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

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CHAPTER 5

DELAYED DIAGNOSIS OF FETAL AND NEONATAL ALLOIMMUNE THROMBOCYTOPENIA: A CAUSE OF PERINATAL MORTALITY AND MORBIDITY

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ABSTRACT

Objective
To evaluate the rate and consequences of a late or missed diagnosis of fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Design
Retrospective analysis of prospectively collected data of a national cohort.

Setting
National referral centre for fetal therapy in the Netherlands.

Population
Twenty-six women with pregnancies complicated by FNAIT and at least one previous pregnancy with a thrombocytopenic child.

Methods
Retrospective analysis of data from our electronic FNAIT database. In a consecutive cohort managed between July 2008 and July 2010, timing of first diagnosis of FNAIT was correlated to severity and outcome in the subsequent pregnancies.

Main outcome measures
Occurrence of delayed diagnosis of FNAIT, and possibly associated intracranial haemorrhage (ICH).

Results
In four of 26 cases, timely diagnostic testing for FNAIT was not performed despite fetal or neonatal thrombocytopenia or ICH. Down's syndrome, dysmaturity and birth trauma were perceived to be the cause of the thrombocytopenia or ICH. In two of these four subsequent, untreated pregnancies, severe fetal ICH occurred. The other 22 women were treated for FNAIT using intravenous immunoglobulin, all children are alive and well.

Conclusions
All neonates with thrombocytopenia at birth should be evaluated for FNAIT. Missing this diagnosis can have severe consequences for subsequent pregnancies.

INTRODUCTION

Thrombocytopenia is a common clinical problem in neonates: 1-5% of newborns present with this problem.[1] Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of thrombocytopenia in otherwise healthy term infants.[2] It is the result of maternal alloimmunisation to antigens on fetal platelets, inherited from the father. The maternal immunoglobulin G (IgG) antibodies cross the placenta and cause destruction of fetal/neonatal platelets, with resultant thrombocytopenia and associated risk of bleeding.

A potentially devastating condition, FNAIT may lead to intracranial haemorrhage (ICH) in the fetus or neonate, often with death or major neurological damage as consequence. The reported incidence of FNAIT ranges from 1: 500[3] to 1:1100.[4] With an annual birth rate of 185 000, the expected number of affected pregnancies in the Netherlands would range between 168 and 370. FNAIT is most often diagnosed after the birth of a clinically affected child with signs of bleeding. Coincidental detection of thrombocytopenia is not uncommon with laboratory tests for other reasons. Further testing then reveals the presence of alloantibodies in the maternal serum.

Currently, preventive measures are only possible in a subsequent pregnancy of women with a previously affected child and known FNAIT. Experience shows that FNAIT is not routinely taken into consideration by paediatricians as a possible cause of neonatal thrombocytopenia

This study was undertaken to evaluate the rate and consequences of a late or missed diagnosis of FNAIT by assessing the clinical presentation of first affected children, the timing of diagnosis and the outcomes of the subsequent children.

PATIENTS AND METHODS

Patients

The Leiden University Medical Centre is the national referral centre for pregnancies complicated by FNAIT in the Netherlands. We retrospectively evaluated prospectively collected data using our FNAIT database and neonatal records from all women and infants treated at our centre between July 2008 and July 2010.

Medical records were evaluated to obtain obstetric history, clinical presentation of the first affected child and timing of diagnosis of FNAIT.

Case definition

Early diagnosis was defined as a diagnosis of FNAIT made following clinical signs or suspicion after birth of a first affected child. Diagnosis was considered delayed if diagnostic testing for FNAIT was not performed after a first clinically affected child, with FNAIT being unknown at the outset of the subsequent pregnancy.

Study outcomes

Antenatal management and outcome in subsequent pregnancies of women with undiagnosed FNAIT in previous pregnancies were compared with those with early diagnosed FNAIT. Primary outcome was the occurrence of fetal or neonatal ICH. Secondary outcomes included other bleeding signs, the cord blood platelet count at birth and type of neonatal treatment.

Statistical analysis

Data are expressed as mean (SD) values for continuous variables or as median (range) for categorical variables. The Fisher's exact test and the Mann-Whitney test were used for comparison as appropriate. A P-value <0.05 was considered significant. Analyses were performed using SPSS 16.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Between July 2008 and July 2010, 26 women were referred to the LUMC for management of pregnancies complicated by FNAIT. Table 5.1 outlines the characteristics of the study group.

Clinical presentation of older siblings

In the older siblings, 16 of the 26 children presented at birth with bleeding manifestations: skin bleeding only in 13, and ICH in three. Nine infants (35%) presented with

Table 5.1 *Characteristics of pregnancies with FNAIT following a previous affected child (n = 26)*

	Early diagnosis of FNAIT (n = 22	Delayed diagnosis of FNAIT* (n = 4)
Parity (before index pregnancy)		
Primiparity	18	3
Multiparity	4	1
Pregnancy loss		
One miscarriage	6	1
Recurrent miscarriage	2	0
Immature delivery	1	1
Type of HPA antibodies		
HPA-1a	17	2
HPA-5b	1	1
HPA-1a and HPA-5b	1	
HPA-1b	1	
HPA-5a		1
HPA-15a	2	

FNAIT fetal and neonatal alloimmune thrombocytopenia; HPA human platelet antigen
**Defined as diagnosis of FNAIT made only during or after the subsequent pregnancy*

asymptomatic thrombocytopenia, detected through blood drawing for other purposes. Seven had severe thrombocytopenia (platelet count <50 x10^9/L) and two infants had moderate thrombocytopenia (50 x10^9/L - 100x10^9/L).

Early diagnosis of FNAIT and primary outcome of index cases

In 22/26 cases, the diagnosis was made directly after birth of the first affected child. Four were multiparous women. Of these four women, two lost their child in the neonatal period due to unrelated congenital anomalies. Thrombocytopenia was first detected in their second child. The other two multiparous women first had asymptomatic children, with symptomatic thrombocytopenic children in the next pregnancy.

Intracranial haemorrhage occurred in one index case (1/22, 5%) of the early diagnosed group, The previous child of this mother had a low platelet count (5x10^9/L), without ICH. Ultrasound at 20 weeks of gestation showed no bleeding. Just before initiation of intravenous immunoglobulin (IVIG) therapy at 28 weeks of gestation, small intracranial bleedings were identified on ultrasound. The IVIG treatment (1.0 g/kg/week) was given as planned, and an asymptomatic child was born at 36 weeks of gestation. Magnetic resonance imaging confirmed several minor bleeding sites. The child is developing normally at 1year of age.

Late diagnosis of FNAIT and primary outcome of index cases

In four of 26 cases, there was a long delay in diagnosing FNAIT. Despite the birth of a child with a low platelet count or ICH, the possible diagnosis of FNAIT was not considered and no tests for FNAIT were performed. In the delayed diagnosis group, two of the four (50%) subsequent children suffered from ICH. One neonate died 2 hours postpartum due to a massive subarachnoidal haemorrhage. The other child had no clinical sequelae at 1 year of age. The four cases are summarised in table 5.2.

Table 5.2 *Characteristics of pregnancies with delayed diagnosis of FNAIT*

Case	A	B	C	D
Parity (at index pregnancy)	G3P2	G2P1	G2P1	G2P1
Clinical presentation of first affected child	ICH	Asymptomatic	Asymptomatic	Asymptomatic
Platelet count of first affected child	Unknown	30 × 10^9/L	67× 10^9/L	11× 10^9/L
Presumed cause of ICH/thrombocytopenia	Birth trauma	Down syndrome	IUGR	IUGR
Gestational age at diagnosis in index pregnancy	20-week scan (diagnosis of ICH)	After birth at 32 weeks (ICH)	35 weeks	13 weeks
Antenatal management of index pregnancy	IVIG 1.0 g/kg/wk for 15 weeks	_	IVIG 1.0 g/kg/wk for 3 weeks	IVIG 0.5 g/kg/wk for 4 weeks*
Clinical outcome of index pregnancy	CS, 38 weeks	CS for fetal distress at 32 weeks	Vaginal birth at 38 weeks. Healthy	CS for fetal distress at 32 weeks. Healthy
Platelet count at birth of index pregnancy	158 × 10^9/L	11 × 10^9/L	16 × 10^9/L	184 × 10^9/L

IUGR intrauterine growth restriction; ICH intracranial haemorrhage; CS caesarean section.
**IVIG planned for 10 weeks but preterm birth.*

Table 5.3 Data on neonatal outcome, antenatal and neonatal treatment and type of delivery in index pregnancies with FNAIT

Pregnancy outcome	Early diagnosis of FNAIT (n = 22)	Delayed diagnosis of FNAIT (n = 4)	P-value
ICH, n (%)	1 (5)	2 (50)	0.051
Perinatal death, n (%)	0	1 (25)	0154
Platelet count at birth, $\times 10^9$/L	66 (6-278)	57 (11-54)	0.561
Severe thrombocytopenia ($<50\times10^9$/L) n(%)	9 (41)	2 (50)	0.386
Haemorrhagic symptoms excluding ICH, n (%)	2(9)	1(25)	0.355
Antenatal treatment			
IVIG, n (%)*	21 (95)	2 complete (50), 1 incomplete, 3 weeks	0.271
Neonatal treatment			
Platelet transfusion only, n (%)	4 (18)	1(25)	0.445
Platelet transfusion and IVIG, n (%)	3 (14)	0	0.592
None, n (%)	15 (68)	3 (75)	0.437
Mode of delivery			
Vaginal, n (%)	13 (59)	1 (25)	0.206
Caesarean section, n (%)	9 (41)	3 (75)	

Values given in numbers (percentage) or median (range)
FNAIT fetal and neonatal alloimmune thrombocytopenia; ICH intracranial haemorrhage; IVIG intravenous immunoglobulin: 0.5 g/kg/wk from 28 weeks when affected sibling had no ICH, or 1.0 g/kg/week from 16 weeks if sibling had ICH.
**In one early diagnosis, a predelivery fetal blood sample was taken followed by one intrauterine platelet transfusion and a vaginal birth.*

Secondary outcomes of index cases

In table 5.3 , the platelet count at birth, bleeding signs other than ICH, antenatal and neonatal treatment are given.

DISCUSSION

In this cohort study of 26 women with FNAIT, delay of diagnosis was identified in four cases (15%). Two of these four fetuses suffered from severe ICH. Several factors were presumed to have caused the low platelets in the previous pregnancies—Down syndrome, intrauterine growth restriction and birth trauma—and kept the clinicians from requesting the appropriate investigations.

The most feared complication of fetal or neonatal thrombocytopenia is ICH. Untreated newborns with FNAIT are reported to be affected by ICH in 7-26% of pregnancies.[6-8] After the birth of a child with ICH, the recurrence rate of ICH is as high as 79% (CI 61-79%).[9-11] Surviving children suffer from severe neurological sequelae including mental retardation, cerebral palsy, cortical blindness and seizures in 14-26%.[5,8] As safe

and nearly 100% effective prenatal treatment is available, using IVIG,[12] it is of clinical importance to detect neonates with FNAIT.

In our study, one ICH occurred in the group with known FNAIT, just before to starting IVIG. This child is now developing normally at 1 year of age. The mother had received IVIG for 8 weeks, which could be the reason for the good long-term outcome. However, as this is the only failure in over 10 years and more than 120 women treated with noninvasive management (IVIG only), we have not changed our policy of starting IVIG at 28 weeks.

The limited number of pregnancies means that our analysis has limited power to detect statistically significant differences. However, these illustrative examples of delayed diagnosis show that missing the diagnosis of FNAIT can have devastating consequences for subsequent children, including perinatal death.

More than one-third of the neonates in our study with FNAIT presented with asymptomatic thrombocytopenia. A Norwegian study showed that in the absence of a routine screening program, only 14% of affected neonates would be identified. [13] Our data confirm their conclusion that for effective prevention of ICH due to FNAIT, routine screening of all pregnant women for human platelet antigen 1a (HPA-1a) antibodies needs to be implemented.

The same recommendation was given by Knight *et al.*[5] following a national study in the UK which showed significantly more children diagnosed with ICH when FNAIT was unknown or unrecognised at the onset of pregnancy compared with pregnancies with known diagnosis of FNAIT (at 1 year of age 10% versus 0% severe disability or death).

The debate on implementation of routine antenatal screening for FNAIT depends mostly on cost-effectiveness. Several studies provide calculations that all reach the conclusion that screening is likely to be cost-effective.[4,8,14,15,16] However, until then, given the serious consequences of missing the diagnosis FNAIT, we recommend platelet antibody detection for all cases with (suspected) antenatal fetal haemorrhage and neonatal thrombocytopenia. We propose a limited serological investigation for antenatally suspected cases, by maternal HPA-1a typing and screening for the clinical important HPA antibodies. This can be extended for newborns with proven thrombocytopenia with a cross-match between maternal serum and paternal platelets, maternal and neonatal (or paternal) HPA typing and platelet autoantibody investigation depending on the differential diagnosis.

CONCLUSION

Delay in diagnosing FNAIT, resulting in withholding appropriate preventive measures in the subsequent pregnancy, may lead to perinatal death or severe brain damage in newborns . We recommend that in all neonates with thrombocytopenia at birth, the diagnosis FNAIT should be considered, followed by appropriate testing. Screening all pregnant women for HPA-type would be even more effective.

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