OBSTETRICS

Antenatal intravenous immunoglobulins in pregnancies at risk of fetal and neonatal alloimmune thrombocytopenia: comparison of neonatal outcome in treated and nontreated pregnancies

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BACKGROUND: Maternal alloantibodies to human platelet antigen-1a can cause severe intracranial hemorrhage in a fetus or newborn. Although never evaluated in placebo-controlled clinical trials, most Western countries use off-label weekly administration of high-dosage intravenous immunoglobulin in all pregnant women with an obstetrical history of fetal and neonatal alloimmune thrombocytopenia. In Norway, antenatal intravenous immunoglobulin is only recommended in pregnancies wherein a previous child had intracranial hemorrhage (high-risk) and is generally not given in other human platelet antigen-1a alloimmunized pregnancies (low-risk).

OBJECTIVE: To compare the frequency of anti-human platelet antigen-1a-induced intracranial hemorrhage in pregnancies at risk treated with intravenous immunoglobulin vs pregnancies not receiving this treatment as a part of a different management program.

STUDY DESIGN: This was a retrospective comparative study where the neonatal outcomes of 71 untreated human platelet antigen-1a-alloimmunized pregnancies in Norway during a 20-year period was compared with 403 intravenous-immunoglobulin-treated pregnancies identified through a recent systematic review. We stratified analyses on the basis of whether the mothers belonged to high- or low-risk pregnancies. Therefore, only women who previously had a child with fetal and neonatal alloimmune thrombocytopenia were included.

RESULTS: Two neonates with brain bleeds were identified from 313 treated low-risk pregnancies (0.6%; 95% confidence interval, 0.2—2.3). There were no neonates born with intracranial hemorrhage of 64 nontreated, low-risk mothers (0.0%; 95% confidence interval, 0.0—5.7). Thus, no significant difference was observed in the neonatal outcome between immunoglobulin-treated and untreated low-risk pregnancies. Among high-risk mothers, 5 of 90 neonates from treated pregnancies were diagnosed with intracranial hemorrhage (5.6%; 95% confidence interval, 2.4—12.4) compared with 2 of 7 neonates from nontreated pregnancies (29%; 95% confidence interval, 8.2—64.1; P=.08).

CONCLUSION: The most reliable data hitherto for the evaluation of intravenous immunoglobulins treatment in low-risk pregnancies is shown herein. We did not find evidence that omitting antenatal intravenous immunoglobulin treatment in low-risk pregnancies increases the risk of neonatal intracranial hemorrhage.

Key words: alloimmunization, antenatal management, human platelet antigen 1a, intracranial hemorrhage, intravenous immunoglobulins, neonatal alloimmune thrombocytopenia, newborn

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) occurs in approximately 1 per 1,000 births and is the single most common cause of severe neonatal thrombocytopenia in otherwise healthy term-born neonates.[1,2] The most critical complication of FNAIT is intracranial hemorrhage (ICH), estimated to occur in 1:10,000 newborns.[3] The major risk factor for ICH because of FNAIT is a previous sibling with ICH,[4] and the recurrence risk of ICH has been reported to be 80%.[5] Maternal alloantibodies against human platelet antigen (HPA)-1a is the most common cause of FNAIT in White people. In this situation, maternal immunoglobulin (Ig)G alloantibodies targeting paternally-inherited HPA-1a antigens on fetal platelets cross the placenta, and they can lead to thrombocytopenia with or without bleeding in the fetus or newborn.[6,7] There is currently no screening program or prophylaxis for FNAIT, so primary prevention is not an option. Secondary prevention, ie, prevention of severe neonatal outcomes of pregnancies where the mother is already alloimmunized, is only possible if the risk of FNAIT is recognized before delivery.

Currently, most Western countries use off-label weekly administration of high-dose intravenous immunoglobulins (IVIg) in pregnant HPA-1a-alloimmunized women to prevent ICH in the fetus or newborn. This costly treatment is generally regarded to be efficacious despite never being documented in a placebo-controlled clinical trial. As IVIg has been used for this condition for decades, it is considered unethical to test the efficacy of IVIg in a placebo-controlled clinical trial.[8] Solid evidence on IVIg's efficacy in preventing severe FNAIT is therefore lacking.[8,9] Yet, this treatment modality has been the core of several clinical guidelines and was recently also recommended by the

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AJOG at a Glance

Why was this study conducted?

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) can lead to intracranial hemorrhage (ICH), with a high recurrence risk. Despite a low level of clinical evidence, most countries recommend giving antenatal intravenous immunoglobulins (IVIg) to all alloimmunized women with a previous FNAIT-affected child to prevent fetal and neonatal ICH.

Key findings

This study systematically compared the frequency of FNAIT-associated ICH in non-IVIg–treated alloimmunized women (n=71) vs a comparable cohort of antenatally IVIg-treated pregnancies (n=403). Our comparison showed a similar risk of neonatal ICH in treated vs nontreated pregnancies, especially for the larger group of low-risk pregnancies (no ICH in previous pregnancy).

What does this add to what is known?

A better evaluation of antenatal IVIg in pregnancies is obtained by stratifying the risk of ICH on the basis of previous obstetrical history. Substituting antenatal IVIg treatment with a non-IVIg management regime may not increase ICH frequency in a low-risk cohort.

International Collaboration for Transfusion Medicine Guidelines.[10]

The Norwegian FNAIT management strategy differs from other Western countries, as IVIg is usually not administered to HPA-1a alloimmunized pregnant women where a previous child had FNAIT without ICH. Previously, antenatal IVIg was not recommended to any woman with an obstetrical history of FNAIT, including those with a previous ICH-complicated pregnancy. However, since 2014, antenatal IVIg has been recommended to pregnant women with a previous history of FNAIT-induced ICH[11] because of some evidence of reduced risk of recurrence.[12] Furthermore, women are offered cesarean delivery 1–2 weeks before term if the anti-HPA-1a levels are ≥3 IU/mL along with compatible platelets available for transfusion in case of neonatal thrombocytopenia and/or clinical signs of bleeding. Cesarean delivery is generally not indicated for HPA-1a-immunized women with lower antibody levels.[11] If antenatal IVIg reduces the incidence of ICH in HPA-1a-alloimmunized pregnancies, one would expect that the clinical outcome of FNAIT in Norway is less favorable than in other countries. To determine if this is the case, we investigated the neonatal outcome (ie, ICH) of the Norwegian management FNAIT program over a 20-year period and compared the results with other published cohorts[9] where antenatal IVIg was given.

Materials and Methods

Study design

The study was a retrospective comparative study where the neonatal outcomes in untreated Norwegian HPA-1a-alloimmunized pregnancies was compared with previously published outcomes of IVIg-treated pregnancies.[9] The study was approved by the Regional Committee for Medical Research Ethics, North Norway (REKNORD 2009/1585). All Norwegian women and their children over the age of 16 years gave informed written consent.

The Norwegian study cohort

Women who delivered at least 1 neonate diagnosed with FNAIT because of HPA-1a-alloimmunization from January 1997 to December 2017 in Norway and those who did not receive antenatal IVIg treatment were included. The cases were categorized as FNAIT if the neonatal platelet count was $<150\times10^9$/L, the child was HPA-1a positive, and the mother had anti-HPA-1a antibodies. If data on neonatal HPA-1a genotype were missing, the pregnancy was defined as HPA-1 incompatible and included if the paternal platelet type was HPA-1aa.

The pregnancies were identified from 2 groups as follows: clinical referrals to the Norwegian National Unit for Platelet Immunology (NNUPI) at the University Hospital of North Norway in Tromsø and participants in a previous Norwegian HPA-1a screening study.[13]

All Norwegian HPA-1a-alloimmunized participants in whom the risk of FNAIT was acknowledged before delivery were followed-up according to the Norwegian clinical guidelines[11], which included repeated fetal ultrasonographic examinations and maternal anti-HPA-1a antibody quantifications. In line with national recommendations, women with high anti-HPA-1a antibody levels (≥3 IU/mL) were delivered by elective cesarean delivery 1–2 weeks before term with immediate access to HPA-1a negative platelets to the newborn if the platelet count was $<35\times10^9$/L or if there were clinical signs of bleeding. If the anti-HPA-1a antibody level was <3 IU/mL, spontaneous vaginal delivery was recommended. The use of antibody levels to determine the mode of delivery was based on the results from a previous large screening and intervention study.[13,14]

Information regarding the demographic characteristics, obstetrical history, and the course and outcome of each pregnancy was retrieved from the medical records of the mothers and neonates. The gestational age at the time of delivery was calculated from the ultrasonographically-determined pregnancy due date. The first pregnancy where FNAIT was diagnosed during the study period was referred to as the index pregnancy, which in most cases coincided with the mother's first child. Index pregnancies from clinical referrals had no identified risk of FNAIT before delivery, whereas the risk of FNAIT was known before birth for all pregnancies from the screening group.

The ICH outcome was assessed by reviewing the medical record of the child. ICH was diagnosed through

ultrasound, computed tomography, or magnetic resonance imaging scanning of the newborn, and it was defined as ICH if the diagnosis was given in the medical journal. Pregnancies where an older sibling had ICH because of FNAIT were defined as high-risk, whereas pregnancies where a previous child had FNAIT without ICH were defined as low-risk. In the cases where no medical record for the child was established during the perinatal period, we concluded that there had been no clinical suspicion of ICH. If we could not verify whether perinatal medical record notes existed or not, these neonates were not included.

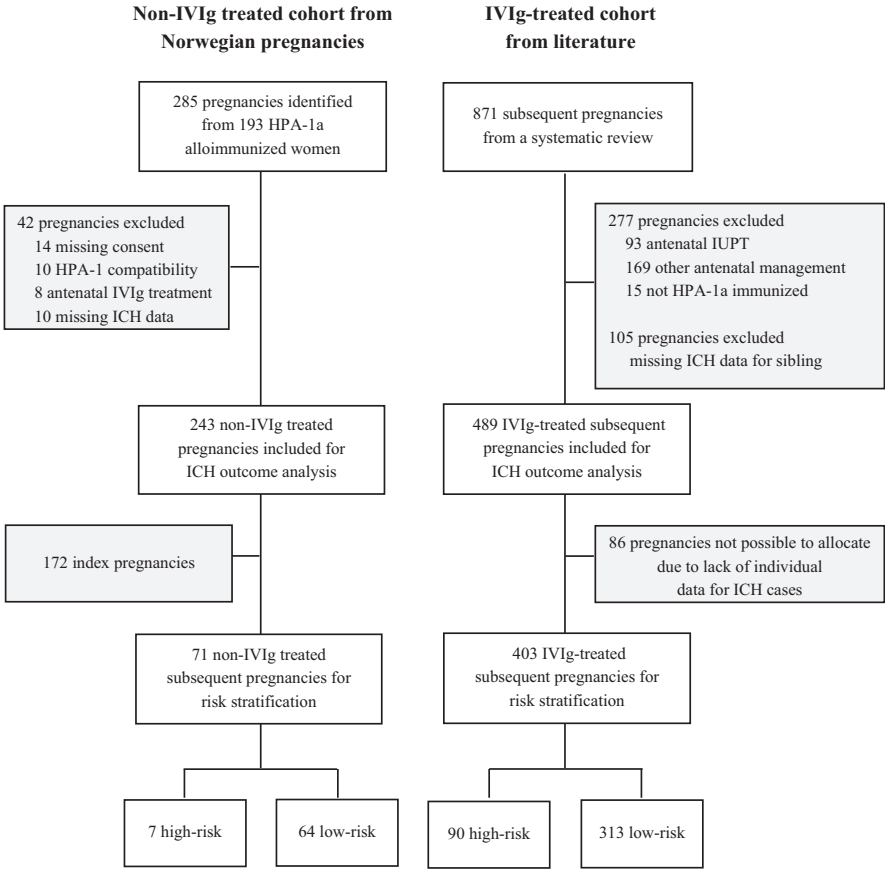
Laboratory results were retrieved from the clinical records at NNUPI and the previous screening study.[13] Platelet typing of the mother, neonate, and father and HPA-1a antibody detection were performed as previously described.[13]

The cohort of historic controls

To evaluate the ICH frequency in IVIg-treated cohorts, we identified the IVIg-treated pregnancies included in the systematic review of antenatal management in FNAIT by Winkelhorst et al from 2017.[9] Non-IVIg–treated pregnancies included in this review were excluded. This review applied the following inclusion criteria: (1) original study; (2) included ≥5 pregnant women with pregnancies at risk for FNAIT or fetuses or neonates diagnosed with FNAIT; (3) treated with either IVIg, steroids, or intrauterine platelet transfusions (IUPT); (4) included any of the outcomes: intracranial hemorrhage and fetal or neonatal platelet count; and (5) published in English. In total, 26 studies were identified.[9] For the current study, pregnancies included by Winkelhorst et al[9] were excluded if IUPT or steroids had been used as single treatment modality, if women were not treated with IVIg during pregnancy, or if FNAIT was caused by alloantibodies other than anti-HPA-1a (details in Supplemental Table 1).The original studies included in the review of Winkelhorst et al[9] were scrutinized to classify the pregnancies as high- or low-risk depending on the presence or absence of a previous sibling with ICH because of FNAIT (Supplemental Table 1). For those papers where it was not possible to perform this classification, the corresponding authors were contacted by e-mail to clarify this. Cases that could not be assigned to high- or low-risk categories were not included. The publications finally included as historic controls ranged in time from 1992 to 2015.

The main outcome was the presence or absence of ICH in the fetus or newborn. On the basis of the antenatal IVIg treatment status, we classified each pregnancy as "treated" or "untreated." We stratified the outcome analysis on whether the pregnancy was high- or low-risk and whether or not the pregnancy was IVIg-treated.

FIGURE
Overview of the study populations



The study includes a non-IVIg cohort of Norwegian HPA-1a immunized pregnancies and a control cohort of IVIg-treated pregnancies from the systematic review by Winkelhorst et al.[9]

HPA, human platelet antigen; *ICH*, intracranial hemorrhage; *IUPT*, intrauterine platelet transfusion; *IVIg*, intravenous immunoglobulin.

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Statistics

Statistical data were analyzed using SPSS software version 25.0 (SPSS Inc, Chicago, IL). The proportions of fetuses or newborns were expressed with corresponding 95% confidence intervals (CIs) calculated according to the "score method."[15] The Fisher exact test was used to test for differences in the numbers of ICH cases between populations. The comparison of platelet counts was performed by the Mann–Whitney test ($P<.05$).

Results

From the Norwegian study population, we identified 193 mothers with at least 1 child diagnosed with FNAIT in a total of

TABLE
Neonatal outcomes stratified on maternal antenatal intravenous immunoglobulins treatment status in subsequent pregnancies

FNAIT Risk group	No antenatal IVIg (Norwegian cohort)		Antenatal IVIg (control group)		
	Pregnancies n	Neonates with ICH n (%, 95% CI)	Pregnancies n	Neonates with ICH n (%, 95% CI)	*P* value[a]
Low-risk	64	0 (0, 0.0–5.7)	313	2 (0.6, 0.2–2.3)	1.00
High-risk	7	2 (29, 8.2–64.1)	90	5 (5.6, 2.4–12.4)	.08

Low-risk indicates pregnancies where a previous child had FNAIT without ICH; High-risk indicates pregnancies where an older sibling had ICH because of FNAIT.

CI, confidence interval; *FNAIT*, fetal and neonatal alloimmune thrombocytopenia; *ICH*, intracranial hemorrhage; *IVIg*, intravenous immunoglobulin; *n*, numbers.

[a] *P* value was calculated by Fisher exact test.

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285 pregnancies. After applying the exclusion criteria, 243 untreated pregnancies (135 pregnancies from clinical referrals and 108 from the screening group) were included for neonatal outcome analysis as outlined in Figure. In total, we identified 18 ICH cases equivalent to 7.4% (95% CI, 4.7–11.4), of which 16 were from index pregnancies. Of the 243 pregnancies, there were 172 index pregnancies; the remaining 71 were classified as subsequent pregnancies. Of the latter, 64 were categorized as low-risk pregnancies, and 7 were classified as high-risk pregnancies (Figure).

In the low-risk group, no ICH cases were identified among untreated pregnancies. Hence, the risk of ICH was 0.0% (95% CI, 0.0–5.7) (Table). Among these low-risk untreated pregnancies, 26 were identified through screening, and 38 were identified from clinical referrals. The neonatal platelet counts from subsequent pregnancies were similar among pregnancies recruited from clinical referrals or screening, though the platelet counts in index neonates identified by screening were significantly higher (median, 30×10^9/L) than index referrals neonates (median, 16×10^9/L; P=.033).

To avoid a false low ICH frequency because of these partly prospective data, we performed a sensitivity analysis, where we evaluated which screening pregnancies would likely have also been identified in a nonscreening setting. Ten of the 26 neonates in the screening group had older siblings with signs of bleeding at birth and neonatal platelet count $<30\times10^9$/L (median, 10×10^9/L). The neonatal platelet counts in these were not significantly different from the index referral neonates (median, 16×10^9/L; P=.07). It is likely that these FNAIT cases would have been identified in the absence of a screening program. Thus, the adjusted estimated risk of ICH, assuming a nonscreening setting, with 48 (38+10) untreated pregnancies in the low-risk FNAIT population would be 0.0% (95% CI, 0.0–7.4).

Among untreated high-risk pregnancies, 2 out of 7 women gave birth to a child with ICH, which is equivalent to a recurrence risk of 29% (95% CI, 8.2–64.1) (Table). Of note, these 2 pregnancies took place before the change in national guidelines in 2014 recommending antenatal IVIg treatment to all high-risk pregnancies.

All women in the high-risk group underwent cesarean delivery. Among the low-risk pregnancies, 58/64 (91%) underwent cesarean delivery. Of these 58, 55 (95%) had anti-HPA-1a antibody levels ≥3 IU/mL.

In the antenatally IVIg-treated control group of 489 subsequent pregnancies (Supplemental Table 1), there were 12 neonates who had ICH. Hence, the overall ICH frequency was 2.5% (95% CI, 1.4–4.2). Two of the studies contributing to these 489 pregnancies included 5 ICH cases.[16,17] For these 5 ICH cases, individual data were missing and could therefore not be categorized (ICH status in the corresponding siblings or maternal treatment modality in the current pregnancy) (Supplemental Table 1). The 86 pregnancies reported in these 2 studies were therefore, not included in risk-stratified analysis. A total of 313 pregnancies were assigned as low-risk, of which 2 children had ICH (Table). Thus, the risk of ICH in the low-risk control group was 0.6% (95% CI, 0.2–2.3). Further, 90 pregnancies were categorized as high-risk pregnancies. In this group, there were 5 cases of ICH (Table), giving a frequency of ICH in the high-risk group of 5.6% (95% CI, 2.4–12.4). Individual platelet counts were not available for the treated population.

A comparison of neonatal outcomes between Norwegian untreated pregnancies with IVIg-treated pregnancy data from historic controls did not reveal any significant differences, neither in the main analysis (Table) nor in the sensitivity analysis. These results indicate that antenatal IVIg does not influence the risk of ICH with certainty if the mother has previously given birth to a child with FNAIT without ICH. For high-risk pregnancies, the risk of ICH was 6 times-lower among IVIg-treated pregnancies (Table).

Comment

Principal findings

The risk of ICH among low-risk FNAIT-pregnancies was similar among the treated and nontreated pregnancies (treated: 2/313, 0.6%; 95% CI, 0.2–2.3 vs nontreated: 0/64, 0.0%; 95% CI, 0.0–5.7). Refraining from antenatal

IVIg treatment did not increase the risk of ICH in low-risk pregnancies.

Results

This study systematically compared the frequency of FNAIT-associated ICH in a cohort of 71 neonates from non-IVIg-treated HPA-1a-alloimmunized women vs a comparable cohort of 403 neonates from IVIg- treated women.

We stratified the outcome analysis systematically on the basis of previous obstetrical history into low-risk and high-risk. As this is an entirely new approach, there are no comparable data, neither for treated nor for untreated pregnancies. Yet, 3 of the 18 studies that were the basis of our IVIg-treated historic controls, also included some untreated HPA-1a-alloimmunized pregnancies who gave birth to children without ICH.[18–20] The outcome from these untreated pregnancies supports our findings.

The observed ICH recurrence risk among untreated high-risk pregnancies in the current study was only 29%, which is considerably lower than a commonly cited narrative literature review which estimated the recurrence rate to be almost 80%.[5] Clinicians are probably more likely to publish a report of recurrent ICH in a subsequent pregnancy than if the subsequent child was born without ICH. Thus, the previous narrative review[5] may most likely have suffered from publication bias, which may have resulted in too high an estimate of recurrence rate.

Clinical and research implications

This study indicates that omitting antenatal IVIg treatment in HPA-1a alloimmunized pregnancies at a low risk of severe FNAIT complications (ie, no ICH in previous children) may not increase the risk of ICH in the newborn. This study therefore challenges the current management guidelines in most Western countries.

Our data may be valuable when consulting a woman with a previous history of HPA-1a-induced FNAIT to allow her to make an informed decision as to whether she should accept antenatal IVIg treatment or not. The risk estimates of ICH because of FNAIT without antenatal IVIg in a low-risk population are shown here for the first time. For women in the high-risk group, the recurrence risk of ICH may be lower than previously reported if it is untreated.[5]

It is worth noting that what is referred to as a nontreated pregnancy in the Norwegian cohort is not the same as no intervention. When the risk of FNAIT is recognized before birth, several measures are taken according to the national Norwegian clinical guidelines, including cesarean delivery 1 to 2 weeks before term and prompt transfusion with compatible platelets to the newborn.[11] The current Norwegian clinical guidelines are based on the non-IVIg intervention protocol used in a previous large screening study in Norway, where the results showed significant reduction in the number of newborns with ICH and intrauterine fetal deaths compared with historic controls.[13] The natural course and ICH recurrence risk without any follow-up or intervention may therefore be higher than the risk reported here, as the clinical effects of the interventions other than antenatal IVIg probably play a role in determining the outcome. This means that the true risk of ICH among the low-risk pregnancies may be higher if no follow-up or intervention was applied. However, our results still imply that a non-IVIg management regime could safely replace IVIg treatment among a low-risk pregnant population. The limited number of untreated high-risk pregnancies calls for cautious interpretation, and we support the continued use of antenatal IVIg for this small group of pregnancies.

Several Western countries are considering screening programs to identify pregnancies at risk of FNAIT.[13,21,22] However, it is an open question as to what antenatal management regime should be applied when a previous obstetrical history of FNAIT is missing to guide risk assessment. Currently, we do not have the risk assessment tools to identify pregnant women in a screening program who would benefit from antenatal IVIg treatment. There are ongoing endeavors to develop laboratory analyses[23–25] that may assist in predicting pregnancies at risk of severe FNAIT, which would benefit from antenatal IVIg treatment. Although international consensus has not been fully reached regarding the predictive value of anti-HPA-1a antibody levels during pregnancy, a systematic review has indicated that antibody levels in a prospective setting are associated with the neonatal platelet count.[24] Whether maternal anti-HPA-1a antibody levels could be useful to assess the need for antenatal IVIg in a prospective setting is not known, but it is an attractive idea. Testing of cell-free fetal DNA obtained from maternal blood for noninvasive prediction of the fetal HPA-1 type has also been suggested[26] as part of a screening program. In short, our data do not imply that no women should be offered IVIg treatment, but we need to learn how to identify those who would benefit from this treatment.

High-dosage IVIg treatment has a negative impact on the quality of life of a significant number of the treated pregnant women.[27–30] Moreover, the antenatal treatment of one HPA-1a-alloimmunized pregnant woman typically involves administration of 1 g/kg/wk IVIg for 20 weeks, which is equivalent to 1.4 kg IgG (assuming a body weight of 70 kg). Obtaining such a quantity requires approximately 310 L of plasma, which in turn requires 4.5 man-months of donor involvement (Supplemental Table 2). It is questionable whether such tremendous donor commitments are justifiable when a significant beneficial effect of IVIg has not been demonstrated in low-risk pregnancies.

Strengths and limitations

Because IVIg has been used for this condition for decades, it is now considered unethical to test the efficacy of IVIg in a placebo-controlled clinical trial.[8] This is problematic from a scientific view, because the pregnancy outcomes without IVIg are not known. Although the sample size of our nontreated cohort limits the statistical power, this is still the only and largest study population of its kind. More systematic data would be optimal, but considering the rarity of

FNAIT and the even rarer serious complications of ICH, it is virtually impossible to examine the effect of IVIg in a controlled clinical trial with ICH as the primary outcome. Hence, the design of the current study is the best possible approach to study this research question.

The Norwegian cohort consisted of both prospectively and retrospectively identified women. Thus, there is a potential risk of bias toward a less severe phenotype in the prospectively recruited group.[13,14] However, the sensitivity analyses for low-risk pregnancies showed no significant difference for ICH outcomes compared with the antenatally IVIg-treated control group, assuming a nonscreening setting. Sensitivity analysis among the Norwegian nontreated pregnancies supports the conclusion that this cohort represents typical FNAIT-pregnancies in severity. It is worth mentioning that all 71 untreated Norwegian pregnancies were representative in terms of their clinical characteristics and management, as national clinical guidelines on antenatal and perinatal management in pregnancies at risk of FNAIT are well-implemented throughout Norway, and all pregnancies included in the study originate from the whole country.

The maternal antibody levels were used to guide the delivery mode in the Norwegian cohort. Almost all neonates in the low-risk group were delivered by cesarean delivery. Even if it is not well-established whether cesarean delivery prevents ICH, this may have influenced the neonatal outcomes. Data on delivery mode within the IVIg-treated cohort were scarce. However, on the basis of the available data, we estimated the frequency of cesarean delivery to be approximately 60%, which is higher than the overall rates in American and European populations. Nevertheless, our main finding is that a non-IVIg management approach in low-risk pregnancies seems to be safe.

Termination of pregnancies because of fetal ICH would result in a lower incidence of neonatal ICH. However, to the best of our knowledge, there have been no terminated pregnancies among Norwegian HPA-1a immunized women because of fetal ICH during the study period. For the IVIg-treated cohort identified through a literature review, this information was not available.

Conclusions

Our study shows the risk estimates of FNAIT-associated ICH in low-risk pregnancies without antenatal IVIg. Bearing in mind the retrospective design and limited sample size of nontreated pregnancies, we did not find evidence that refraining from antenatal IVIg treatment increased the risk of ICH in low-risk pregnancies. Thus, we believe that the current study provides the most reliable data hitherto for the evaluation of IVIg treatment in low-risk pregnancies. ■

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J.K.K. belongs to a group of founders and owners of Prophylix AS—a Norwegian biotech company that has produced a hyperimmune antihuman platelet antigen (HPA)-1a immunoglobulin G (IgG) (NAITgam) for the prevention of HPA-1a-alloimmunization and fetal and neonatal alloimmune thrombocytopenia (FNAIT). J.K.K. is also a consultant for Rallybio IPA, LLC—a US biotech company that will continue the development of NAITgam until licensure. H.T. reports previous payment from Prophylix AS related to a patent on a monoclonal anti-HPA-1a antibody and is funded as a research consultant by Janssen since August 2021. H.T. will also be a local study site principal investigator in a planned multicenter natural history study on FNAIT sponsored by Rallybio. The other authors report no conflict of interest.

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SUPPLEMENTAL TABLE 1

IVIg-treated pregnancies, data extracted from Table in Winkelhorst et al,[1] 2017

References in Winkelhorst et al,[1] 2017	Study period year	Treatment	Overall pregnancies N	Low-risk (no ICH in sibling)		High-risk (ICH in sibling)		Reason for exclusion				
				N	ICH (n)	N	ICH (n)	Excluded (N) total	Other antenatal management	IVIG+ IUPT	not anti-HPA-1a	ICH in sibling not reported
Randomized controlled trials												
Paridaans et al,[2] 2015	2005–2007	IVIG 0.5 g	12	11	0			1			1	
		IVIG 1 g	11	11	0							
Berkowitz et al,[3] 2007	2001–2006	IVIG 2 g	37[a]	37[a]	1							
		IVIG 1 g + steroids	36	36	1							
Berkowitz et al,[4] 2006	1994–2001	IVIG (all)	40	36	NAC	4	NAC					
		IVIG + steroids (high)	19	16	NAC	3	NAC					
		Steroids (standard)	20					20	20			
Bussel et al,[5] 1996	1990–1993	IVIG	28	41	0	6	0	3			3	
		IVIG + steroids	26			4	0					
Prospective studies												
Kanhai et al,[6] 2006	1998–2003	IVIg ± IUPT	7			4	0	3		3		
Bertrand et al,[7] 2006	1984–2004	IUPT predelivery	2					2	2			
		IVIG ± IUPT	4	4	0							
		IVIG + steroids	13	11	0	2	0					
Radder et al,[8] 2004	1988–1999	IVIg ± IUPT	37					37		26		11
		FBS ± IUPT	13					13	13			
Silver et al,[9] 2000	1992–1997	IVIG	8					8				8
		Fetal IVIG	2					2	2			
Lynch et al,[10] 1992	1984–1989	IVIG	9	4	0	4	0	1		1		
		IVIG + steroids	9	5	0	3	0	1			1	
Retrospective studies												
Lugt et al,[11] 2015	2006–2012	IVIG 1 g (all)	5	2	0	2	0	1	1			
		IVIG 0.5 g (standard)	17	17	0							

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SUPPLEMENTAL TABLE 1

IVIg-treated pregnancies, data extracted from Table in Winkelhorst et al,[1] 2017 *(continued)*

References in Winkelhorst et al,[1] 2017	Study period year	Treatment	Overall pregnancies N	Low-risk (no ICH in sibling)		High-risk (ICH in sibling)		Reason for exclusion				
				N	ICH (n)	N	ICH (n)	Excluded (N) total	Other antenatal management	IVIG+ IUPT	not anti-HPA-1a	ICH in sibling not reported
Bertrand et al,[12] 2011	1981–2009	IVIG	27					27				78[b]
		IVIG + steroids	51[b]					51[b]				
		Steroids	11					11	11			
Mechoulan et al,[13] 2011	2002–2007	IVIG	17	16	0	7	0					
		IVIG + steroids	6									
Bussel et al,[14] 2010	1994–2008	IVIG 1 g	5			5	1					
		IVIG 1 g steroids	19			16	2	3		1	2	
		IVIG 2 g	4			4	0					
		IVIG 2 g + steroids	9			9	1					
Giers et al,[15] 2010	1997–1999	Fetal IVIG + IUPT	10					10	10			
te Pas et al,[16] 2007	2000–2005	IVIG	13	8	0	3	0	2		2		
van den Akker et al,[17] 2007	1989–2005	IVIG (all)	52[c]	47[c]	0	5	0					
		FBS + IVIG (all)	33	22	0	11	0					
		FBS + IUPT (standard)	13					13	13			
Ghevaert et al,[18] 2007	1998–2005	IUPT ± IVIG ± steroids	40					40		40		
		IVIG and/or steroids	7					7	4			3
		No treatment	8					8	8			
Yinon et al,[19] 2006	1999–2005	IVIG	24	17	0			7			7	
		No treatment	6					6	6			
Tiblad et al,[20] 2003	1991–2001	IVIG	9	9	0							
		IUPT	3					3	3			
		No treatment	6[d]					6	6			
Birchall et al,[21] 2003	1988–2001	IVIg ± IUPT	18	8	0	4	1	6		6		
		IUPT weekly	30[c]					30[c]	30[c]			
		FBS ± single IUPT	7					7	7			

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SUPPLEMENTAL TABLE 1

IVIg-treated pregnancies, data extracted from Table in Winkelhorst et al,[1] 2017 *(continued)*

References in Winkelhorst et al,[1] 2017	Study period year	Treatment	Overall pregnancies N	Low-risk (no ICH in sibling)		High-risk (ICH in sibling)		Reason for exclusion				
				N	ICH (n)	N	ICH (n)	Excluded (N) total	Other antenatal management	IVIG+ IUPT	not anti-HPA-1a	ICH in sibling not reported
Sainio et al,[22] 1999	1988–1998	IVIg ± IUPT	11	2	0			9		9		
		IUPT	4					4	4			
Kaplan et al,[23] 1998	1984–1994	IVIG	27	20	NAC	7	NAC					
		Steroids	10					10	10			
Kornfeld et al,[24] 1996	1985–1991	IVIG + IUPT	4					4		4		
		IVIG	6	5	0	1	0					
Murphy et al,[25] 1994	NR	IVIG + IUPT ± steroids	8					8	8			
		IUPT + steroids	7					7	7			
Wenstrom et al,[26] 1992	1989–1991	IVIG	2					2				2
		IVIG + steroids	4					4			1	3
Kaplan et al,[27] 1988	NR	IUPT	4					4	4			
		IVIG + IUPT	1					1		1		
Total			871	385	2	104	5	382	169	93	15	105

FBS, fetal blood sampling; *HPA*, human platelet antigen; *ICH*, intracranial hemorrhage; *IUPT*, intrauterine platelet transfusion; *IVIg*, intravenous immunoglobulin; *n*, number of cases; *NAC*, not able to classify ICH (not clear if antenatal IVIg was administrated during the pregnancies[4], ICH status in older sibling were not reported[4,23]); *NR*, not reported.

[a] 4 twin pregnancies; [b] 3 twin pregnancies; [c] 1 twin pregnancy; [d] ICH-status for older sibling in 1 FNAIT case was not reported. After exclusion, 489 pregnancies are included as historic IVIg-treated controls.

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SUPPLEMENTAL TABLE 2
Calculation on the basis of an antenatal intravenous immunoglobulin-dosage of 1 g/kg/wk in a person weighing 70 kg

Variables	Formula	Value
Weekly amount of IVIg	a	70 g
Number of treatment weeks	b	20
Total dosage of IgG	c = a×b	1400 g
Amount of plasma per plasmapheresis	d	0.65 L
Amount of extractable IgG per L plasma	e	4.5 g/L
Amount of plasma for treatment of 1 woman	f = c/e	311 L
Number of apheresis procedures for treatment of 1 woman	g = f/d	479
Time for 1 apheresis procedure	h	1.5 h
Number of apheresis hours for treatment of 1 woman	i = h×g	718 h
One man-month	j	160 h
Number of man-months for treatment of 1 woman	i/j	4.49

IgG, immunoglobulin G; *IVIg*, intravenous immunoglobulin.

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