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

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CHAPTER 9

FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA, MANAGEMENT AND OUTCOME OF A LARGE INTERNATIONAL RETROSPECTIVE COHORT

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ABSTRACT

Objective

To evaluate the management and outcome of a large international cohort of cases of pregnancies complicated by fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Methods

This was an observational prospective and retrospective cohort study of all cases of FNAIT entered into the international multicenter No IntraCranial Haemorrhage (NOICH) registry during the period 2001–2010. We evaluated human platelet antigen (HPA specificity, antenatal and postnatal interventions performed and clinical outcome.

Results

A total of 615 pregnancies complicated by FNAIT from 10 countries were included. Anti-HPA-1a was the most commonly implicated antibody. Antenatal treatment was administered in 273 pregnancies (44%), varying from intrauterine platelet transfusion to maternal administration of immunoglobulins, steroids or a combination of those. Intracranial haemorrhage was diagnosed in 23 fetuses or neonates (3.7%). Overall perinatal mortality was 1.14% (n=7).

Conclusion

This study presents the largest cohort of cases of FNAIT published. Our data show that antenatal treatment for FNAIT results in favourable perinatal outcome. Over time, in most centres, treatment for FNAIT changed from an invasive to a complete non-invasive procedure.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by an immunological process in which the mother produces an antibody-mediated response against a platelet-specific antigen [human platelet antigen (HPA)] that she herself lacks but that is present on the fetal platelets, inherited from the father.[1] The mother's antibodies, of the IgG (immunoglobulin) type, can cross the placenta and bind to fetal platelets. The antibody-coated platelets are subsequently removed from the fetal circulation by the reticuloendothelial system, which results in fetal thrombocytopenia. These same antibodies also may inhibit platelet production.[2] The proportion of individuals belonging to a particular platelet antigen type varies according to ethnicity. The immunodominant antigen in Caucasians is HPA-1a, which is responsible for 85% of the FNAIT cases, followed by HPA-5b in 10%.[3] Two percent of the Caucasians is HPA-1a negative. The reported incidence of FNAIT ranges from 1:350 to 1:1000.[4] The most severe complication is intracranial haemorrhage (ICH), leading to lifelong handicap or even death. The clinical outcome is often more severe than that of neonatal ICH from other causes.[3-6] The majority of ICH bleedings seem to occur by the end of the 2nd trimester.[7]

Without routinely screening for HPA antibodies, the disease is nowadays diagnosed after birth of the first affected child. Subsequently, antenatal treatment can only be offered in following pregnancies to avoid recurrence of severe FNAIT.

The aim of this study was to analyse management and outcome of the largest international cohort of FNAIT-cases to date, with emphasis on the different treatment modalities.

MATERIAL AND METHODS

Data collection

The No IntraCranial Haemorrhage (NOICH) registry database (http://www.NOICH.org) was initially set up in 2001 for the NOICH study, an international multicentre randomized controlled trial comparing 0.5 with 1.0 g intravenous immunoglobulins (IVIG) for the prevention of bleeding in the fetus and neonate at risk for FNAIT. This study was prematurely ended in 2008 due to lack of inclusion.[8] The registry was kept open for fetal treatment centres worldwide to enter data on pregnancies complicated by FNAIT. Data were entered both retrospectively and prospectively by 13 tertiary referral centres from 10 different countries around the world (fig. 9.1.) An observational cohort study of these data was performed.

Cases

A case was defined as affected by FNAIT if incompatibility between maternal and paternal/fetal HPA type was confirmed and maternal anti-HPA antibodies were detected.

Initially, cases were entered into the database for inclusion of the NOICH randomized trial. All non-randomized and non-eligible cases from the participating centers were included as well. After having prematurely ended the trial the contributing centres kept collecting cases. These were mainly referred patients known to be at risk of FNAIT because of a previous affected child. Some cases originated from a previous Norwegian screening study of FNAIT.[9]

Fetuses and neonates with major congenital or chromosomal abnormalities were excluded.

Outcome

The primary outcome variables were HPA specificity, maternal/ neonatal demographic characteristics and clinical outcome. Cases affected by ICH were not extensively described; we refer to our previous published paper for characteristics of the ICH group.[7] In that study, both older and younger siblings with ICH were also identified and included, resulting in a cohort of 43 cases. In the current study we focus only on the ICH case that were originally included in the NOICH regisitry, explaining the lower number (n=23) described in this paper.

Secondary outcome variable were antenatal and postnatal interventions performed in pregnancies complicated by FNAIT. Outcomes of pregnant women with a previous child with ICH, considered as at high risk, are described separately.

To set up the database, approval was given by the Leiden University Medical Centre's Medical Ethics Committee (MEC PP04.203) and by each centre's respective Institutional Review Board.

Statistical analysis

Categorical data are summarized as actual numbers and percentages. Continuous data reported are presented as medians or means values with ranges. The analysis was done using independent samples t-test. A p value of 0.05 was considered statistically significant. Data analysis was generated using SPSS software (version 20; SPSS Inc., Chicago, IL, USA).

RESULTS

The NOICH registry database contained data on 615 pregnancies complicated by FNAIT; part of these were registered prospectively: 23 for inclusion into the NOICH trial[8], and 177 as a result of the screening study in Norway.[9]

Figure 9.1 shows the contribution of the participating centres, a major part of which are situated in Norway, Sweden, and the Netherlands. The HPA antibody specifics are outlined in table 9.1, with anti-HPA-1a being the most commonly implicated antibody (88%). The maternal and neonatal demographics are shown in table 9.2; the cohort comprised 100 (19%) primiparous and 499 (83%) multiparous women. Of the

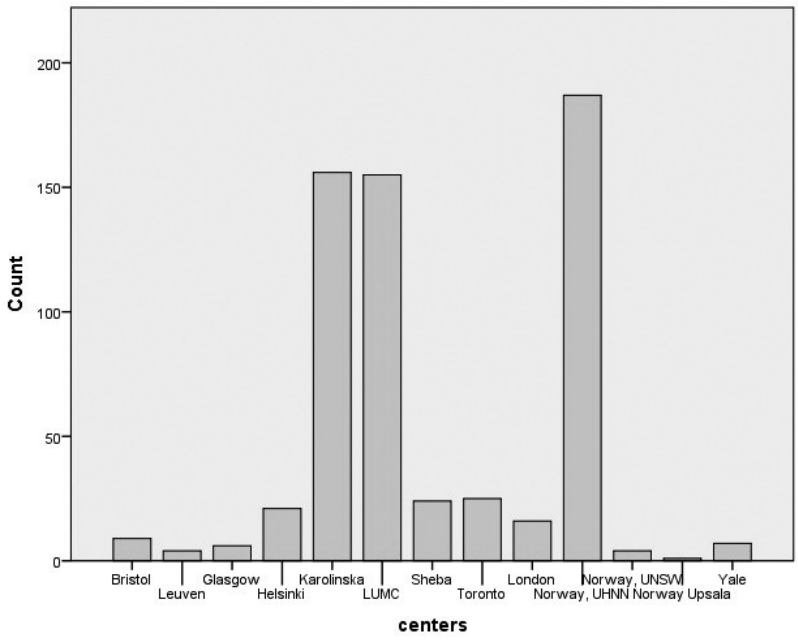

Figure 9.1
Participating centres. LUMC = Leiden University Medical Centre; UHNN = University Hospital North Norway; UHSW = University Hospital South Nor-way.

Table 9.1 HPA specifics

HPA type	Cases, n(%)	Mean PC $\times 10^9$/L	ICH, n
HPA-1a	544 (88)	105	19
HPA-5b	23 (3.6)	136	2
HPA-3a	7 (1.1)	147	
HPA-5a	4 (0.6)	184	
HPA-15a	5 (0.8)	200	
HPA-1a + -5b	18 (3)	94	2
HPA-1a + other*	5 (0.8)		
Negative	2 (0.03)		
Unknown	7 (1.1)		
Total	615		

HPA=Human platet antigen, PC= platelet count, ICH=intracranial hemorrhage

Table 9.2 *Maternal and neonatal demographic*

Pregnancy type	
Singleton	599 (97)
Multiple	16 (3)
Parity[a]	
Primiparous	100 (19)
Multiparous	499 (83)
History	
FNAIT[b]	343 (56)
IUFD	24 (7)
ICH	50 (15)
Mode of delivery[c]	
Vaginal	240 (39)
Instrumental	4 (0.7)
Elective Caesarean	289 (50)
Emergency Caesarean	46 (7.5)
Birthweight[d], g	
Mean (range)	2985 (400-4775)
Gestational Age, weeks	
mean (range)	37 (24-42)
Sex[e]	
Boys	229 (55)
Girls	188 (45)
Platelet count at birth[f]	
Mean (range) $\times$ 10^9/L	108 (1-104)
$<30 \times 10^9$/L	191 (31)
$< 50 \times 10^9$/L	235 (43)
50-100 $\times$ 10^9/L	78 (14)
100-150 $\times$ 10^9/L	59 (11)
$>150 \times 10^9$/L	172 (32)
Petechiae	100 (17)
Petechiae and PC $\times$ 10^9/L	81 (81)
ICH n(%)	23 (3.7)
IUFD n(%)	4 (0.7)

FNAIT= fetal and neonatal alloimmune thrombocytopenia, ICH=intracranial haemorrhage, IUFD= intrauterine fetal death
Values are presented as n (%) unless specified otherwise. a 17 cases missing. b 154 cases missing. c 36 cases missing. d 71 cases missing. e 198 cases missing. f 40 cases missing.

multiparous women, 343 were known to be at risk because of a previous history of FNAIT. This group contained 50 siblings with ICH (15%) and 23 cases of fetal demise (7%), which can be classified as high-risk pregnancies.

Almost all pregnancies were singleton pregnancies (97%). Of the 575 pregnancies with a known mode of delivery, 240 (39%) deliveries were by vaginal route, including 4 assisted by ventouse or forceps. Three hundred thirty-five (50%) caesarean sections were performed, of which 289 were elective. Most deliveries were after 32 weeks of gestation (98%). The mean birth weight was found to be 2985 g, with a mean gestational age of 37 weeks. The neonates were boys in 55% of the cases. When comparing boys and girls there was no significant difference in mean platelet count at birth (102×10^9/L in both groups) or in mean birth weights (2990 vs 2951 g). Severe thrombocytopenia ($<50\times10^9$/L) was found in 235 cases (43%) including 191 (31%) neonates with platelet counts of less than 30×10^9/L. Skin bleeding was reported in 94 (18%) cases, in most of these cases severe thrombocytopenia was found (94%).

Adverse Perinatal Outcomes

In the database 4 cases of intrauterine fetal death (IUFD) and 3 neonatal deaths were found, giving an overall perinatal mortality of 1.14%. In these cases no antenatal treatment had been given. Twenty-three neonates (4.5%) were affected by ICH, 9 were first-born children. Of the other 14 cases, 4 had a sibling affected by ICH due to FNAIT.

HPA-1a was the concerning antigen in the majority of cases (83%); in the other 4 cases, HPA-5a, HPA-5b, and a combination of HPA-1a/-5b was found. Nine of the neonates with ICH were treated during pregnancy; in 4 pregnancies treatment was started after ICH had been found. This is described in more detail in the next section.

A high proportion of the pregnancies complicated by ICH ended preterm: 12 of 23 children (52%) were born before 37 weeks, and 2 children were born before 28 weeks of gestation. Two children suffering from ICH died in utero and 1 post term. The neonates with ICH were male in the majority (76%) of cases. Furthermore 2 cases of intra-abdominal bleeding were found, 1 ending in IUFD at 24 weeks of gestation. In both pregnancies no antenatal treatment had been given.

Antenatal interventions

In 273 pregnancies some form of antenatal treatment was given, varying from cordocentesis with intrauterine platelet transfusions (IUPT) to maternal administration of intravenous immunoglobulins (IVIG), steroids or a combination of those (table 9.3). In most pregnancies (n=138) single treatment with IVIG was given, in 24 cases with 0.5 and in 102 cases with 1.0 g/kg per week (n=12 unknown). In 124 pregnancies invasive treatment was offered. The two groups were comparable according the definition of high-risk FNAIT. There was no difference in number of ICH or IUFD in previous sibling between the invasive and non-invasive group [26/124, 21% vs. 28/138 (20%), p=1.0].

The number of cordocentesis performed differed per centre. This ranged from 0% (0 per offered treatments in Scotland and Norway) to 100% (Canada). If we have a closer

Table 9.3 *Antenatal therapy*

	Cases n (%)	Mean PCat birth (range) $\times 10^9$/L	ICH n	IUFD n
FBS	21(3)	131 (5-302)	0	1
FBS + IVIG + steroids	20 (3)	144 (17-277)	2	0
FBS+IVIG	75 (12)	166 (12-391)	2	0
FBS +steroids	8 (1)	71 (4-166)	1	0
IVIG + steroids	8 (1)	70 (2-298)	0	0
IVIG	138 (22)	122 (4-354)	4	1
Steroids	3 (0.5)	270*	0	0
No treatment	338 (55)	86 (1-405)	14	2
Unknown	4			

FBS=fetal bloodsampling, IVIG= immunoglobulins, PC= platelet count, ICH= intracranial hemorrhage, IUFD=intrauterine fetal death
**= 1 case*

look at the major contributing centres in the database that performed cordocentesis during the study period (in the Netherlands and Sweden), a decline is seen in invasive procedures over the years (from 22% in 2005 to 0% in 2008, 2009 and 2010). One single centre performed cordocentesis up to 2009 (Canada; n=25).

There were 9 cases of ICH reported in the antenatally treated group. Looking at the data in more detail, 5 cases of ICH occurred in the invasive procedure group; in 4 patients it seems likely that invasive therapy with fetal blood sampling (FBS) and serial IUPT (with IVIG or steroids) had been started before the diagnosis of ICH was made during ultrasound examination. In 1 case ICH was found and subsequently invasive therapy was given.

The other 4 cases of ICH had been diagnosed before any antenatal treatment was given. In these pregnancies treatment with IVIG was started to prevent further worsening of bleeding. One of these pregnancies ended in IUFD 1 week after IVIG treatment had been started.

In the single FBS group, 1 IUFD was reported, seen 1 week after the first IUPT. It is unclear whether this was related to spontaneous fetal bleeding or to a complication of the procedure.

Outcomes of High-Risk Pregnancies

Th clinical outcomes of the high-risk pregnancies (n=73) are outlined in table 9.4. Fifty-six cases received antenatal treatmen (26 invasive versus 30 non-invasive). In this high-risk group, 3 cases of ICH were found (4.2%), 1 resulting in IUFD. In 1 of these pregnancies antenatal treatment was given (IVIG+ serial IUPT); in the other 2 cases IVIG was started after the diagnosis of ICH.

Table 9.4 *Clinical outcome in the high-risk group*

	Cases, n (%)	Median PC at birth (range) $\times 10^9$/L	ICH,n	IUFD, n
Total high-risk cases	73	96 (1 - 391)	3	1[a]
Platelet count < 50 X 10^9/L	18 (25)			
Platelet count < 30 X 10^9/L	16 (16)			
Antenatal treatment	**56**			
FBS+IVIG+steroids	4	70 (17 - 170)		
FBS+IVIG	21	181 (21 - 391)	1	
FBS	1	253		
IVIG+steroids	3	60 (2 - 296)		
IVIG	27	63 (10 - 340)	2	1[a]

FBS=fetal blood sampling, IVIG=immunoglobulins, ICH=intracranial hemorrhage, IUFD=intrauterine fetal death
[a] 1case suffering from ICH ended in IUFD

DISCUSSION

In this study we evaluated treatment and outcome of more than 600 cases of FNAIT, the largest cohort of cases of FNAIT published on thus far. The majority of cases were collected after a first affected pregnancy. The overall frequency of ICH in our study group is 3,7%, which is lower than previously reported.[10] This might well be explained by the several antenatal interventions performed in this group.

Antenatal treatment

Different treatment regimens were offered to avoid recurrence of any burden, divided into invasive (n=124) and non-invasive (n=138). An important observation was that, although rare, all bleeding complications (n=5) occurred in the invasively treated group (FBS+IUPT). No ICH cases were reported in the non-invasive group (maternal administration of IVIG). Although the exact cause of the adverse outcome in the invasively treated group could no be reliably assessed, at least we can conclude that there appears to be no benefit from invasive treatment over a non-invasive approach. Previous studies have calculated a cumulative risk of fetal loss per pregnancy of 6% directly related to complications of FBS and IUPT.[11,12]

Overall we can state that non-invasive antenatal treatment with maternal administration of IVIG appears successful in protecting fetuses and neonates from bleeding (138 cases treated, 0 cases of ICH reported). Furthermore, our study clearly indicates that over the years the invasive diagnostic and treatment approach in FNAIT has been almost completely replaced by safer non-invasive protocols.

Several reports have been published on IVIG treatment for FNAIT with a close to 100% success in preventing bleeding complications in fetuses and neonates.[13-18] Until now, the working mechanism of IVIG is not clear. Most likely, it acts on various levels,

i.e.in maternal serum, at the level of placental transfer of IgG and in the fetal blood, blocking Fc-receptors on macrophages.[19] Recent research by Yougbaré et al (2015) supports the hypothesis that IVIG may aid in protection against bleeding through a direct effect on endothelial cells, instead of merely causing a rise in platelets.[20] They showed that impairment of angiogenesis rather than thrombocytopenia is the critical cause of ICH in FNAIT. In their murine-model study, ICH only occurred in fetuses and neonates with anti–β3 integrin–mediated, but not anti-GPIbα–mediated FNAIT, despite similar levels of thrombocytopenia in both groups. Only anti–β3integrin–mediated FNAIT reduced brain and retina vessel density, impaired angiogenic signaling, and increased endothelial cell apoptosis. This might be an explanation for the phenomenon of 'non-responders', i.e. fetuses not responding to IVIG with platelet counts remaining below 50×10^9/L, reported to be around 20%.[21]

Outcomes in High-Risk Pregnancies

Most reports support the assumption that pregnant women with a previous child with an intracranial bleeding compose the highest-risk group; the ICH recurrence rate in subsequent pregnancies is reported to be around 79%.[22] Therefore, most clinicians caring for such pregnancies choose for a more aggressive approach as compared with the group in which the affected sibling did not have an ICH.

In our study, 73 FNAIT cases with a previous sibling with ICH or IUFD were reported; 56 of them received antenatal treatment with 1 case ending in ICH and finally IUFD. In this pregnancy, invasive therapy was given (combination FBS+serial IUPT with IVIG). In this high risk group 30 cases were treated completely non-invasively (all with IVIG, 3 in combination with steroids) and no ICH occurred.

FNAIT and Fetal gender

In our large data set of pregnancies affected by FNAIT, 55% of fetuses/neonates were male. Interestingly, in the group of children with ICH, the proportion of males was much higher (76%). A study by Tiller et al. showed a clear association between the levels of maternal HPA-1a antibodies and reduced birth weight in boys.[23] How the sex of the offspring is involved in FNAIT remains to be explored.

The strengths of our study are its large sample size,which is 3 times larger than the previously largest series[24], the input of data by multiple international centres and the variation in interventions performed. The results obviously need to be interpreted with care, given the limitation that a large part of the data was collected retrospectively, and a selection bias cannot be ruled out. More reliable data can only be obtained from prospective population screening studies.

CONCLUSION

Pregnancies affected by FNAIT, even with a severe history, now have an excellent prognosis. Our data confirm that there appears to be no benefit from invasive diagnostic or therapeutic procedures. Non-invasive management using IVIG with or without additional steroids prevents bleeding in the fetus or neonate in virtually all cases. Remaining issues for future research are timing and optimal dose of IVIG, the role of gender, and long-term neurologic outcome of the surviving affected children.

In several countries, preparations are being made to implement population screening studies of FNAIT.

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