bjh research paper

The incidence and outcomes of fetomaternal alloimmune thrombocytopenia: a UK national study using three data sources

Marian Knight,[1] Matthias Pierce,[1] Dave Allen,[2,3] Jennifer J Kurinczuk,[1] Patsy Spark,[1] David J Roberts[2,3] and Michael F Murphy[2,3]

[1]National Perinatal Epidemiology Unit, University of Oxford, Oxford, [2]NHS Blood and Transplant, and [3]Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

Received 20 October 2010; accepted for publication 14 November 2010

Correspondence: Dr Marian Knight, Senior Clinical Research Fellow, National Perinatal Epidemiology Unit, University of Oxford, Old Road Campus, Oxford OX3 7LF, UK.
E-mail: Marian.knight@npeu.ox.ac.uk

Summary

Fetomaternal alloimmune thrombocytopenia (FMAIT) is the most common cause of severe neonatal thrombocytopenia in otherwise well, term infants. First pregnancies are often severely affected. This descriptive, population-based national study was undertaken in order to inform the case for antenatal screening. Cases were identified using three sources and capture-recapture techniques used to generate a robust incidence estimate. One hundred and seventy three cases were identified between October 2006 and September 2008. An extra 20 cases were estimated from capture-recapture analysis, giving an estimated incidence of clinically detected FMAIT of 12·4 cases per 100 000 total births (95%confidence interval: 10·7, 14·3). Fifty-two cases (30%) were known at the start of pregnancy; 120 (70%) were unknown ($n = 115$) or unrecognized ($n = 5$). Unknown cases were more likely to experience a haemorrhagic complication (67% vs. 5%) ($P < 0·001$) and more likely to have an intracranial haemorrhage (20% vs. 4%) ($P = 0·014$) than known cases receiving antenatal management. In view of the incidence of severe disease identified, further assessment of the case for antenatal screening is important. There were a number of cases in which the significance of a history of FMAIT in a previous sibling was not recognized and there is a need to raise awareness of the importance of this diagnosis.

Keywords: fetomaternal alloimmune thrombocytopenia, incidence, epidemiology, cohort.

Fetomaternal alloimmune thrombocytopenia (FMAIT) is the most common cause of severe neonatal thrombocytopenia in otherwise well, term infants (Dreyfus *et al*, 1997). The condition results from a fetomaternal incompatibility in human platelet alloantigens (HPAs), most commonly HPA-1a, and can lead to serious bleeding, intracranial haemorrhage (ICH) and sometimes death of the fetus or infant (Serrarens-Janssen *et al*, 2005). The fetal and neonatal thrombocytopenia caused by anti-platelet antibodies is analogous to the fetal and neonatal anaemia caused by anti-red cell antibodies in haemolytic disease of the fetus and newborn (HDFN). The incidence of clinically affected infants is estimated to be 1 in 15 000 births in European populations (Williamson *et al*, 1998; Serrarens-Janssen *et al*, 2005). In contrast to HDFN, first pregnancies are often severely affected and the diagnosis is usually made with the birth of a first affected infant. There is therefore a current debate about the utility of screening for the condition antenatally. In order to fully assess the case for antenatal screening, information to allow assessment of the burden of disease as well as disease outcomes on a population basis is vital (Murphy *et al*, 2002). However, this information is currently lacking (Kamphuis *et al*, 2010).

Additionally, there are considerable controversies in the optimal management of FMAIT-affected pregnancies (Murphy & Bussel, 2007). There is no standard approach to the antenatal management of affected pregnancies, and in particular, there is no clear approach to the management of first affected pregnancies identified by antenatal screening. This descriptive, population-based national study was undertaken in order to estimate the incidence of clinically detected FMAIT, describe the outcomes up to 1 year of age, and assess the impact of antenatal management on disease outcomes.

First published online 07 January 2011
doi:10.1111/j.1365-2141.2010.08540.x

Material and methods

Case identification

Cases were identified using three different sources between October 2006 and September 2008: the UK Obstetric Surveillance System (UKOSS) (Knight *et al*, 2005), the British Paediatric Surveillance Unit (BPSU) (2004) and the NHS Blood and Transplant (NHSBT) Platelet Immunology Laboratories (NHSBT-Filton, UK).

The UKOSS is an active surveillance system that identifies cases of rare disorders of pregnancy through a monthly mailing to nominated reporting midwives, obstetricians and anaesthetists in all consultant-led maternity units in the UK. Although a small proportion of women in the UK deliver at home or in midwifery-led units, all women with a known diagnosis of FMAIT would be managed in a consultant unit; this study therefore effectively covers the entire cohort of births in the UK. The UKOSS methodology is described in detail elsewhere (Knight *et al*, 2005). UKOSS reporting clinicians were asked to return a report card each month indicating whether there had been any women with a pregnancy affected by FMAIT delivered in their unit in that month. They were also required to return a 'nil report' if there had been no cases. In response to a report of a case, clinicians were sent a data collection form asking for further anonymous details of the case, including demographic, management and outcome information.

The BPSU is an active surveillance system which uses a similar methodology to UKOSS to identify cases of rare paediatric disorders through all paediatricians in the UK (British Paediatric Surveillance Unit 2004). Reporters were asked to notify any infants born with FMAIT in the study period. Negative reports were also sought. In addition to the birth form, BPSU clinicians were sent a form shortly after the first birthday of the infants reported, in order to collect details of outcomes at 1 year of age.

This project also identified cases from the NHSBT Platelet Immunology database. Infants with confirmed FMAIT were identified through a sequential database interrogation process. In the first stage, information on all infants tested for maternal fetal platelet antigen incompatibility was retrieved; subsequently these cases were examined individually to determine whether the diagnosis of FMAIT was confirmed. Note that this database only contained information about cases occurring in England and North Wales. As the clinical information available from this database was limited, where a case was identified that had not been reported through either UKOSS or BPSU, a data collection form was sent to the relevant UKOSS or BPSU clinician in order to obtain full clinical details.

With the exception of date of birth, which was collected from BPSU clinicians (with regulatory approval), all details collected were anonymous. Thus for the capture-recapture analysis, cases were matched across the three sources using simple identifiable fields – place of delivery/birth, mother's year of birth and date of birth/delivery. Once identical fields were found; each unmatched case was checked against the other sources and non-exact matches were considered (for example, mother's year of birth 1 year different). This process was repeated until no further matches could be found.

The denominator population under observation is total births to women in the UK during the same defined period; an estimated 1 559 411 total births. The birth figures used to estimate the prevalence were obtained from the Office for National Statistics for England and Wales (2008,2009,2010), the General Register Office for Scotland (2007, 2008, 2009) and the Northern Ireland Statistics and Research Agency (2009).

Case definition

UKOSS reporting clinicians were asked to report all pregnant women with a previous child affected by FMAIT or pregnant women otherwise known to be alloimmunized with a platelet-incompatible fetus confirmed on testing.

BPSU reporters were asked to identify any infant born during the study period with maternal/fetal platelet antigen incompatibility confirmed on testing, usually in the presence of maternal antibodies AND one of the following:

1 Cord platelet count at birth $<50 \times 10^9$/l
2 Haemorrhagic complications before or after birth (for example, intraventricular haemorrhage, gastrointestinal bleed, bruising or petechiae)
3 Antenatal therapy with maternal steroids, intravenous immunoglobulin or fetal platelet transfusion

Cases identified from the NHSBT database were infants in whom there was a maternal-fetal platelet incompatibility confirmed on testing of maternal and fetal/neonatal samples following clinical referral.

Statistical analysis

The cases were examined in three distinct groups according to the expected capture sources:

1 Live born cases in which maternal-fetal platelet incompatibility was unknown, or its significance unrecognized, at the start of pregnancy, which we would expect to be identified only through BPSU and NHSBT;
2 Live born cases in which a potential for maternal-fetal platelet incompatibility was known at the start of pregnancy and subsequently confirmed, which we would expect to be identified through all three sources;
3 Cases in which the pregnancy was terminated, had a second trimester fetal loss (directly as a consequence of FMAIT) or the infant stillborn, which we would expect to be identified only through UKOSS and NHSBT.

The data were first analysed using the two source capture-recapture method, assuming independence of sources (Hook & Regal, 1995). A three-source analysis was also carried out on

live born cases known at the start of pregnancy from within NHSBT regions to assess the independence of the sources. Bayes information criterion was used to evaluate the interactions (dependence) between sources in a log-linear model.

The estimated total numbers of cases from the three capture-recapture estimates were combined to generate an estimated overall total number of cases from which to calculate a prevalence estimate. Confidence intervals for the estimated totals arising directly from a capture-recapture model were calculated using a goodness of fit test (Regal & Hook, 1984). Where the estimated number of cases was extrapolated from a capture-recapture estimate, bootstrap methods were used to obtain a sampling distribution. Ninety five percent confidence intervals (95% CI) were calculated by taking percentiles of this distribution. For calculation of the confidence intervals for the associated birth prevalence estimates, in order to accommodate two sources of error, bootstrap methods were used as developed by Tilling *et al* (2001).

Data for cases known at the start of pregnancy were compared with those unknown at the start of pregnancy using the Chi squared test, Fisher's exact test or Wilcoxon rank sum test as appropriate. Statistical significance was assumed at $P < 0{\cdot}05$. All analyses were performed using STATA 10SE STATACORP LP, College Station, Texas, USA.

Ethics committee approval

This study was approved by the London Research Ethics Committee (study reference numbers 05/MRE02/83 and 06/MRE02/53)

Results

In total, 173 cases meeting the case definition were identified through the three sources. An extra 20 cases were estimated from capture-recapture analysis, resulting in an estimated UK-wide incidence of clinically detected FMAIT of 12·4 cases per 100 000 total births [95% CI: 10·7, 14·3]. Fifty-two cases (30%) were known and recognized at the start of pregnancy, 120 (70%) were unknown ($n = 115$) or unrecognized ($n = 5$) at the start of pregnancy. For one case we were unable to determine whether or not it was recognized. The five unrecognized cases each had a previous sibling affected by FMAIT. The significance of this diagnosis was not recognized until the birth of the affected sibling (the index case in our study) in four cases; in one case the diagnosis in the woman's first born infant was considered unproven and after discussion she was not managed antenatally for FMAIT, although her next infant was subsequently born with a low platelet count and the diagnosis confirmed (the index case in our study).

Information on 22 cases was available only from the NHSBT database; we therefore have limited clinical data on these cases. Table I shows the clinical characteristics of the 151 cases identified through the two other sources. Eighty-one percent of cases were due to anti-HPA-1a, 7% due to anti-HPA-5b, 5% were associated with both anti-HPA-1a and anti-HPA-5b and 7% with other HPA antibodies; there was no significant difference in the frequency of antibodies in cases where FMAIT was recognized at the outset of pregnancy or was unknown or unrecognized at the outset. Cases known at the outset of pregnancy were more likely to be delivered by caesarean

Table I. Clinical characteristics of infants with FMAIT ($n = 151$).

Characteristic	FMAIT known at outset of pregnancy *n* (%)*	FMAIT unknown or unrecognized *n* (%)*	*P*	Total
Total	45 (30%)	106 (70%)	<0·001†	
Antigen incompatibility			0·45	
HPA-1a/b	38 (84%)	82 (80%)		120 (81%)
HPA-5a/b	3 (7%)	8 (8%)		11 (7%)
HPA-1a/b and HPA-5a/b	3 (7%)	4 (4%)		7 (5%)
Other	1 (2%)	9 (9%)		10 (7%)
Delivery‡				
Vaginal	8 (18%)	72 (70%)	<0·001	80 (54%)
C-section	36 (82%)	31 (30%)		67 (46%)
Platelet count at birth ($\times 10^9$/l)‡				
Median (interquartile range)	124 [56, 252]	17 [9, 32]	<0·001§	26·5 [12, 69]
$<20 \times 10^9$/l	2 (5%)	58 (57%)	<0·001	60 (42%)
Time to discharge (median days, IQR)¶	6 [4, 16]	7 [4, 10]	0·91§	6 [4, 10]
Gestation at delivery (median weeks, IQR)‡	35 [33, 36]	39 [38, 40]	<0·001§	38 [35, 40]

*Percentages of those with complete data.
†Binomial test for equal proportions.
‡Excludes two pregnancy terminations and one miscarriage.
§Ranksum test.
¶$n = 121$ as data obtained only for BPSU reported cases.
IQR, interquartile range.

section (82% vs. 30%, $P < 0{\cdot}001$), had higher platelet counts at birth (Fig 1) and were less likely to have a platelet count below 20×10^9/l at birth than cases not known at pregnancy outset (2% vs. 58%, $P < 0{\cdot}001$). The gestation at delivery is illustrated in Fig 2. Infants tended to be born earlier in the known group compared to the unknown (median 35 vs. 39 weeks, $P < 0{\cdot}001$).

Among fetuses known to be affected at the start of pregnancy, 36 (82%) were delivered preterm; 89% of these were delivered by caesarean section. Of those with data, 14 (74%) were delivered by caesarean electively and 5 (26%) as an emergency. Eleven (79%) of the infants delivered preterm electively were delivered early for fetal indications to minimize the risks of FMAIT. Two (40%) of the five infants born prematurely by emergency caesarean were delivered following complications of intrauterine transfusion (IUT).

Cases known at the outset of pregnancy were managed with a variety of therapies antenatally. Intravenous immunoglobulin (IvIg) alone ($n = 17$, 38%) and a combination of IvIg, maternal corticosteroids and IUT ($n = 14$, 31%) were the most common management strategies, followed by a combination of IUT and IvIg ($n = 5$, 11%), maternal corticosteroids and IvIg ($n = 4$, 9%) and IUT alone ($n = 1$, 2%). Three women (7%) received no antenatal therapy and for one woman (2%) antenatal management was unknown.

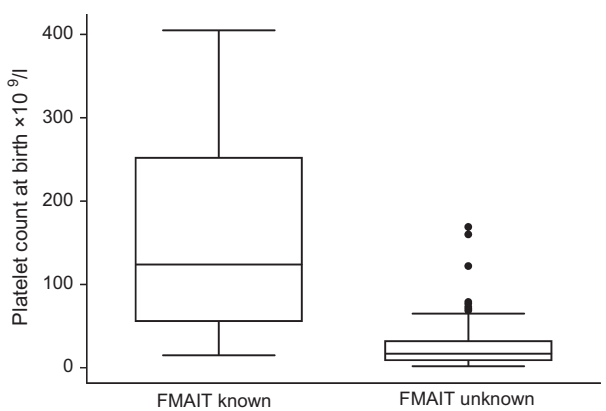

Fig 1. Platelet counts at birth in infants with FMAIT known or unknown at the outset of pregnancy.

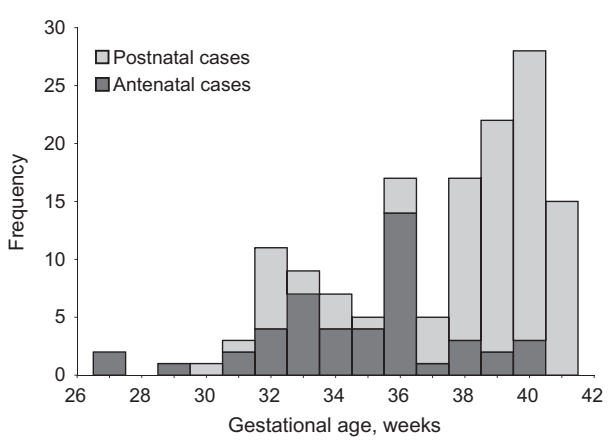

Fig 2. Gestational ages at delivery for cases of FMAIT known (antenatal) and unknown (postnatal) at the outset of pregnancy.

One hundred and sixty-six (96%) of the infants were live born. Cases not known at the outset of pregnancy were more likely to experience a haemorrhagic complication (67% vs. 5% respectively) ($P < 0{\cdot}001$) and more likely to have an intracranial haemorrhage (20% vs. 4% respectively) ($P = 0{\cdot}014$) than cases known at the outset of pregnancy (Table II). Twenty-two percent of infants in whom the diagnosis was not known or recognized at the outset of pregnancy suffered a severe complication (pregnancy miscarriage, termination, perinatal death or intracranial haemorrhage) compared with 8% of infants in whom the diagnosis was known at pregnancy outset ($P = 0{\cdot}041$). There were four infants with a severe outcome in pregnancies known to be affected with FMAIT. Two of these cases were managed with intravenous immunoglobulin, steroids and intrauterine transfusion (IUT) without improvement in platelet count, one was stillborn the day following an IUT and one had an intracranial haemorrhage (ICH). One was not reported to have had any antenatal management, although the pregnancy was recognized to be affected by FMAIT, and the infant was stillborn at 35 weeks following an ICH. We do not have the details of antenatal management in one case; the pregnancy miscarried.

In total, 24 (15%) infants had an intracranial haemorrhage. One of these infants was stillborn and in two the ICH was diagnosed antenatally and considered to be so severe that the pregnancies were terminated. The remaining 21 infants were liveborn. The five infants in whom FMAIT was unrecognized although they had a known affected sibling, were all born with very low platelet counts (median 11×10^9/l, range 8–23). Four of the five had reported bleeding complications although none were reported to have an ICH. There were no statistically significant differences in outcomes between these cases and the unknown cases.

We obtained 1-year follow-up information about 116 (79%) of the 146 liveborn infants reported through UKOSS or BPSU. The birth characteristics of these infants and those for whom we have no follow-up information are shown in Table III. The characteristics of those with follow-up and those without are very similar, the only exceptions being that the group without follow-up contained a higher proportion of infants in whom FMAIT was known at the outset of pregnancy (50% vs. 24%, $P = 0{\cdot}006$) and a higher proportion of infants managed antenatally with intravenous immunoglobulin alone (60% vs. 29%, $P = 0{\cdot}045$). The 1-year follow-up information shows that there were no infant deaths or reported disability in the group known at the outset of pregnancy (95%CI 0–10%) compared with two deaths (2%) and seven infants with disability (9%) in the group who were not known to have FMAIT ($P = 0{\cdot}11$); the overall rate of death or disability up to age 1 year in the group not known to have FMAIT was 10% (95% CI 5–19%)

Table II. Outcomes at birth in cases of FMAIT (n = 173).

Characteristic	FMAIT known at outset of pregnancy n = 52 (%)*	FMAIT unknown or unrecognized n = 120 (%)*	P	Total (n = 173)†
Pregnancy outcome				
Livebirth	49 (94%)	116 (97%)		166† (96%)
Stillbirth	2 (4%)	0		2 (1%)
Second trimester fetal loss	1 (2%)	1 (1%)		2 (1%)
Termination	0	3 (2%)		3 (2%)
Any diagnosed haemorrhagic complication (n = 144)‡	2 (5%)	68 (67%)	<0·001	70 (49%)
Haemorrhagic complication excluding ICH (n = 123)‡	1 (2%)	49 (60%)	<0·001	50 (49%)
Known intracranial haemorrhage	2 (4%)	22 (20%)	0·014	24 (15%)
Any severe outcome (perinatal death, second trimester loss, termination or ICH or related cerebral abnormality)	4 (8%)	25 (22%)	0·041	29 (17%)

Note that categories are not mutually exclusive.
*Percentages of those with data.
†Includes one case for which we were unable to determine the known/unknown status.
‡Data for the infants identified through UKOSS and BPSU only (n = 144, excluding five antenatal losses and two cases with missing data).
ICH, intracranial haemorrhage.

Table III. Comparison of characteristics of cases with 1 year of follow up (n = 116) and those without (n = 30).

Characteristic	Without follow up (n = 30) (26%)	With follow up (n = 116) (74%)	P
Known at outset of pregnancy			
Yes	15 (50%)	28 (24%)	0·006
No	15 (50%)	88 (76%)	
Incompatibility			
HPA-1a	26 (87%)	91 (80%)	0·39
HPA-5b	0 (0%)	10 (9%)	
HPA-1a and HPA-5b*	2 (7%)	5 (5%)	
Other	2 (7%)	8 (7%)	
Antenatal management, any (n = 43)			
IvIg alone	9 (60%)	8 (29%)	0·045
Steroids, IUT and IVIg	3 (20%)	10 (36%)	0·29
IUT and IvIg	0	5 (18%)	0·15*
Steroids and IvIg	2 (13%)	2 (7%)	0·51
IUT alone	0	1 (3%)	0·65*
None	1 (7%)	1 (4%)	0·58*
Gestational age at delivery[median weeks, IQR]	38·6 [36·1, 40]	38 [35, 40]	0·43†
Very preterm births (<32 weeks gestation)			
Yes	1 (3)	4 (4)	0·94
No	29 (97)	106 (96)	
Platelet count following birth, (median [quartiles])	24·5 [13, 69]	28 [12, 69]	0·58†
Platelets $<20 \times 10^9$/l	13 (46%)	47 (41%)	0·57
Time to discharge [median days, IQR]‡	7 [4, 8]	6 [4, 11]	0·76
Any diagnosed haemorrhagic complication	13 (45%)	57 (50%)	0·65
Any severe outcome	5 (17%)	17 (15%)	0·73
Severe outcome in known case	0	1 (4%)	0·67*
Severe outcome in unknown case	5 (33%)	16 (18%)	0·18

*Fishers exact test.
†Ranksum test.
‡Includes only cases identified through BPSU (n = 121).
IvIg, intravenous immunoglobulin; IUT, intrauterine transfusion, IQR, interquartile range.

(Table IV). Two of the infants had severe global developmental delay and visual impairment, four had motor impairment, one of whom also had visual problems, and one had visual problems alone. Four cases of death or disability occurred in infants not reported to have had an ICH.

Using the proportion of disability and deaths after 1 year amongst those infants with an ICH as a predictor for the number of disabilities or deaths in those that were not followed up, we estimated that an extra three cases would have had a disability or died after 1 year in the group not known to have FMAIT. We also estimated the total proportion of deaths or disability amongst pregnancies affected by FMAIT, but unknown at the time, including antenatal loses, as 13% (95% CI: 8–21%).Using the same methodology we predicted one extra child with a disability or death in the known group, resulting in a mortality/disability estimate of 8%, with a test for a true difference between these estimates yielding a *P* value of 0·29.

Discussion

The incidence of clinically detected FMAIT, as estimated from this study of a cohort of over 1·5 million births, is 12 cases per 100 000 total births, or one in every 8000 total births. Of these infants an estimated one in every 25 will die antenatally, whether through miscarriage, stillbirth or pregnancy termination, and an estimated one in 12 will either die before the age of 1 year or be severely disabled by age 1 year. Taking the diagnosed incidence into account, this means that eight infants born every year in the UK will either die or be severely disabled at 1 year of age as a consequence of FMAIT. These figures are irrespective of whether FMAIT was known at the outset of pregnancy and thus represent the overall burden of disease diagnosed by 1 year of age.

This compares with an estimated incidence of clinically detected FMAIT of one case in 7700 births in Norway (Tiller *et al*, 2009) and an estimated one case in 16 500 births in Ireland (Davoren *et al*, 2002) and contrasts with an incidence of approximately one case in every 1–2000 births estimated from prospective screening studies (Williamson *et al*, 1998; Turner *et al*, 2005; Kjeldsen-Kragh *et al*, 2007). We used three sources to identify cases and adjusted our estimates using statistical capture-recapture techniques; it is thus unlikely that the differences we observed compared with the prospective screening studies represent an under-ascertainment of cases. This study thus suggests, alongside these previous studies, that in absolute terms, more cases are detected in antenatal screening studies than in prospective observational studies such as ours. However, this observation needs careful interpretation, particularly in relation to fetal/infant outcomes, in order to inform further the current debate concerning antenatal screening. Current antenatal screening techniques are limited by their ability to distinguish between clinically significant cases of FMAIT and cases with no or minor clinical consequences, and thus have the potential to overdiagnose clinically significant FMAIT.

A large prospective screening study of over 24 000 pregnancies in East Anglia (Williamson *et al*, 1998) reported an incidence of severe thrombocytopenia due to FMAIT of 1 in 1100 births and of fetal/neonatal haemorrhage of 1 in 15 400 births. Given the small size of this study and therefore the uncertainty around the estimated incidences, the results for fetal/neonatal haemorrhage are compatible with our figure of approximately 1 in 60 000 pregnancies and emphasize the significant rate of poor outcomes. In addition, we followed cases where possible to 1 year of age to estimate the disease burden in terms of death or disability and not simply as the presence of severe haemorrhage. We estimate from our follow-up data that death or severe disability at age 1 year as a consequence of FMAIT occurs in approximately 1 in every 100 000 total births. These data on the burden of disease are important figures when considering the potential impact of antenatal screening.

Outcomes at birth were significantly better among infants in whom the diagnosis of FMAIT was known and recognized at the onset of pregnancy compared with infants in whom FMAIT was unknown or unrecognized. Although the difference in outcome at 1 year of age between the two groups was 0% vs. 10% for severe disability or death this was not statistically significant. It should be noted, however, that all the adverse outcomes we observed were in infants in whom FMAIT was undiagnosed during pregnancy, and that due to the small number of cases this analysis has limited power to detect as statistically significant a difference that may in reality exist. We obtained follow up information for a lower proportion of the infants in whom FMAIT was known at the outset of pregnancy (65%) compared to infants in whom FMAIT was not known (85%). This may be because clinicians have assumed that infants born following antenatal management are unlikely to have problems. Other studies which have

Table IV. Outcomes at 1 year of age in infants affected by FMAIT (n = 116).

Characteristic	FMAIT known at outset of pregnancy n = 28 (24%)	FMAIT unknown or unrecognized n = 88 (76%)	P
Disability at 1 year of age	0 (0%)	7 (8%)	0·19*
Infant death	0 (0%)	2 (2%)	0·59*
Disability or death at 1 year	0 (0%)	9 (10%)	0·11*

*Fisher's exact test.

followed infants treated antenatally for FMAIT have reported few long term problems; none of 48 infants in a Dutch study had long-term disability (Radder *et al*, 2004) and none of 71 infants in a study from the US had disability secondary to ICH, although three had long-term visual problems (Ward *et al*, 2006), suggesting that follow-up of this group of infants may still be important to identify mild disabilities.

The differences in outcomes between the recognized and unrecognized groups emphasize the importance of adequate history-taking at the start of pregnancy. The severity of disease in a previous affected sibling is known to predict how severely a fetus or infant will be affected in the next pregnancy (Bussel, 2009). In this study, five infants (4% of the unknown/unrecognized group) with a previously affected sibling were not managed antenatally for FMAIT; in four of these cases the significance of the prior history was not recognized and hence the pregnancy was not managed appropriately. There is clearly a need for raised awareness of the importance of this prior diagnosis amongst staff caring for women in early pregnancy in the UK.

We were only able to follow-up 79% of infants to 1 year of age, which may be regarded as a limitation of this study. However, the characteristics of infants followed-up and those not followed-up were similar, and in particular, infants with poor outcomes at birth were not under-represented amongst those followed-up; it is therefore unlikely that we have underestimated morbidity at 1 year of age. This study therefore demonstrates a significant burden of morbidity at 1 year in the unknown/unrecognized group. The study does not, however, provide robust evidence to inform the debate on different antenatal management strategies, as the number of infants managed antenatally was small, a number of different strategies were used and adverse outcomes were few. Nevertheless, these data do show that antenatal management is not always effective and provide further information about the severe complications that may be associated with it.

Randomized controlled clinical trials will always provide the highest level of evidence of effectiveness of any therapeutic intervention, but conducting a trial can be challenging in the context of a rare condition, such as FMAIT, hence there is a place for multinational collaborative studies. The recent establishment of the International Network of Obstetric Survey Systems (2010) to conduct collaborative studies of rare pregnancy disorders may provide one route to such studies; we believe there may be a place for a similar collaboration amongst haematologists to further facilitate high quality multinational research on uncommon conditions.

In view of the significant morbidity due to FMAIT identified by this study, there is clearly a place for further assessment of the case for antenatal screening for the condition. Perhaps the most challenging areas to be addressed include the development of a better screening test which reliably predicts clinically significant FMAIT, as well as determining what is the most safe and effective management for cases identified in a screening program without a past history. Current debates range around assessment of whether maternal antibody amount (Bessos *et al*, 2009) or specificity (Rayment *et al*, 2009) can be used to predict clinical disease in the infant and further research focusing on this area is particularly important. There is no consistent approach to management of pregnancies identified as affected in large screening studies to date (Williamson *et al*, 1998; Turner *et al*, 2005; Kjeldsen-Kragh *et al*, 2007). In the most recently reported of these studies (Kjeldsen-Kragh *et al*, 2007), caesarean section was carried out in alloimmunized women 2–4 weeks prior to term; only 2/170 pregnancies managed in this way were associated with ICH, which included 55 HPA–1a positive infants with platelet counts $<50 \times 10^9$/l. This was less than was found in an analysis of all previously published prospective antenatal screening studies.

In summary, this national study shows that FMAIT is an important cause of death and severe disability up to age 1 year in the UK. Infants in whom the condition is known at the outset of pregnancy have significantly better outcomes than infants in whom the condition is unknown or unrecognized. We identified a number of cases in which the significance of a history of FMAIT in a previous sibling was not recognized and there is a need to raise awareness of the importance of this diagnosis in relation to the antenatal management of subsequent pregnancies. The information from this study clearly indicates that FMAIT fulfils a number of the key criteria for appraising the validity of a screening programme (UK National Screening Committee, 2010). In view of the incidence of severe disease we have identified, further assessment of the case for antenatal screening is therefore important, and future research should be aimed at identifying a clinically predictive screening test as well as to determine optimal antenatal management of screen-positive cases.

Acknowledgements

This study would not have been possible without the collaboration of UKOSS and BPSU reporting clinicians throughout the UK and the staff of the NHS Blood and Transplant (NHSBT) Histocompatibility and Immunology (Platelet Immunology) Laboratories. We acknowledge the BPSU, supported by the Department of Health, for facilitating the paediatric data collection.

This project was funded by a grant from the charity Wellbeing of Women. UKOSS and the BPSU are independent programs which are part-funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department of Health or the BPSU. The research benefited from additional funding by the United Kingdom National Health Service R&D Directorate through the National Institute of Health Research (NIHR) and the National Institute for Health Biomedical Research Centre Programme.

Author contributions

MK and MFM designed the study, coordinated data collection, coded the data, supervized the analysis, writing and editing of the paper. MP carried out the analysis and contributed to writing the paper. DA analysed the NHSBT data, contributed to data collection and writing of the paper. JJK and DJR assisted with the design of the study, data collection and contributed to the analysis and writing of the paper. PS assisted with data coding, conducted validation of the data and analysis and contributed to the writing of the paper.

Disclosure of conflict of interest

None to declare.

References

Bessos, H., Killie, M.K., Seghatchian, J., Skogen, B. & Urbaniak, S.J. (2009) The relationship of anti-HPA-1a amount to severity of neonatal alloimmune thrombocytopenia – Where does it stand? *Transfusion and Apheresis Science*, **40,** 75–78.

British Paediatric Surveillance Unit (2004) *British Paediatric Surveillance Unit*. Available at:http://bpsu.inopsu.com/. Accessed 20 July 2010.

Bussel, J. (2009) Diagnosis and management of the fetus and neonate with alloimmune thrombocytopenia. *Journal of Thrombosis and Haemostasis*, **7**(Suppl. 1)**,** 253–257.

Davoren, A., McParland, P., Barnes, C.A. & Murphy, W.G. (2002) Neonatal alloimmune thrombocytopenia in the Irish population: a discrepancy between observed and expected cases. *Journal of Clinical Pathology*, **55,** 289–292.

Dreyfus, M., Kaplan, C., Verdy, E., Schlegel, N., Durand-Zaleski, I. & Tchernia, G. (1997) Frequency of immune thrombocytopenia in newborns: a prospective study. Immune Thrombocytopenia Working Group. *Blood*, **89,** 4402–4406.

General Register Office for Scotland (2007) Scotland's Population 2006: The Registrar General's Annual Review of Demographic Trends. General Register Office for Scotland, Edinburgh.

General Registers Office (2008) Scotland's Population 2007: The Registrar General's Annual Review of Demographic Trends. General Register Office for Scotland, Edinburgh.

General Registers Office (2009) Scotland's Population 2008: The Registrar General's Annual Review of Demographic Trends. General Register Office for Scotland, Edinburgh.

Hook, E.B. & Regal, R.R. (1995) Capture-recapture methods in epidemiology: methods and limitations. *Epidemiologic Reviews*, **17,** 243–264.

INOSS (2010) *The International Network of Obstetric Survey Systems*. Available at: http://www.npeu.ox.ac.uk/inoss. Accessed 23 June 2010.

Kamphuis, M.M., Paridaans, N., Porcelijn, L., De Haas, M., van der Schoot, C.E., Brand, A., Bonsel, G.J. & Oepkes, D. (2010) Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. *British Journal of Obstetrics and Gynaecology*, **117**(11): 1335–43.

Kjeldsen-Kragh, J., Killie, M.K., Tomter, G., Golebiowska, E., Randen, I., Hauge, R., Aune, B., Oian, P., Dahl, L.B., Pirhonen, J., Lindeman, R., Husby, H., Haugen, G., Gronn, M., Skogen, B. & Husebekk, A. (2007) A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood*, **110,** 833–839.

Knight, M., Kurinczuk, J.J., Tuffnell, D. & Brocklehurst, P. (2005) The UK Obstetric Surveillance System for rare disorders of pregnancy. *British Journal of Obstetrics and Gynaecology*, **112,** 263–265.

Murphy, M.F. & Bussel, J.B. (2007) Advances in the management of alloimmune thrombocytopenia. *British Journal of Haematology*, **136,** 366–378.

Murphy, M.F., Williamson, L.M. & Urbaniak, S.J. (2002) Antenatal screening for fetomaternal alloimmune thrombocytopenia: should we be doing it? *Vox Sanguinis*, **83**(Suppl. 1)**,** 409–416.

Northern Ireland Statistics and Research Agency (2009) *Registrar General Annual Report 2008*. Northern Ireland Statistics and Research Agency, Belfast.

Office for National Statistics (2008) *Birth Statistics 2006 Series FM1 No.35*. Office for National Statistics, Newport.

Office for National Statistics (2009) *Birth Statistics 2007 Series FM1 No.36*. Office for National Statistics, Newport.

Office for National Statistics (2010) *Birth Statistics 2008 Series FM1 No.37*. Office for National Statistics, Newport.

Radder, C.M., de Haan, M.J., Brand, A., Stoelhorst, G.M., Veen, S. & Kanhai, H.H. (2004) Follow up of children after antenatal treatment for alloimmune thrombocytopenia. *Early Human Development*, **80,** 65–76.

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.

Regal, R.R. & Hook, E.B. (1984) Goodness-of-fit based confidence intervals for estimates of the size of a closed population. *Statistics in Medicine*, **3,** 287–291.

Serrarens-Janssen, V.M., Steegers, E.A., van den Bos, A., van Heijst, A.F., Pereira, R. & Semmekrot, B.A. (2005) Experiences with fetomaternal alloimmune thrombocytopenia in the Netherlands over a 2-year period. *Acta Obstetrica et Gynecologica Scandinavica*, **84,** 203.

Tiller, H., Killie, M.K., Skogen, B., Oian, P. & Husebekk, A. (2009) Neonatal alloimmune thrombocytopenia in Norway: poor detection rate with nonscreening versus a general screening programme. *British Journal of Obstetrics and Gynaecology*, **116,** 594–598.

Tilling, K., Sterne, J.A. & Wolfe, C.D. (2001) Estimation of the incidence of stroke using a capture-recapture model including covariates. *International Journal of Epidemiology*, **30,** 1351–1359; discussion 1359–1360.

Turner, M.L., Bessos, H., Fagge, T., Harkness, M., Rentoul, F., Seymour, J., Wilson, D., Gray, I., Ahya, R., Cairns, J. & Urbaniak, S. (2005) Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. *Transfusion*, **45,** 1945–1956.

UK National Screening Committee (2010) *Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme*. Available at: http://www.screening.nhs.uk/criteria. Accessed 19 October 2010.

Ward, M.J., Pauliny, J., Lipper, E.G. & Bussel, J.B. (2006) Long-term effects of fetal and neonatal alloimmune thrombocytopenia and its antenatal treatment on the medical and developmental outcomes of affected children. *American Journal of Perinatology*, **23,** 487–492.

Williamson, L.M., Hackett, G., Rennie, J., Palmer, C.R., Maciver, C., Hadfield, R., Hughes, D., Jobson, S. & Ouwehand, W.H. (1998) The natural history of fetomaternal alloimmunization to the platelet-specific antigen HPA-1a (PlA1, Zwa) as determined by antenatal screening. *Blood*, **92,** 2280–2287.