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

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CHAPTER 2

SCREENING IN PREGNANCY FOR FETAL OR NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: SYSTEMATIC REVIEW

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ABSTRACT

Background

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a potentially devastating disease, which may lead to intracranial haemorrhage (ICH), with neurological damage as a consequence. In the absence of screening, FNAIT is only diagnosed after bleeding symptoms, with preventive options limited to a next pregnancy.

Objectives

To estimate the population incidence of FNAIT and its consequences to prepare for study design of a screening programme.

Search strategy

An electronic literature search using MEDLINE, EMBASE and Cochrane database, and references of retrieved articles. No language restrictions were applied.

Selection criteria

Prospective studies on screening for human platelet antigen 1a (HPA-1a) alloimmunisation in low risk pregnant women.

Data collection and analysis

Two reviewers independently assessed studies for inclusion and extracted data. Main outcome data were prevalence of HPA-1a negativity, HPA-1a immunisation, platelet count at birth and perinatal ICH. We aimed to compare outcome with and without intervention.

Main results

HPA-1a alloimmunisation occurred in 294/3028 (9.7%) pregnancies at risk. Severe FNAIT occurred in 71/227 (31%) of immunised pregnancies, with perinatal ICH in 7/71 (10%). True natural history data were not found, as interventions were performed in most screen-positive patients.

Author's conclusion

Screening for HPA-1a alloimmunisation detects about two cases in 1000 pregnancies. The calculated risk for perinatal ICH of 10% in pregnancies with severe FNAIT is an underestimation, because studies without interventions were lacking. Screening of all pregnancies together with effective antenatal treatment such as intravenous immunoglobulin may reduce mortality and morbidity associated with FNAIT.

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a potentially devastating condition, which may lead to intracranial haemorrhage (ICH) in the fetus or neonate, often with death or major neurological damage as a consequence. In Caucasians, between 1.6% and 4.6% are negative for human platelet antigens (HPA) 1bb or 1a.[1] In this group, 85% of immunisations are caused by alloantibodies against HPA- 1a. Older literature suggests that most immunisations occur during pregnancy.[2-4] Recently, a large prospective study showed that most immunisations probably occurred during or shortly after birth.[5] The immunoglobulin G (IgG) antibodies against fetal HPA-1a can cross the placenta and cause destruction of fetal platelets. The chance of immunisation is correlated with maternal expression of human leucocyte antigen (HLA) DRB3*0101 type. Typing for this antigen may contribute to identifying the pregnancies at risk for FNAIT.[6]

Several studies aimed to identify a threshold of HPA-antibody level in the maternal serum below which severe FNAIT would not occur but with conflicting results.[7-9]

The reported incidence of FNAIT ranges from 1:350[10] to 1:1000[11] in the largest studies. The most severe complication is intracranial haemorrhage (ICH), leading to perinatal mortality in 1-7% and to surviving children with often severe neurological sequelae including mental retardation, cerebral palsy, cortical blindness and seizures in 14-26% of affected pregnancies. [4,12-14] Reviewing all published cases of ICH due to FNAIT, Spencer and Burrows found that 80.5% originated before birth.[4]

The recurrence rate of FNAIT in a subsequent pregnancy is estimated at 90%.[14] Radder et al. reviewed the scarce literature on ICH risk in subsequent, untreated pregnancies. In women with a previous child with ICH, the estimated recurrence risk was between 61-97%.[15] Furthermore, similar to red cell alloimmunisation, the severity of FNAIT is assumed to increase with each pregnancy.[14,16,17]

In the absence of screening, the disease is only diagnosed after the birth of symptomatic neonates, i.e. fetal or neonatal bleeding, or occasionally by chance in the case of neonatal blood tests for other reasons. As a consequence, antenatal treatment is currently provided only for women with a previously affected child. In such a pregnancy, preventive measures, such as fetal blood sampling with platelet transfusion or weekly intravenous infusions with immunoglobulins (IVIG), are taken. Until recently, insufficient specificity of the diagnostic tests and the risks of treatment precluded the introduction of population-based screening programmes. However, laboratory methods have improved, and IVIG treatment without any invasive testing was shown, at least in women with a previous affected child, to be both safe and effective.[18]

As a preparation to introduce a provisional national screening programme for FNAIT in a general population of pregnant women, we performed a systematic review of the literature.

METHODS

Research questions

We aimed to review all prospective screening studies in cohorts of low-risk pregnant women, where HPA-typing was performed to identify pregnancies at risk for FNAIT. The time range of publication was January 1980 to October 2008. Study data were pooled to the extent that study populations seemed comparable. The specific research questions were first: what is the incidence of HPA-1a negativity among pregnant women, what proportion of these women form HPA alloantibodies during pregnancy, what proportion of their offspring is affected by FNAIT, and how severely are they affected? Second, what are the effects of interventions in screen-positive pregnant women?

Definitions

HPA-1a status is defined straightforwardly, but the definition of FNAIT manifestations varies in the literature. Thrombocytopenia, in adults and children as well as in fetuses is defined as a platelet count < $150x10^9$/L. Severe thrombocytopenia, associated with an increased risk of bleeding is commonly defined as a platelet count < $50x10^9$/L, and therefore has been used in many studies on FNAIT as a single endpoint. However, only a minority of fetuses or neonates with such a low platelet count actually suffer from bleeding complications. The key complication of the disease to be prevented is ICH. However, even the use of ICH as an endpoint has become controversial through the application of ever-improving imaging modalities, which now may detect minute areas of haemorrhage that may be clinically irrelevant. The truly meaningful endpoint would be neurodevelopment, to be assessed later in life, e.g. Bayley score at 2 years of age or later. For our literature review, we aimed to identify studies that at least provided information of the incidence of HPA-1a negativity, HPA-alloantibodies, neonatal platelet counts and signs of bleeding in the newborns. As a definition of severe FNAIT we used a platelet count < $50x10^9$/L.

Search and study selection

Relevant literature was identified using the electronic bibliographic databases PubMed, Embase, and Cochrane. We used the following keywords: 'mass screening' [MESH] OR screen* AND 'Thrombocytopenia, neonatal alloimmune'[MESH] OR NAITP OR Alloimmune thrombocytopenia. We accepted original articles, short communications and letters to the editor. In addition a search was performed from the reference list of all identified articles. When needed, we contacted authors for additional, unpublished information. There were no language restrictions.

We subsequently excluded all non-prospective studies. Studies were excluded when screening was not done by HPA-typing, or when screening was applied in a specific or high-risk population.

Two of the authors (M.K. and N.P.) initially screened all the titles and abstracts of papers, identified by the review search strategy, for relevance. Only studies which were

obviously irrelevant were excluded at this stage. All other studies were assessed on the basis of their full text for inclusion versus exclusion by two reviewers independently (M.K. and N.P.) using the criteria indicated above. Discrepancies were to be resolved by discussion with a third reviewer but this proved to be unnecessary.

Methodological quality

The methodological quality of the articles included was assessed by evaluating the explicitness and clarity of the study question, level of detail of the selection criteria for pregnancies included and excluded, details of the laboratory tests used, details on the interventions offered and carried out both antenatally and postnatally, appropriateness of the methods used to detect fetal and neonatal bleeding complications and pregnancy outcome. An important aspect of screening studies is the assessment of the incidence of the disease in the screen-negative group. Therefore, we evaluated whether the studies reported platelet counts and bleeding complications in the HPA-1a- positive group, and in the HPA-1a- negative women without (detectable) HPA antibodies. Completeness of follow-up and explanation of reasons for loss to follow up were critically evaluated.

Outcome variables

We extracted the following primary outcome data: number of HPA-1a negative women detected by the screening, the incidence in that subgroup of HPA-alloantibody formation during pregnancy, number of fetuses and neonates with severe thrombocytopenia defined as a platelet count $<50x10^9$/L, incidence of intrauterine fetal death probably related to FNAIT, incidence of fetal or neonatal ICH, combined adverse outcome defined as perinatal mortality and morbidity associated with severe thrombocytopenia. In addition, we evaluated the use of HLA-typing, in particular assessment of the presence or absence of HLA-DRB3*0101, which is associated with the risk of antibody formation in HPA-1a-negative pregnant women.

From the selected articles, we only used the data on those pregnancies from which all relevant data on primary outcomes were available.

Some screening studies aimed to describe the natural history of the disease, while others included some type of intervention either antenatally, postnatally or by adapting the mode of delivery.

We planned to compare the total group of women screened without intervention with the group in which an intervention was carried out. We planned in addition to analyse the primary outcome parameters related to the types of interventions, divided in the following categories: antenatal transplacental medical treatment (IVIG and/or steroids), intrauterine platelet transfusions, altered time and mode of delivery (near-term caesarean section), availability of postnatal matched platelets for transfusion and/or IVIG.

Statistical analysis

Descriptive analysis of the outcome parameters was performed by dividing the total number of women with the outcome parameter by the total number of women screened. We compare the odds of having a fetus or neonate with ICH in women with HPA alloantibodies with and without any intervention, by calculating odds ratios and 95% confidence intervals.

RESULTS

The initial search of the databases revealed 660 studies. During the first screening 639 studies were excluded and 21 remaining studies were assessed on the basis of their full text for inclusion or exclusion using the criteria described above. After critical appraisal of the full text of the remaining 21 articles, ten studies were included in our review.[2,3,10-12,19-23] The main reason for exclusion was the use of case-finding through platelet counting in umbilical cord blood at birth or in neonates, with further analysis in those with low platelet counts instead of identifying pregnancies at risk by HPA-1a typing. The process of literature searching and study selection is illustrated in figure 2.1.

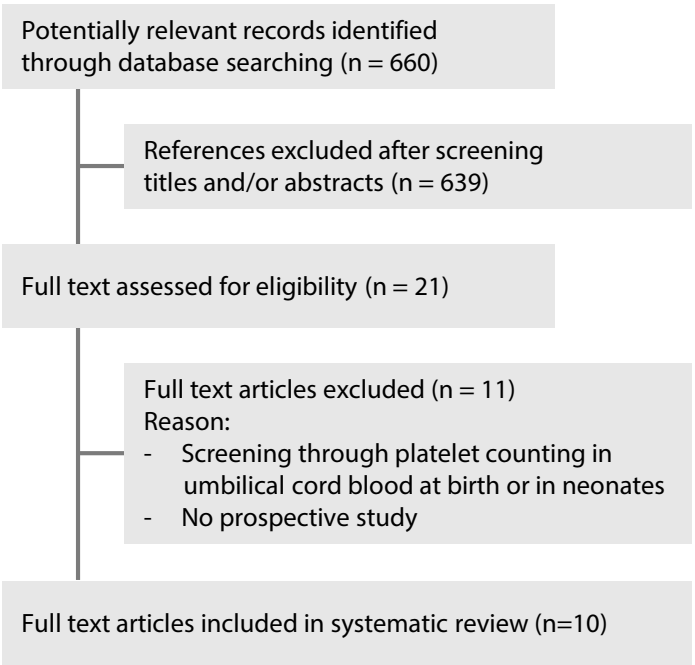

Figure 2.1 *Process from initial search to final inclusion*

No randomised controlled trials were found. Two of the ten studies were case-control studies, comparing outcome of the HPA-1a-negative women identified through the screening program with outcome of pregnancies of HPA-1a-positive women.[11,22] The other studies fulfilling our selection criteria were prospective cohort studies.

In the ten selected studies, a total number of 176 084 low-risk pregnancies comprised the screened populations with a range from 860 to 100 448. In table 2.1, the primary outcome data obtained from these ten studies are listed. In all studies, except one[20] both primigravida and multiparous women were included.

Table 2.1 *Outcome of screening studies for FNAIT included in the analysis*

Author, year	Women screened	HPA 1a negative (%)	Antenatal anti-HPA (%)	Intervention	Severe NAIT * (%)	ICH	IUFD
Mueller-Eckhardt 1985	1211	26 (2.1)	2/26 (7.7)	None	0	0	0
Reznikoff-Etievant 1988	860	27 (3.1)	0	None	0	0	0
Blanchette 1990	5000	81 (1.6)	3/50 (6.0)	NTCS, PP	1/3 (33)	1	0
Doughty 1995	3473	74 (2.1)	1/68 (1.5)	IUPT, IVIG, PP	2/1* * (100)	0	0
Durand-Zaleski 1996	2066	52 (2.5)	4/45 (8.9)	IVIG,ST	2/4 (50)	0	0
Williamson 1998	24417	598 (2.4)	36/385 (9.4)	PP	8/31 (26)	1	1***
Davoren 2003	4090	53 (1.3)	2/34 (5,9)	IUPT,PP	2/2 (100)	0	0
Maslanka 2003	8013	144 (1.8)	12/112 (10.7)	IUPT+IVIG	3/12 (25)	1	
Turner 2005	26506	327/19 127 (1.7)	25/318 (7.9)	PP	5/25 (20)	0	0
Kjeldsen-Kragh 2007	100448	2111 (2.1)	210/1990 (10.6)	NTCS, PP	48/147**** (33)	2	1*****
Total	**176 084**	**3493/168 705 (2.1)**	**294/3028 (9.7)**		**71/227 (31)**	**5**	**2**

ICH, intracranial haemorrhage; IUFD, intrauterine fetal death; PP, postpartum matched platelets available; IUPT, intrauterine platelet transfusion;
IVIG, antenatal intravenous immunogloblins; ST, antenatal corticosteroids.
The denominator in the columns differs as the result of drop-out or loss to follow up for these variables in the studies.
**Severe FNAIT was defined as a platelet count <50x10^9/L.*
***One pregnancy with two severely affected twin children.*
****IUFD related to fetal blood sampling in fetus with severe thrombocytopenia.*
*****Excludes second immunised pregnancies and those with HPA-1a-negative neonates.*
******One IUFD in a twin born at 31 weeks, with the other twin having severe thrombocytopenia.*

Methodological quality

A wide variation was found in the amount of detail provided on all major aspects. The articles ranged from a one page letter[21] to an 11-page report.[11] Only one paper[20] reported a sample size calculation, most others chose a fixed time period (e.g. 1 year), or lacked details on the basis for the size of the study population.

The primary investigators of all ten papers were haematologists or other specialists working in transfusion medicine, which might explain the generally detailed descriptions of the laboratory investigations. The various tests were either clearly described or references to the appropriate literature were provided in all papers.

Although all studies aimed to include only low-risk pregnant women, some series contained patients with previously affected pregnancies. Turner et al[11] found 3 women in their screened group with previously affected pregnancies, and excluded those from further analysis. Williamson et al[10] included two HPA-1a-negative women in their study group who were at first not typed as such but were known to have had affected children. In addition, one of the 33 women with positive HPA antibodies in their series had a diagnosis of NAIT in a previous child. Davoren et al[22] also included a woman who reported having had a previous child with petechiae at birth and a platelet count of 6 x 10^9/L. The index pregnancy in the study again ended in the birth of a child with petechiae, bruising and cord blood platelet count of 6 x 10^9/L. Kjeldsen-Kragh et al[23] included 16 women twice in their screening study, of which 14 gave birth in the second pregnancy again to an HPA-1a-positive child. These pregnancies are described separately in their article. Informed consent was commonly only obtained after identification of HPA-1a negativity, for follow-up and possible intervention.

The relative lack of obstetricians and paediatricians as co-authors could be the explanation for the absence or only rudimentary description of fetal examinations, obstetric management, clinical evaluations of the newborns and follow-up.

HPA-antibody detection

There was a large variation in maternal serum testing for antibody formation. In three studies the frequency of sampling was left unstated.[3,12,19] In the other studies the frequency ranged from twice during the pregnancy[20] to every 4 weeks.[23] Several women were found to have antibodies already at the first-trimester booking sample, all were multiparous. In the cohort reported by Williamson et al[10] eight women developed HPA-antibodies during their first pregnancy, two of whom already at 17 weeks of gestation. In the series by Turner et al[11], five of the 25 HPA-1a immunised women developed antibodies in their first pregnancy, two at 21 weeks, and the other three after 28 weeks of gestation.

Interventions

In the two smallest studies describing a total of 2071 pregnancies, no interventions in the screen-positive group were used. In the smallest study, none of the HPA-1a negative women developed HPA-1a antibodies.[19] In the study by Mueller-Eckhardt et al.[12] two women developed HPA-1a alloantibodies, both neonates had platelet counts

above 80 x 10^9/L. In the other eight studies, one or more types of interventions were offered to all HPA-1a alloimmunised pregnant women, a true nonintervention group was lacking.[2,3,10,11,19,20,22,23] Therefore, we had to omit the planned comparative analysis of the odds of having an affected child with or without intervention.

The eight studies in which interventions were performed in the screen-positive group used a wide variety of treatments, summarised in table 2.1. Only postnatal intervention, consisting of having matched platelets available for urgent transfusion, was used in two studies.[10,11] In six studies[3,11,20-23] one or more fetuses were treated with platelet transfusions, IVIG, corticosteroids or a combination of these. Two studies explicitly stated the offer of elective near-term caesarean section for women with HPA-antibodies.[2,23] In only two of the other eight studies, caesarean section rates in pregnancies with known HPA-antibodies were given. They were 36% in the study by Williamson et al.[10], and 33% in the study by Davoren et al.[22]

Perinatal mortality and neonatal morbidity

In the total study cohort where screening was applied 71 pregnancies were affected by severe FNAIT, with two perinatal deaths and five infants FNAIT-related ICH. Severe FNAIT occurred in the first pregnancy in 15/71 (21%), including three of the seven cases with adverse perinatal outcome (table 2.2). ICH was detected postnatally in four of five neonates, but all except one almost certainly occurred well before birth. Details on mode of delivery and platelet counts of this group are given in table 2.3.

Table 2.2 *Characteristics of all pregnancies complicated by severe FNAIT (platelet count < 50x10^9/L) in the ten screening studies*

Author, year	Primiparous	Multiparous
Mueller-Eckhardt 1985	0	0
Reznikoff-Etievant 1988	0	0
Blanchette 1990	0	1 (1 ICH)
Doughty 1995	0	2*
Durand-Zaleski 1996	2	_
Williamson 1998	4 (1 ICH)	3 (1 IUFD**)
Maslanka 2003	2 (1 ICH)	1
Davoren 2003	1	2
Turner 2005	0	5
Kjeldsen-Kragh 2007	6 (1 ICH)	42 (1 ICH, 1 IUFD)
Total	**15 (3 (ICH)**	**56 (2 ICH, 2 IUFD)**

ICH, intracranial haemorrhage; IUFD, intrauterine fetal death.
**One pregnancy with two severely affected twin children.*
***Death occurred after haemorrhage following fetal blood sampling at 29 weeks in an anaemic hydropic fetus with 6×10^9/L platelets.*
****Excludes pregnancies where mother has a previous affected child.*

Table 2.3 *Characteristics of the five HPA-1a alloimmunised pregnancies complicated by fetal or neonatal intracranial haemorrhage*

Case No. Author,yr	GA and mode of delivery	Detection of ICH	Occurrence of ICH	Platelet count	Long-term outcome*
1 Blanchette 1990	38 weeks, CS	Postnatal day 2	Antenatal < 36 wks	9 x 10^9/L	Mild cerebral palsy
2 Williamson 1998	37 weeks, CS	Postnatal day 1	Antenatal < 35 wks	4 x 10^9/L	Hydrocephaly, spasms, hypertonia, delayed development, mild optic atrophy
3 Maslanka 2003	38 weeks?	Postnatal	Antenatal likely < 36 wks**	34 x 10^9/L	Central neurological coordination dysfunction, recovered after rehabilitation
4 Kjeldsen-Kragh 2007	38 weeks, CS	Postnatal day 3	unknown	26 x 10^9/L	No clinical sequelae at 5 years
5 Kjeldsen-Kragh 2007	34 weeks, CS	Antenatal	Antenatal < 34 wks	13 x 10^9/L	Epilepsy with daily seizures at 7 months

GA gestational age; ICH intracranial haemorrhage; CS caesarean section
**Outcome description literally cited from publications.*
***Case 3 had fetal blood sampling at 36 weeks, platelet count 34×10^9/L followed by two intrauterine platelet transfusions, 119×10^9/L platelets at birth, gestational age and mode of birth unknown.*

HLA-typing

In four of the ten studies HLA-DRB3*0101 type was determined in the whole cohort.[3,10,11,21] These results are summarised in table 2.4. In the study Norwegian study of Kjeldsen-Kragh et al[23], only HPA-1a immunised women were HLA DRB3*0101 typed. They found that 12 of the 150 HPA-1a immunised women were HLA-DRB3*0101 negative.

Table 2.4 *Results of HLA DRB3*0101 typing in HPA-1a negative pregnant women*

Author, year	Prevalence of DRB3*0101 in HPA-1a negative women (%)	HPA-immunisation in DRB3*0101 positive women (pos. predictive value) (%)	No HPA-immunisation in DRB3*0101 negative women (neg. predictive value) (%)
Doughty 1995	22/71 (31)	2/22 (10)	49/49 (100)
Williamson 1998	123/385 ((32)	43/123 (35)	261/262 (99.6)
Maslanka 2003	41/122 (34)	12/41 (29)	81/81 (100)
Turner 2005	107/303 (35)	18/107 (17)	189/196 (96.4)
Total	**293/881 (33)**	**75/293 (26)**	**580/591 (98.1)**

HLA human leucocyte antigen; HPA human platelet antigen

DISCUSSION

Our analysis of studies describing screening pregnant women for FNAIT provides a pooled estimate of the naive prevalence among pregnant women of HPA-1a negativity (2.1%) and an estimate of the risk of negative women to show antenatal HPA-antibody formation (9.7%). The pooled data confirm that a significant proportion of severe disease occurs already in the first pregnancy. However, none of the studies reported on the true natural history of the disease. Understandably, the investigators offered interventions to women in whom they detected HPA antibodies, with the aim of reducing the incidence of the true clinical disease, which is fetal or neonatal bleeding. It seems safe to assume that the incidence of 31% severe fetal or neonatal thrombocytopenia in HPA-immunised women, with 10% severe adverse outcome, is an underestimation of the true risk in nonscreened populations. This was recently confirmed by a study from Norway, where the authors compared the detected infants with FNAIT in two groups, nonscreened versus a screened population of pregnant women. Their reported detection rate of FNAIT without screening was only 14% of the expected rate.[24]

Better estimations are unavailable because no randomised studies have been published. The largest and most recent study compared the outcome of a cohort with a historic control group for which they used outcome data from published screening studies.[9] About half of these studies were also included in our analysis, with the above described limitation of using interventions. The other half of their historic control group were studies screening 'low-risk' or 'randomly selected' neonates for thrombocytopenia, with subsequent maternal HPA-antibody testing in case of low platelet counts. Prenatal interventions were obviously not performed in this group, but postnatal treatment was generally available. The authors acknowledged the limitations of their control groups; however they considered a truly randomised design withholding intervention to one study-arm to be unethical. We conclude from our literature review that more reliable data on the natural history are both unavailable and not likely to be collected.

For many years, clinicians treating ICH in newborn children due to FNAIT considered antenatal screening as a measure to reduce the disease burden[2,25,26]. Our review adds essential information to this ongoing debate. Severe FNAIT occurs in about 40 per 100 000 pregnancies (of the estimated 210 HPA-1a immunised women) with, despite several interventions, severe ICH in three or four children per 100 000 pregnancies screened. The majority of these bleedings occurred *in utero*, before 36 weeks of gestation. Permanent neurological handicap in this group was common, associated with severe burden for affected individuals and their families, and with high costs for society. In previous literature reviews, estimated risks for ICH in HPA-immunised pregnancies ranged from 7 to 26%, which would mean three to ten per 100 000.[15] Again we must stress the fact that these figures are likely to be underestimations. This disease therefore seems to have enough burden of disability to consider a prevention program.

Although we consider the data of this review valuable for the design of a screening programme, several questions remain. The first aspect in a screening programme is to

how to identify women at risk for FNAIT. To timely select the 2.1% HPA-1a negative pregnant women, screening should start in the first trimester, the obvious choice being the use of the universally accepted 'booking sample'. Laboratory methods for large-scale, rapid, reliable and cheap assessment of HPA-1a antigens are needed. In most studies we reviewed, either an enzyme-linked immunosorbent assay or flow cytometry was used for phenotyping with, in more recent studies, a polymerase chain reaction-based method either as primary test or to confirm HPA-1a negativity. Large-scale primary genotyping could become cost-effective, however. Recent studies used a modified monoclonal antibody immobilisation of platelet antigens technique for antibody detection and quantification. Collaboration between reference laboratories in this field has let to highly reproducible results with this method.[27]

An option to optimise selection would be to assess the fetal HPA-type. About 30% of fathers are either HPA-1a negative (2%) or heterozygous HPA-1a1b. Recently, a reliable method became available for fetal HPA-typing using free fetal DNA in maternal plasma (M. de Haas, personal communication). This test would omit the use of paternal testing or amniocentesis for fetal testing. Its use, however logical, depends again on careful cost-effectiveness evaluation.

Whether or not to further narrow the screen-positive group by testing for HLA DRB3*0101 can only be determined by a detailed cost-effectiveness analysis, and also depends on logistic possibilities. As we showed in our review, a remarkably consistent prevalence of 33% was found. Although HPA-antibody formation is rare in DRB3*0101 negative women, the positive predictive value of only 26% questions its usefulness in a screening program. In the large Norwegian study, 10% of HPA-immunised women were found to be DRB3*0101 negative, again raising doubt on the value of testing for this allele.[23]

Furthermore as in any other screening programme it is significant to identify the window or presymptomatic stage of the disease. From the published data, we could not reliably determine the time between (detection of) antibody formation and occurrence of ICH. In many multiparous women, antibodies were already present early in pregnancy, whereas in first pregnancies several women had detectable antibodies already in the second trimester. In this large cohort of women without a previous affected child, the earliest ICH was detected at 34 weeks of gestation. It seems likely therefore, that a case finding strategy aiming to detect HPA-immunisation allows time for interventions preventing the clinical disease, which is fetal ICH.

A final option to further select the group requiring intervention would be to use a certain threshold of HPA-antibody level in the maternal serum. Only a few studies in our review discussed this subject, with conflicting conclusions.

Another as yet unsolved question in the debate on screening for FNAIT is what to offer the screen-positive group. From our review it seems clear that ICH may occur *in utero*, which makes antenatal intervention necessary. The large Norwegian study shows that near-term caesarean section with matched platelets available may reduce, but not eliminate, perinatal death and severe handicap due to ICH. Until recently, most ante-

natal interventions included the use of serial fetal blood sampling. The procedure-related fetal loss risks involved however, are 2-6%, which in a screening program would mean losing more fetuses to the intervention then would be saved from ICH-related adverse outcome.[28-30] Only recently, it was shown that at least in women with FNAIT and a previous affected child, non-invasive treatment using IVIG given to the pregnant women weekly in the third trimester was 100% effective and probably safe to mother and child.[8,18] If this intervention could be shown to be equally effective in first affected pregnancies, which theoretically seems likely, this would mean an important step towards an effective screening programme.

An interesting issue for debate is what to offer the HPA-1a negative women who do not become immunised during pregnancy. Killie et al.[31] recently reported that more than 75% of the immunisations occur during or after labour. Ideally, for this group, we would like to offer a prophylactic drug similar to anti-D in Rhesus immunisation. The development and testing of prophylactic drugs is likely to take many years before widespread clinical application is possible, so a management strategy for immunised women is urgently needed.

The choice for an elective caesarean section in pregnancies with FNAIT is another subject of debate. One study specifically addressed this subject, and concluded that there was insufficient evidence to support this choice.[32] Most studies in our review lacked sufficient information to reach any conclusion. None of the incidneces of ICH seemed to have occurred intrapartum, and such occurrences are extremely rare in the literature as well.[32] Two studies that reported mode of delivery had caesarean section rates around 35%, which is much higher than expected in a normal population. The Norwegian investigators defended their choice with three arguments. The first was the ability to deliver the child 2- 4 weeks prior to term. This is obviously also possible with the currently quite effective prostaglandin induction. Second, they refer to a radiologic study in which 26% of neonates born vaginally had signs of haemorrhage on magnetic resonance image, compared to 0% in the group delivered by caesarean section.[33] However, most of these bleeds were small subdural hematomas; none were symptomatic and most disappeared within 5 weeks. A more recent larger study by Rooks et al.[34] with a similar design showed the presence of such haematomas in neonates born after caesarean section. This type of bleeding is thought to originate from tearing of small veins by the (normal) movement of the skull bones during labour and delivery, and are quite different from intraventricular and intraparenchymal bleeding commonly seen in ICH due to FNAIT.[34] The third argument was that planned caesarean section would provide time for the blood bank to prepare matched platelets. This is, however, a matter of logistics and would be equally true for planned induction of labour. In conclusion, although not proven to be safer, we cannot exclude that elective caesarean section may prevent ICH. This intervention however is associated with maternal morbidity and increased risk of complications in subsequent pregnancies. A choice for elective caesarean section in a screening programme would, depending on country and culture, have consequences for acceptability for both pregnant women and clinicians.

Implementation of routine antenatal screening for FNAIT obviously depends on cost-effectiveness. Several studies provided calculations all reaching the conclusion that screening is likely to be cost-effective.[11,20,35,36] The major determinants of the costs are the initial HPA-typing, antibody detection in those at risk, and costs of interventions. Although these costs are considerable, even in the most expensive strategy (e.g. offering IVIG to all immunised women), they are easily outweighed by the savings assuming that most cases of perinatal ICH can be prevented. For a population of 200 000 pregnancies per year, such as in the Netherlands, the estimated costs of HPA-1a screening would be around 1 million euros/year. Testing the 4000 HPA-1a women for fetal HPA-type and presence of antibodies is probably feasible for 250 000 euro. If we elect the most costly intervention programme, around 350 women annually would receive IVIG for the last 10 weeks of pregnancy, which would cost around 5 million euros. Including costs of organisation a rough estimate of such a programme thus would be in the order of 7 million euros/200 000 pregnancies screened. The obvious benefits are prevention of cases of life-long severe neurological morbidity such as cerebral palsy, blindness, deafness, seizures and mental retardation.

Using calculations made for children with neurological handicap due to kernicterus, with an estimated annual additional cost of 50 000 euros, a conservative estimated life expectancy of 40 years and a conservative estimate of ten handicapped children born each year as a result of FNAIT, an 80% effective prevention programme could be cost-effective if total costs are below 16 million euros annually, or 2 million euros per case prevented. Given the estimated annual costs for a screening program in the Netherlands of 7 million euros, cost-effectiveness is reached when 4 cases of ICH are prevented each year. Assuming a high effectiveness of the proposed intervention programme, at least double that number are expected to be prevented, leading to net savings of at least 9 million euros per year.

In conclusion this review showed that severe FNAIT occurs in about 40 per 100 000 pregnancies. Despite several interventions severe ICH occurred in three or four children per 100 000 pregnancies screened**.** Large prospective studies without any intervention were not found, which means that the incidence of ICH in non-screened populations is likely to be higher. The majority of neonates with ICH had severe and life-long neurological sequelae. Intervention studies using antenatal IVIG suggest that ICH due to HPA-1a alloimmunisation is preventable without known risk for mother or child. These data indeed indicate that large-scale screening studies including comparison of several interventions are warranted.[37] Given the devastating outcome in severely affected pregnancies, such programs are likely to do more good than harm, and may be cost-effective.

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