



Universiteit
Leiden
The Netherlands

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

Kamphuis, M.M.

Citation

Kamphuis, M. M. (2017, May 23). *Fetal and neonatal alloimmune thrombocytopenia : towards implementation of screening in pregnancy*. Retrieved from <https://hdl.handle.net/1887/49219>

Version: Not Applicable (or Unknown)

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/49219>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden

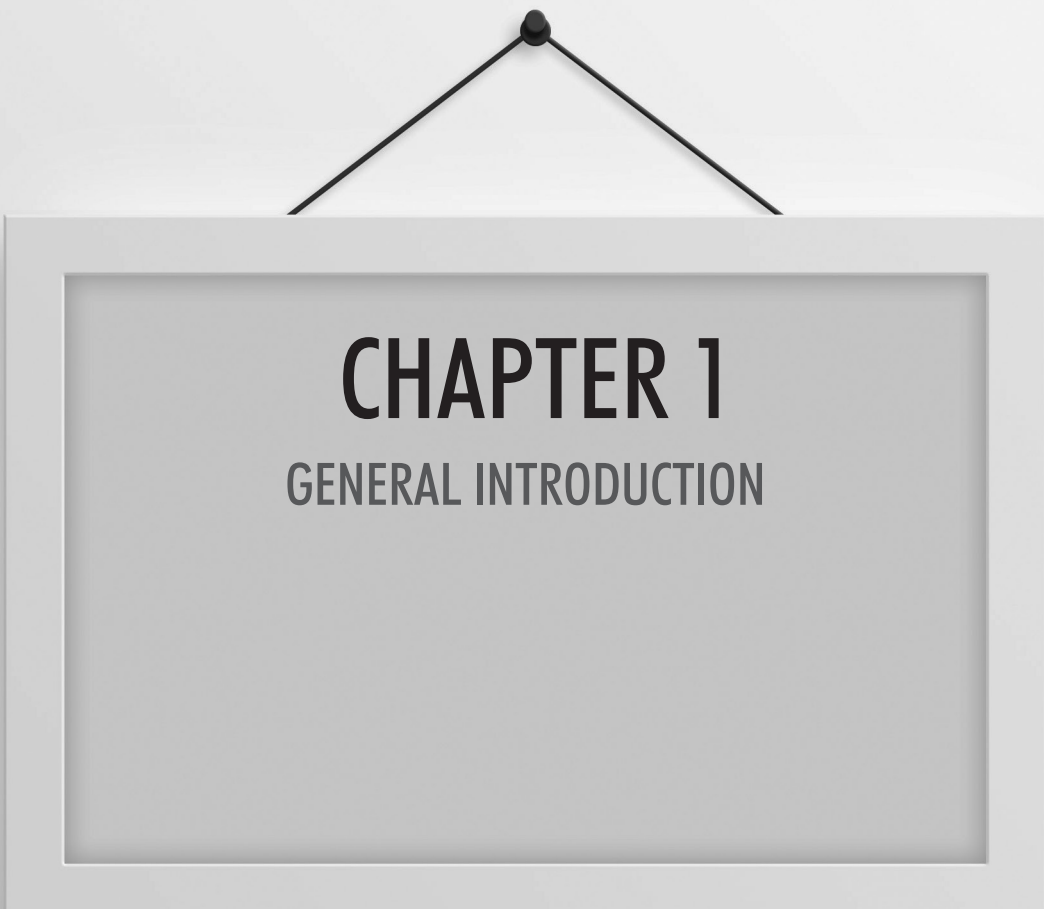


The handle <http://hdl.handle.net/1887/49219> holds various files of this Leiden University dissertation

Author: Kamphuis, Marije

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

Issue Date: 2017-05-23



CHAPTER 1

GENERAL INTRODUCTION

GENERAL 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. The fetal platelet antigens are expressed as early as 16–18 weeks of gestation.¹ The mother's antibodies [of the immunoglobulin G (IgG) 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 race. The immunodominant antigen in Caucasian individuals is HPA-1a, which is responsible for 85% of the FNAIT cases, followed by HPA-5b.^{3,4} Two percent of the Caucasians is HPA-1a negative. The reported incidence of FNAIT is estimated to be one in 1000–2000 births.^{5–7}

FNAIT is a potentially devastating condition with intracranial haemorrhage (ICH) as most feared complication, which can lead to severe neurological sequelae including mental retardation, cerebral palsy, cortical blindness, seizures or even death. The clinical outcome seems to be more severe than for neonatal ICH from other causes.^{8,9} However true specific data about the long-term neurodevelopmental, cognitive outcome and development of children suffering from ICH due to FNAIT is scarce.

Available data indicate that 50–80% of ICH cases happen in utero, and then mainly during the third trimester.⁴ The highest risk for FNAIT-related complications in subsequent pregnancies seems to be among fetuses/neonates with siblings that experienced antenatal ICH, with a reported recurrence rate of 90%.^{4,10} Among siblings with severe FNAIT and no ICH, data are still unclear, ranging from no risk to a 66% recurrence rate.^{11,12} Furthermore, similar to red cell alloimmunisation, the severity of FNAIT is assumed to increase with each pregnancy, although strong evidence is lacking.

For several years, fetal blood sampling with intrauterine platelet transfusion was the standard treatment for FNAIT. However, in-utero platelet transfusion is an invasive procedure that carries a risk of fetal loss, especially for fetuses with a low platelet count.¹³ Currently, administration of immunoglobulins (IVIG) to the pregnant mother, a varying degree of intrauterine monitoring and specific measures around birth is mainly offered to women affected by FNAIT.^{14,15} There is no consensus about the dosage of IVIG, it varies from 0.5 (Netherlands), 1.0 (Sweden) to 2.0 g/kg per week in the USA. Some centres, particularly in the USA add steroids to the IVIG treatment. Other interventions, which may be used in conjunction to fetal therapy, are induction of labour, near term caesarean section, and delivery in a tertiary care centre with match platelets available for transfusion.

With the current lack of screening programs, the diagnosis of FNAIT is usually only established following the birth of a clinically affected child with signs of bleeding or coincidentally when thrombocytopenia is found with laboratory test for other reasons. As

a consequence, antenatal treatment modalities are nowadays only provided for women with a previously affected child.

If we truly want to prevent the burden of this disease, all at risk pregnancies should be identified in time to start effective preventive treatment and reduce severe adverse outcomes. This can only be realised when routine screening for HPA-type is offered. The question remains if the time is ripe to implement such a screening program or whether we need more detailed information about incidence, pathogenesis and natural course of this rare disease. The studies described in this thesis were designed to contribute to the implementation of a screening and intervention program for FNAIT.

OUTLINE OF THIS THESIS

The general aim of the studies described in this thesis is to contribute to the decision about implementation of screening for FNAIT in the healthcare program for pregnant women.

In chapter 2 a systematic review of the literature on antenatal screening studies for FNAIT is given. It provides a pooled estimate of the naive prevalence among pregnant women of HPA-1a negativity, the risk of HPA-antibody formation, thrombocytopenia and risk of adverse outcome.

In chapter 3 we systematically assessed the reported prevalence of severe thrombocytopenia in newborns secondary to NAIT with sub analysis of ICH due to NAIT.

In chapter 4 an overview is given on the current management of fetal and neonatal allo immune thrombocytopenia (FNAIT).

In chapter 5 we evaluated 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 subsequent children.

In chapter 6 we characterised pregnancies where the fetus or neonate suffered from ICH with special focus on clinical and laboratory characteristics and time of bleeding onset.

In chapter 7 the results of the NOICH trial are reported. This randomised trial comparing a lower dose of IVIG of 0.5 g/kg to the standard dose of 1 g/kg showed no difference in frequency of neonatal ICH, platelet counts at birth, need for neonatal treatment and levels of cord blood levels of IgG. Unfortunately this trial had to be stopped prematurely, resulting in insufficient power to prove equivalence of the lower dose to the standard dose.

In chapter 8 we describe a cohort study that shows that treatment in pregnancies with FNAIT with a previous affected child without ICH, in a weekly dose of 0.5g/kg or 1.0 g/kg results in comparable neonatal platelet counts at birth and incidence of severe thrombocytopenia.

In chapter 9 we analysed the management and outcome of the largest international cohort of FNAIT-cases to date, with emphasis on different treatment modalities. Non-in-

vasive management using IVIG with or without additional steroids prevents bleeding in the fetus or neonate in virtually all cases.

In chapter 10 we aimed to determine the long-term outcome and cognitive development of a group of children with ICH due to FNAIT to clearly outline the burden of this disease.

In chapter 11, a general discussion of the overall results is presented. Furthermore, future perspectives and proposals for research are given.

REFERENCES

1. Kaplan C. Platelet alloimmunity: the fetal/neonatal alloimmune thrombocytopenia. *Vox Sang* 2002;83Suppl 1:289-91.
2. Warwick RM, Vaughan J, Murray N, Lubenko A, Roberts I. In vitro culture of colony forming unit-megakaryocyte (CFU-MK) in fetal alloimmune thrombocytopenia. *Br J Haematol* 1994;88:874-7.
3. Porcelijn L, Van den Akker ES, Oepkes D. Fetal thrombocytopenia. *Semin Fetal Neonatal Med* 2008;13:223-30.
4. Spencer JA, Burrows RF. Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis. *Aust N Z J Obstet Gynecol* 2001;41:45-55.
5. Blanchette VS, Chen L, de Friedberg ZS, Hogan VA, Trudel E, Decary F. Alloimmunization to the PIA1 platelet antigen: results of a prospective study. *Br J Haematol* 1990;74:209-15.
6. Dreyfus M, Kaplan C, Verdy E, Schlegel N, Durand Zaleski I, Tchernia, G, et al. Frequency of immune thrombocytopenia in newborns: a prospective cohort study. *Blood* 1997;89:4402-6.
7. Williamson LM, Hackett G, Rennie J, Palmer CR, Maciver C, Hadfield R, et al. The natural history of fetomaternal alloimmunization to the platelet specific antigen HPA-1a (PIA1, Zwa) as determined by antenatal screening. *Blood* 1998;92:2280-7.
8. Mao C, Guo J, Chituwo BM. Intraventricular haemorrhage and its prognosis, prevention and treatment in term infants. *J Trop Pediatr* 1999;45:237-40.
9. Jocelyn LJ, Casiro OG. Neurodevelopmental outcome of term infants with intraventricular haemorrhage. *Am J Dis Child* 1992;146:194-7.
10. Radder CM, Brand A, Kanhai HH. Will it ever be possible to balance the risk of intracranial haemorrhage in fetal or neonatal alloimmune thrombocytopenia against the risk of treatment strategies to prevent it? *Vox Sang* 2003;84:318-25.
11. Killie MK, Husebekk A, Kjeldsen-Kragh J, Skogen B. A prospective study of maternal anti-HPA 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. *Haematologica* 2008;93:870-877.
12. Gaddipati S, Berkowitz RL, Lumbet AA, Lapinski R, McFarland JG, Bussel JB. Initial fetal platelet counts predict the response to intravenous gammaglobulin therapy in fetuses that are affected by PLA1 incompatibility. *Am J Obstet Gynecol* 2001;185:976-980.
13. Daffos F, Capella-Pavlovsky M, Forestier F. Fetal blood sampling during pregnancy with use of a needle guided by ultrasound: a study of 606 consecutive cases. *Am J Obstet Gynecol* 1985;153:655-60.
14. Van den Akker ESA, Oepkes D, Lopriore E, Kanhai HHH. Noninvasive antenatal management of fetal and neonatal alloimmune thrombocytopenia: safe and effective. *BJOG* 2007;114:469-73.
15. Berkowitz RL, Lesser ML, McFarland JG, Wissert M, Primiani A, Hung C, et al. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomized controlled trial. *Obstet Gynecol*. 2007;110:249-55.

