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

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CHAPTER 6

FETAL INTRACRANIAL HAEMORRHAGES CAUSED BY FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: AN OBSERVATIONAL COHORT STUDY OF 43 CASES FROM AN INTERNATIONAL MULTICENTRE REGISTRY

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ABSTRACT

Objective
To characterise pregnancies where the fetus or neonate was diagnosed with fetal and neonatal alloimmune thrombocytopenia (FNAIT) and suffered from intracranial hae-morrhage (ICH), with special focus on time of bleeding onset.

Design
Observational cohort study of all recorded cases of ICH caused by FNAIT from the international No IntraCranial Haemorrhage (NOICH) registry during the period 2001-2010.

Setting
13 tertiary referral centres from nine countries across the world.

Participants
37 mothers and 43 children of FNAIT pregnancies complicated by fetal or neonatal ICH identified from the NOICH registry was included if FNAIT diagnosis and ICH was confirmed.

Primary and secondary outcome measures
Gestational age at onset of ICH, type of ICH and clinical outcome of ICH were the primary outcome measures. General maternal and neonatal characteristics of pregnancies complicated by fetal/ neonatal ICH were secondary outcome measures.

Results
From a total of 592 FNAIT cases in the registry, 43 confirmed cases of ICH due to FNAIT were included in the study. The majority of bleedings (23/43, 54%) occurred before 28 gestational weeks and often affected the first born child (27/43, 63%). One third (35%) of the children died within 4 days after delivery. 23 (53%) children survived with severe neurological disabilities and only five (12%) were alive and well at time of discharge. Antenatal treatment was not given in most (91%) cases of fetal/ neonatal ICH.

Conclusions
ICH caused by FNAIT often occurs during second trimester and the clinical outcome is poor. In order to prevent ICH caused by FNAIT, at risk pregnancies must be identified and prevention and/or interventions should start early in the second trimester.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of intracranial haemorrhage (ICH) in relation to thrombocytopenia in term born infants.[1] FNAIT is caused by maternal alloantibodies directed against fetal platelets due to incompatibility in human platelet antigens (HPAs). ICH due to FNAIT is reported to occur in 1: 12 500 – 25 000 births.[2,3] The clinical outcome is often more severe than for neonatal ICH from other causes.[1,4] The ICH recurrence rate in subsequent pregnancies is reported to be 79%.[5] Therapies have been developed that can reduce the incidence of ICH, such as weekly high-dose intravenous immunoglobulin (IVIG).[6,7,8] It is therefore considered important to identify ICH caused by FNAIT in order to treat the mother in subsequent pregnancies. Gestational age at time of bleeding onset is a key factor when antenatal treatment options are discussed since treatment to prevent ICH needs to be started before ICH is likely to occur. No study has specifically addressed this. Identifying common denominators of human HPA-alloimmunised pregnancies complicated by ICH may serve as a future tool to help identify pregnancies at high risk.

The No IntraCranial Haemorrhage (NOICH) registry is a multinational registry including 592 pregnancies complicated by FNAIT from 13 tertiary referral centres across the world. This study presents the results of an in-depth evaluation of all recorded cases of ICH caused by FNAIT from this registry. The aim of the study was to characterize pregnancies where the fetus or neonate suffered from ICH with special focus on clinical and laboratory characteristics and time of bleeding onset.

MATERIALS AND METHODS

Study design and inclusion criteria
All centres that had registered FNAIT cases in the NOICH registry from 2001-2010 were invited to participate in this observational cohort study. Pregnancies recorded in the NOICH registry as complicated by fetal or neonatal ICH were identified, and included if both the diagnosis of FNAIT and ICH were confirmed. STROBE guidelines were followed as appropriate.

A case was defined as FNAIT if: 1) Incompatibility between maternal and paternal/ fetal HPA type was confirmed and maternal anti-HPA antibodies were detected, 2) HPA-incompatibility between the mother and father was confirmed and the fetus/ neonate suffered ICH and 3) anti-HPA antibodies were detected in the mother but data on fetal/ paternal HPA genotype was missing.

Neuroradiological images were recovered and reviewed as electronic copies in a picture archiving and communication system (PACS) using standard display programs. One Norwegian participant and two of the Dutch participants had MR-studies performed in utero. All available neuroradiological images were re-evaluated for this study by an experienced independent paediatric neuroradiologist (OF). The focus of the neu-

roradiological evaluation was primarily to confirm the ICH diagnosis, second to use imaging to assist in assessing time of bleeding onset and finally to classify the type of bleeding. When images were not available, written reports of the imaging evaluations for the patient files by others were used to evaluate if the ICH diagnosis was correct. Cases where an ICH could not be confirmed were not included in the study.

In cases where information from normal imaging preceding abnormal imaging results was available we were certain of a window in time during which the haemorrhage did occur. In most participants we did not have the benefit of initial normal imaging. Here we used instead well recognised imaging principles[9] in judging the age of haemorrhage from its appearance on CT or MRI and estimated time of onset of bleed from this assessment. According to the classification commonly used in the study of causes of cerebral palsy we classified the haemorrhages as either intraventricular (IVH) and/or periventricular (PVH) or as parenchymal, in brain parenchyma not associated with the central ventricular system.[10] The neuroradiological information of likely time of onset was matched to all other clinical information available.

In cases where the fetus or neonate died, autopsy reports were retrieved and studied to evaluate whether ICH diagnosis was certain or unlikely. All reports from post-mortem examinations were evaluated by an experienced perinatal pathologist (NP). Only cases evaluated to be certain ICH were included.

Laboratory data

All laboratory data except maternal anti-HPA-1a antibody levels were collected from the NOICH registry database (http://www.NOICH.org).

Maternal anti-HPA-1a antibody levels, except for the Finnish cases (four pregnancies), were measured at the National reference laboratory of clinical platelet immunology in Tromsø, Norway, by quantitative MAIPA.[11] Reproducibility between Norwegian and Finnish quantitation was secured by double analysis of some sera samples in both Norway and Finland. In cases where several anti-HPA-1a antibody level measurements were available, the highest maternal anti-HPA-1a antibody level measured during pregnancy or postpartum was included in the study.

The lowest platelet count recorded in the fetus or new-born before any platelet transfusions were given, was included.

Clinical data

Clinical data was mainly collected from the NOICH registry database (http://www. NOICH.org). Additional clinical information was retrieved from the original medical records by each country coordinator.

The pregnancy where ICH was detected for the first time was referred to as the index case. A subsequent ICH event was defined if ICH was recorded in any subsequent pregnancies after the index ICH case.

Statistics

All data were analysed using SPSS software (V.18.0 SPSS Inc, Chicago, Illinois, USA). The P<0.05 was considered significant. Means with 95% confidence intervals (CI) or median with range were calculated for all continuous variables. Independent sample t-test and Kruskal-Wallis test were used as appropriate. One-way of variance test was used to test clinical outcome in relation to time of bleeding onset.

RESULTS

From the NOICH registry recording 592 FNAIT cases, 66 pregnancies from 57 women were initially identified with suspected ICH. In 23 cases ICH or FNAIT diagnosis could not be confirmed. In total, 43 confirmed cases of ICH due to FNAIT were recorded from 37 mothers. The 43 cases studied were included from the Netherlands, Finland, Sweden, Norway and the UK (figure 6.1).

Laboratory characteristics of ICH cases

HPA-1a alloimmunisation was found to be the cause in 39 of 43 ICH cases (91%). Anti-HPA-5b antibodies were found in two further cases. In one woman with records of two ICH cases, incompatibility in the gpla/IIa system was confirmed and in one of her ICH pregnancies anti-HPA-5a antibodies were detected.
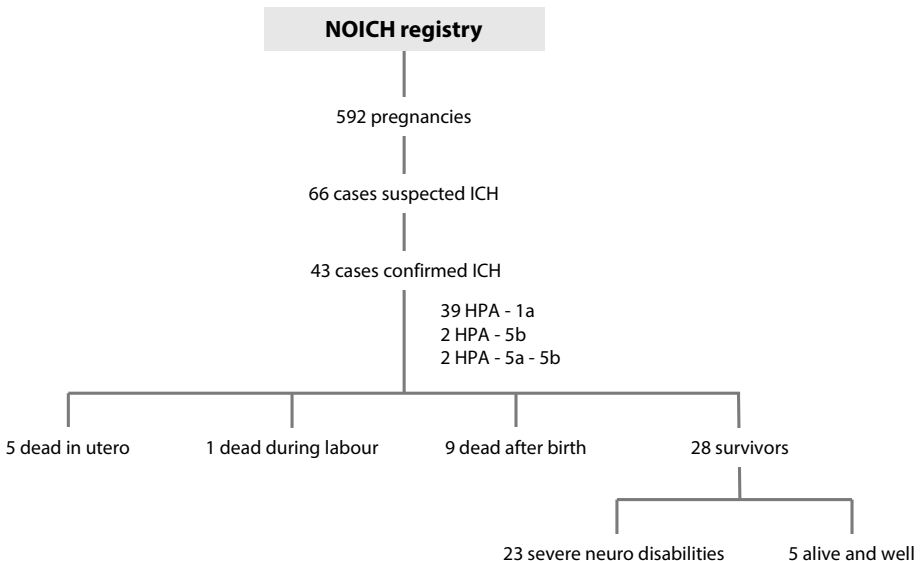
6

NOICH registry

592 pregnancies

66 cases suspected ICH

43 cases confirmed ICH

39 HPA - 1a
2 HPA - 5b
2 HPA - 5a - 5b

5 dead in utero   1 dead during labour   9 dead after birth   28 survivors

23 severe neuro disabilities   5 alive and well

Figure 6.1
Flow diagram of the study population

Data on maternal anti-HPA-1a antibody levels during pregnancy or after delivery were available for 15 (35%) of the FNAIT pregnancies complicated by ICH. The median (range) highest anti-HPA-1a antibody level was 105 IU/mL (39 to 264 IU/mL). In two pregnancies we have serial anti-HPA-1a antibody level measurements starting in the first trimester, and in both these pregnancies the anti-HPA-1a antibody levels fell from the first to the third trimester. The ICH occurred between 28 and 34 weeks in these pregnancies. The median anti-HPA-1a antibody levels measured during the first, second, third trimesters and postpartum did not differ significantly from each other or from the overall median highest antibody level (data not shown).

The median (range) lowest fetal/ neonatal platelet count for ICH cases was 8×10^9/L (1 to 27). In comparison, median (range) neonatal platelet count for previous or subsequent pregnancies where no ICH was detected, was 17×10^9/L (1 to 199) and significantly higher when compared with ICH cases (Kruskal-Wallis test, P=0.004).

Clinical characteristics of ICH pregnancies

Maternal characteristics for all ICH cases are shown in table 6.1. In the group of the 37 index cases, 26 (70%) cases were first born children. However, most mothers had been pregnant before they had their first child: Eight women had one or more first trimester miscarriages and six women had one or more second trimester losses. For two women, we lack data on gravida status. The mothers were primigravidae in only 10/37 (27%) index cases. In total, ten mothers (23%) experienced one or more second trimester miscarriages (altogether 20) before or after the ICH case.

Table 6.1 *Maternal characteristics of ICH-affected pregnancies*

Maternal characteristic	
Maternal age in years, mean (95% CI)	29.3 (27.6-31.0)
Obstetrical history	
Primigravida, n (%)	10 (23)
First-born child, n (%)	27 (63)
2nd trimester miscarriage, n (%)	10 (23)
Pre-eclampsia in this pregnancy, n (%)	3 (7)
Vaginal delivery of ICH neonate, n (%)	22* (51)
Caesarean section of ICH neonate, n (%)	20* (47)
Fetal/ maternal treatment	
IVIG, n (%)	4 (9)
Steroids, n (%)	1 (2)
Intrauterine platelet transfusion, n (%)	3 (7)
No treatment	36 (84)

ICH intracranial haemorrhage; IVIG intravenous immunoglobulin.
*Mode of delivery was not known for one ICH pregnancy

Antenatal treatment was given in 4/43 (9%) of the pregnancies complicated by fetal/ neonatal ICH. In three cases IVIG was given, two of these fetuses received additional intrauterine platelet transfusions. One mother received corticosteroids as single treatment from 6 weeks gestation onwards, due to two previous second trimester miscarriages (not identified as FNAIT related). For the 37 index cases, only one mother received antenatal treatment. In this case, IVIG treatment was started from week 7 due to autoimmune thrombocytopenia in the mother.

Twenty out of 43 mothers with pregnancies complicated by fetal/ neonatal ICH were delivered by caesarean section (CS); CS was performed in nine cases with abnormal fetal cerebral ultrasound (US) as main indication.

A high proportion of the pregnancies complicated by ICH were ended preterm: 29 out of 43 children (67%) were born before 37 weeks and 4 children were born before 28 weeks. Abnormal US scan with detection of ICH was the main reason for premature delivery (table 6.2).

Five (12%) of the infants died in utero and one (2%) died during labour. Neonatal characteristics of the live-born children are shown in table 6.3. Nine children died within the first four days after delivery. Most of the survivors developed neurological sequelae: 8 infants were diagnosed with cerebral palsy, 10 were reported to be moderate/ severely mentally retarded or severely disabled, 7 neonates were reported to have epilepsy and 4 were blind or with severely reduced vision. In addition, one case of autism and one case of impaired hearing were reported. More than one neurological complication was reported in several cases. Five (14%) of surviving neonates with ICH were reported to be alive and well at time of discharge after delivery, but data on long-term clinical outcome is missing (figure 6.1).

The fetuses/ neonates were male in the majority (65%) of ICH cases. There was no significant difference in maternal anti-HPA-1a antibody levels, birth weight, APGAR scores or platelet counts when comparing boys and girls (Independent sample t test, P>0.05).

Ten (23%) ICH neonates were below the 10th percentile for birth weight and defined as small for gestational age (SGA) according to standard growth curves. All SGA cases except one were boys.

Table 6.2 *Preterm birth*

Reason for preterm delivery	Number of pregnancies (% of total)
Abnormal US scan (ICH detected)	15* (52)
Intrauterine fetal demise	5* (17)
Intrauterine growth restriction/ pre-eclampsia	3 (10)
Spontaneous preterm birth	4 (14)
Not known	2 (7)
Total	29** (100)

*One case was a complication during cordocentesis
**Including one twin pregnancy
ICH intracranial haemorrhage

Table 6.3 *Clinical outcome characteristics of ICH cases*

Characteristic	Result
All ICH cases	
Gestational age at delivery, median (range) in weeks	35 (23-42)
Birth weight, mean (SD) in grams	2274 (832)
Sex, female/ male	14/28
Stillborn	6 (14)
Live-born children	37 (86)
APGAR score <7 after 5 minutes, n (%)	8 (23)
Lowest platelet count (range) x10^9/L*	8.9 (1-27)
Neonatal death, n (%)	9 (21)
Alive and well at discharge, n (%)	5 (12)
Alive with neurological sequelae, n (%)	23 (53)

*Data available for 32 pregnancies
ICH intracranial haemorrhage

Bleeding characteristics

Neuroradiological studies were used to review and confirm 19 ICH cases. The remaining 24 ICH cases were confirmed using descriptions of radiographic material by local radiologists.

The estimated time of bleeding onset for each ICH case is shown in figure 6.2. The figure demonstrates that many bleedings started early, and that in most cases several weeks passed between bleeding onset and delivery. More than half (23/43, 54%) of the bleedings happened around gestational week 28 or earlier. In 16 (70%) of the 23 cases with bleeding onset before the third trimester we do not know the exact time of bleeding onset, only that the bleeding started no later than 28 weeks (figure 6.2). Twenty-nine of 43 bleedings (67%) started before 34 gestational weeks. No cases of intrapartum ICH bleedings were confirmed. The time of bleeding onset in the 10 primigravid cases were not different from the multigravid ICH cases.

There was no difference in clinical outcome in relation to time of bleeding onset (data not shown). However, it is noteworthy that perinatal death occurred in two girls (14%) where the bleedings were found to have happened before 30 weeks. In boys, perinatal death occurred in 13 (46%) cases with bleedings happening also at a later gestational age.

Intraparenchymal haemorrhages were found in 11 out of 13 cases where the bleeding occurred during the third trimester or after delivery. Figure 6.3A illustrates intraparenchymal haemorrhage.

In five cases, multiple bleeding episodes were found. All second bleedings occurred after 33 weeks (range 33 to 37 weeks). These five cases were all due to HPA-1a alloimmunisation.

Fifteen ICH cases were classified as intraparenchymal and 13 cases as IVH/ PVH (figure 6.3B). Five cases were classified as miscellaneous (figure 6.3C), whereas 10 cases could not be classified. Among cases where ICH was found to occur before 28 weeks, all but one case was found to be IVH/PVH.
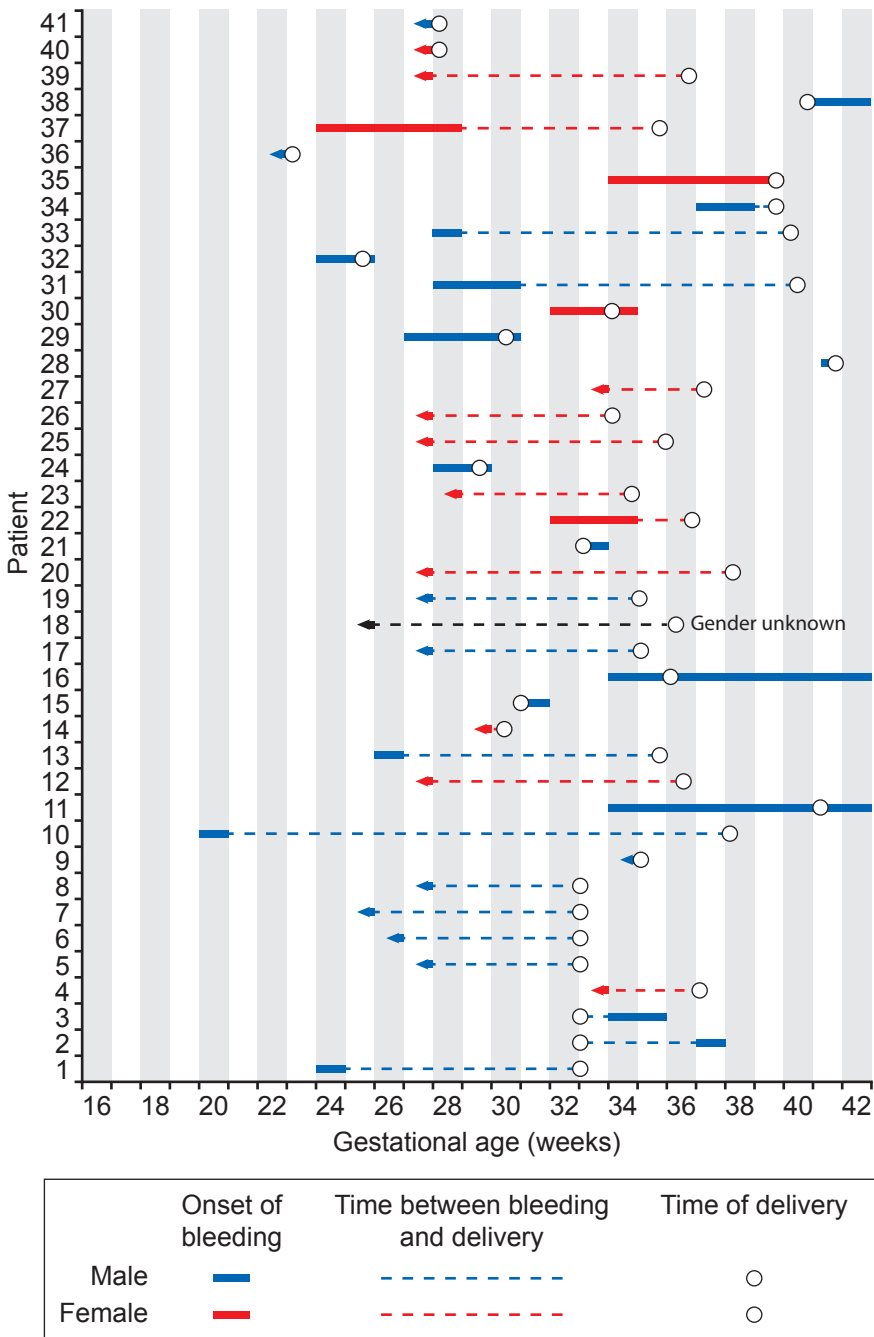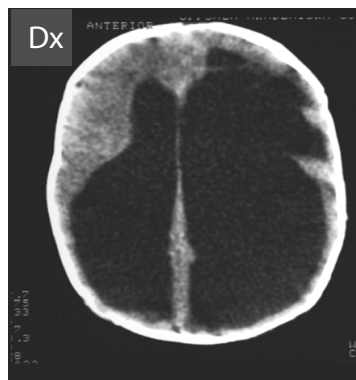
Figure 6.2
Estimated time period for onset of ICH is shown for 41 cases of ICH caused by FNAIT. An arrowhead to the left indicates that the earliest time of onset cannot be estimated, only that the bleeding occurred before the gestational age indicated on the x-axis.
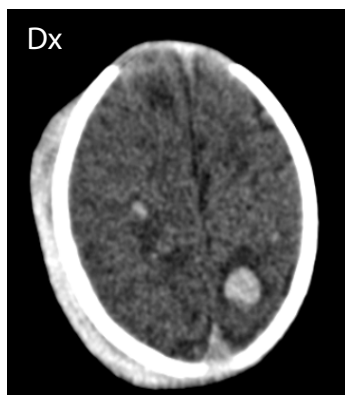
a) Intraparenchymal hemorrhage

b) Intraventricular hemorrhage

c) Miscellaneous (Multiple intraparenchymal hemorrhages)

Figure 6.3

(A) CT scan shows a very large intraparenchymal haemorrhage with mass effect and occupying most of the right frontal lobe in a term baby. Note a second but smaller haemorrhage on the left side adjacent to the ventricle but separate from this. The attenuation of both haemorrhages indicates that the haemorrhage is several weeks old at the time of imaging. We estimated the right haemorrhage to be 4 - 6 weeks old and the left still a couple of weeks older. The pregnancy was considered normal, and no IVIG treatment was given. A live boy was born vaginally at 40 gestational weeks with petecchiae. The platelet count was 6x109/L.

(B)This CT shows marked ventriculomegaly, partly due to hydrocephalus, partly due to loss of brain tissue in the left hemisphere. Note the very large ventricle on the left side occupying most of the left hemicranium. The shape of the left lateral ventricle is irregular and that of residual from a previous intraventricular haemorrhage with a paraventricular atrophic defect caused by an old periventricular haemorrhagic infarction. This pattern is pathognomonic for this condition even though no actual blood can be detected. The interpretation of this image is that of an intraventricular haemorrhage associated with a periventricular hemorrhagic infarction timed at 28 – 30 gestational weeks or earlier. Hydrocephalus was diagnosed intrapartum because of breech presentation. A live boy was born at term with a platelet count of 4x109/L. The child has severe cerebral palsy and a hydrocephalus shunt.

(C)The CT scan shows multiple focal intraparenchymal haemorrhages throughout both cerebral hemispheres. Most haemorrhages are quite small. Note also the extensive extracranial subgaleal haemorrhage overlying the right hemicranium. All bleedings are of same age and maximum seven days old. It was noted that the fetus was small on US scan at 25 weeks, but otherwise the pregnancy was considered normal. At 42 weeks a live boy was born vaginally, with multiple petecchiaes and multiple retinal bleedings. The platelet count at delivery was 14x109/L, with nadir value 8x109/L. He received platelet transfusions. At time of discharge the boy was described as alive and well, but we do not have data on long-term clinical outcome.

Treatment and clinical outcome in subsequent pregnancies

ICH was detected in six (23%) subsequent pregnancies. One woman had records of ICH in two subsequent pregnancies after the index ICH case. In most subsequent pregnancies (20/26, 77%), no ICH was found.

In 19/ 26 (73%) of subsequent pregnancies, the mothers received antenatal treatment (IVIG). The intravenous immunoglobulin schedules varied greatly, with a median starting time at 18 weeks (range 16-35 weeks). In the six cases where ICH was detected in subsequent pregnancies, three received IVIG treatment. However, in one of these cases IVIG treatment was started *after* ICH was detected. Therefore, IVIG treatment failed to prevent ICH in two (11%) out of 19 cases. These two treatment failures were from the same woman. It should be commented that the obstetrical history of this woman is particularly severe with regards to FNAIT complications. The ICH recurrence rate was therefore 11% in IVIG treated pregnancies. Compared with historical data reporting 79% risk of ICH recurrence in FNAIT,[5] our data indicate that IVIG was effective in preventing ICH.

In seven cases, no IVIG treatment was given during a subsequent pregnancy after ICH was detected in a previous pregnancy. Five of these untreated pregnancies come from Norway, where IVIG is not routinely given as treatment during HPA alloimmunised pregnancies. ICH occurred in three of these seven cases.

DISCUSSION

The main findings of this study are that the majority of ICH bleedings occurred by the end of the second trimester and that clinical outcome was devastating for most cases. The high frequency of bleedings occurring before 28 weeks indicates that the fetus may be severely affected already in the second trimester.

This is the largest study to date on fetal/ neonatal ICH caused by FNAIT. For the first time, time of bleeding onset was assessed using clinical information together with radiographic imaging and autopsy reports. The in-depth study of both laboratory and clinical information was done in close collaboration between obstetricians, immunologists, perinatal pathologists and specialists in neuroradiology. Limitations of this study include that it is a retrospective cohort study, being subject to confounding and information bias. A bias toward inclusion of the more severe ICH phenotype may be considered. The ICH cases in this study were collected from five different countries and therefore reflect several institutions' clinical experiences. There is obvious heterogeneity in antenatal treatment for FNAIT between these countries. However, since most of the patients affected by fetal ICH did not receive antenatal treatment, we consider the study population uniform and representative of a larger population.

Some earlier studies have suggested the onset of bleedings to be in the third rather than the second trimester,[3,12] and are in variance with this study. The judgment of the onset of cerebral bleeding in this study was cautious, and the onset was probably in many cases even earlier than we report. However, previous studies included too few

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cases to address this question in an adequate manner. Also, and more importantly, other studies report the gestational age when the ICH was diagnosed, and did not assess when the bleeding may have occurred. In a recent study by Bussel et al,[13] antenatal management to prevent recurrence of ICH caused by FNAIT was studied. Gestational age at the time of ICH is reported in this study, but without any data with regard to how the timing of ICH was assessed. These data are therefore difficult to assess, but in support of our data they report that as many as 8/37 (22%) of ICH cases in their study population occurred before 28 gestational weeks. Most of the ICH cases occurred in boys, and the bleedings were more often lethal when the fetus was male. The finding that 80% of the SGA neonates in our population were boys supports the recently published observation that birth weight in boys, but not in girls, was associated with maternal anti-HPA-1a antibodies.[14] Data on maternal anti-HPA-1a antibody levels in FNAIT pregnancies complicated by fetal/ neonatal ICH have not been published before.

Fetal ICH due to FNAIT often occurred in the first child. Most ICH cases will therefore not be recognised in time for treatment or prophylactic measures if we do not identify pregnancies at risk before the onset of the bleeding. The high number of first-born children in the study population may not necessarily mean that the risk of ICH caused by FNAIT is genuinely higher in the first-born child. The distribution could be skewed towards nulliparous women since these women may choose not to have more children due to high recurrence risk. Further, most of these women received antenatal treatment during the subsequent pregnancy thereby reducing the incidence of ICH in the younger siblings. Nevertheless, this finding challenges the current management strategy where antenatal treatment is given in subsequent pregnancies after FNAIT has been diagnosed in the first child. A majority of these children will suffer from bleeding already in the second trimester or in the early part of the third trimester. Possible interventions to reduce risk of ICH need to be introduced before the 20th week of gestation. In most children the ICH was either fatal or induced severe disabilities. Our findings therefore support the idea of identifying HPA-1bb mothers with anti-HPA-1a antibodies in all pregnancies[3,15] and working towards a prophylactic approach to prevent the immune response against HPA-1a**.**[16,17] The rate of prematurity and CS was high in our study. Many of these patients required delivery before term due to problems related to the fetal ICH such as fetal distress, lack of fetal movements, abnormal ultrasound scan etc. Thus, the present study does not indicate that FNAIT per se is associated with an increased risk for prematurity.

There were no confirmed cases of ICH occurring intrapartum in this study, and only two bleedings occurred after delivery. This could suggest that mode of delivery may not be so important in the prevention of ICH. However, the high CS rate in this study population may have contributed to the low number of intrapartum bleedings. Whether or not delivery by CS prevents ICH needs to be further addressed.[3,18] The present study suggests that IVIG treatment during pregnancy is protective in regard to ICH in most cases, which is in accordance with previous studies.[13] However, it is an open question whether IVIG would have protected the first born child from ICH, or whether there

is a genuine increased risk of ICH in the first born child. Further, it remains to be estab-lished if there is also a milder phenotype of ICH with discrete symptoms and better outcome. This question can only be addressed in prospective studies including general screening and repeated fetal US examinations. The maternal anti-HPA-1a antibody lev-els were extremely high among ICH cases in this study. Maternal anti-HPA-1a antibody levels may therefore be useful to identify pregnancies at risk for fetal ICH, but these findings need to be evaluated in larger prospective studies. Finally, why boys seem to be more susceptible to maternal anti-HPA-1a antibodies is currently not known and needs further investigation.

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