Screening for Fetomaternal Alloimmune Thrombocytopenia

A report for the UK National Screening Committee

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Introduction

1. Thrombocytopenia is a shortage of platelets. Fetomaternal alloimmune thrombocytopenia (FMAIT) is thrombocytopenia in the fetus or neonate due to maternal antibodies against platelet-specific antigens (HPAs) that a fetus has inherited from his/her father. These antibodies can cross the placenta from mother to baby and if they cause severe thrombocytopenia this can result in intracranial haemorrhage (ICH) or intra-uterine fetal death (IUFD). ICH is fatal in 1-7% of cases, with surviving children experiencing severe neurological damage, including mental retardation, cerebral palsy, cortical blindness and seizures in 14-26% of affected pregnancies (Kamphuis et al 2010). In infants where ICH is not present, the outcome is usually favourable with the platelet count returning to normal within 8-10 days (Kaplan 2008).

2. FMAIT accounts for approximately 3% of all fetal and neonatal thrombocytopenias and 27% of cases of severe fetal and neonatal thrombocytopenia (Serrarens-Janssen et al 2008). Most of the other cases are caused by infection or congenital thrombocytopenia (Arnold et al 2008). Screening for FMAIT would not detect these other causes of thrombocytopenia, and they are not considered further in this review.

3. FMAIT is analogous to the fetal and neonatal anaemia caused by anti-red cell antibodies in haemolytic disease of the fetus and newborn (HDFN). It is usually suspected after the occurrence of neonatal (or rarely fetal) bleeding resulting in the detection of thrombocytopenia. Occasionally it is suspected after the incidental detection of thrombocytopenia on a blood count done for some other reason. Confirmation of the diagnosis requires the identification of maternal antibodies directed against HPAs.

4. The aim of screening pregnant women for FMAIT is to detect the condition during the mother’s first affected pregnancy, to reduce the risk of ICH or IUFD for that baby and subsequent babies. Currently the first affected baby in a family is only recognised after it has suffered a clinically evident episode of bleeding.

5. The current UK policy not to screen for FMAIT is based on a previous review of the evidence (Murphy and Williamson 2002). The policy was last reviewed in 2006. To inform this review a literature search covering the period January 2002 to 7th January 2011 was carried out by the UKNSC (Coles 2011), with a particular focus on the following areas where the previous review identified gaps in evidence:

- The long-term effects of ICH
- Predictors of severe clinical disease
- The lack of a clear approach to antenatal therapy for women who have antibodies to HPA-1a but no previously affected pregnancies
- The absence of any RCTs of screening for FMAIT

Further details of the search strategy are given in Appendix 1.
**The Condition**

The condition should be an important health problem

6. The most serious potential consequences of FMAIT are ICH and IUFD. Other complications include bleeding into other organs such as the gut, the scalp, and the eyes (Davoren et al 2002). FMAIT-related ICH and IUFD occur only among babies with severe thrombocytopenia. However, only a minority of babies with severe thrombocytopenia suffer from bleeding complications (Kamphuis et al 2010).

7. The incidence of these serious consequences appears to be much lower than has been predicted from studies of screening for FMAIT. Arnold et al (2008) conceptualized FMAIT as a pyramid, using HPA-1a incompatibility as an example (Figure 1). In each tier the expected number of affected pregnancies and babies per 10,000 Caucasian women is given.

Figure 1: Pyramid model of fetal and neonatal alloimmune thrombocytopenia (Arnold et al 2008).

8. The base layer of the pyramid estimates the proportion of all pregnant women who are HPA-1a negative and who are therefore potentially at risk. The second layer represents the proportion of at risk women who have detectable anti-HPA-1a antibodies on antenatal screening. The third layer represents the proportion of these women who have a baby with severe thrombocytopenia, and the fourth level represents the proportion of severely thrombocytopenic babies that suffer an ICH.

9. Arnold et al’s figures are mostly consistent with the pooled estimates published in a recent systematic review of population-based screening studies (Kamphuis et al 2010). Kamphuis et al estimated the prevalence of HPA-1a negativity among pregnant women as 2.1%, of whom

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1 The platelet antigen HPA-1a is the leading cause of FMAIT in the Caucasian population and has been implicated in about 80% of serologically confirmed neonatal alloimmune thrombocytopenia cases.
9.7% show antenatal HPA-antibody formation; 31% of these have severe FMAIT, of whom 10% suffer from perinatal ICH. This latter figure from Kamphuis et al (2010) probably underestimates the risk of ICH, because in most of the included studies various forms of treatment were offered to mothers of babies with FMAIT, to try to prevent ICH. In a UK study using active surveillance systems and capture-recapture techniques to identify clinically detected cases (Knight et al 2011), 116 babies had FMAIT that was not recognized early in pregnancy through a history of a previous affected sibling, and of these 116 babies 22 (20%) suffered an ICH. This is consistent with Arnold et al’s estimate of 20%.

10. Studies of clinically detected cases of FMAIT have identified substantially lower numbers of cases than studies of screened populations (Davoren et al 2002, Turner et al 2005). In a Norwegian study with geographic controls, the detection rate in the non-screened population was only 14% of that in the screened population (Tiller et al 2009).

11. If the estimates derived from screening studies are applied to a UK birth cohort of 700,000 births one would expect to find approximately 1400 pregnancies with maternal anti-platelet antibodies each year, in 420 (30%) of which the fetus would have severe thrombocytopenia. However Knight et al (2011) estimated the incidence of clinically-detected FMAIT in the UK as only 12.4 (95% CI 10.7 – 14.3) per 100,000 births (or 1.2 per 10,000 births), equivalent to approximately 85 babies per year. Furthermore, 30% of the cases occurred in pregnancies with a previous sibling history of FMAIT, where screening would be of no value as they were already identifiable as at risk for FMAIT.

12. It is unclear to what extent these major discrepancies between the numbers predicted from screening studies and the numbers that are clinically diagnosed represents over-diagnosis through screening, or under-diagnosis by paediatricians in the absence of screening. Without screening, FMAIT is diagnosed as a result of fetal or neonatal bleeding, or occasionally incidentally by blood counts performed for another reason (Kamphuis et al 2010). Cases of severe thrombocytopenia with ICH have been reported without any other overt signs of bleeding (Uhrynowska et al 1997, Bussel et al 2005).

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

13. Requisites for the occurrence of FMAIT include alloimmunisation, where maternal antibodies are produced in response to the ‘foreign’ fetal platelet antigens, and for these antibodies to cross the placenta and cause fetal platelet destruction and thrombocytopenia (Bussel & Primiani 2008). However, there are still aspects of the natural history of FMAIT that are not fully understood, particularly predicting how severe the clinical expression will be.

\[2 \text{ Expected number of babies each year with FMAIT} = 700,000 \times 2\% \times 10\% = 1400\]
14. Incompatibility for HPA-1a causes about 80% of serologically confirmed cases of FMAIT in the Caucasian population (Arnold et al 2008; Bussel and Primiani 2008), but is rarer in other populations. Incompatibilities for HPA-5b and HPA-15a are responsible for the majority of the remaining 20% of cases. (Arnold et al 2008). The HPA-1a platelet antigen is therefore the obvious target for screening in Caucasian populations.

15. HPA-1a alloimmunisation can occur during a first affected pregnancy (Kumpel et al 2008, Kamphuis et al 2010). In the largest screening study to date, only 25% of women developing HPA-1a antibodies were alloimmunised during pregnancy, and the majority were alloimmunised after delivery (Killie et al 2008). However, there are several case reports of FMAIT resulting in ICH in first pregnancies (personal communication from Professor Murphy).

**All the cost-effective primary prevention interventions should have been implemented as far as practicable**

16. Primary prevention may become possible in future if sensitisation prophylaxis (analogous to anti-D for the prevention of HDFN) is shown to be effective for preventing FMAIT, but this is not yet the case.

**If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications**

17. This is not relevant to screening for FMAIT.
The Test

There should be a simple, safe, precise and validated screening test

HPA antigen typing
18. Women who are negative for the relevant HPA antigens can be identified using a variety of methods, including enzyme-linked immunosorbent assay (ELISA) (Garner et al 2000), polymerase chain reaction (Kjaer et al 2002) or flow cytometry (Killie et al 2004). The HPA antigen status of the fetus can also be determined from fetal DNA in maternal plasma, and if the fetus is HPA-1a negative no further follow-up is necessary. However this has not yet been developed as a routine laboratory test (Hussebek 2009). Scheffer et al (2011) report 100% sensitivity and 100% specificity for this test, albeit in a limited sample of 34 pregnancies.

HLA DRB3*0101 typing
19. The largest screening study to date found that 90% of women with anti-HPA antibodies, and all those with severely affected children, carry the human leukocyte antigen (HLA) DRB3*0101 (Killie et al 2009). By incorporating this step in the testing pathway, the number of women who need to be tested for anti-HPA antibodies can be reduced. The literature search for this review did not identify any formal assessments of the performance of this test.

Anti-HPA antibody detection
20. There are a number of potential tests for the detection of HPA antibodies and there are several descriptions of new tests within the recent published literature. The monoclonal antibody immobilization of platelet antigen (MAIPA) assay and the radioimmunoprecipitation (RIP) assay have allowed for the detection of alloantibodies with specificity for platelet antigens at low levels of expression (Arnold et al 2008), though RIP is still primarily a research tool rather than a routinely used diagnostic assay. Other than the MAIPA assay, the Platelet Immunofluorescence Test (in Europe), solid-phase adherence assays (in Japan) and various forms of Antigen Capture ELISA (in the USA) are the main diagnostic assays (Allen, Ouwehand et al 2007).

21. The ability of laboratories to correctly identify HPA antibodies was tested in a study in involving 42 laboratories in 23 countries, including two in the UK. The MAIPA was the most common in-house test used by 20 laboratories. Most (over 90%) of participants were able to accurately determine platelet antibody specificity for antibodies against HPA-1a, HPA-3a, HPA-5b and HPA-5a. However the accuracy was lower for HPA-1b (85%) and HPA-3b (20%) (Wu et al 2010).

The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

22. Given the large potential for over-diagnosis through screening it is important to find a reliable predictor of severe clinical disease which might be used to select pregnancies for aggressive intervention. In the largest screening study to date, a maternal antibody level above 3.0 IU/mL in either week 22 or 34 of pregnancy had a sensitivity and specificity of 93% and 63%,
respectively, for predicting severe FMAIT (Killie et al 2008). Bertrand et al (2011) claim that severe FMAIT can be predicted using a formula that incorporates both maternal antibody levels and the gestation at which the antibody levels are measured, but their study has some methodological problems. It is based on cases referred to specialist centres not a general maternity population, and the proposed test might perform rather differently in the two contexts; and the test data (maternal antibody levels) and the outcome measure (neonatal platelet counts) would both have been modified by the various treatments that were used (IVIG and/or steroids), which makes the relationship between test and outcome almost impossible to interpret. Other studies (Turner et al 2005, Ghevaert et al 2007) have failed to find a link between the level of maternal anti-HPA-1a antibody and the severity of neonatal thrombocytopenia. Possible explanations for these different results include differences in the method of antibody detection, the timing of the antibody screening and threshold values of antibody concentrations (Arnold et al 2008; Bessos et al 2009), and differences in design between retrospective and prospective studies (Killie et al 2011). Killie et al (2010) have also reported that the level of anti-HPA 1a antibody reported varies significantly when different monoclonal antibody reagents are used. There is current debate about whether the specificity of maternal antibody, rather than its amount, can best predict clinical disease in the infant (Rayment et al 2009). Further research is required to evaluate how well the level and /or the specificity of maternal anti-HPA-1a antibodies predict which cases of FMAIT will be more severe, and therefore more likely to benefit from medical intervention.

The test should be acceptable to the population

23. No studies were identified that specifically look at the acceptability of testing for FMAIT, but the test is analogous to screening to prevent haemolytic disease of the fetus and newborn (HDFN), which has been implemented successfully in the UK since 1969 (Royal College of Obstetricians and Gynaecologists 2011). Testing for FMAIT has been used without controversy in the various screening studies that have been published (e.g. Kjeldsen-Kragh et al 2007).

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

24. There is no general agreement on how to handle women with anti-HPA1a antibodies with no previous history of FMAIT. Fetal blood sampling (FBS) was previously used to diagnose and monitor the fetal platelet response, but has been largely abandoned because it is generally considered that the risks outweigh the benefits (Arnold et al 2008). Serial fetal ultrasounds can be performed to monitor for signs of fetal distress which would indicate a need for treatment escalation (Arnold et al 2008), but by the time ICH is seen on ultrasound it is too late for fetal treatment, except consideration of termination of pregnancy.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

25. This is not relevant to screening for FMAIT.
The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

26. The previous review for NSC on this topic (Murphy and Williamson 2002) concluded that antenatal treatment appears to have the potential to improve the outcome of severely affected cases of FMAIT, but noted that there was uncertainty regarding the most appropriate antenatal intervention for the management of pregnancies found to be affected by FMAIT during a screening programme. The following two sections describe the evidence for two types of treatment that have been proposed for the management of pregnancies found to be affected by FMAIT during a screening programme.

Antenatal administration of intravenous immunoglobulin (IVIG) or corticosteroids

27. Virtually all the published evidence on the effects of giving mothers IVIG or corticosteroids is derived from their use in second or subsequent affected pregnancies. However, the review by Kamphuis (2010) lists three studies that employed antenatal IVIG or corticosteroids in first affected pregnancies (Doughty et al 1995, Durand-Zaleski et al 1996, Maslanka et al 2003).

28. Doughty et al (1995) report a single case of a mother who had had two previous unaffected pregnancies, but whose fetus during the third pregnancy was found to be mildly thrombocytopenic at 30 weeks of gestation (platelet count 120 x 10⁹/l). She received weekly IVIG and the fetal platelet count rose to 210 x 10⁹/l prior to vaginal delivery; no further treatment was required.

29. The screening study by Durand-Zaleski et al (1996) found two women with FMAIT. One was treated with IVIG after fetal thrombocytopenia was detected; few details are provided, except that the ‘treatment was effective and permitted vaginal delivery’. The second mother was treated with corticosteroids, but required an emergency Caesarean section following a haemorrhage caused by the fetal blood sampling that was being used to monitor the effects of treatment. The baby had severe thrombocytopaenia at birth (platelet count 26 x 10⁹/l), but survived.

30. The screening study by Maslanka et al (2003) found two mothers with FMAIT, one of whom was treated using in utero platelet transfusions for her fetus, combined with high-dose IVIG for the mother on four occasions. The baby’s platelet count rose from 19 x 10⁹/l at 28 weeks of gestation to 237 x 10⁹/l at birth.

31. In summary, the published evidence on the effects of giving IVIG or corticosteroids to mothers with screen-detected FMAIT is limited to three mothers who received IVIG and one who received corticosteroids. None of the studies involved controls, one of the mothers who received IVIG also received other treatment that would have raised the fetal platelet count (in utero platelet transfusions), and one of the babies suffered temporary harm from the intervention (requiring emergency Caesarean section). From these data it is impossible to
know whether giving IVIG or corticosteroids to mothers with screen-detected FMAIT is effective.

32. Given the dearth of evidence on the effects of giving IVIG or corticosteroids to mothers with screen-detected FMAIT, it is reasonable to consider evidence obtained from its use in second or subsequent affected pregnancies. A Cochrane review found that there are no RCTs which demonstrate that IVIG is an effective treatment for FMAIT in any pregnancies, screen-detected or otherwise (Rayment et al 2011). Such efficacy is assumed, on the basis of data from 27 non-randomized observational studies, brief details of which are provided by Rayment et al (2011). The use of control groups appears to be limited to one study (Kaplan et al 1998) which compared the effects of IVIG and corticosteroids; otherwise the evidence for IVIG in FMAIT appears to be limited to uncontrolled case series. The authors state that ‘there is conflicting evidence on its efficacy in preventing ICH, with some reports documenting good results (Lynch 1992; Bussel 1996; Bussel 1997) and others reporting failure of IVIG to prevent haemorrhage, particularly in severely affected fetuses (Zimmermann 1992; Kroll 1994; Murphy 1994; Sainio 1999). However, in the latter cases only IVIG 1 g/kg/week was utilised.’

Elective Caesarean section +/- neonatal transfusion with platelets

33. Kjeldsen-Kragh et al (2007) assessed the effect of a protocol that offered elective Caesarean section at 36-38 weeks to all women with antibodies to HPA1a, together with preparation of platelets from HPA1a–negative donors for immediate transfusion of the newborn baby if petechiae were present and/or the platelet count was less than 35 x 10^9/L. The protocol subsequently proposed by the same group (see Appendix 2) is more conservative than that used in their screening study, in that it recommends elective Caesarean section only for women with antibodies to HPA1a > 3.0 IU/mL, rather than all women with any level of antibodies to HPA1a. The rationale for the approach used by Kjeldsen-Kragh et al (2007) was three-fold. First, that elective Caesarean section would cause less trauma to the baby’s head than vaginal delivery. Second, that shortening the pregnancy would reduce the period of time when the fetus would be exposed to harmful antibodies. Third, that elective Caesarean section would allow the blood bank time to prepare a compatible platelet concentrate for the newborn baby.

34. The evidence for the effectiveness of this strategy is problematic, for several reasons. It depends on comparison with historic controls from up to 15 different studies; it is a matter of debate which of these 15 studies can provide the most appropriate controls, and which provide ‘test’ data; and the numbers of cases of ICH or IUFD across all the studies are quite small, so a minor change in the data can have a substantial effect on the results. A review of the ultrasound pictures from the children studied by Kjeldsen-Kragh et al (2007) has concluded that one of the two children originally diagnosed as having an ICH did not have an ICH after all (personal communication from Professor Kjeldsen-Kragh). A similar review has not been undertaken for cases of ICH diagnosed in the historic control studies, which is one of the many difficulties of relying on these as controls.
35. The original paper by Kjeldsen-Kragh et al (2007) used 15 previous prospective screening studies as historical controls (comparison A in Table 1), but six of them involved fetal blood sampling (FBS), which has been largely abandoned because the risks outweigh the benefits. A better comparison, therefore, would be between the test intervention (elective Caesarean section +/- neonatal transfusion with platelets) and historical control studies that did not involve fetal blood sampling. Kjeldsen-Kragh et al (2007) also suggested using a different set of six of the original 15 studies as a comparison group (comparison B in Table 1). However, two of these control studies (Dreyfus et al 1997, de Moerloose et al 1998) employed FBS, and the results change when these are excluded (comparison C in Table 1).

Table 1: Various comparisons between intervention and control groups, depending on the judgements made about which study belongs in which group

<table>
<thead>
<tr>
<th>Various comparisons between intervention and historical control groups</th>
<th>Number of babies with ICH or IUFD / number of babies with severe FMAIT</th>
<th>p value (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective CS +/- platelet transfusion</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>A: Original comparison in Kjeldsen-Kragh et al (2007)</td>
<td>3/57</td>
<td>&lt;0.05 (3.96)</td>
</tr>
<tr>
<td>B: Alternative comparison in Kjeldsen-Kragh et al (2007)</td>
<td>2/57</td>
<td>&lt;0.02 (6.12)</td>
</tr>
<tr>
<td>C: Same as B, but excluding 2 control studies that employed FBS</td>
<td>2/57</td>
<td>&lt;0.05 (4.21)</td>
</tr>
<tr>
<td>D: Same as C, but assigning data from Blanchette et al (1990) to the intervention group</td>
<td>3/58</td>
<td>&gt;0.05 (2.95)</td>
</tr>
</tbody>
</table>

36. It is also a matter of judgement whether data from the Canadian study by Blanchette et al (1990) should be included among the historic controls (as in Kjeldsen-Kragh et al 2007), added to the ‘test’ intervention data from Kjeldsen-Kragh et al (2007), or ignored. The similarity between the management protocols of Blanchette et al (1990) and Kjeldsen-Kragh et al (2007) suggests that their data should be combined. However, Kjeldsen-Kragh has argued (personal communication) against this for several reasons: The prevalence of HPA 1a-negativity is less common in Canada than Norway (1.6% vs. 2.1%); the proportion of severely thrombocytopenic children was lower in Canada than Norway (1/5,000 vs. 57/100,448); Blanchette et al did not quantify antibodies to HPA1a; and they did not intervene with Caesarean section until relatively late in pregnancy (38 weeks’ gestation). Blanchette et al (1990) found only one baby with severe FMAIT, and this child suffered an ICH despite being managed using a protocol of elective Caesarean section +/- neonatal transfusion with platelets. If these data are assigned to the ‘test’ intervention, the apparent benefit of elective

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3 Although not statistically significant, the proportion of babies with severe FNAIT who suffered ICH or IUFD is slightly higher in the six studies that involved fetal blood sampling (5/24) than on the eight studies that involved neither fetal blood sampling nor the test intervention of elective Caesarean section and postpartum transfusion with matched platelets if necessary (4/26).
Screening for fetomaternal alloimmune thrombocytopenia

Caesarean section +/- neonatal transfusion with platelets is no longer statistically significant (comparison D in Table 1).

37. Many clinicians believe it is now impossible to carry out a placebo-controlled RCT of either IVIG or preterm Caesarean section for FMAIT, because it would be difficult not to treat women whose fetus might be considered at significant risk of ICH. However, Norway, Denmark and the Netherlands all have different national guidelines for the antenatal management of FMAIT, reflecting current uncertainty about the effectiveness of the treatments involved, and a non-randomised controlled trial is planned, following these different national guidelines. Women in Norway will be offered preterm Caesarean section, and women in the Netherlands will be offered IVIG. Women in Denmark will not be offered any treatment, but umbilical cord blood samples will be tested for thrombocytopenia so that further investigations can be carried out to establish if the cause is maternal anti-HPA-1a (personal communication from Professor Jens Kjeldsen-Kragh).

38. This study may generate further evidence regarding the effectiveness of IVIG or preterm Caesarean section, compared with no treatment, and could potentially guide the design of an RCT of screening for FMAIT. The ethical difficulties inherent in an RCT of treatment would not arise in an RCT of screening, because all women who are randomized to be screened and who test positive would be offered the recommended treatment.

Neonatal transfusion with platelets

39. The literature search for this review did not identify any RCTs of transfusion with platelets to prevent ICH in newborn babies with FMAIT. Current UK guidelines include an unreferenced statement that transfusion with HPA-1a and 5b-negative platelet concentrates will be effective (in raising the neonatal platelet count) in around 95% of cases of FMAIT (Kelsey et al 2003). In a non-randomised study among newborns affected by anti-HPA-1a or HPA-5b mediated NAIT, Allen, Verjee et al (2007) found that transfusion with HPA-1a/-5b negative platelets achieved a larger and more sustained increase in the platelet count than transfusion with random donor platelets.

Long term effects

40. Although the main complication of FMAIT that intervention seeks to prevent is ICH, even the use of ICH as an endpoint has become controversial through the application of ever-improving imaging modalities, which now may detect minute areas of haemorrhage that may be clinically irrelevant. Kamphuis et al (2010) argue that a more meaningful endpoint would be a measure of neurodevelopment some time later, such as the Bayley score at two years of age or later. Knight et al (2011) used a composite endpoint of mortality and significant disability at 1 year of age.

41. This review did not identify any studies that can definitively answer the question of whether early intervention improves outcomes in childhood. Ward et al (2006) measured the
developmental outcomes at around four years of age of children with FMAIT whose mothers had been treated with antenatal IVIG and / or steroids, and compared them with older siblings with FMAIT who had not been treated. Unfortunately the results are impossible to interpret, because the data suffer from selection bias (treated siblings that were born very prematurely were excluded from the study) and severe confounding (untreated siblings were nearly twice as old as their siblings when assessed, so had longer for problems to become manifest).

42. Knight et al (2011) obtained one year follow up data on 116 out of 146 identified cases of FMAIT. The rate of death or disability at one year was non-significantly lower in the group where FMAIT was recognised early in pregnancy, and therefore treated, than in those where it was unknown or unrecognized (0/28 vs. 9/88, p=0.11). Although this was not a randomised comparison, knowledge that the effects of FMAIT are typically more severe for a second affected fetus than the first (Bussel & Primiani 2008) implies that these results indicate that antenatal intervention for FMAIT may reduce the incidence of disability at one year.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

43. The literature search did not identify any UK guidelines that recommend administration of IVIG or corticosteroids to women with screen-detected FMAIT. Recent Department of Health (2011:19) guidelines do not recommend the administration of IVIG to women with screen-detected FMAIT, though they do recommend IVIG for FMAIT in the following three circumstances:

- Thrombocytopenia or spontaneous haemorrhage in the fetus
- Thrombocytopenia with or without haemorrhage in the neonate
- Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific allo-antibodies that are known or suspected to cause this condition (most commonly HPA-1a or HPA-5b).

Women who are found to have anti-HPA1a antibodies on screening but have no previous history of FMAIT would not meet any of the above criteria.

44. A 2007 guideline commissioned by the National Advisory Committee on Blood and Blood Products of Canada and Canadian Blood Services recommends treatment with IVIG for women found to have platelet alloantibodies on screening (Anderson et al 2007). The authors acknowledged that the evidence to support their recommendation was limited and weak in quality. They argued that treatment should be recommended anyway, because they thought the quality of the evidence is unlikely to improve, the condition is very rare and the consequences are frequent and extremely serious. Their proposed policy is therefore based almost entirely on an absence of evidence.

45. Hussebek et al (2009) have proposed a treatment protocol that recommends elective Caesarean section +/- neonatal transfusion with platelets for screen-detected FMAIT (see Appendix 3). It does not recommend IVIG for screen-detected FMAIT. This protocol is not endorsed by any professional body in the UK.
Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

46. No relevant studies were identified on this topic.
The Screening Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

47. There have been no randomised controlled trials of screening for FMAIT.

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

48. Arnold et al (2008) concluded that management of FMAIT requires an individualized patient-based approach rather than population-based screening. Publications from the Norwegian group that have conducted the largest studies of screening for FMAIT have concluded that it does not fully meet the criteria presented by the WHO and that it is still not time for general screening for antibodies to HPA-1a antigens (Hussebek et al 2009). Likewise, Knight et al (2011) concluded that, although FMAIT fulfils a number of the UKNSC criteria, further assessment of the case for antenatal screening is required.

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

49. There is not yet any convincing evidence that a screening programme would produce clinical benefits. It could cause harm through substantial over-diagnosis of FMAIT.

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

50. Killie et al (2007) used data from the large Norwegian screening study (Kjeldsen-Kragh et al 2007) to model the cost-effectiveness of screening for FMAIT, and concluded that screening was cost saving as long as HPA 1 typing cost less than €20/test. However, since there is not yet any convincing evidence that a screening programme would produce clinical benefits, analysis of cost-effectiveness is premature.
Implications for policy

It is not currently appropriate to start a screening programme for FMAIT because:

- There is not yet consistent evidence that the level or specificity of maternal anti-HPA-1a antibodies can reliably predict which cases of FMAIT will be more severe, and therefore more likely to benefit from medical intervention.

- Without such a test there is substantial potential for over-diagnosis and unnecessary intervention. If the estimates derived from screening studies are applied to a UK birth cohort of 700,000 births one would expect to find approximately 1400 cases of FMAIT each year, of which 420 would have severe thrombocytopenia. However the number of babies with clinically-detected FMAIT appears to be only about 85 per year. These figures indicate that the babies of most women who would be identified as screen-positive if a programme were started are born healthy, without receiving any medical intervention.

- There is not yet any convincing evidence that medical intervention improves the outcomes of pregnancies that are identified through antenatal screening. The non-randomised controlled trial that is planned across Norway, Denmark and the Netherlands may generate further evidence regarding the effectiveness of IVIG or preterm Caesarean section, compared with no treatment.

- Neither IVIG nor preterm Caesarean section is recommended by any UK guidelines as treatment for screen-detected FMAIT.

- No RCT of screening has been conducted.
Implications for research

Potential areas for research include:

- Further evaluation of how well the level and/or the specificity of maternal anti-HPA-1a antibodies predict which cases of FMAIT will be more severe, and therefore more likely to benefit from medical intervention.

- Demonstrating through an RCT of screening for FMAIT (not an RCT of treatment for FMAIT) that screening improves outcomes. The ethical difficulties inherent in an RCT of treatment would not arise in an RCT of screening, because all women who are randomized to be screened and who test positive would be offered the recommended treatment. Depending on the findings of the non-randomised controlled trial that is planned across Norway, Denmark and the Netherlands, the recommended treatment might be IVIG or preterm Caesarean section. Given the relatively low incidence of severe FMAIT, a very large study population would be needed. Knight et al (2011) have proposed the establishment of a multinational collaboration amongst haematologists to facilitate studies of uncommon conditions such as FMAIT. Given the possibility of widespread under-diagnosis of FMAIT, reliable ascertainment of outcomes in an RCT of screening would probably require measurement of the platelet count in all newborns in the control arm of the trial. The ethics and acceptability of this would need careful consideration.

- If therapeutic antibodies are shown to be effective for preventing FMAIT in animal models, the optimum timing and dosages will need to be established, and the cost-effectiveness of screening and intervention will need to be estimated.

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4 The re-analysis of the data presented in Appendix 3 suggests that the approach favoured by Kjeldsen-Kragh et al (2007) (elective Caesarian section at 38 weeks +/- platelet transfusion for newborn babies) may reduce the risk of ICH and IUFD by approximately fifty per cent when compared with other interventions that have been used in FMAIT screening studies (excluding those that employed fetal blood sampling). A population of approximately 800,000 women (i.e. approximately the entire number of births each year in the UK) would be needed for a study that has 90 per cent power to detect a fifty per cent difference in the risk of ICH and IUFD at a significance level of five per cent. Such a large study is unlikely to be feasible, so it would be useful to discuss with clinical experts the value of a study with an alternative endpoint.

5 Proof of principle has recently been documented in a preclinical study where sensitisation was prevented in a mouse model by administration of anti-platelet antibodies (Tiller et al 2012). Anti-HPA 1a for clinical usage has now been approved by the European Medicines Agency as an orphan drug for FNAIT. Prophylaxis Pharma AS is collaborating with a large pharmaceutical company for production of this drug which will be tested in a randomized controlled clinical trial after completion of phase I/II studies. (personal communication from Dr Kjeldsen-Kragh).
Appendix 1

Knowledge update on screening for fetal and neonatal alloimmune thrombocytopenia

Paula Coles, Information Scientist

26th January 2011

Background: The current policy not to screen for fetal and neonatal alloimmune thrombocytopenia is based on the following review:

Murphy, MF, Williamson, LM & Urbaniak, SJ Antenatal screening for fetomaternal alloimmune thrombocytopenia: should we be doing it? Vox Sanguinis 2002; 83(Suppl 1): 409-16

Sources searched: Medline (OvidSP), Embase, Maternity and Infant Care, Cinahl, Web of Science and the Cochrane Library.


Search strategy: Medline OvidSP. Similar searches carried out in other databases

1. Thrombocytopenia, neonatal alloimmune/ (87)
2. Alloimmune thrombocytopenia.tw (628)
3. FMAIT.tw (24)
4. FMAIT.tw (31)
5. NAITP.tw (32)
6. 1-5/OR (671)
7. Limit 6 to year=”2002-current” (280)

The strategy was kept fairly simple due to the wide-ranging scope of the review which would focus on assessment against the UK NSC screening criteria, particularly those shortcomings identified in the previous review:

• Incidence of the condition
• Predictors of severe clinical disease
• Interventions
  ▪ There is a lack of clear approach to antenatal therapy for anti-HPA-1a women without previously affected pregnancies
  ▪ No agreed pathway for optimal management in women with previously affected pregnancies
• Long-term effects
• No randomized controlled trials (RCTs) of screening programmes

All searches were carried out on 7th January 2011.

Inclusions and exclusions

Results: The above strategy retrieved 280 citations from Medline. A similar search was conducted in Embase, the Cochrane Library, Maternity and Infant Care, Cinahl and Web of Science.
The above search strategies retrieved 1284 references in total. After duplicates references were removed a total of 630 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for fetal and neonatal alloimmune thrombocytopenia. Of these, 211 references were deemed to be relevant. A simple search of the clinical trials database (http://www.clinicaltrials.gov) retrieved one additional relevant reference. Therefore, a total of 212 references have been included in this knowledge update and are classified into the categories below according to the NSC criteria. There will inevitably be some overlap between categories.

<table>
<thead>
<tr>
<th>Systematic reviews and meta-analyses</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines</td>
<td>4</td>
</tr>
<tr>
<td>Non-systematic reviews</td>
<td>24</td>
</tr>
<tr>
<td>The condition</td>
<td>52</td>
</tr>
<tr>
<td>• Incidence/prevalence (17)</td>
<td></td>
</tr>
<tr>
<td>UK and Ireland (3)</td>
<td></td>
</tr>
<tr>
<td>Europe (8)</td>
<td></td>
</tr>
<tr>
<td>Canada (3)</td>
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<td>Australia (1)</td>
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<td>Brazil (1)</td>
<td></td>
</tr>
<tr>
<td>Japan (1)</td>
<td></td>
</tr>
<tr>
<td>• Predictors of outcomes (13)</td>
<td></td>
</tr>
<tr>
<td>• HPA allele frequencies (22)</td>
<td></td>
</tr>
<tr>
<td>UK and Ireland (1)</td>
<td></td>
</tr>
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<td>Europe (5)</td>
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<td>Argentina (1)</td>
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<td>Role of rare polymorphisms (4)</td>
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</tr>
<tr>
<td>The test</td>
<td>45</td>
</tr>
<tr>
<td>• Reviews (3)</td>
<td></td>
</tr>
<tr>
<td>• HPA-typing (17)</td>
<td></td>
</tr>
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</table>
Updated literature search for Fetal and neonatal alloimmune thrombocytopenia, January 2011 – March 2012

The search strategies that were run for the 2011 knowledge update in January 2011 were re-run in the same databases on 14 March 2012. The results retrieved from each database are displayed below.

<table>
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<td>Medline</td>
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<td>Embase</td>
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<td>The Cochrane Library</td>
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<tr>
<td>Maternity &amp; Infant Care</td>
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<tr>
<td>Cinahl</td>
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<tr>
<td>Web of Science</td>
<td>54</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

After duplicates were removed, 113 unique references remained. These have been sifted for relevance to screening for fetal and neonatal alloimmune thrombocytopenia using the same questions as the previous update. 42 references were deemed to be relevant.
Appendix 2
Screening flow chart proposed by Hussebek (2009)
## Appendix 3

Numbers of cases with severe complications of severe FMAIT in 16 prospective studies (modified from Table 4 in Kjeldsen-Kragh et al 2007):

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Employed fetal blood sampling?</th>
<th>Employed elective Caesarean section &amp; post-partum platelets?</th>
<th>Total no. of pregnant women</th>
<th>No. of neonates with severe FMAIT</th>
<th>Intracranial haemorrhage</th>
<th>Intrauterine deaths</th>
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<tbody>
<tr>
<td>Mueller-Eckhardt et al 1985</td>
<td></td>
<td></td>
<td>1,211</td>
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<td>0</td>
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<tr>
<td>Reznikoff-Etievant et al 1988</td>
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<td></td>
<td>860</td>
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<tr>
<td>Blanchette et al 1990</td>
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<td>5,000</td>
<td>1</td>
<td>1</td>
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<td>Burrows et al 1993</td>
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<td>15,471</td>
<td>10</td>
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<td>1</td>
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<tr>
<td>Panzer et al 1995</td>
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<tr>
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<td>Dreyfus et al 1997</td>
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<tr>
<td>de Moerloose et al 1998</td>
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<td></td>
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<td>1</td>
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<tr>
<td>Williamson et al 1998</td>
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<tr>
<td>Sainio et al 2000</td>
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<tr>
<td>Uhrynowska et al 1997</td>
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<td></td>
<td>26,275</td>
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<tr>
<td>Davoren et al 2003</td>
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<td>4,090</td>
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<tr>
<td>Maslanka et al 2003</td>
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<tr>
<td>Turner et al 2005</td>
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<td>26,506</td>
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<tr>
<td>All studies published before Kjeldsen-Kragh et al 2007</td>
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<td>136,814</td>
<td>51</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Kjeldsen-Kragh et al 2007</td>
<td>y</td>
<td></td>
<td>100,448</td>
<td>57</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

| All studies that employed elective Caesarean section & post-partum platelets | y | 105,448 | 58 | 3 | 1 |
| All studies that employed fetal blood sampling | y | 51,989 | 24 | 3 | 2 |
| All studies that employed neither fetal blood sampling nor elective Caesarean section | | 79,825 | 26 | 3 | 1 |
References


Rayment, R., Kooij, T.W., Zhang, W., Siebold, C., Murphy, M.F., Allen, D., Willcox, N. & Roberts, D.J. (2009) Evidence for the specificity for platelet HPA-1a alloepitope and the presenting HLA-DR52a of diverse antigen-specific helper T cell clones from alloimmunized mothers. Journal of Immunology 183: 677–686


