodies.[1,2]

The diagnosis of FNAIT is most often made after the delivery of a child with thrombocytopenia, with or without signs of haemorrhage. Previous obstetric history serves as a basis for antenatal management.[3,4] ICH or severe thrombocytopenia in the previous neonate is considered useful to predict an increased risk of severe FNAIT in subsequent pregnancies. In many western countries intravenous immunoglobulin (IVIG) is administered antenatally to the mother when the risk of FNAIT is considered to be high.[5–8]

The treatment is considered effective when the neonatal platelet count is increased in a subsequent pregnancy compared with the previous FNAIT pregnancy.[7] The common opinion has been that without antenatal treatment, the severity of FNAIT would be worse in subsequent pregnancies.[4,9] In the FNAIT literature, such a statement is often given without references at all, or with references that do not convincingly support this. Except for the recurrence risk of ICH,[3,10] the natural course of FNAIT in subsequent pregnancies has never been systematically studied.

In Norway, IVIG has not been used regularly as part of the antenatal treatment protocol of FNAIT. In most pregnancies maternal anti-HPA-1a antibody levels during pregnancy, and platelet counts in the newborn, therefore represent the natural course of HPA-1 immunisation and FNAIT. Since a large Norwegian screening and intervention study stopped including new pregnancies in 2004, several of the participants have become pregnant again and have followed a similar antenatal management programme as described in the previous screening and intervention study.[11] The maternal anti-HPA-1a antibody levels and the neonatal platelet counts are therefore directly comparable.

The aim of this study was to assess subsequent pregnancies in previously HPA-1a immunised women in order to describe the natural course of FNAIT over several pregnancies in the same woman.

Methods

Study population

In this prospective observational follow-up study, all HPA-1a immunised women from the Norwegian screening and intervention study who gave birth to one or more children from 2004 until August 2012, were identified.[11] Non-immunised (no detectable anti-HPA-1a antibodies) HPA-1bb women from the screening study were not included. HPA-1a compatible pregnancies (HPA-1bb children) were excluded. If the neonatal platelet type was missing, the pregnancy was also excluded to ensure that no HPA-1 compatible pregnancies were included.

Antenatal management strategy

Maternal anti-HPA-1a antibody levels at around 22 and 34 weeks of gestation, and at 6 weeks postpartum, were included for analyses. The risk of severe neonatal thrombocytopenia was considered to be high if maternal anti-HPA-1a antibody levels during pregnancy were ≥3 iu/ml. In such high-risk pregnancies, the child was delivered by elective caesarean section around 2 weeks before term, and the neonate was immediately transfused with HPA-1a negative platelets if the platelet count was below 35×10^9/l, or if the child had bleeding symptoms. None of the pregnant women received IVIG treatment.

Clinical data

The pregnancy included as part of the screening study was defined as the index pregnancy. All pregnancies identified after the screening study are referred to as subsequent pregnancies.

Medical records from all subsequent pregnancies were retrieved from the hospital(s) where the pregnancy was followed and where the child was born. General obstetrical data, such as gravidity, parity, maternal age at time of delivery, gestational age at time of delivery, and sex of the neonate, were obtained from the medical records of the patients. Gestational age at time of delivery was calculated from ultrasound-determined pregnancy due date and delivery date. Data on ICH in the fetus or newborn were assessed for all subsequent pregnancies, but no cases of ICH were found. The risk of ICH is reported to correlate with neonatal platelet count; therefore, neonatal platelet count was used as a surrogate outcome variable.

To assess the sequential newborn platelet counts, we categorised neonatal platelet counts in three groups according to the severity of thrombocytopenia: severe ($1–49 \times 10^9$/l) or moderate thrombocytopenia ($50–149 \times 10^9$/l), and normal platelet count ($\geq 150 \times 10^9$/l). The groups were compared in index and subsequent pregnancies.

Maternal anti-HPA-1a antibodies

The quantitation of anti-HPA-1a antibodies was performed using a modified monoclonal antibody immobilisation of platelet antigens (MAIPA) assay.[12]

An antibody level of 3 iu/ml discriminated between high- and low-risk pregnancies.

In this study, postpartum immunised pregnancies are defined as cases where maternal anti-HPA-1a antibodies were detected for the first time after delivery and were not detectable during pregnancy. Pregnancies where HPA-1a seroconversion was confirmed by a documented antibody-negative test early in pregnancy, followed by an antibody-positive test later in the same pregnancy, were defined as cases where HPA-1a alloimmunisation occurred during pregnancy. In cases where anti-HPA-1a antibodies were detected in all tests taken during pregnancy, the time of immunisation was not known.

Platelet typing

HPA-1 typing was performed using fluorogenic probes and a modified FAST 5′ nuclease assay (NA).[13] In cases where HPA-1 typing of the neonate was missing, DNA was obtained from buccal cells (Omni swabs; Whatman, GE Healthcare UK Limited, Buckinghamshire, UK). The purification of DNA was performed using a DNA isolation kit (QIAamp 96 Spin Blood kit; QIAGEN Inc., Valencia, CA, USA).

Statistics

Means (mean or median) and dispersion (95% confidence intervals or range) were calculated for all continuous variables. All data were analysed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant. An independent-sample Student's t test, Mann–Whitney test or ANOVA was used to compare means/medians for continuous variables. A linear mixed model was employed to assess associations between increasing parity or maternal anti-HPA-1a antibody levels and neonatal platelet counts. In the linear mixed model, the platelet count in the newborn was included as dependent variable. The dependency between repeated measures (i.e. several pregnancies for each mother) was controlled for by adding a compound symmetry covariance structure to the model. Parity was included as a factor with fixed effects. Maternal age, gestational age at time of delivery, fetal sex, and maternal anti-HPA-1a antibody level were included as covariates. Maternal anti-HPA-1a antibody levels in these models used the highest anti-HPA-1a antibody level measured before delivery, and until 24 hours after delivery. To obtain linearity, the antibody level was log-transformed when included as a continuous independent variable.

Results

Clinical characteristics

During the study period, 50 women were identified with at least one subsequent pregnancy after the index pregnancy. In total, 62 subsequent pregnancies were identified. After excluding HPA-1 compatible pregnancies or pregnancies where HPA-1 incompatibility could not be confirmed, 45 HPA-1a incompatible subsequent pregnancies were included in the study (Figure 1).

Almost half (47%) of the women were pregnant with their second child during the first subsequent pregnancy, indicating that more than half of the women were multiparous already in the index pregnancy (Table 1). The index pregnancy is therefore not necessarily the same as the first pregnancy or first child. In our study population, the premature delivery rate was 36%, with 16/45 subsequent pregnancies ending before 37 weeks of gestation (Table 1). The premature rate was similar for index pregnancies (36%). Data on reasons for prematurity were not available. The caesarean section delivery rate in subsequent pregnancies was high (82%), and was comparable with the mode of delivery of their older screened siblings (88%). There was one case of fetal ICH identified in the index pregnancies (intrauterine fetal death detected at 30 weeks of gestation). No cases of ICH were recorded for subsequent pregnancies (Table 1).

Neonatal platelet counts and maternal anti-HPA-1a antibody levels in subsequent pregnancies

Not all HPA-1a alloimmunised women gave birth to children affected by FNAIT: 19/50 (38%) of index neonates and 13/45 (29%) of neonates from subsequent pregnancies had normal neonatal platelet counts. The unadjusted neonatal platelet count in children from subsequent pregnancies was not significantly different compared with neonatal platelet counts in their older sibling when assessing all HPA-1a alloimmunised pregnancies (irrespective of neonatal platelet count), the pregnancies where the index children had FNAIT, or when assessing the group where the index children had normal neonatal platelet count, respectively (ANOVA test, $P > 0.05$, data not shown). Likewise, there were no significant differences between index- and subsequent HPA-1a alloimmunised pregnancies when comparing adjusted neonatal platelet counts (adjusted for maternal age, parity, gestational age at time of delivery, sex of the fetus, and maternal anti-HPA-1a antibody levels in a linear mixed model, as described in the Methods section). In the aforementioned analyses, postpartum immunised index pregnancies were not included.

To assess the possible impact of parity itself on the development of FNAIT, a linear mixed model was employed as described previously. In this model, the estimated increase in neonatal platelet count per birth was 26×10^9/l; however, this was not significantly different comparing the first-born child with their younger siblings ($P = 0.2$). Likewise, the confounding variables of maternal age, gestational age at time of delivery, and sex of the fetus were not significantly associated with neonatal platelet counts in this model (data not shown).

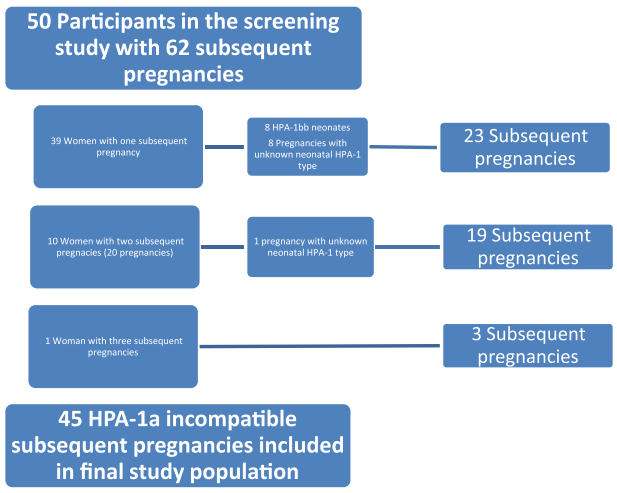

Figure 1. Overview of the study population. A total of 50 index pregnancies and 45 subsequent pregnancies were included in the final study population.

Table 1. Maternal and neonatal characteristics of subsequent pregnancies

Maternal characteristics	
Maternal age, mean (SD) years	33.0 (4.3)
Para 1, *n* (%)*	16 (47)
Maternal anti-HPA-1a antibody level, mean (range) iu/ml**	25 (0–182)
Mode of delivery, *n* caesarean sections (%)	37 (82)
Neonatal characteristics	
Gestational age at delivery in weeks^{days}, mean (range)	37^4 (32^5–40^4)
Premature deliveries, number of children born <37^0 weeks of gestation (%)	16 (36)
Birthweight, mean (range) grams	3122 (2250–4946)
Sex of the fetus, *n* boys (%)	20 (44)
Platelet count at birth, mean (range) × 10^9/ml***	115 (4–425)
Fetal/intracranial haemorrhage, *n* (%)	0 (0)

*Status during first subsequent pregnancy only (n = 34).
**Highest anti-HPA-1a antibody level measured during pregnancy and within 24 hours postpartum.
***Nine missing cases.

We also studied whether the individual patterns of neonatal platelet counts in each woman's child changed from one pregnancy to the next by classifying platelet counts into three groups, as described in the Methods section. For this analysis, the index pregnancy was compared with the first subsequent pregnancy. We had such paired data for 29 index and subsequent pregnancies. Overall, the neonatal platelet count in the subsequent pregnancy was increased to a category with higher platelet count in 18% of cases, unchanged (same category) in 52% of cases, and worse in 30% of cases compared with the corresponding index pregnancy. If we repeat these calculations including only pregnancies where the index child had FNAIT, two-thirds of younger siblings had higher or unchanged platelet counts and one-third had lower platelet counts.

If we just look at the subsequent pregnancies where the index pregnancy children had severe thrombocytopenia, ten of 14 (71%) subsequent pregnancies remained unchanged with severe thrombocytopenia, and four younger siblings improved to moderate thrombocytopenia (three cases) or normal platelet counts (one case). If we add maternal anti-HPA-1a antibody levels into this analysis, an interesting pattern was revealed: in cases where the platelet count remained low in the subsequent pregnancy, the maternal anti-HPA-1a antibody level in the subsequent pregnancy was higher (mean [SD], 64 [62] iu/ml, n = 10) compared with the index pregnancy (mean [SD], 20 [26] iu/ml, n = 18). In the four cases where the newborn platelet count was improved (i.e. to moderate thrombocytopenia or normalized in the subsequent pregnancy), data on maternal antibody level were available for three cases. In all these three cases the anti-HPA-1a antibody level fell by 38–82% compared with the index pregnancy.

In four index pregnancies where the child had moderate thrombocytopenia, one younger sibling had normal platelet count, two retained moderate thrombocytopenia, and in one case the platelet count was slightly lowered (35 × 10^9/l).

In 15 cases where the index child had normal platelet count (no FNAIT), the majority of younger siblings (10/15, 67%) also had a normal platelet count at birth. In five subsequent pregnancies FNAIT occurred: two with moderate and three with severe thrombocytopenia (platelet count of 4, 11 and 40 × 10^9/l, respectively). In conformity with the other platelet group antibody patterns, we found a clear increase in maternal anti-HPA-1a antibody levels when the platelet count was lower in younger siblings: the mean (SD) antibody level in subsequent pregnancies was 13 (12) iu/ml compared with 3 (10) iu/ml in the index pregnancies. When the platelet count remained normal in the subsequent pregnancy, the maternal antibody level was low and unchanged (range 0–4 iu/ml).

All index pregnancies classified as low risk with regard to maternal anti-HPA-1a antibody levels (<3 iu/ml) were also low risk in the subsequent pregnancies. Likewise, if the index pregnancy was at high risk (≥3 iu/ml), all corresponding subsequent pregnancies were also at high risk. We also found a significant association between maternal anti-HPA-1a antibody level and neonatal platelet counts after adjusting for confounding factors (maternal age, parity, gestational age at time of delivery, sex of the fetus, and maternal anti-HPA-1a antibody level) in a linear mixed model including both index and subsequent pregnancies ($P < 0.001$).

Time of immunisation

Postpartum immunised pregnancies were compared with cases where immunisation positively occurred during pregnancy in order to study whether different times of primary immunisation influenced the severity of FNAIT in

subsequent pregnancies. Maternal anti-HPA-1a antibody levels were known for five subsequent pregnancies where the mother was immunised after the index pregnancy, and for nine women who were primigravidae and immunised during the index pregnancy. For the remaining pregnancies we do not know the time of first immunisation. The median highest anti-HPA-1a antibody level in subsequent pregnancies from postpartum immunised women was 4 iu/ml (range 0–31 iu/ml). In comparison, the median highest anti-HPA-1a antibody level in subsequent pregnancies of women who were immunised during the index pregnancy was 35 iu/ml (range 0–182 iu/ml). The difference in median anti-HPA-1a antibody level was not statistically significant (Mann–Whitney test, $P = 0.2$). Correspondingly, the median neonatal platelet count in subsequent pregnancies after postpartum immunisation was 47×10^9/l ($n = 3$, range 4–79×10^9/l). The median platelet count in nine subsequent pregnancies of antepartum immunised women was 35×10^9/l (range 5–349×10^9/l). The difference in neonatal platelet counts when mothers were immunised during pregnancy compared with postpartum immunisation was not significantly different (Mann–Whitney test $P = 0.6$).

Discussion

Main findings

Previous severe FNAIT, with or without bleeding complications, is currently used clinically to determine the risk of severe FNAIT in subsequent pregnancies, and as such serves as the major basis for planning antenatal management. The underlying assumption is that FNAIT gets worse in younger siblings; however, the evidence for this foundation is questionable. In this prospective study, the natural course of FNAIT in several subsequent pregnancies is reported for the first time. Our data do not support the common opinion that the outcome after HPA-1a alloimmunisation generally gets worse in the next pregnancy. One should therefore be cautious to interpret increased neonatal platelet count in a subsequent FNAIT pregnancy as documentation of antenatal treatment effect. Our data show that younger siblings of FNAIT-affected children had unchanged or higher neonatal platelet counts *without* antenatal treatment in two-thirds of subsequent pregnancies. Larger studies are needed to clarify whether the efficacy of IVIG in the treatment of HPA-1a-immunised women is overrated. The most recent Cochrane study also questions the effect of antenatal IVIG treatment on neonatal platelet counts.[14] Importantly, it has been reported that IVIG might protect against ICH, irrelevant of platelet count.[10,15] This suggests that ICH may be triggered by additional mechanisms. We, along with others, recommend that IVIG should be given as treatment when a previous child has suffered FNAIT-induced ICH.

Strengths and limitations

As the inclusion of participants in the current study was based on the former Norwegian screening study,[11] the study population is considered to be representative of a larger study population. A similar management protocol and interventions were employed for the index and subsequent pregnancies. The only intervention performed before the neonatal platelet count was measured at the time of birth was to deliver the mother by elective caesarean section around 2 weeks before the due date. It is possible that the neonatal platelet counts may have been lower if the child was born spontaneous vaginally 2–3 weeks later because of the longer exposure time of maternal anti-HPA-1a antibodies to fetal platelets; however, the difference in platelet counts between the index pregnancy and the subsequent pregnancies would probably not be affected by this. The relative differences of neonatal platelet counts reported in this study may therefore qualify as describing the true natural course of HPA-1a immunisation from one pregnancy to the next.

Intracranial haemorrhage (ICH) is the clinical outcome of main concern regarding FNAIT; however, as only one ICH case occurred in the index pregnancy study population, and no ICH cases in the subsequent study population were detected, the recurrence risk of FNAIT-induced ICH could not be assessed. Retrospective data report this to be very high, however.[3,10] Importantly, our data include prospective FNAIT cases and may not be applicable in a retrospective setting, and therefore not applicable to FNAIT cases with previous brain bleeds.

It has been suggested that HPA-1a immunisation occurring during pregnancy may be different from immunisation taking place in connection with delivery.[15,16] When immunisation occurs in connection with delivery, maternal antibodies are detectable for the first time in the postpartum period. Maternal anti-HPA-1a antibody levels and corresponding neonatal platelet counts in subsequent pregnancies from postpartum immunised pregnancies were compared with pregnancies where the mother was immunised during pregnancy. The trend that maternal anti-HPA-1a antibody levels in the subsequent pregnancy seem to be higher when the mother was immunised during pregnancy, compared with mothers who were immunised postpartum, is interesting, even though the results did not reach statistical significance. Because of the sample sizes the statistical power to detect a significant difference is very weak, and we therefore cannot conclude from our data that there is no difference between these groups. We would welcome more data to clarify this issue.

Interpretation

Current clinical practice is to give high-dose IVIG antenatal treatment to all women where the risk of FNAIT is

considered high, based on obstetric history. A risk stratification to avoid unnecessary use of IVIG has been suggested by Pacheco et al.[17] They propose individualised treatment based on patient history and the presence of maternal anti-platelet antibodies and the corresponding platelet antigen on fetal cells. Our data further indicate that maternal anti-HPA-1a antibody levels during pregnancy may aid in identifying subsequent pregnancies where one expects severe thrombocytopenia as before, or cases where the women may be reassured that the outcome looks more promising this time. More data are needed to assess whether maternal anti-HPA-1a antibodies may be used as an additional parameter in risk assessment and contribute to a more selective use of antenatal IVIG.

Conclusion

The natural course of FNAIT in subsequent pregnancies using prospective data is reported for the first time. Our data do not support the idea that siblings necessarily have worse outcomes than the first-born child with low platelet counts.

Practical and research recommendations

The use of clinical history as the primary guideline for antenatal follow-up means that the primary at-risk pregnancies are not assessed before birth, when complications caused by severe FNAIT may already have occurred. To identify all pregnancies at risk of FNAIT, one should implement screening of all pregnant women. This study welcomes a discussion of the widespread use of IVIG in subsequent FNAIT pregnancies where the previous child did not have ICH.

Disclosure of interests

BS, AH, MK, and JKK have financial relationships with Prophylix. Pharma AS, a small medical company aiming to develop a FNAIT prophylaxis.

Contribution to authorship

HT, MK, AH, BS, and JKK all contributed to planning and designing the study. HT and MK performed the study and analysed the data. HT and MK wrote the article, with contributions from AH, BS, and JKK.

Details of ethics approval

The study was approved by the Regional Committee for Medical Research Ethics, North Norway, approval no: 5.2008.770. The experiments were undertaken with the understanding and appropriate informed consent of each participant.

Funding

This work was supported by a grant from the North Norwegian Health Authorities.

Acknowledgement

We would like to thank Professor Tom Wilsgaard, Department of Community Medicine, University of Tromsø (UiT), for guidance and supervision on the statistical analysis of the data. ■

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