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ORIGINAL ARTICLE

Contemporary management of neonatal alloimmune thrombocytopenia: good outcomes in the intravenous immunoglobulin era: results from the Australian neonatal alloimmune thrombocytopenia registry

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Abstract

Objective: To describe the natural history, antenatal and postnatal therapy, and clinical outcomes of Australian patients with fetomaternal/neonatal alloimmune thrombocytopenia (NAIT) recorded in the Australian NAIT registry.

Methods: Analysis of registry data of Australian mothers treated antenatally for NAIT and any fetus/newborn with thrombocytopenia (TCP) and maternal human platelet antigen (HPA) antibodies.

Results: Ninety four potential cases (91 pregnancies; three twin pregnancies) were registered between December 2004 and September 2015 with 76 confirmed or treated as NAIT. NAIT was frequently unanticipated (44 cases, 58%), whilst 32 cases (42%) were anticipated due to personal or family history. In 70/76 cases, the diagnosis of NAIT was made based on HPA antibody results; anti-HPA-1a was most commonly detected (58/70, 82%), followed by anti-HPA-5b (5/70, 7%). Intracranial haemorrhage (ICH) was detected in seven cases (9%). Maternal antenatal therapy resulted in improved clinical outcomes. For antenatally treated cases, whilst 10/29 (34%) neonates had severe TCP, only one ICH was detected.

Conclusions: This study provides data on contemporary "real world" management of Australian mothers and babies with NAIT. Antenatal IVIG therapy was associated with better neonatal outcomes. Maternal side-effects and treatment costs were substantial.

Keywords

Fetomaternal/neonatal alloimmune thrombocytopenia, human platelet antigen, intracranial haemorrhage, neonatal thrombocytopenia, intravenous immunoglobulin

History

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Introduction

Fetomaternal/neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of isolated severe thrombocytopenia (TCP) in an otherwise well neonate. NAIT is rare, affecting between 1:1000 and 1:2000 pregnancies and can cause catastrophic bleeding [1]. There is a high risk of recurrence in future pregnancies, and these may be managed antenatally with intravenous immunoglobulin (IVIG) and corticosteroids to reduce the severity of TCP and bleeding.

Rarity of this disease makes accrual of evidence to support prospective studies challenging. The Australian NAIT registry was established in 2009 to collect nationally consistent data on women and their children with a history of NAIT. The registry aims to better define the incidence, natural history and clinical outcomes of pregnancies and children with NAIT in Australia. In this study, we describe current treatment strategies and outcomes of patients with NAIT in Australia from the national registry.

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Methods

Patient identification

Data collection commenced in March 2009 at eight hospitals. Ethics approval permits retrospective data entry, to allow us to data capture on the first child affected by NAIT in the family that may have prompted maternal antenatal IVIG therapy.

Case inclusion criteria are mothers treated antenatally for NAIT (with or without human platelet antigen (HPA) antibodies) and any newborn with postnatally identified TCP and maternal HPA antibodies. Cases were classified as

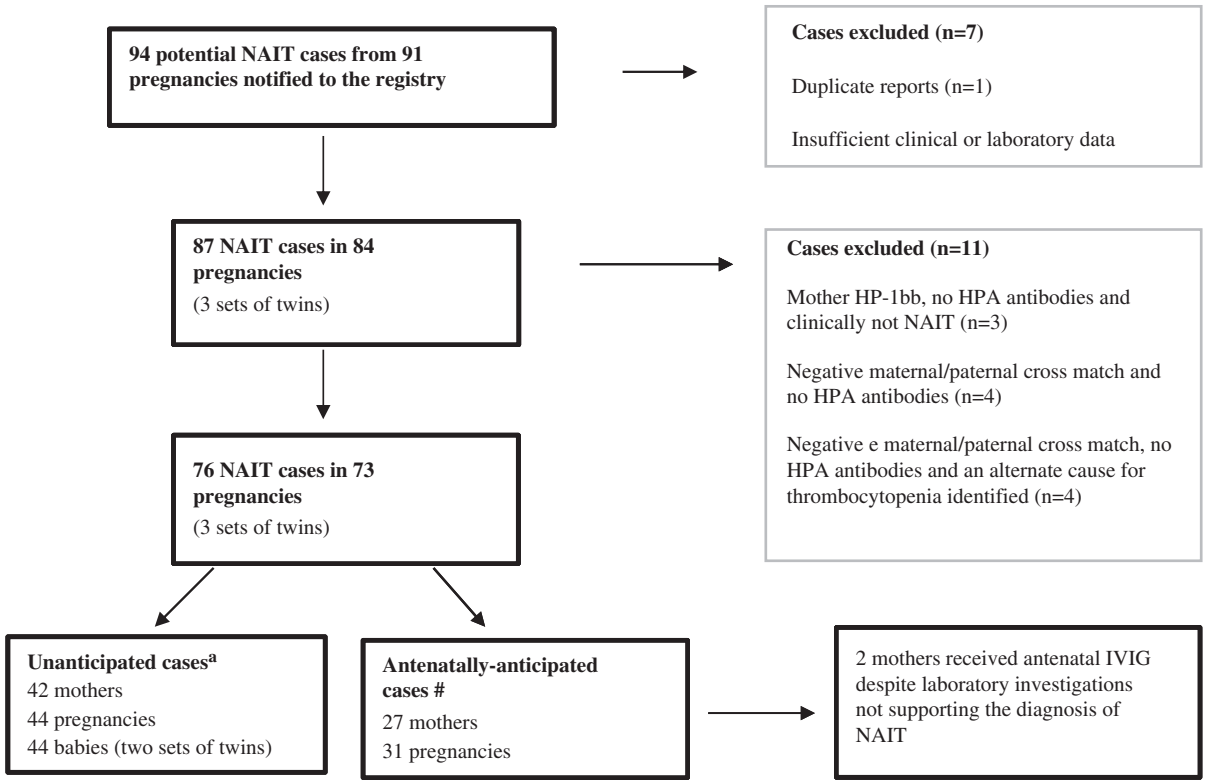

Figure 1. Flowchart of cases notified to the registry. [a]Fifteen mothers were cases in both the antenatally anticipated group and not-anticipated groups in sequential pregnancies.

confirmed NAIT on the basis of a positive maternal/paternal crossmatch and presence of HPA-antibodies. Registry cases are identified by treating clinicians at participating sites. To ensure eligible cases at participating sites are registered, registry staff cross-reference cases with NAIT diagnostic investigations performed at four centralised laboratories and the Australian Red Cross Blood Service (ARCBS) for the issue of IVIG.

Data collection

Data are recorded for the following categories: maternal demographics, clinical case description, laboratory investigations, antenatal therapy, neonatal demographics, postnatal features, therapy and outcome. ARCBS provides the results of HPA and human leukocyte antigen (HLA) genotyping and antibody investigations (platelet immunofluorescence tests, glycoprotein binding ELISA assays and HLA antibody testing).

Data analysis

For continuous variables, normally distributed data are presented as mean ± standard deviation (SD), while non-normally distributed data are presented as median and interquartile range (IQR). Categorical variables are presented as number and proportion. Comparison of outcomes for cases that were antenatally anticipated versus unanticipated was performed, with a p value of <0.05 considered as statistically significant.

Ethics approval

Ethics approval for participation in the registry was granted from the Human Research Ethics Committees (HREC) of Monash University, the ARCBS and the 26 participating hospitals.

Results

Registry cases

Ninety-four potential NAIT cases (91 pregnancies) were notified to the NAIT registry from 26 sites between December 2004 and September 2015. Six potential cases were excluded because of insufficient data, one due to duplicate reports, and 11 because investigations were not confirmatory of NAIT, the neonate was not thrombocytopenic, or another cause for TCP was evident. These 76 cases were the result of 73 pregnancies (three twin pregnancies) in 55 mothers (Figure 1).

Maternal demographics

Median maternal age at delivery was 30.3 years (IQR 27.3–34 years). Four mothers with HPA antibodies were thrombocytopenic (platelet count $< 150 \times 10^9$/L) at delivery.

Laboratory investigations

Positive maternal–paternal platelet crossmatch was seen in 74/76 cases, and in 70 the diagnosis of NAIT was made due to detection of HPA antibodies. Two mothers were included on the registry because they received antenatal treatment based on clinical history, despite a negative crossmatch and no documented HPA antibodies. This did not strictly meet our definition of NAIT, however we included them in the analysis of registry patients receiving antenatal therapy. In four cases, the maternal/paternal crossmatch was positive, however cognate HPA antibodies were not identified.

Table 1. Perinatal outcomes and comparison between antenatally anticipated NAIT cases and unanticipated cases.

	Overall registry population ($n = 76$)	Antenatally anticipated ($n = 32$)	Unanticipated ($n = 44$)	p values (anticipated versus unanticipated)
Number of live babies	74	32	42	
Nulliparous	13	1 (3%)	12 (30%)	0.001
Birthweight (g) Mean ± SD	2859 ± 669	2775 ± 639	2932 ± 695	0.33
Gestation (weeks) Median (IQR)	37 (35, 39.5)	36 (35, 37)	39 (36.5, 40)	<0.001
Median first platelet count ($\times 10^9$/L) Median (IQR)	33.5 (14, 135)	139.5 (65.5, 237.5)	17.5 (7.5, 28)	<0.001
Median lowest platelet count ($\times 10^9$/L) Median (IQR)	23 (9.5, 99.5)	107 (41.5, 212)	15.5 (5.5, 22.5)	<0.001
Cesarean section	44	28 (88%)	16 (38%)	<0.001
Intracranial hemorrhage	7	1 (3%)	6 (14%)	0.12
Required postnatal therapy	39	10 (31%)	29 (67%)	0.002
Required postnatal platelet transfusion	34	7 (22%)	27 (63%)	<0.001

IQR: interquartile range; SD: standard deviation.

In pregnancies affected by antibodies with confirmed HPA-antibody specificity, anti-HPA-1a (58/70; 82%) and anti-HPA-5b in five cases (7%) were most commonly detected. Rarer antibodies identified included anti-HPA-3a, HPA-1b, HPA-5a, antibody to GPIV (CD36) and a possible anti-HPA-9b.

In 20/27 antenatally anticipated cases with HPA antibodies, there was homozygous paternal expression of the implicated HPA antigen, in four heterozygous expression and in three cases paternal samples were unavailable.

Antenatally anticipated and unanticipated cases

In 58% (44 fetuses or neonates) of cases, the diagnosis of NAIT was unanticipated, whilst 42% (32 cases; 31 pregnancies) were antenatally anticipated due to a previous NAIT-affected baby, or in one case due to a positive family history (Figure 1). Of the 27 antenatally-anticipated mothers, 26 had a history of a NAIT-affected baby with three intrauterine fetal deaths (IUFDs), two antenatal intracranial haemorrhage (ICH), three severely affected neonates and 16 mildly affected neonates from previous pregnancies. One case was antenatally anticipated due to a family history of NAIT; she had anti-HPA-1a and a sister with a NAIT-affected baby.

Antenatal therapy

Of the 31 antenatally anticipated pregnancies, two mothers did not receive antenatal IVIG; one due to maternal choice and one because fetal blood sampling (FBS) confirmed a normal platelet count. Twenty-nine mothers received antenatal IVIG; Intragam P (CSL Behring, King of Prussia, PA) was the most commonly prescribed. Most mothers (90%) received weekly IVIG (median dose 1 g/kg). One mother received alternate week IVIG, despite a previous baby with an antenatal ICH. Two mothers initially received weekly IVIG, this was increased to twice weekly (from 18 and 28 weeks, respectively) for prior history of antenatal ICH. IVIG was commenced at a median of 18.7 weeks gestation [IQR 15.4–22.3], with two mothers commencing IVIG at less than 12 weeks because of prior affected pregnancies with antenatal ICH. Two mothers required dose change or cessation of their IVIG regimens due to intolerance or severe side effects and two additional mothers were not compliant with weekly IVIG.

Ten mothers received antenatal prednisolone as adjunctive therapy to IVIG; five because of previous antenatal ICH. Two mothers received antenatal prednisolone instead of IVIG, because of associated side effects. Median daily prednisolone dose was 50 mg (0.75 mg/kg). Steroids commenced at a median gestation of 25.5 weeks (range 7.6–34 weeks). One mother commenced steroids prior to 16 weeks (7.6 weeks) and this appeared related to a previous early antenatal ICH.

Four of the 29 antenatally anticipated mothers had antenatal procedures (FBS or amniocentesis). One mother had amniocentesis for fetal genotyping, which resulted in her not receiving IVIG. One had FBS with platelet transfusion (previous baby with antenatal ICH) and two had FBS without platelet transfusion.

Neonatal details

Perinatal outcomes are shown in Table 1. There were 74 live births (37 female, 37 male) and two IUFD due to NAIT. Two neonatal deaths were reported, one directly attributable to NAIT from severe ICH and one unrelated to NAIT (sepsis in an extremely preterm baby). Antenatally anticipated NAIT cases were born earlier; median gestational age (GA) of 36 weeks versus 39 weeks in unanticipated cases ($p < 0.001$). However, there was no significant difference in birthweight. Median first and lowest platelet counts of antenatally anticipated cases were statistically higher than in unanticipated cases (Table 1). Median day for the lowest platelet count was day 0 (range day 0–18).

Mode of delivery

Mode of delivery was reported for 74 neonates; 23 (31%) were vaginal delivery, four (5%) ventouse, one (1%) forceps, 29 (39%) Caesarean section (prior to onset of labour), 15 (20%) Caesarean section (after onset of labour) and two (3%) IUFD. Caesarean section rates were significantly higher in antenatally anticipated cases (88% versus 38%; $p < 0.001$).

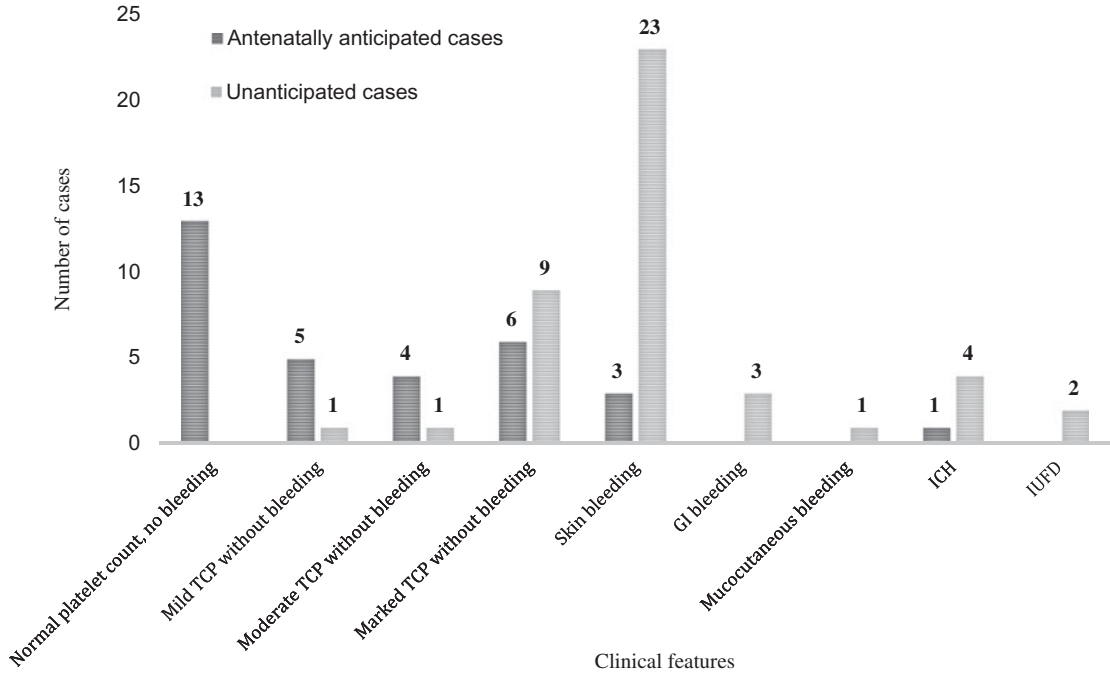

Figure 2. Clinical features in the 76 fetal and neonatal cases leading to the diagnosis of NAIT. TCP: thrombocytopenia; GI: gastrointestinal; ICH: intracranial hemorrhage; IUFD: intrauterine fetal death.

Clinical features – unanticipated cases

Of the 44 unanticipated cases, the most common clinical feature leading to investigation for NAIT was skin bleeding, including petechiae and bruising (23/44 [52%]) followed by incidental TCP without clinical symptoms (11/44 [25%]). ICH including antenatal diagnosis (IUFD) and postnatal diagnoses were identified in 6/44 (14%) (Figure 2).

Clinical features – antenatally anticipated

Of the 32 antenatally anticipated cases, 13/32 (41%) of babies had no clinical features and a normal platelet count, and 15/32 (47%) had no clinical features with mild, moderate or marked TCP (Figure 2). Three babies (9%) had evidence of skin bleeding and one baby had an ICH (small grade 1 intraventricular haemorrhage) without other clinical features. In this case, the mother received weekly IVIG during her pregnancy and delivered at 36 weeks by elective Caesarean section. At birth the neonate's platelet count was 3×10^9/L and ICH was detected by screening cranial ultrasound.

Intracranial haemorrhage

ICH was detected in 7/76 cases (9.2%); however, three additional mothers reported a prior history of antenatal ICH.

Postnatal therapy

Thirty-nine neonates received postnatal treatment; of these, 23 received both platelets and IVIG, five received IVIG only, 11 received platelets only and one neonate received platelets, IVIG and five days of IV methylprednisolone. Significantly fewer antenatally anticipated cases required either postnatal platelets (22% versus 63%, $p < 0.001$) or any postnatal therapy (31% versus 67%, $p = 0.002$) compared to unanticipated cases. Five neonates, despite platelet counts of $<30 \times 10^9$/L, did not receive postnatal therapy. Thirty-four neonates received a total of 76 postnatal platelet transfusions, median one per neonate. Five neonates received more than five platelet transfusions in addition to postnatal IVIG. Twenty-eight neonates received IVIG at median dose 1.04 g/kg and median one dose per neonate.

Almost 50% of platelets transfused were random donor platelets (i.e. non-HPA-matched), whilst 25 of the 76 platelet transfusions were HPA-matched. Median platelet increment was higher with HPA-matched platelets compared with random donor platelets (170×10^9/L versus 43×10^9/L, $p < 0.001$).

Discussion

This study provides data on contemporary ''real world'' management of Australian mothers and babies with a diagnosis of NAIT and highlights several important themes in this rare but potentially devastating condition.

Diagnosis

Australia does not have a screening program for NAIT and hence the diagnosis was most commonly made after the birth of an affected neonate. Studies reporting NAIT incidence based on antenatal screening are likely to report higher rates of NAIT, because asymptomatic neonates will be identified [1]. In our series, 58% of cases were identified following delivery; skin manifestations of bleeding were most commonly noted and the lowest platelet counts were seen on day one of life.

HPA specificity

A suspected HPA-antibody was detected in 92% of registry cases of which the frequency of anti-HPA1a, -5b and -3a was similar to published Australian and international

literature [2,3]. Davoren et al. in an analysis of 1162 diagnostic NAIT investigations found maternal anti-HPA-1a in the majority of confirmed cases (79%), followed by anti-HPA-5b (9%), anti-HPA-3a (2%) and HPA-1b (4%) [3]. An Australian retrospective review reported anti-HPA-1a in 17/20 pregnancies (11/13 mothers) and anti-HPA-5b in 2/13 mothers. However, recent Australian laboratory testing data demonstrated a lower frequency of anti-HPA-1a, partly due to detection of anti-5b antibodies in 30% of cases [4].

Antibodies to CD36 are rarely reported as a cause of NAIT [5]. We found one case of NAIT secondary to antibodies against CD36. Approximately 5% of individuals of Asian or African ethnicity will have platelets deficient in CD36 and these individuals are at risk of alloimmunisation during pregnancy if exposed to CD36-positive fetal platelets [5].

Difficulties in the diagnosis of NAIT

Clinicians face a number of challenges in refuting or confirming the diagnosis of NAIT. Eleven women notified to the registry had non-confirmatory laboratory investigations and in four an alternate aetiology for the TCP was identified. Many perinatal and maternal conditions are associated with neonatal TCP and rates of TCP are very high in neonates admitted to the neonatal intensive care unit [6]. Therefore, laboratory investigations for NAIT must take into account the clinical presentation of the fetus/neonate.

Three cases were excluded because, whilst the mother was HPA-1bb, anti-HPA-1a antibodies were not detected. Approximately 2% of Caucasian women are homozygous for HPA-1b and therefore are at risk of alloimmunisation, however only 10% of these women will produce anti-HPA-1a [1].

Maternal–paternal crossmatch may be positive in the setting of maternal platelet autoantibodies, HLA antibodies and ABO incompatibility. Conversely, the crossmatch may be negative in the setting of non-paternity, if the methodology is not sufficiently sensitive, or if the maternal samples were not appropriately timed (taken before an antibody is detectable or after it has gone). Antibodies against HPA-3 can also be difficult to detect using standard techniques [7]. Complete NAIT investigations may not be able to be conducted when paternal samples are not available.

In the four cases where the maternal/paternal crossmatch was positive and specific anti-HPA antibodies were not detected, three mothers had HLA antibodies detected. The role of anti-HLA Class I antibodies in NAIT remains contentious, however cases of HLA-mediated NAIT have been reported and there is increasing evidence that high-titre antibodies against paternal HLA types can cause catastrophic neonatal ICH [8].

Family history

Data from the registry and elsewhere suggest a role for offering antenatal screening to mothers with a first-degree relative with a history of a NAIT-affected baby. One baby notified to the registry died from a postnatally detected ICH secondary to anti-HPA-1a, and was subsequently found to have a maternal first degree relative who lost a baby due to NAIT. In another case, a mother with detectable anti-HPA-1a had a sister with a NAIT-affected baby; she was treated successfully with antenatal IVIG and gave birth to a healthy baby. Screening includes parental HPA genotyping and HPA antibody testing, and if HPA incompatibility and potential for NAIT is identified, then serial HPA antibody monitoring should be considered, and antenatal treatment commenced if antibodies detected.

The importance of family history has been examined before. Bussel et al. in their study of 107 fetuses with alloimmune TCP, identified two mothers in their first pregnancy because of a sister with a neonate with NAIT [9].

Perinatal mortality and morbidity

NAIT remains a significant cause of perinatal mortality and morbidity. Four deaths were reported to the registry, including two antenatally detected ICH that resulted in fetal death and one postnatally detected ICH. In these cases, anti-HPA-1a was detected in 9/10 cases and anti-HPA-5b in one case. Similarly, Tiller et al. reported anti-HPA-1a in (91%) 39/43 ICH cases and anti-HPA-5b in two cases [10].

Maternal ABO group may play a role in the risk of severe NAIT due to anti-HPA-1a [11]. Ahlen et al. found that of their HPA-1a alloimmunised patients, 20% of group O women had a child with severe NAIT compared with 47% of group A women [11]. In our study, maternal blood group was A in seven (78%) cases of ICH with anti-HPA-1a, group O in one and group B in one case.

Antenatal treatment strategies

No randomised controlled trials have directly compared intrauterine platelet transfusions (IUPT) and maternal IVIG therapy for treatment of NAIT. Historically, FBS with IUPT was the main treatment strategy for the fetal management of NAIT. However, more recently IVIG treatment has replaced IUPT as the primary treatment choice. FBS and IUPT can cause severe complications including bleeding, infection, preterm delivery and death [12,13]. Due to short platelet life span, transfusions are required weekly and each procedure holds a significant risk. Our study found small numbers of antenatal procedures performed. In four cases with heterozygous paternal expression of the HPA, only one amniocentesis was performed to determine fetal genotype. Use of IVIG in the other three cases may have been avoided if fetal genotyping had been performed. Recently, noninvasive fetal HPA-1a genotyping using targeted massively parallel sequencing of cell-free maternal plasma to detect fetal and maternal alleles has been reported. This offers the potential for safe and noninvasive HPA-genotyping for alloimmunised mothers with partners with heterozygous or unknown HPA-1a expression [14].

Bussel et al. first reported the successful use of antenatal IVIG (1 g/kg weekly) with or without steroids in seven pregnant women with a history of severely affected babies [15]. All seven treated fetuses had platelet counts $>30 \times 10^9$/L and none had ICH [15]. In 2010, they demonstrated that a risk-stratified approach consisting of antenatal therapy of IVIG 1–2 g/kg/week beginning at approximately 12 weeks gestation was effective in preventing ICH in the highest

risk pregnancies (those with a history of an antenatal ICH). Only five ICH occurred in 37 treated fetuses, when all 33 mothers had previous affected babies with ICH [16]. Today, antenatal weekly IVIG, with or without steroids, is considered optimal antenatal treatment [17]. Management is typically stratified based on the presence or absence of previous antenatal ICH, the timing and gestation of ICH. In those at highest risk of ICH, treatment should start at 12 weeks [16]. This correlates with when fetal platelets become phenotypically mature [18]. Lower doses of IVIG may be appropriate in mothers without a history of antenatal ICH. Paridaans et al. randomised 23 women with a history of a previously affected baby without ICH to low dose (0.5 g/kg) IVIG or standard dose (1 g/kg) IVIG [19]. The trial was stopped early due to poor recruitment; however no instances of ICH or death occurred and median platelet count in the low dose group was 81 versus 110×10^9/L in the standard group, $p = 0.64$ [19].

We have found that antenatally anticipated pregnancies treated with IVIG, had better clinical outcomes and less postnatal therapy requirements than unanticipated cases. Whilst 10/29 (34%) antenatally treated neonates had severe TCP, there was only one instance of ICH (a small grade 1 intraventricular haemorrhage) and three cases of documented clinical bleeding. Intraventricular haemorrhage is commonly seen in preterm neonates, however most healthy term neonates do not have cranial imaging performed. A study of healthy, healthy term neonates for the presences of ICH, found 20/505 (4%) neonates had asymptomatic germinal matrix haemorrhage, which is similar to our rate of 1/29 (3%) in our series [20].

Consistent with international series, some fetuses and newborns have a more severe phenotype and, despite maternal therapy have profound TCP, clinical signs of bleeding and may require prolonged treatment with platelet transfusion and or IVIG. Kamphuis and Oepkes reported that 20% fetuses do not respond to IVIG and their platelet counts remain $<50 \times 10^9$/L [21]. Tiller's review of fetal ICH found antenatal IVIG treatment failure in one woman (two pregnancies) out of 19 antenatally treated cases [10].

Our study noted a number of challenges in the administration of maternal IVIG, including refusal of treatment and side effects, necessitating dose change or cessation. Antenatal IVIG has generally been considered safe and well-tolerated with negligible adverse effects [12,17]. However serious side effects including maternal haemolysis have been reported [2,22].

The total amount of IVIG given to these 29 mothers was very costly. At a cost of $AUD61/g (excluding the cost of plasma collection) the total cost of IVIG received by these women was more than $AUD2 million [23]. Product cost alone of IVIG per antenatally-treated pregnancy was approximately $AUD72 000. Despite the costs of therapy, the impacts for a child with permanent neurological injury from ICH measured by financial cost, mortality and morbidity are likely to be significant.

Postnatal treatment

There is no evidence to define the optimal trigger for platelet transfusion in term or preterm neonates with suspected NAIT. Guidelines directing neonatal platelet transfusion practice vary considerably, and are largely consensus rather than evidence-based. Platelet transfusion triggers of $<25 \times 10^9$/L [24] and $<30 \times 10^9$/L [25] in neonates with suspected NAIT and the absence of bleeding have been suggested. Management of the neonate with NAIT focuses on timely platelet transfusion for symptomatic clinical bleeding or significant TCP. We found five neonates did not receive platelet transfusion or IVIG, despite a platelet count of $<30 \times 10^9$/L. Our results indicate that random platelets gave sufficient platelet increment to treat bleeding and therefore provide time to source HPA-matched platelets. IVIG was frequently used to treat TCP, however difficulties were noted around vial size and baby's weight, resulting in product wastage.

Strengths and limitations of this study

Strengths of our study include the large number of recent cases with comprehensive clinical and laboratory data from a large number of institutions across Australia, supporting generalisability of our findings. Limitations include the observational study design, and possible reporting bias, with more severe cases with worse outcomes more likely to be reported. Our results indicate that clinicians had difficulty making the diagnosis of NAIT, and therefore unrecognised cases may have been missed.

In summary, we present the largest study of NAIT cases from Australia. Perinatal morbidity and mortality was high, with an ICH rate of 9%. Most cases were not anticipated and there were differences in management and outcomes of antenatally anticipated versus unanticipated cases. Maternal IVIG therapy was successful in improving neonatal clinical outcomes, but was not infrequently associated with adverse effects, and was costly. Long-term patient outcome data have not been collected to date, and this area deserves further research. We noted clusters of NAIT cases within families and propose that screening for mothers with first-degree relatives who are affected with NAIT should be considered.

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Declaration of interest

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