Neonatal Alloimmune Thrombocytopenia

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1. Objective

These clinical guidelines are intended to provide information on the diagnosis, laboratory investigation and clinical management of fetal/neonatal alloimmune thrombocytopenia (NAIT) for medical and scientific staff providing platelet immunology services within the NHS Blood and Transplant (NHSBT) Services.

2. Introduction

Prospective studies have revealed that severe neonatal thrombocytopenia (<50x10^9/L) is more frequent than has been previously assumed with an estimated incidence of 1:1000. Alloantibodies against platelet specific alloantigens or human platelet antigens (HPA) are the most frequent cause in otherwise well neonates delivered at term.[1-5] Premature neonates are however more likely to have thrombocytopenia as a result of placental insufficiency or infection.

A diagnosis might be made coincidentally by the finding of a low platelet count on a full blood count performed for an alternative reason. Once it has been established that a mother has HPA antibodies, the management of subsequent pregnancies requires specialised care.

In Denmark and Norway, screening programmes have been established to detect women with anti-platelet alloantibodies and have been coupled with management by early delivery by caesarean section.[30, 31] These policies are claimed to be cost-effective but their application remains uncertain, especially given the wide divergence of opinion on management of women with anti-platelet alloantibodies (see below).

HPA alloantibodies can be formed if an HPA alloantigen is present on fetal platelets but absent from maternal platelets. NAIT is the platelet homologue of haemolytic disease of the newborn (HDN). In contrast to HDN, no antenatal screening is in place to detect women at risk of HPA alloimmunisation as there is as yet no evidence that screening would lead to a significant reduction in morbidity and mortality. Furthermore, NAIT often occurs in primagradivae[28].

The diagnosis of NAIT should be suspected if a pregnancy is complicated by:

- obvious signs of bleeding in the newborn
- *in utero* cerebral bleeds, ventriculomegaly or cerebral cysts[6]
- hydrops fetalis[6]

2.1 Fetal/neonatal thrombocytopenia

Thrombocytopenia caused by maternal HPA alloantibodies is an under-diagnosed condition of the fetus/neonate. HPA antigens are often uniquely expressed on platelets and not on other blood cells. Maternal alloantibodies against an HPA antigen are the most frequent cause of severe thrombocytopenia ($<50x10^9$/L) in the otherwise healthy neonate.[1]

In Caucasoid populations, the two most important alloantigens are HPA-1a and HPA-5b of the HPA-1 and -5 systems, respectively. HPA-1a (PI^{A1}, Zw^a) antibodies complicated 1:347 pregnancies (250-509, 95% confidence intervals) and severe fetal/neonatal thrombocytopenia ($<50x10^9$/L) ensued in 1:1100 birth (684-2910, 95% confidence intervals).[5] About 80% of NAIT cases are caused by anti-HPA-1a and 15% anti-HPA-5b; other HPA antibodies are only detected occasionally.[3,4,7]

2.2 Platelet (HPA) alloantigens

Platelets have their own alloantigens (blood groups) which are expressed on the platelets but not on other blood cells. To date, 28 HPA systems have been identified comprising of 34 antigens have been described.[8,33] The molecular basis of these bi-allelic polymorphisms has been resolved and in all but one system the difference between the two alleles is based on a single nucleotide polymorphism (SNP). The HPA alloantigens are most abundant on platelets but are also expressed on other haematopoietic cells, unlike the HLA class I antigens which are expressed in a functional form on all cells (except erythrocytes where some HLA class I antigens, HLA A2, B7, B17, may be found but are not functional as far as antigen presentation is concerned). The maternal HPA alloantibody status of a mother with a history of autoimmune thrombocytopenia should be determined if the neonate is severely thrombocytopenic i.e. $<50x10^9$/l.

2.3 Classification of HPA alloantibodies

HPA alloantibodies can be classified according to their immunoglobulin class, either being IgG or IgM and also by the HPA alloantigen recognised. Only maternal HPA antibodies of the IgG class can cross the placenta, bind to fetal platelets and cause fetal thrombocytopenia.

2.4 Prediction of severity

There is no laboratory parameter which reliably predicts the severity of fetal/neonatal thrombocytopenia caused by HPA antibodies in an individual case. Prediction of severity frequently relies on the history of previously affected pregnancies and determination of the fetal platelet count. However, in a HPA alloimmunised pregnancy, two tests described below can potentially aid clinical management.

2.4.1 Zygosity of the father

If the father is heterozygous for the relevant HPA antigen then there is a 50% chance that his offspring will be negative. Determination of the fetal HPA group in the first trimester using PCR amplification of DNA obtained from cultured amniocytes from 14 weeks gestation onwards should be considered where the previous child was affected. HPA typing of free fetal DNA isolated from maternal blood is not currently available in the UK.

2.4.2 Titre of antibody

Some screening studies have suggested that the chance of severe disease may be increased if the third trimester anti-HPA-1a titre is high. Severe disease can however also occur at a lower titre and the titre of the antibody can fluctuate during pregnancy, so the elucidation of the titre is of limited clinical value. The clinical significance of HPA antibody titres has not been agreed and titres are therefore not performed by NHSBT laboratories.[5, 9, 23, 24,34]

2.5 Indications for laboratory testing

2.5.1 When to suspect NAIT in the fetus

- if fetal thrombocytopenia is incidentally discovered
- if there is a fetal ICH, hydrocephalus or ventriculomegaly or cerebral cysts
- if there is a family history of NAIT
- if there is unexplained fetal anaemia
- if there are unexplained, recurrent miscarriages after the first trimester
- if testing for NAIT is performed for another reason, i.e. in a screening study, and it unexpectedly reveals definite or potential NAIT

2.5.2 When to suspect NAIT in the neonate

- if neonatal thrombocytopenia is incidentally discovered and confirmed
- if there is a family history of NAIT
- if there are signs or symptoms of bleeding

2.5.3 Diagnosis of NAIT in the neonate

Commonly the infant affected with previously unsuspected NAIT is a full-term baby presenting with widespread petechiae at or few hours after birth; ecchymoses may also be present. Visceral haemorrhages, especially ICHs, are uncommon but not rare. Generally the mother has no past history of thrombocytopenia, other than possibly gestational thrombocytopenia, and the pregnancy was uneventful.

A careful examination of the infant shows no sign of infection, congenital anomalies, or disseminated intravascular coagulation i.e. abnormal coagulation results.

If thrombocytopenia is suspected, then a blood count including platelet count should be obtained. The clinical diagnosis of NAIT is strongly supported by severe thrombocytopenia (<50 x 10^9/l) and otherwise normal blood count. In patients with NAIT, the platelet count is typically low at birth, but may reach a nadir on Day 3 or 4. Response to platelet transfusion as a diagnostic tool is controversial since there may be a short term response to random donor (antigen incompatible) platelets in a significant percentage of cases.[25] However, detailed measurements show antigen-negative platelets have a significantly greater response rate and half-life than random platelets.[26]

3. Platelet laboratory testing for NAIT

The diagnosis of NAIT requires the demonstration of maternal platelet alloantibodies that react against platelet-specific antigens present in the father and infant but not in the mother.

Normally testing requires:
From the mother: 6 EDTA + 6 ml clot
From the father: 6 ml EDTA
From the cord / neonate: 1ml EDTA anticoagulated blood.
Correctly labelled samples must be sent to the following address accompanied by properly completed NHSBT Histocompatibility & Immunogenetics (H&I) request form, 3D (Platelet Immunology) for each family member:
Histocompatibility and Immunogenetics
NHSBT Filton
North Bristol Park
Northway
Filton
Bristol BS34 7QH
UK
Detection of maternal platelet-specific antibodies should be carried out by two techniques, the indirect platelet immunofluorescence test (PIFT) and the monoclonal antibody immobilisation of platelet antigens (MAIPA) assay using a panel of HPA-typed platelets.

The parents and infant are also genotyped for the HPA-1, -2, -3, -4 -5, -6, -9 and -15 alloantigens. If the initial tests for HPA–1a antibodies are negative and the mother is HPA-1b1b, then an alternative monoclonal antibody and double the ratio of serum to platelets is used for the MAIPA assay. If these additional tests are negative, the serum of the mother may be tested against paternal platelets by both PIFT and MAIPA assay in a crossmatch so that alloantibodies against low-frequency alloantigens and

private antigens (i.e. non-HPA-1, 2, 3, 4, 5, 6, 9, 15 antigens) can be detected. A crossmatch will only be performed, after discussion with NHSBT Medical and Laboratory staff, if there is a strongly clinical suspicion of NAIT with negative routine serology. Only one example of an antibody against a low-frequency antigen was detected in 2500 cases of suspected NAIT.

For these crossmatch tests, further blood samples are required:
From the mother: 6 ml clot
From the father: 3 x 6 ml EDTA anticoagulated blood, which must reach the laboratory within 72 hours of venesection to arrive at the H&I laboratory in Filton (Monday to Friday).

It should also be noted that in up to 30% of cases of NAIT associated with fetomaternal incompatibility for the HPA-1a antigen, maternal HPA-1a antibodies may not be detectable. However, some studies have shown that the choice of monoclonal antibody (MoAb) used to capture GPIIb/IIIa in the MAIPA assay is critical and falsely negative results may be obtained if the epitope recognized by the MoAb is blocked by the human antibody. Others have reported that an increased serum:cell ratio is required to detect low levels of antibody. Sometimes the antibodies that were not detectable at the time of delivery become detectable a few weeks or months after delivery.

Out of hours testing is unnecessary as HPA-1a(-), -5b(-) platelets can be provided immediately from selected NHSBT sites to support the infant without the results of laboratory investigations but these should be initiated on the next routine working day (Mon-Fri excluding bank holidays). HPA-1a(-), -5b(-) platelets are the treatment of choice in 95% of suspected NAIT cases in Caucasians.

4. Management during pregnancy

The management of a pregnancy in a HPA alloimmunised mother is dependent on:

- the outcome of previous pregnancies
- previous neonatal platelet counts
- specificity of the HPA antibody
- zygosity of the father. A sample of the amniotic fluid can be used for fetal genotyping where the father is heterozygous for the cognate antigen.

Generally, if a previous child has been severely affected (platelet count $<50x10^9$/L), then a subsequent infant expressing the offending HPA antigen is usually equally or more severely affected.

The recommendations made in the following section are made in the absence of UK guidelines and of the results of only one randomised study on the most effective antenatal treatment.

The choice of the most appropriate treatment for HPA alloimmunised pregnant women is the responsibility of the Consultant Obstetrician in charge, although management is multidisciplinary. Advice from a Consultant Haematologist, and a Fetal Medicine expert is needed. The H&I Consultant and the NHSBT H&I laboratory at Filton in Bristol need to remain closely involved to ensure optimal transfusion support for mother and fetus/neonate.

The approach to antenatal management[10-19, 27-29] is reviewed below and ranked from a conservative approach to a more interventionist one:

4.1 General measures

- The mother should be advised to avoid any non steroidal anti-inflammatory drugs as well as aspirin.
- The delivery should be planned and a Caesarean section should be considered.
- If labour begins spontaneously, it would probably be wise to avoid the use of scalp electrodes.
- The blood centre should be informed that there is a risk of delivery of a thrombocytopenic infant so that compatible platelets can be available at the local blood centre
- HPA compatible platelets should be available at the local blood centre and transported by “blue light” delivery if there is any neonatal bleeding (HPA-1a and -5b negative platelets should be available routinely)

4.2 Intravenous immunoglobulin (ivIgG) to the mother

- This is first line antenatal treatment.

- The dose is 1g/kg body weight at weekly intervals, usually from 20 weeks of gestation onwards – some fetal medicine specialists may use a lower dose of 0.5g/kg and may start treatment between 12 and 20 weeks of gestation depending on the history of NAIT in previous pregnancies
- A beneficial effect of ivIgG on the fetal/neonatal platelet count occurs in about 67% of cases.[14,19] An initial increase in the fetal platelet count may not be maintained.
- There is debate about the need to carry out fetal blood sampling (FBS) to assess the platelet count. Many centres do this at 28 weeks (usually after 8 weeks treatment with IvIgG)
- The Dutch approach has been to avoid FBS completely, treat all women with previous NAIT with IvIg and deliver by caesarean section at 34-36 weeks.[29] The results of 98 pregnancies (16 with previous ICH) appear to be good. This approach has been adopted by some centres in the UK. However, debate still continues regarding the cost-benefit of the conservative and the interventionist approaches. In absence of definitive evidence, the balance struck between these approaches depends on the clinicians at the Fetal Medicine Unit taking into account the severity of the previous ICH, previous experience with FBS and IUT and the patient themselves.

4.3 Failure of response to maternal IvIgG

- Consider doubling the dose of IvIgG, and/or adding corticosteroids (prednisolone 0.5mg/kg body weight)
- Fetal blood sampling may be repeated after 2-4 weeks.
- If the increased intensity of radical treatment is ineffective, then it may be necessary to discontinue radical treatment and switch to weekly fetal platelet transfusion.

4.4 Intrauterine intravascular transfusion of HPA compatible platelets

- FBS combined with transfusion of compatible platelets is a procedure carrying a significant risk of fetal morbidity and mortality[12,17]
- Transfusion of platelets has more complications when compared with red cell transfusions for HDN (e.g. bradycardia, post-needle withdrawal cord bleeds)
- Transfusion of platelets is recommended when FBS is carried out in a suspected or known case of NAIT where the platelet count is unknown[17] – some fetal medicine units have the facility of rapid blood counts and can avoid transfusing platelets if the platelet count is satisfactory.
- Weekly transfusions of compatible platelets may be needed if other treatment fails (see above).

5. Planning of the delivery

Delivery should be planned and the obstetrician should inform both the local Haematologist and Paediatrician that delivery is imminent. The Medical Consultant at the blood centre should be informed, as soon as the date of a planned delivery is known. Appropriate blood products can then be arranged for mother and baby (see below).

5.1 After delivery

- A cord platelet count should be performed, and if <100x10^9/L should be confirmed on a venous sample. Inspect the neonate for skin or mucosal bleeding.
- If the platelet count is <30x10^9/L or if there are signs of bleeding with a low count it is strongly recommended to transfuse HPA compatible donor platelets. HPA-1a and -5b negative platelets are always available and should be provided, even if the antibody specificity is not known.
- Following the transfusion of platelets an incremental platelet count should be measured approximately one hour after the transfusion is complete and subsequently at least daily until the platelet count has been demonstrated not to be falling. The platelet counts should be documented and reported to the platelet immunology laboratory.
- IvIgG is not recommended as first line treatment. Small and non-randomised studies have shown that the infusion of IvIgG produces a rise in the platelet count in 75% of cases.[20] However, there is a delay of 24-48 hours before a satisfactory count is achieved.[20] This is in contrast to the immediate effect of the transfusion of HPA compatible donor platelets.
- Some experts would consider the use of IvIgG as adjunct therapy to random platelets if no compatible platelets are available or if the duration of severe thrombocytopenia is protracted and multiple transfusions have been given. It should be given at 1g/kg body weight on two consecutive days.
- A cerebral ultrasound scan of the baby within the first week of life should be considered if the platelet count is <50x10^9/L and is recommended when the platelet count is <30x10^9/L.

5.2 Transfusion advice

Patients including pregnant women and mothers with HPA antibodies are at risk of post transfusion purpura (PTP) and should be transfused with HPA compatible red cells and platelets if these are readily available and will not result in the delay of an urgent transfusion

5.2.1 Antibody card and information sheet

The NHSBT H&I Reference laboratory will issue an HPA antibody card for patients with HPA antibodies in case they require further transfusions in the future. An information leaflet for women with pregnancies affected by NAIT can be downloaded from http://hospital.blood.co.uk/library/pdf/diagnostic_services/INF283.pdf.

5.2.2 For the mother

Red cell concentrates obtained from donors negative for the relevant HPA antigen should be made available at delivery if the risk of transfusion is high. This should be discussed with the Obstetrician.

In an emergency situation where antigen negative RBCs are not available standard leucodepleted ABO and RhD compatible RBCs that are Kell negative should be provided. The risk of PTP from this approach is very low as residual platelets and leucocytes are effectively removed by leucodepletion processes.

5.2.3 For the neonate

- HPA compatible donor platelet concentrates are the treatment of choice.[21,22, 26]
- Where NAIT is suspected on clinical grounds, random platelets may be used, if clinically indicated, in neonates either suffering or thought to be at risk of serious haemorrhage, while HPA-1a and -5b negative platelets are sourced.[25, 32]
- HPA-1a and -5b negative platelets are routinely available from the Colindale, Tooting, Manchester, Sheffield and Filton Blood Centres. These should be issued for the treatment of thrombocytopenic baby with suspected NAIT without waiting for serological confirmation of the diagnosis. If only RhD positive HPA selected platelets are available for a female neonate who is RhD negative, anti-D 50iu (sc or iv) should be administered per neonatal pack of platelets transfused.
- A single dose of HPA compatible platelets for neonatal use (1/4 of an adult dose) is generally adequate to achieve a lasting correction of the platelet count. However, in 20-30% of cases more than one transfusion is required to keep the platelet count above $30x10^9$/L. If fetal transfusions have been given then all blood products for the neonate should be irradiated. (All HPA-1a and -5b negative platelets from accredited donors are irradiated when the packs are split.)
- Maternal platelets should only be used if no appropriate donor product is available. This may be necessary in rare cases in which the antigen or antigen combination that must be avoided is of very high incidence in the donor population. Removal of plasma and replacement by platelet suspension medium must be performed, and mandatory microbiological tests must be passed. Maternal platelets should be irradiated. In practice this is very rarely needed

5.2.4 *For the fetus*

- HPA compatible, hyperconcentrated platelets (> 2 x 10^9/ml) are available for IUT. This is not a standard product and ideally at least 7 days notice is required to ensure the appropriate donors are available. They contain < 2.5 x 10^6 leucocytes/unit, are CMV seronegative, require irradiation and expire 24 hrs after collection.

6 Dealing with problems with hyperconcentrates

Platelet hyperconcentrates for IUT expire at the end of day 1 after collection. Consequently if there are problems with a hyperconcentrate, there is often no option to provide an alternative donor for a planned procedure. If the risk of delaying the procedure until another component is available is too great it may be possible to use a neonatal donation from one of the stock holding centres providing the consultant in charge of the FMU is in agreement.

The concentration of platelets in hyperconcentrates for IUT are 2-4 $x10^{12}$/L while neonatal platelets contain 1-2 x 10^{12}/L. The consultant performing the intrauterine transfusion will need to calculate the

volume to transfuse accordingly. On the rare occasions that a neonatal pack is used for intrauterine transfusion, the platelet concentration of the neonatal pack used will not be automatically stated on it and arrangements have to be made for this testing if required. If the neonatal platelets are more than 24 hours old there may be a fall in pH and other biochemical changes.

In the event of a problem during normal working hours (Monday to Friday, 09.00 to 17.30 hours), please inform H&I in Filton.

In the event of a problem out of normal working hours, please contact the on-call patient facing NHSBT medical consultant and the on call H&I consultant.

The following is a list of some of the common problems that may affect a hyperconcentrate and some suggested remedies – this is not an exhaustive list.

Problem	Suggested action
Platelet hyperconcentrate has a platelet count of less than 2-4 x 10^{12}/litre or a volume outside of the recommended 50-100mL range	Discuss with medical consultant FMU and hospital blood bank. Issue under medical concession. Inform H&I Filton. The fetal medicine specialist can calculate the volume to transfuse if they know the concentration of the pack
Isolated high titre anti-A or anti-B in the donor sample, when historical results are negative	Review results on PULSE. If the ABO type of the fetus is known, it may be apparent that the high titre anti-A and / or anti-B are of no significance. If the risk is low then the component may be issued under medical concession.
Isolated positivity in red cell antibody screening performed using neat donor plasma against standard screening cells (known as paediatric antibodies "PANTS")	Check with the most senior member of staff in the testing department whether it is a false positive result. Request urgent antibody screening and identification by the local RCI department . If negative on retesting or only antibodies that will not affect fetal red cells are present the pack can be issued under medical concession.
CMV IgG positive	DO NOT ISSUE
The official accompanying paperwork (FRM 604) is not with the hyperconcentrate	Contact department which last tested the donation.e.g. CDU, quality monitoring, processing, issues.

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The donation is RhD positive and the fetus is known to be RhD negative	This will have been agreed in advance with the FMU and NHSBT medical consultants . Fetuses and babies up to 4 months of age rely on maternal antibodies and do not produce their own so this poses minimal risk to the baby. Concessionary issue can be undertaken.
The donation is RhD positive and the mother is RhD negative	The mother should be given prophylactic anti-D (if not already immunised) in accordance with prophylactic guidelines
Bag leaking	DO NOT ISSUE

In all cases, please advise H&I Filton of the problem and the resultant action taken.

References

1. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia [see comments]. *N Engl J Med* 1993;329:1463-6.
2. Dreyfus M, Kaplan C, Verdy E, Schlegel N, Durand Zaleski I, Tchernia G. Frequency of immune thrombocytopenia in newborns: a prospective study. Immune Thrombocytopenia Working Group. *Blood* 1997;89:4402-6.
3. von dem Borne AE, Ouwehand WH. Immunology of platelet disorders. *Baillieres Clin Haematol* 1989;2:749-81.
4. Warkentin TE, Smith JW. The alloimmune thrombocytopenic syndromes. *Transfus Med Rev*. 1997;11:296-307.
5. Williamson LM, Hackett G, Rennie J et al. The natural history of feto-maternal alloimmunisation to the platelet-specific antigen HPA-1a (PLA1, Zwa) as determined by antenatal screening. *Blood* 1998;92:2280-2287.
6. Murphy MF, Hambley H, Nicolaides K, Waters AH. Severe fetomaternal alloimmune thrombocytopenia presenting with fetal hydrocephalus. *Prenat Diagn* 1996;16:1152-5.
7. Mueller-Eckhardt C, Kiefel V, Grubert A, et al. 348 cases of suspected neonatal alloimmune neonatal thrombocytopenia. *Lancet* 1989;1:363-6.
8. Metcalfe P, Watkins NA, Ouwehand WH et al. Nomenclature of human platelet antigens. *Vox Sang* 2003;85:240-5.
9. Jaegtvik S., Husebekk A., Aune B., Oian P., Dahl L.B., & Skogen B. Neonatal alloimmune thrombocytopenia due to anti-HPA-1a antibodies: the level of maternal antibodies predicts the severity in the newborn. *Br J Obstet Gynaecol* 2000;107:691-694.
10. Bussel JB, Zabusky MR, Berkowitz RL, McFarland JG. Fetal alloimmune thrombocytopenia. *N Engl J Med* 1997;337:22-6.
11. Kaplan C, Daffos F, Forestier F et al. Management of alloimmune thrombocytopenia: antenatal diagnosis and in utero transfusion of maternal platelets. *Blood* 1988;72:340-3.
12. Murphy MF, Waters AH, Doughty HA et al. Antenatal management of fetomaternal alloimmune thrombocytopenia - report of 15 affected pregnancies. *Transfus Med* 1994;4:281-92.
13. Kroll H, Kiefel V, Giers G et al. Maternal intravenous immunoglobulin treatment does not prevent intracranial haemorrhage in fetal alloimmune thrombocytopenia. *Transfus Med* 1994;4:293-6.
14. Bussel JB, Berkowitz RL, McFarland JG, Lynch L, Chitkara U. Antenatal treatment of neonatal alloimmune thrombocytopenia. *N Engl J Med* 1988;319:1374-8.
15. Bussel JB, Berkowitz RL, Lynch L, Lesser ML, Paidas MJ, Huang CL, McFarland JG. Antenatal management of alloimmune thrombocytopenia with intravenous gammaglobulin: a randomized trial of the addition of low dose steroid to IVIg in fifty-five maternal-fetal pairs. *Am J Obstet Gynecol* 1996; 174, 1414-1423.

16. Overton TG, Duncan KR, Jolly M, Letsky E, & Fisk NM. Serial aggressive platelet transfusion for fetal alloimmune thrombocytopenia: platelet dynamics and perinatal outcome. *Am J Obstet Gynecol* 2002; 186, 826-831.
17. Paidas MJ, Berkowitz RL, Lynch L, Lockwood CJ, Lapinski R, McFarland JG, & Bussel JB. Alloimmune thrombocytopenia: fetal and neonatal losses related to cordocentesis. *Am J Obstet Gynecol* 1995; 172, 475-479.
18. Radder CM, Brand A, & Kanhai HHH. A less invasive treatment strategy to prevent intracranial hemorrhage in fetal and neonatal alloimmune thrombocytopenia. *Am J Obstet Gyneco.* 2001; 185, 683-688.
19. Birchall J, Murphy MF, Kaplan C, Kroll H. European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. *Br J Haematol* 2003;122:275-88.
20. Mueller-Eckhardt C, Kiefel V, Grubert A. High dose IgG treatment for neonatal alloimmune thrombocytopenia. *Blut* 1989;59:145-6.
21. Murphy MF, Verjee S, & Greaves M. Inadequacies in the postnatal management of fetomaternal alloimmune thrombocytopenia. *Br J Haematol* 1999; 105, 123-126.
22. Ranasinghe E, Walton JD, Hurd CM, Saul L, Smith G, Campbell K, & Ouwehand WH. (2001) Provision of platelet support for fetuses and neonates affected by severe fetomaternal alloimmune thrombocytopenia. *Br J Haematol* 2001;113, 40-42.
23. Killie MK, Husebekk A, Kaplan C, Taaning E & Skogen B. Maternal human platelet antigen-1a antibody level correlates with the platelet count in the newborns: a retrospective study. *Transfusion* 2007; 47:55-58.
24. Ghevaert C, Campbell K, Stafford P, Metcalfe P, Casbard A, Smith GA, Allen D, Ranasinghe E, Williamson LM, Ouwehand WH. HPA-1a antibody potency and bioactivity do not predict severity of fetomaternal alloimmune thrombocytopenia. *Transfusion.* 2007; 47, 1296-305
25. Kiefel V, Bassler D, Kroll H, Paes B, Giers G, Ditomasso J, Alber H, Berns M, Wiebe B, Quenzel EM, Hoch J and Greinacher A. Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT) *Blood* 2006; 107, 3761-3763.
26. Allen D, Verjee S, Rees S, Murphy M, Roberts DK. Platelet transfusion in neonatal alloimmune thrombocytopenia. *Blood* 2007; 109:388-389
27. Murphy MF, Bussel JB. Advances in the management of alloimmune thrombocytopenia. *Br J Haematol* 2006; 136, 366-78
28. Ghevaert C, Campbell K, Walton J, Smith GA, Allen D, Williamson LM, Ouwehand WH, Ranasinghe E Management and outcome of 200 cases of fetomaternal alloimmune thrombocytopenia. *Transfusion.* 2007; 47, 901-10
29. van den Akker ES, Oepkes D, Lopriore E, Brand A, Kanhai HH. Noninvasive antenatal management of fetal and neonatal alloimmune thrombocytopenia: safe and effective. *BJOG.* 2007;114, 469-73.
30. Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R, Aune B, Øian P, Dahl LB, Pirhonen J, Lindeman R, Husby H, Haugen G, Grønn M, Skogen B, Husebekk A. A screening

and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood.* 2007 Aug 1;110(3):833-9

31. Killie MK, Kjeldsen-Kragh J, Husebekk A, Skogen B, Olsen JA, Kristiansen IS.Cost-effectiveness of antenatal screening for neonatal alloimmune thrombocytopenia. *BJOG.* 2007; 114, 588-95. Erratum in: *BJOG*. 2007; 114, 1453.
32. Win, N. Provision of random donor platelets (HPA-1a positive) in neonatal alloimmnune thrombocytopenia due to HPA-1a alloantibodies. *Vox Sang* 1996:71:130-131.
33. http://www.ebi.ac.uk/ipd/hpa/table2
34. Bertrand G, Drame M, Martageix C, Kaplan C. Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia. *Blood* 2011:117: 3209-3213.