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Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal Alloimmune Thrombocytopenia: A systematic review

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Abstract

BACKGROUND AND OBJECTIVES: In Caucasians, fetal/neonatal alloimmune thrombocytopenia (FNAIT) is most commonly due to maternal HPA-1a antibodies. HPA-1a typing followed by screening for anti-HPA-1a antibodies in HPA-1bb women may identify first pregnancies at risk. Our goal was to review results from previous published studies to examine whether the maternal antibody level to HPA-1a could be used to identify high-risk pregnancies.

MATERIALS AND METHODS: The studies included were categorized by recruitment strategies: screening of unselected pregnancies or samples analyzed from known or suspected FNAIT patients.

RESULTS: Three prospective studies reported results from screening programs and 10 retrospective studies focused on suspected cases of FNAIT. In 8 studies samples for antibody measurement, performed by the monoclonal antibody immobilization of platelet antigen (MAIPA) assay, and samples for determining fetal/neonatal platelet count were collected simultaneously. In these 8 studies, the maternal antibody level correlated with the risk for severe thrombocytopenia. The prospective studies reported high negative predictive values (88-95%), which would allow for the use of maternal anti-HPA-1a antibody level as a predictive tool in a screening setting, in order to identify cases at low risk for FNAIT. However, due to low positive predictive values reported in prospective as well as retrospective studies (54-97%), the maternal antibody level is less suited for the final diagnosis and for guiding antenatal treatment.

CONCLUSION: HPA-1a antibody level has the potential to predict the severity of FNAIT.

Keywords: alloimmune thrombocytopenia, maternal HPA-1a antibodies, MAIPA, platelet, bleeding

INTRODUCTION

The frequency of severe fetal and neonatal alloimmune thrombocytopenia (FNAIT) ($<50\times10^9$/L) secondary to HPA-1a antibodies has been reported to be approximately 1/2500 pregnancies.[1] Clinically, a fetus or neonate with severe FNAIT often displays unexpected bleeding during pregnancy or within a few hours of delivery.

Without screening of all pregnancies, there is currently no way to predict the occurrence of FNAIT other than identification of a sibling with FNAIT. Using the obstetric history as a predictor, with a diagnostic sensitivity of only 13%, the majority of severe FNAIT cases are not detected until after delivery.[2] . Thus in a non screening situation, Tiller et al. reported that only 7-8 cases of FNAIT were detected per year compared with 53 cases when screening was applied.[3]

Development of non-invasive diagnostic tools that can be used to discriminate between pregnancies in need of antenatal treatment is crucial. The current approach by identifying neonates with FNAIT postnatally, precludes antenatal treatment and/or precautions during delivery, whereas an antenatal screening program would ideally allow both antenatal intervention and immediate treatment of severe FNAIT at birth of an affected neonate.

The challenge of an antenatal screening program is, however, to identify women in whom the risk of severe FNAIT is sufficiently high to justify active treatment during pregnancy to minimize the risk of bleeding complications secondary to FNAIT, whilst not exposing women with milder cases to unnecessary interventions.

The aim of this systematic review is to examine if a relationship can be identified between maternal anti-HPA-1a alloantibody concentration and fetal/neonatal platelet count, which could potentially serve as a non-invasive strategy to identity high-risk pregnancies.

METHODS

Study selection and data extraction

The search was applied to the electronic databases MEDLINE, EMBASE and the Cochrane Library from 1946 to January 12, 2016 (**Appendix A**). Data were independently extracted by two authors (NS, ST).

The included studies met the following criteria: 1) an original study, 2) five or more pregnant women, 3) platelet count and HPA-1a antibody determination, and 4) published in English. Details from each included study are summarized in Appendix B. The included studies were divided into two categories: 1) 'Prospective studies' of 'unselected women' identified by an FNAIT screening program (HPA-1 typing followed by anti- HPA-1a antibody screening), and 2) 'Retrospective studies' of 'selected women' due to an FNAIT child.

All thrombocytopenic neonates ($<150\times10^9$/L) from these studies were included in this review, even those without clinical signs of bleeding.

Assessment of quality

The assessment of the quality of individual primary studies was based on the checklist developed by Fowkes and Fulton and considered the following; whether 1) there was an adequate description of the study population, 2) all eligible patients were screened, 3) a normal sample was included, 4) there were clear definitions of associations, 5) reproducibility of testing was assessed 6) missing data were reported.[4] The considerable heterogeneity in the measurement of study outcomes did not permit conduction of a meta-analysis; therefore, we performed a descriptive review of included studies. Strategies for inclusion of study subjects, the type of laboratory assay used and the time point of both maternal and fetal sampling were specially taken into consideration when analyzing the data.

RESULTS

Study selection and characteristics

A total of 5,940 publications were identified (**Figure 1**). Of these, 4,692 were screened after duplicates were removed and 93 full-text articles were assessed for eligibility. Sixty-six of the 93 did not report the population or outcome of interest and three were not published in English.

Finally, thirteen of the 27 studies had complete data[2, 5-16], the remainder were duplicates[17-21], did not address HPA-1a antibodies[22-25], screened all neonates[26], or did not have a sufficient sample size[27-30]. Three studies were prospective[2, 5, 7] and ten studies were retrospective.[6, 8-16] **Appendix B** describes the 13 studies that were included in this review. **Appendix C** details the 14 studies that were not included.

The assessment of the quality of studies is shown in **Figure 2**. Nine studies adequately described the study population.[2, 5-9, 11, 13, 15] Six studies included samples from non-FNAIT cases[2, 5, 8-10, 12] and screened eligible patients.[2, 5-8, 12]

Four studies reported missing data[2, 4, 8, 10] and three studies assessed reproducibility of testing.[2, 8, 11]

The majority of studies defined severe FNAIT as platelets $<50\times10^9$/L. Severe FNAIT was not defined in three studies.[10, 12, 15]

The studies differed in three key aspects: i) the assays used, ii) the time point at sampling and iii) the populations screened. Ten studies used the MAIPA assay.[2, 5, 6, 8-11, 13, 14, 16] Other methods used were ELISA[7, 12, 16], the platelet immunofluorescence test (PIFT)[2, 10, 12, 15] the ^{51}Cr release test[12] and the chemiluminescence assay.[8]

Antibody testing was scheduled across various weeks of gestation. Antibody measurement was conducted once in five studies[8-10, 14, 16], and more than once in seven studies.[2, 5, 7, 11-13, 15] The frequency of antibody testing was not reported in one study.[6]

Three studies conducted HPA-1 typing followed by antibody screening and quantitation in unselected pregnancies.[2, 5, 7] Ten studies analyzed samples of known or suspected FNAIT.[6, 8-16]

The assay and time point of sampling were taken into consideration when summarizing and discussing the results i.e. evaluating studies that used the same laboratory methods, as well as evaluating results from retrospective studies that reported antibody concentrations and fetal or newborn platelet counts at the same time point when possible.

Lastly, the results were grouped and described separately i.e. prospective screening studies of unselected pregnancies and studies including newly diagnosed FNAIT patients and/or follow-up of women with a history of FNAIT, i.e. retrospective studies.

Prospective screening studies on unselected pregnancies

Details of the three prospective studies that screened and reported quantitative results from unselected immunized pregnancies (a total of 235/125 000 screened pregnancies) are presented in **Table 1**.[2, 5, 7] None of these women was treated with intravenous immune globulin (IVIG) during pregnancy. Severely thrombocytopenic neonates (with or without bleeding symptoms) were treated with compatible platelet transfusion immediately after birth.

Antibody level to predict FNAIT: Williamson described that fetal thrombocytopenia ($<50\times10^9$/L) in the third trimester was associated with maternal HPA-1a antibody level (titers ≥1:32, positive predictive value (PPV) 75% and negative predictive value (NPV) 88%).[5] Killie also reported a correlation between neonatal platelet count ($<50\times10^9$/L) and maternal HPA-1a antibody level at the time of delivery, R^2=0.49. [2] The PPV and NPV of severe FNAIT ($<50\times10^9$/L) using an antibody level of 3 IU/mL when screening unselected pregnancies were 54% (95% CI 43-63%) and 95% (95% CI 86-98%), respectively.[2] In 76 pregnancies with maternal HPA-1a antibody levels <3 IU/mL, four neonates were severely thrombocytopenic (platelet counts of 16, 30, 36 and 45×10^9/L) but did not have any bleeding symptoms.[2] Both studies used MAIPA to analyze the HPA-1a antibody levels.[2, 5] The third study by Bessos did not find any correlation between newborn platelet counts and the HPA-1a antibody concentration using an in-house ELISA for HPA-1a antibody quantitation, R^2=0.14.[7] However, a correlation between antibody level and platelet count was identified in a comparable subsequent study using MAIPA, R^2=0.42. In this study, Bessos reanalyzed 14 samples from their previous study together with 12 samples from the study by Killie 2008 **(Table 1)**.[19] Hence, all studies (n=3) reported that the maternal antibody level at delivery correlated with the newborn platelet count when using quantitative MAIPA.

Retrospective studies on suspected FNAIT

The ten studies focusing on suspected patients with FNAIT included a total of 566 women with HPA-1a antibodies.[6, 8-16] These studies included patients who were treated antenatally with either IVIG (with or without steroids) or with intrauterine platelet transfusions. Eight of the ten studies reported either titration or quantification of HPA-1a antibodies **(Table 2).** In the four studies that reported results obtained from the second trimester, blood samples were collected from the pregnant mother and the fetus at the same time points; whereas in the five studies that reported results from sampling at birth and/or the 3rd trimester, samples were only collected simultaneously in three studies.[6, 8-13, 15]

Antibody level to predict severity of FNAIT: Three studies investigated the HPA-1a antibody level by titration of the samples using either PIFT or ELISA.[10, 12, 15] One of these studies[15] did not examine if there was any correlation between antibody titer and platelet count while the two other studies[10, 12] indicated that there was no correlation between the HPA-1a antibody level and neonatal platelet count. Five studies quantified maternal HPA-1a antibodies by quantitative MAIPA.[6, 8, 9, 11, 13] Four of these five studies, which included a total of 313 pregnancies, identified a statistically significant relationship (p-values: 0.002-0.046) between HPA-1a antibody level and fetal or neonatal platelet count ($<20\times10^9$/L or $<50\times10^9$/L, see Table 2).[6, 9, 11, 13] From the four studies that reported an association, Sainio did not find a statistically significant correlation in samples taken postnatally in 72 index patients, but identified a statistically significant correlation between maternal HPA-1a antibody level during the second trimester and the corresponding fetal platelet count.[11] In addition, maternal HPA-1a antibody level was significantly higher for those delivering neonates with bleeding symptoms (ICH or mild bleeding symptoms) than in mothers of neonates with FNAIT that there were no evidence of bleeding. Killie reported a significant difference in maternal antibody levels at delivery between cases where neonates were severely thrombocytopenic and neonates with normal platelet count.[9] Bertrand reported that an antibody level of ≥250 AU/mL (corresponding to 31 IU/mL[18]) correlated with severe thrombocytopenia in the fetus before the start of treatment (p=0.0021).[6] At this level, PPV and NPV for a platelet count of 50×10^9/L or less were 94% and 60%, respectively.[6] The same group subsequently reported that in pregnancies treated with IVIG, a mean antibody level throughout pregnancy (area under the curve, AUC) >23 IU/mL correlated with treatment failure (newborn platelet count ≤50×10^9/L).[13] By using an antibody level of 23 IU/mL as cut-off, the PPV and NPV of therapy failure were 67 and 86%, respectively.

The last of the five studies included 97 newly diagnosed and 36 patients with known FNAIT, and did not find any relationship between anti-HPA-1a antibody levels and platelet count in newly diagnosed patients.[8] However, in 22/36 patients who were treated antenatally, maternal HPA-1a antibody levels were reported to correlate with fetal platelet count (after fetal blood sampling [FBS]). The correlation co-efficient was not reported. Overall four of five studies, which used quantitative MAIPA found that the maternal antibody level in second trimester correlated with the fetal platelet count in second trimester (4/5). The last study did not investigate fetal platelet count during second trimester, but reported that maternal antibody level measured at time of delivery correlated with platelet count in the newborn.[9]

It is not known if and how antenatal IVIG treatment potentially affects measurements of anti-HPA-1a antibodies. However, a decrease in HPA-1a antibody concentrations has been observed during pregnancies of IVIG-treated women [6] as well as in untreated women [2], suggesting that the decrease in antibody level may not be associated with IVIG therapy.

DISCUSSION

Main findings

In this descriptive systematic review, we found that most studies quantifying HPA-1a antibodies by the MAIPA assay reported a correlation between antibody level and severity of FNAIT; whereas studies in which antibody analysis was done by PIFT or ELISA could not document such a relationship, suggesting that these methods may not be as suitable for quantitative analysis. This is supported by the study by Bessos who compared ELISA and MAIPA and found that the severity of FNAIT was significantly associated with the HPA-1a antibody level when using MAIPA, but not when an in-house ELISA was used.[19] Another important finding was that timing of the blood sample for antibody determination from mother and fetus/newborn seems essential since a correlation was only observed in those studies that reported the same time point for fetal/newborn platelet count sampling and maternal antibody detection/quantitation.

Results from prospective screening studies using the MAIPA technique[2, 5] (a total of approximately 125,000 pregnancies) showed that among 256 HPA-1a-immunized pregnancies, HPA-1a antibody levels in the third trimester or at delivery correlated with the newborn platelet count, suggesting that the maternal HPA-1a antibody level in the third trimester has the potential to be used as a predictive tool, and used as guideline for mode of delivery and to have compatible HPA-1bb platelets available in case of bleeding in the neonate.

A significant association (all $p<0.05$) between the fetal platelet count and maternal antibody level quantified by MAIPA could also be demonstrated in pregnancies known to be at risk of FNAIT due to a previous child with FNAIT, when maternal and fetal sampling was performed at the same time during the second trimester.[6, 8, 9, 11] The low PPV and NPV would not allow for the use of maternal antibody level to determine a final diagnosis of severe FNAIT (defined as $<20\times10^9$/L or $<50\times10^9$/L in the studies) or to be used to establish treatment regimens. Bertrand suggests that the maternal antibody level throughout pregnancy (area under the curve, AUC) might be used to follow the effect of IVIG treatment.[13]

Strength and limitations

A strength of this systematic review is that study populations were categorized by FNAIT risk and compared separately; i.e. results from studies screening unselected pregnancies (prospective studies) and from studies focusing on newly diagnosed FNAIT patients and pregnancies with a known risk of FNAIT (retrospective studies). This has been an important bias in previous study reports. In retrospective studies, cases have been selected who have been diagnosed with FNAIT in the fetus/newborn, and thus, it is not surprising that the majority of these women will have higher antibody levels than women in prospective studies, since the latter studies included all HPA-1a-immunized women irrespective of fetal/neonatal symptoms. It is

therefore not surprising there is a better chance of finding an association between antibody levels and fetal/neonatal platelet counts in prospective studies, as compared with retrospective studies, and similarly, it is not surprising that an effort of defining a clinically relevant antibody cut-off level will differ between these two patient populations.

In general, measurements reported as fluorescence intensity, optical density, titer or arbitrary units would depend on the in-house assay sensitivity and would not allow for comparison between laboratories. Results could only be compared directly when an international standard was used as a reference and measurements were reported in IU/mL. As a result, there are two major limitations of the studies included in this review that make it difficult to draw definitive conclusions. Firstly, different methods were used to quantify anti-HPA-1a levels and the number of studies reporting HPA-1a antibody level in IU/mL was small (4/13). Secondly, the time of sampling varied considerably. Samples taken at different time points cannot be compared directly, primarily because the transfer of maternal IgG across the placenta varies with gestational age. The transfer of normal and pathogenic IgG from the mother to her fetus begins as early as the end of the first trimester and increases as the pregnancy advances.[31] Therefore, the amount of HPA-1a antibodies to which the fetus is exposed, may be related to both maternal antibody concentration and gestational age.

The studies in the current review correlated antibody concentration and platelet count using a low platelet count as a surrogate for bleeding risk. Bleeding is indeed much more common in neonates with very low platelet counts but many fetuses with low platelet counts seem not to bleed. Both a defective hemostatic system as well as endothelial damage are necessary requirements for bleeding to occur. Thus, isolated thrombocytopenia, as such, may not cause harm in the newborn unless the endothelium is damaged. This may explain why some newborns with severe thrombocytopenia do not bleed. Recently, it was demonstrated that HPA-1a antibodies in women who have had a fetus/child with FNAIT-associated ICH bind to αVß3 on endothelial cells, and that these antibodies *in vitro* can induce endothelial apoptosis. These antibodies were not present in HPA-1a-immunized women whose fetus/child had FNAIT but no ICH.[32] Unfortunately, the current MAIPA assays do not distinguish between these different specificities of the HPA-1a antibodies. Moreover, the reactivity of antibodies measured by MAIPA or similar techniques is always a composite of antibody amount, specificity and avidity. Moreover, the exact binding sites (epitopes) for the HPA-1a antibodies would be important, since binding sites might alter binding to and/or signaling through the fibrinogen receptor, and thus may have influence on FNAIT severity and bleeding tendency.[33] Further, low avidity antibodies can have biological effects as they are not washed away *in vivo* as opposed to *in vitro*, and such antibodies may account for those few cases where a fetus/child bleeds despite the MAIPA assay only detected low levels of anti-HPA-1a.

Implications

FNAIT has been regarded as the platelet counterpart of hemolytic disease of the fetus and newborn (HDFN). For decades, measurement of the maternal anti-D level, either as titer or as IU/mL, has been used in Europe and North America to determine when an RhD-immunized woman is referred to a fetal medicine unit for monitoring and eventual treatment. An RhD-

alloimmunized pregnant woman is referred to a fetal medicine unit for monitoring the middle cerebral artery peak systolic velocity (MCA PSV) when the antibody level exceeds 4 IU/mL. Invasive investigation or treatment may be required when the anti-D level exceeds 15 IU/mL, but this is ultimately determined by the MCA PSV levels.[34-36]. . Results from the prospective studies suggest that HPA-1a antibody levels might have a comparable future role as predictor for fetuses with increased risk for FNAIT. As there remains interlaboratory variation in measurement in the measurement of the anti-D titer [37], some of the inconsistencies in anti-HPA-1a antibody titer we found in some of reports may represent a similar occurrence. Although a gold standard imaging modality is not yet available, and there is a lack of consensus on how to treat risk pregnancies that are identified by screening, anti-HPA-1a levels may identify pregnancies to be referred to specialists in fetal-maternal medicine. Hence, if screening for FNAIT is implemented, measurements of HPA-1a antibody levels could potentially be used for risk stratification of pregnancies and could guide the clinicians in order to avoid invasive procedures in pregnancies with low risk, and for planning the route of delivery and treatment of high risk pregnancies. Preliminary data suggest [36,37] an antibody cut-off of 3 IU/mL may potentially be used for risk assessment.

Studies have shown that by standardizing quantitative MAIPA and by expressing anti-HPA-1a levels in IU/mL, it is possible to obtain comparable results across laboratories[38, 39], and therefore, the differences in HPA-1a antibody cut off level (3 IU/mL at delivery vs 30 IU/mL in the second trimester[6, 8]) between prospective and retrospective studies may not necessarily be due to inter-laboratory variability. Instead, the difference between the identified antibody threshold may be due to variable trans-placental transportation of IgG during pregnancy. In the second trimester, the fetal IgG level is only 5%-10% of the maternal IgG concentration; whereas, later in the third trimester, IgG concentration is almost identical in the mother and fetus.[40] It is also important to be aware that maternal antibody levels increase shortly after delivery and post-partum sampling cannot be used to study the correlation between maternal antibody levels and newborn platelet count.

Although the HPA-1a-antibody concentration, as measured by the MAIPA assay, appears to be associated with the degree of thrombocytopenia in FNAIT, there are shortcomings which make it difficult to predict individual risk for bleeding. Thus, more studies are needed to define antibody characteristics that give higher PPV or NPV for bleeding risk; preferentially predictive values in the same range as MCA PSV for the prediction of anaemia in women who are RhD-immunized. Future studies should be prospective, should report the exact time point of sampling (which ideally would also be standardized), should perform quantitative HPA-1a analysis by the MAIPA assay, should report HPA-1a antibody levels in IU/mL using WHO HPA-1a international standards[41], and should measure the antibody concentration prior to antenatal treatment as well as during antenatal treatment.

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AUTHORSHIP

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38   Bertrand G, Jallu V, Gouet M, et al.: Quantification of human platelet antigen-1a antibodies with the monoclonal antibody immobilization of platelet antigens procedure. *Transfusion* 2005; 45: 1319-23.

39   Bertrand G, Bakchoul T, Javela K, et al.: Interlaboratory workshop on anti-HPA-1a alloantibody quantification with the mAb-specific immobilization of platelet antigen technique. *J Thromb Haemost* 2012; 10: 1172-4.

40   Malek A, Sager R, Kuhn P, et al.: Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol* 1996; 36: 248-55.

41   Allen D, Rigsby P, Bessos H, et al.: Collaborative study to establish the first international standard for quantitation of anti-HPA-1a. *Vox Sang* 2005; 89: 100-4.

TABLES

Table 1 Characteristics and performance; samples collected by screening unselected pregnancies

Table 2 Characteristics and performance; samples collected retrospectively from known or suspected FNAIT cases

FIGURE

Figure 1 Flow diagram of included studies

Figure 2 Quality assessment of included studies

Table 1 Characteristics and performance; samples collected by screening unselected pregnancies

First author, year of publication (number of pregnancies screened)	No. of pregnancies	Method	Time of sampling	Platelet count cut-off	Positive predictive value	Negative predictive value	Antibody cut-off	R^2	p value
Williamson LM, 1998 (24 417)	25	MAIPA	3rd trimester	$<50\times10^9$/L	75%	88%	Titer: 32	-	0.004
	17	MAIPA	2nd trimester		-	-	Titer: 32	-	0.05
	13	MAIPA	1st trimester		-	-	Titer: 32	-	NS
Killie MK, 2008 (100 448)	161	MAIPA	At birth and at weeks 22 and 34	$<50\times10^9$/L	54%	95%	3 IU/mL	0.49	0.001
Bessos H, 2005 (26 506)	28	ELISA	At birth	NR	-	-	-	<0.01	NS
Bessos H, 2008*	26	MAIPA	At birth	NR	-	-	-	0.42	0.002

MAIPA, monoclonal antibody immobilization of platelet antigen; NR, not reported; NS, not significant; R^2, coefficient of determination.

 *The study compared results from 26 samples (from Bessos et al. 2005 and Killie et al. 2008) blindly quantified by both ELISA

and MAIPA. This study was not included in the systematic review since it includes duplicates from Bessos et al. 2005 and Killie et al. 2008.

Table 2 Characteristics and performance; samples collected retrospectively from known or suspected FNAIT cases

First author, year of publication	No. of pregnancies	Method	Time of sampling	Platelet count cut-off	Positive predictive value	Negative predictive value	Antibody cut-off	R^2	p value
McFarland JG, 1989	17	PIFT/ ELISA	1st, 2nd & 3rd trimester	NR	-	-	-	-	NR
Proulx C, 1994	36	ELISA	At birth	NR	-	-	-	<0.01	NS
Bertrand G, 2006	27	MAIPA	2nd & 3rd trimester	$\leq 50 \times 10^9/L$	94%	60%	31 IU/ mL	-	0.002
Killie MK, 2007	102	MAIPA	At birth	$<25 \times 10^9/L$ & 25- $150 \times 10^9/L$	-	-	-	-	0.007
Ghevaert C, 2007	97	MAIPA	At birth	$<50 \times 10^9/L$	-	-	-	-	NS

	22	MAIPA	2nd & 3rd trimester	$<20\times10^9$/L	90%	66%	30 IU/mL	-	-
Sainio S, 2013	72	MAIPA	At birth	$<20\times10^9$/L	80%	17%	-	-	0.074
	16	MAIPA	2nd trimester	$<20\times10^9$/L	90%	31%	-	-	0.047
Bertrand G, 2014	27	MAIPA	2nd & 3rd trimester	$<50\times10^9$/L	67%	86%	23 IU/mL	-	<0.001
Kanhai HH, 1996	19	PIFT	2nd & 3rd trimester	NR	-	-	-	-	NR

ELISA, enzyme-linked immunosorbent assay; MAIPA, monoclonal antibody immobilization of platelet antigen; NR, not reported;

NS, not significant; PIFT, platelet immunofluorescence test; R^2, coefficient of determination.

Identification

Records identified through database searching (n = 5940)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 4692)

Screening

Records screened (n = 4692)

Records excluded (n = 4599)

Eligibility

Full-text articles assessed for eligibility (n = 93)

Full-text articles excluded (n = 66)
- Population or outcome of interest not reported, n = 63
- Non English, not accessible, n = 3

Included

Studies included on HPA Alloantibody Screening (n = 27)

Full-text articles excluded (n = 14)
- < 5 patients with HPA-1a antibodies (n=4)
- Results from samples reported in other studies (n=4)
- Incomplete data set (n=5)
- Symptomatic cases instead of unselected pregnancies screened by a prospective study (n=1)

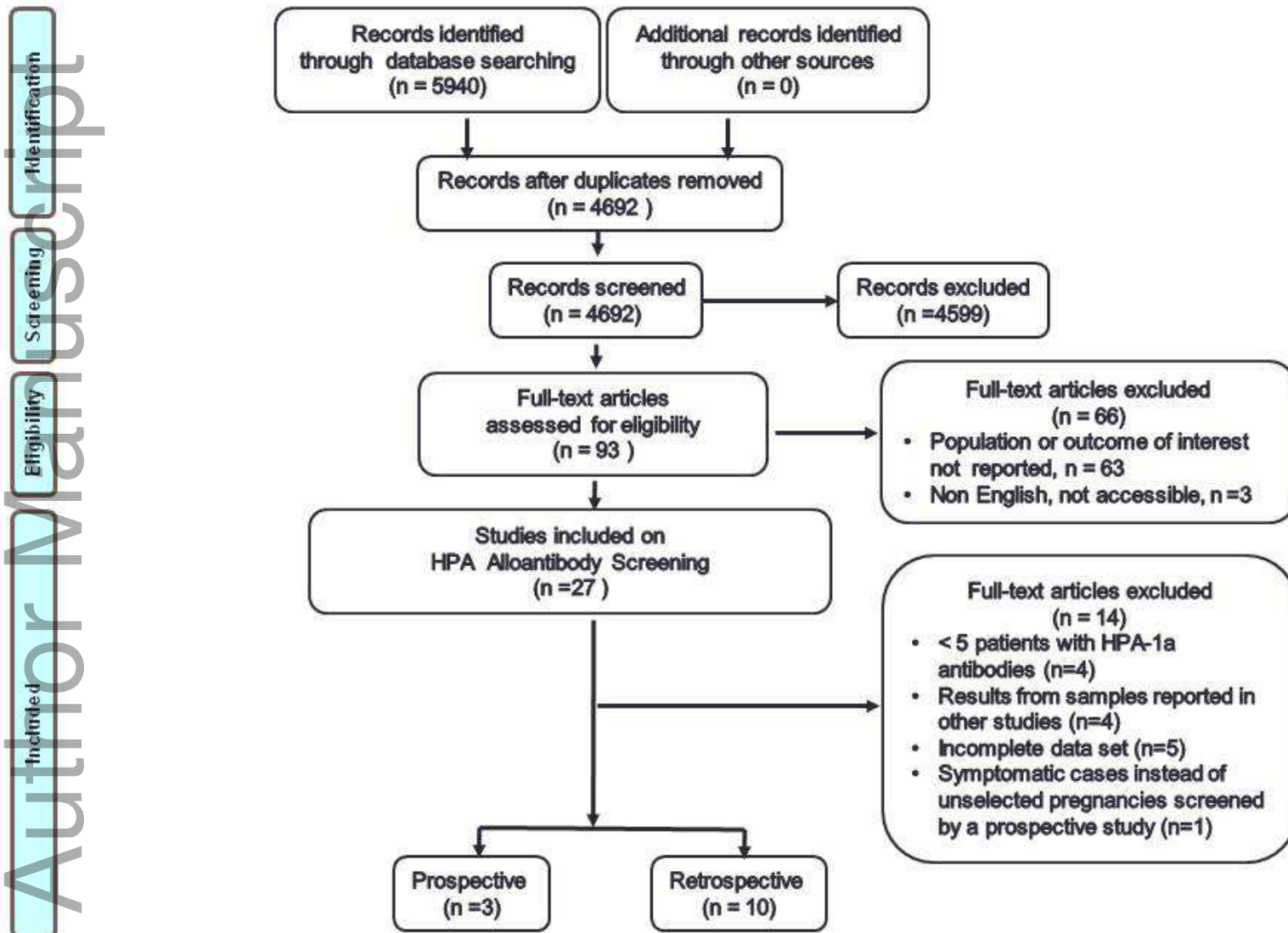Prospective (n = 3)

Retrospective (n = 10)
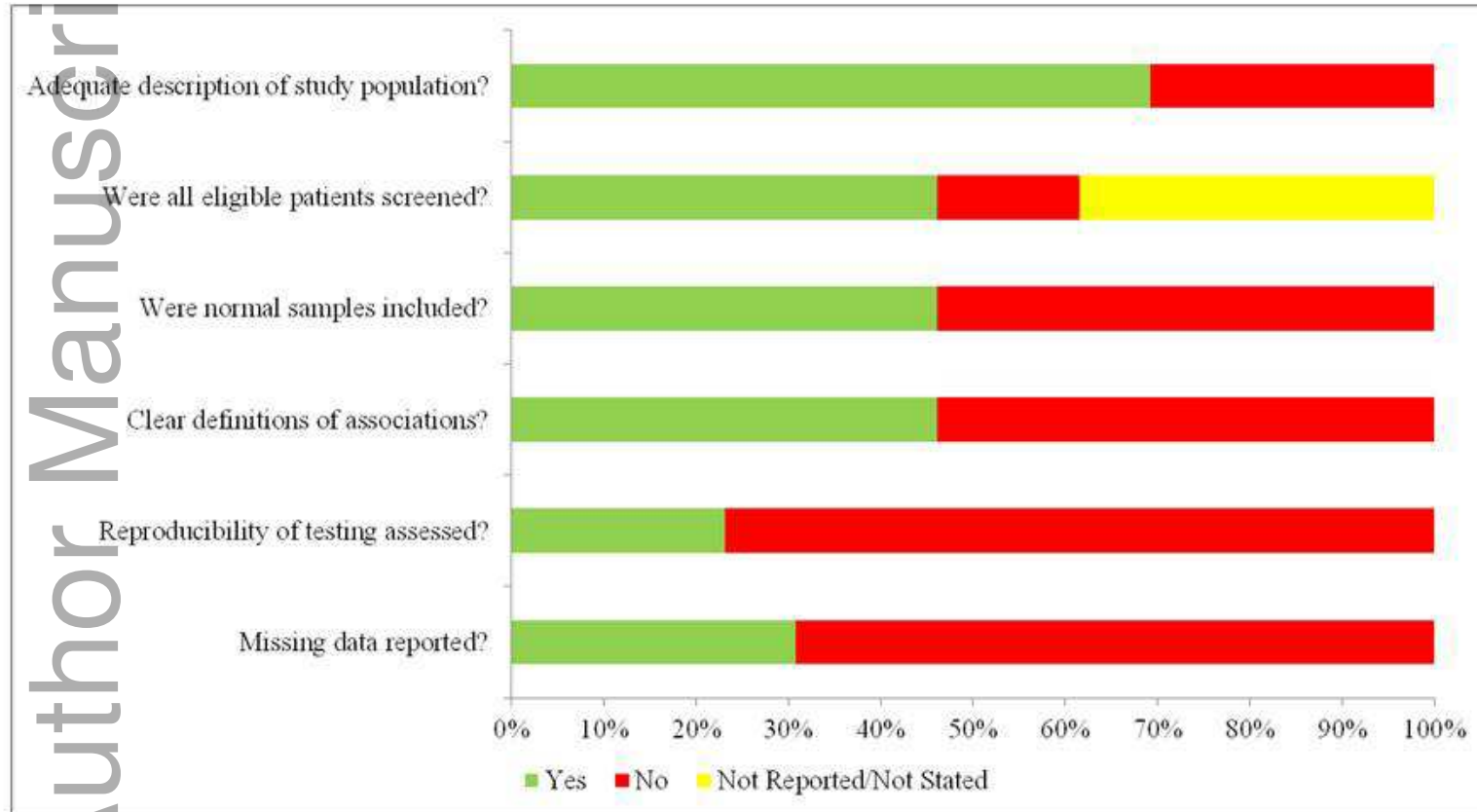
Figure 1 Flow diagram of included studies

Figure 2 Quality assessment of included studies

APPENDIX A: Search Strategy

MEDLINE

1. thrombocytopenia, neonatal alloimmune/
2. thrombocytopenia/
3. limit 2 to "newborn infant (birth to 1 month)"
4. infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or infant, extremely premature/
5. Exp Fetus/
6. (fetus* or foetus* or fetal* or foetal* or neonat* or newborn* or infan* or prematur* or preemie* or "pre term" or "pre-term" or lbw or elbw or sga or vlbw or nicu*).mp.
7. 3 or (2 and (4 or 5 or 6))
8. (((fetal or foetal or fetus* or foetus* or neonat*) adj5 thrombocytopen*) or NAIT or FNAIT or FMAIT).mp.
9. or/1,7-8
10. immunoglobulins, intravenous/
11. immunoglobulin g/ or IgG/ or Immunoglobulins/ or (immunoglobulin* or sandoglobulin* or sandoglobin* or "immune globulin*" or gamimmune or endobulin* or venoglobulini or gammagard or venoglobulin or "intraglobin f" or intraglobin or "globulin-n" or "globulin n" or alphaglobin or privigen or "flebogamma dif" or gamunex or globulinn or venimmune or flebogamma or flebogammadif or gamastan or "gamma globulin*" or "gamma immunoglobulin*" or "gamma-globulin*" or gammagee or gammaglobulin* or gammar or gammimune or gamulin or globuman or Ig or igam or igc or immunogammaglobulin* or intragam or "intraglobin f" or panglobulin* or tegelin* or "c 425" or c425 or "c-425" or cytotect or "gamimune n" or "gamma g" or "gamma globulin g" or gammagard or gammaglobulin* or "ig g" or IgG or octagam or pentaglobin or polygam or polyglobin or "gamma g1" or "gamma g2").mp.
12. administration, intravenous/ or infusions, intravenous/ or injections, intravenous/ or (intravenous or iv or infusion* or administrat*).mp.
13. 11 and 12

14   (iveegam or gammonativ or "intravenous ig" or ivig or "glovenin i" or isiven or iveegam or ivega or veinoglobulin or vivaglobin* or gammonativ or kiovig or privigen).mp.

15   or/10,13-14

16   9 and 15

17   Antigens, Human Platelet/ or ("platelet-specific antigen*" or "antigen* platelet-specific" or (human adj5 platelet* adj5 antigen*) or (platelet adj5 alloantigen*) or HPA or HP-A).mp.

18   9 and 17

19   Maternal-Fetal Exchange/ or ("maternal-fetal exchange" or (transplacental adj5 (transfer* or exposure* or exchange*))).mp.

20   platelet transfusion/

21   blood component transfusion/ and blood platelets/

22   Blood Transfusion, Intrauterine/

23   ((intrauterine or fetus* or foetus* or fetal* or foetal* or cord or platelet*) adj5 transfusion*).mp.

24   or/19-23

25   9 and 24

26   exp adrenal cortex hormones/ or glucocorticoids/ or dexamethasone/ or dexamethasone isonicotinate/ or prednisone/

27   ("adrenal cortex hormone*" or "adrenal cortical hormone*" or ((adreno or adrenal) adj2 (cortex or cortical) adj2 steroid*) or corticosteroid* or adrenocortical or "cortical steroid*" or "cortico steroid" or glucocorticoid*).mp.

28   (dexamethasone or adrecort or adrenocot or "aeroseb dex" or aflucoson or aflucosone or alfalyl or anaflogistico or arcodexan or arcodexane or artrosone or azium or bidexol or calonat or cebedex or cetadexon or colofoam or corsona or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or dacortina fuerte or dacortine fuerte or dalalone or danasone or decacortin or decadeltosona or decadeltosone or decaderm or decadion or decadran or decadron or decadronal or decadrone or decaesadril or decaject or decameth or decamethasone or decasone or decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or desacort or desacortone or desadrene or desalark or desameton or desametone or desigdron or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or

"dexa scherosan" or "dexa scherozon" or "dexa scherozone" or dexacen or dexachel or dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabroson or dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or dexametason or dexamethasone or dexameth or dexamethasone or dexamethazon or dexamethasone or dexamethonium or dexamonozon or dexan or dexane or dexano or "dexa-p" or dexapot or dexascheroson or dexascherozon or dexascherozone or dexason or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or dexpak or dextelan or dextrasone or dezone or dibasona or dexamethasone or esacortene or "ex s1" or exadion or exadione or firmalone or "fluormethyl prednisolone" or fluormethylprednisolon* or fluormone or fluorocort or fluorodelta or fluoromethylprednisolon* or fortecortin or gammacorten or gammacortene or grosodexon or grosodexone or hexadecadiol or hexadecadrol or hexadiol or hexadrol or isnacort or "isopto dex" or "isopto maxidex" or isoptodex or isoptomaxidex or "lokalison f" or loverine or luxazone or marvidione or maxidex or mediamethasone or megacortin or mephameson or mephamesone or metasolon or metasolone or methazon or methazone or methazonion or methazonione or methylfluorprednisolone or "metisone lafi" or mexasone or millicorten or millicortenol or "mk 125" or mymethasone or nisomethasona or novocort or "nsc 34521" or nsc34521 or "oftan-dexa" or opticorten or opticortinol or oradexan or oradexon or oradexone or orgadrone or ozurdex or pidexon or policort or posurdex or "predni f tabline" or "predni-f" or "prednisolone f" or prodexona or prodexone or sanamethasone or santenson or santeson or sawasone or solurex or spoloven or sterasone or thilodexine or triamcimetil or vexamet or visumetazone or visumethazone).mp.

29   (prednison* or ancortone or biocortone or colisone or cortan or corcortancyl or cortidelt or cortiprex or cutason or dacorten or dacortin or "de cortisyl" or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or "dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or "delta dome" or "delta e" or "delta prenovis" or deltacorten* or deltacortisone or "delta-cortisone" or deltacortone or deltasone or deltison or deltisona or deltra or "di adreson" or diadreson or drazone or encorton or encortone or enkortolon or enkorton or fernisone or hostacortin or insone or kortancyl or "liquid pred" or lodotra or "me-korti" or meprison or metacortandracin or meticorten or meticortine or nisona or "sc 10023" or nsc10023 or orasone or orisane or panafcort or panasol or paracort or

pehacort or precort or precortal or "predni tablinen" or "prednicen-m" or prednicorm or prednicot or prednidib or predniment or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or sone or steerometz orsterapred or ultracorten orurtilone or winpred).mp

30   dexamethasone acetate/ or (decadron or "decadron-la" or "dexi siozwo" or supertendin).mp.

31   "dexamethasone ester".mp

32   (auxiloson or auxison or dosauxison or "he 111" or he111 or voren).mp.

33   or/26-32

34   9 and 33

35   16 or 18 or 25 or 34

EMBASE

1   neonatal alloimmune thrombocytopenia/

2   thrombocytopenia/

3   limit 2 to infant <to one year>

4   newborn/ or prematurity/ or "immature and premature labor"/ or low birth weight/ or extremely low birth weight/ or small for date infant/ or very low birth weight/

5   fetus/

6   (fetus* or foetus* or fetal* or foetal* or neonat* or newborn* or infan* or prematur* or preemie* or "pre term" or "pre-term" or lbw or elbw or sga or vlbw or nicu*).mp.

7   3 or (2 and (4 or 5 or 6))

8   (((fetal or foetal or fetus* or foetus* or neonat*) adj5 thrombocytopen*) or NAIT or FNAIT or FMAIT).mp.

9   or/1, 7-8

10   immunoglobulin/iv or immunoglobulin g/iv or immunoglobulin g1/iv or immunoglobulin g2/iv or immunoglobulin g2a/iv or immunoglobulin g2b/iv or immunoglobulin g3/iv or immunoglobulin g4/iv or ((immunoglobulin g/ or IgG/ or Immunoglobulins/ or (immunoglobulin* or sandoglobulin* or sandoglobin* or "immune globulin*" or gamimmune or endobulin* or venoglobulini or gammagard or venoglobulin or "intraglobin f" or intraglobin or "globulin-n" or "globulin n" or alphaglobin or privigen or "flebogamma dif" or gamunex or globulinn or venimmune or flebogamma or flebogammadif or gamastan or "gamma globulin*" or "gamma

immunoglobulin*" or "gamma-globulin*" or gammagee or gammaglobulin* or gammar or gammimune or gamulin or globuman or Ig or igam or igc or immunogammaglobulin* or intragam or "intraglobin f" or panglobulin* or tegelin* or "c 425" or c425 or "c-425" or cytotect or "gamimune n" or "gamma g" or "gamma globulin g" or gammagard or gammaglobulin* or "ig g" or IgG or octagam or pentaglobin or polygam or polyglobin or "gamma g1" or "gamma g2")) and iv.fs.).mp.

11 (iveegam or gammonativ or "intravenous ig" or ivig or "glovenin i" or isiven or iveegam or ivega or veinoglobulin or vivaglobin* or gammonativ or kiovig or privigen).mp.

12 or/10-11

13 9 and 12

14 thrombocyte antigen/ or ("platelet-specific antigen*" or "antigen* platelet-specific" or (human adj5 platelet* adj5 antigen*) or (platelet adj5 alloantigen*) or HPA or HP-A).mp.

15 9 and 14

16 fetomaternal transfusion/ or ("maternal-fetal exchange" or (transplacental adj5 (transfer* or exposure* or exchange*))).mp.

17 thrombocyte transfusion/ or (platelet adj2 transfus*).mp.

18 (blood component therapy/ or blood transfusion/) and (thrombocyte/ or platelet*.ti,ab.)

19 intrauterine blood transfusion/

20 ((intrauterine or fetus* or foetus* or fetal* or foetal* or cord or platelet*) adj5 transfusion*).mp.

21 or/16-20 [****Transfusion terms****] ()

22 9 and 21

23 exp corticosteroid/ or glucocorticoid/ or dexamethasone/ or dexamethasone isonicotinate/ or prednisone/ or ("adrenal cortex hormone*" or "adrenal cortical hormone*" or ((adreno or adrenal) adj2 (cortex or cortical) adj2 steroid*) or corticosteroid* or adrenocortical or "cortical steroid*" or "cortico steroid" or glucocorticoid*).mp.

24 (dexamethasone or adrecort or adrenocot or "aeroseb dex" or aflucoson or aflucosone or alfalyl or anaflogistico or arcodexan or arcodexane or artrosone or azium or bidexol or calonat or cebedex or cetadexon or colofoam or corsona or cortastat or cortidex or cortidexason or cortidrona or cortidrone or cortisumman or dacortina fuerte or dacortine fuerte or dalalone or danasone or decacortin or decadeltosona or

decadeltosone or decaderm or decadion or decadran or decadron or decadronal or
decadrone or decaesadril or decaject or decameth or decamethasone or decasone or
decaspray or decasterolone or decdan or decilone or decofluor or dectancyl or
dekacort or delladec or deltafluoren or deltafluorene or dergramin or deronil or
desacort or desacortone or desadrene or desalark or desameton or desametone or
desigdron or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or
"dexa scherosan" or "dexa scherozon" or "dexa scherozone" or dexacen or dexachel or
dexacort or dexacortal or dexacorten or dexacortin or dexacortisyl or dexadabroson or
dexadecadrol or dexadrol or dexagel or dexagen or dexahelvacort or dexakorti or
dexalien or dexalocal or dexame or dexamecortin or dexameson or dexamesone or
dexametason or dexamethasone or dexameth or dexamethasone or dexamethazon or
dexamethasone or dexamethonium or dexamonozon or dexan or dexane or dexano or
"dexa-p" or dexapot or dexascheroson or dexascherozon or dexascherozone or
dexason or dexasone or dexinoral or dexionil or dexmethsone or dexona or dexone or
dexpak or dextelan or dextrasone or dezone or dibasona or dexamethasone or
esacortene or "ex s1" or exadion or exadione or firmalone or "fluormethyl
prednisolone" or fluormethylprednisolon* or fluormone or fluorocort or fluorodelta or
fluoromethylprednisolon* or fortecortin or gammacorten or gammacortene or
grosodexon or grosodexone or hexadecadiol or hexadecadrol or hexadiol or hexadrol
or isnacort or "isopto dex" or "isopto maxidex" or isoptodex or isoptomaxidex or
"lokalison f" or loverine or luxazone or marvidione or maxidex or mediamethasone or
megacortin or mephameson or mephamesone or metasolon or metasolone or methazon
or methazone or methazonion or methazonione or methylfluorprednisolone or
"metisone lafi" or mexasone or millicorten or millicortenol or "mk 125" or
mymethasone or nisomethasona or novocort or "nsc 34521" or nsc34521 or "oftan-
dexa" or opticorten or opticortinol or oradexan or oradexon or oradexone or orgadrone
or ozurdex or pidexon or policort or posurdex or "predni f tabline" or "predni-f" or
"prednisolone f" or prodexona or prodexone or sanamethasone or santenson or
santeson or sawasone or solurex or spoloven or sterasone or thilodexine or
triamcimetil or vexamet or visumetazone or visumethazone).mp.

25   (prednison* or ancortone or biocortone or colisone or cortan or corcortancyl or
cortidelt or cortiprex or cutason or dacorten or dacortin or "de cortisyl" or decortancyl
or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or
"dellacort a" or "delta 1 dehydrocortisone" or "delta cortelan" or "delta cortisone" or

"delta dome" or "delta e" or "delta prenovis" or deltacorten* or deltacortisone or "delta-cortisone" or deltacortone or deltasone or deltison or deltisona or deltra or "di adreson" or diadreson or drazone or encorton or encortone or enkortolon or enkorton or fernisone or hostacortin or insone or kortancyl or "liquid pred" or lodotra or "me-korti" or meprison or metacortandracin or meticorten or meticortine or nisona or "sc 10023" or nsc10023 or orasone or orisane or panafcort or panasol or paracort or pehacort or precort or precortal or "predni tablinen" or "prednicen-m" or prednicorm or prednicot or prednidib or predniment or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or sone or steerometz orsterapred or ultracorten orurtilone or winpred).mp.

26   dexamethasone acetate/ or (decadron or "decadron-la" or "dexi siozwo" or supertendin).mp.

27   "dexamethasone ester".mp.

28   (auxiloson or auxison or dosauxison or "he 111" or he111 or voren).mp.

29   or/23-28

30   9 and 29

31   13 or 15 or 22 or 30

Cochrane Central Register of Controlled Trials

1   thrombocytopenia, neonatal alloimmune/ or neonatal alloimmune thrombocytopenia/

2   thrombocytopenia/

3   infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or infant, extremely premature/ or newborn/ or prematurity/ or "immature and premature labor"/ or low birth weight/ or extremely low birth weight/ or small for date infant/ or very low birth weight/

4   exp fetus/

5   (fetus* or foetus* or fetal* or foetal* or neonat* or newborn* or infan* or prematur* or preemie* or "pre term" or "pre-term" or lbw or elbw or sga or vlbw or nicu*).mp.

6   2 and (3 or 4 or 5)

7   (((fetal or foetal or fetus* or foetus* or neonat*) adj5 thrombocytopen*) or NAIT or FNAIT or FMAIT).mp.

8   1 or 6 or 7

Author Manuscript

Appendix B Characteristics and Outcomes of Samples Collected

Author, Year; Country, Center	Implicated HPA antigen	Method of antibody determination	Antibody Concentration Threshold,	Frequency of antibody screening	# screened / # of pregnant women with HPA antibody / # of pregnancies included	Platelet count that correlated with antibody titre	Sensitivity (%) / Specificity (%)/ PPV (%)/ NPV (%)	Summary
Prospective								
Killie M, 2008; Norway, single center[2]	1a	MAIPA PIFT	>3 IU/mL	Every 4 weeks	1,990/161/161	$<50\times10^9$/L	93/ 63/ 54/ 95	The maternal antibody level (IU/mL) at delivery correlated with the degree of FNAIT (p<0.001).
Bessos H, 2005; Scotland, multi center[6]	1a	ELISA	NR	Samples obtained from various gestational ages	327/28/22	NR	NR	The maternal antibody level did not correlate with the degree of FNAIT (R=-0.046).

Williamson L, 1998; UK, multi center[4]	1a	MAIPA	≥1:32	HLA-DRB3*0101 positive: week 26, 30, 36; HLA-DRB3*0101 negative: week 28-34	24,417/46/387	$<50\times10^9$/L	NR/ NR/ 75/ 88	The maternal antibody titre at last trimester correlated with the degree of FNAIT (p=0.004).
Retrospective								
Bertrand G, 2014; France, single center[12]	1a	MAIPA	>23 IU/mL	Every 3-5 weeks	55/55/55	$<50\times10^9$/L	76/ 79/ 67/ 86	The maternal antibody level (IU/mL) during pregnancy correlated with the degree of FNAIT (p<0.0001).
Sainio S, 2013; Finland, multi center[10]	1a	MAIPA	NR	Index pregnancies, postnatally;	129/84/129	$<20\times10^9$/L	Subsequent pregnancies	Index pregnancies: The maternal antibody level

				Subsequent pregnancies, first and second trimesters			NR/ NR/ 90/ 31	(IU/mL) postnatally did not correlate with the degree of FNAIT (p=0.074). Subsequent pregnancies: The maternal antibody titers at second trimester correlated with the degree of FNAIT (p=0.046).
Giers G, 2010; Germany, single center[13]	1a, 3a, 4b, 5b	MAIPA	NR	Prior to intrauterine transfusion	57/57/57	NR	NR	No quantitative measurements
Ghevaert C, 2007;	1a	MAIPA CL	>30 IU/mL	Index pregnancies,	133/117/133	$<20\times10^9$/L	Subsequent pregnancies	Index pregnancies:

UK, multi center[7]				postnatally; Subsequent pregnancies, first, second and third trimesters			NR/ NR/ 90/ 66	The maternal antibody level (IU/mL) postnatally did not correlate with the degree of FNAIT (p-value NR). Subsequent pregnancies: The maternal antibody level (IU/mL) at second trimester correlated with the degree of FNAIT (p-value NR)
Killie MK, 2007; Norway, multi center[8]	1a	MAIPA	NR	At delivery	108/102/102	$<25\times10^9$/L		NR	The maternal antibody level (IU/mL) at delivery correlated with

								the degree of FNAIT ($p<0.007$).
Bertrand G, 2006; France, single center[5]	1a	MAIPA	≥250 AU/mL	NR (FBS and maternal antibody detection at the same time points)	27/19/27	$<50\times10^9$/L	<28 weeks 80/ 88/ 89/ 78	The maternal antibody level (AU/mL) correlated with the severe FNAIT ($p<0.0021$).
Proulx C, 1994; Canada, not reported[9]	1a	ELISA PIFT	NR	Shortly after delivery	40/40/40	NR	NR	The maternal antibody titer did not correlate with the degree of FNAIT ($r=0.001$).
Kanhai H 1996; The Netherland, single center[14]	1a, 3a, 5a, n=1 unknown	PIFT	NR	Before and after every FBS	19/18/15	NR	NR	No report of any correlation between antibody titer and FNAIT
Taaning E,	1a, 5b,	ELISA	NR	Following	59/32/19	NR	NA	No quantitative

1994; Denmark, not reported[15]	unknown			delivery				measurements
McFarland JG, 1989; United States, not reported[11]	1a, 3a, n=5 unknown	PIFT ^{51}Cr release test ACE-ELISA	NR	Samples obtained from various gestational ages	25/22/14	NR	NR	No report of any correlation between antibody titer and FNAIT

ACE-ELISA, antigen capture enzyme-linked immunosorbent assay; CL, chemiluminiscence; ELISA, enzyme-linked immunosorbent assay; FBS, fetal blood sampling; FNAIT, fetal/neonatal alloimmune thrombocytopenia; HLA, human leukocyte antigen; HPA, human platelet antigen; PPV, positive predictive value; NPV, negative predictive value; MAIPA, monoclonal antibody immobilization of platelet antigen; PIFT, platelet immunofluorescence test; NA, not applicable; NR, not reported

Appendix C Excluded studies in the final analysis

Author, Year	Reasons for exclusion
Fratellanza G, 2006[25]	Screening of selected pregnancies
Davoren A, 2003[27]	Anti-HPA-1a (3 patients)
Jaegtvik S, 2000[19]	Anti-HPA-1a (24 patients); data reported in Killie 2008[2]
Ohto H, 2000[24]	Anti-HPA-5b; no anti-HPA-1a
Doughty HA, 1995[28]	Anti-HPA-1a (2 patients)

Panzer S, 1995[23]	Anti-HPA-5b; no anti-HPA-1a
Blanchette V, 1990[26]	Anti-HPA-1a (3 patients, 2 patients prior to birth, 1 postpartum)
Bertrand G, 2011[17]	Anti-HPA-1a (75 patients). The same samples have been reported in Bertrand 2014[12]
Killie MK, 2010[16]	Data already included in Killie 2008[2]
Bessos H, 2008[18]	Anti-HPA-1a (26 patients); results from 12 samples has been reported in Killie 2008[2]
Kaplan C 1988[29]	Anti-HPa-1a (5 patients)
Ohto H, 2004[22]	Anti-HPA-4b and anti-HPA-5b; no anti-HPA-1a
Kurtz M, 1999[21]	Anti-HPA-5b; no anti-HPA-1a
Mawas F, 1997[20]	14 of 27 samples (all anti-HPA-1a) were from Williamson 1998[4]

HPA indicates human platelet antigen.

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Kjaer, M;Bertrand, G;Bakchoul, T;Massey, E;Baker, JM;Lieberman, L;Tanael, S;Greinacher, A;Murphy, MF;Arnold, DM;Baidya, S;Bussel, J;Hume, H;Kaplan, C;Oepkes, D;Ryan, G;Savoia, H;Shehata, N;Kjeldsen-Kragh, J;Allard, S;Bianco, C;Callum, J;Compernolle, V;Fergusson, D;Fung, M;Greinacher, A;Hume, H;Lieberman, L;Murphy, MF;Nahirniak, S;Pavenski, K;Pink, J;Shehata, N;So-Osman, C;Stanworth, SJ;Szczepiorkowski, ZM;Tanael, S;Wood, E

Title:
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