Review Article

A review of pathophysiology and current treatment for neonatal alloimmune thrombocytopenia (NAIT) and introducing the Australian NAIT registry

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Fetomaternal or neonatal alloimmune thrombocytopenia (NAIT) is a rare but serious condition associated with significant fetal and neonatal morbidity and mortality. The most useful predictor of severe disease is a history of a sibling with an antenatal intracranial haemorrhage. However, NAIT can occur during the first pregnancy and may not be diagnosed until the neonatal period. Antenatal treatment options include maternal intravenous immunoglobulin (IVIG) and corticosteroid treatment, fetal blood sampling (FBS) and intrauterine platelet transfusion (IUT) and early delivery. FBS (with or without IUT) can be used to direct and monitor response to therapy, and to inform mode and timing of delivery. However, this procedure is associated with significant risks, including fetal death, and is generally now reserved for high-risk pregnancies. This review highlights the current understanding of the epidemiology and pathophysiology of NAIT and summarises current approaches to investigation and management. It also introduces the newly established Australian NAIT registry. Owing to the relative rarity of NAIT, accruing sufficient patient numbers for studies and clinical trials at an institutional level is difficult. This national registry will provide an opportunity to collect valuable information and inform future research on this condition.

Key words: fetal diseases/diagnosis, fetal diseases/therapy, infant – newborn, pregnancy, thrombocytopenia – neonatal alloimmune/diagnosis, thrombocytopenia – neonatal alloimmune/therapy.

Introduction

Fetomaternal or neonatal alloimmune thrombocytopenia (NAIT) is a rare but serious condition associated with significant fetal and neonatal morbidity and mortality. In this article, we highlight the current understanding of the pathophysiology of NAIT and review present approaches to investigation and management. We also introduce the new Australian NAIT Registry. Owing to the relative rarity of NAIT[1] and the difficulty in accruing sufficient patient numbers for studies and clinical trials at an institutional level, this national registry will provide valuable information and inform future research on this condition.

Although commonly known as NAIT, the significance of fetal involvement has led to the alternative name fetomaternal alloimmune thrombocytopenia (FMAIT). These terms may be used interchangeably, and the term NAIT will be used for this review.

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Pathophysiology and Natural History of NAIT

Neonatal thrombocytopenia (defined as a platelet count of $<150 \times 10^9$/L) occurs in approximately 0.5–0.9% of newborns[1] and severe thrombocytopenia (platelet count of $<20 \times 10^9$/L) in <0.1% of newborns.[2] NAIT is a relatively rare condition with an incidence of approximately 1–1.5 in 1000 live births and is the most common cause of severe thrombocytopenia ($<20 \times 10^9$/L) in newborns.[1,3,4]

Neonatal alloimmune thrombocytopenia is caused by maternal alloantibodies directed against incompatible fetal platelet antigens inherited from the father. In the setting of an antigen-negative mother, transplacental passage of maternal immunoglobulin G (IgG) antibodies results in the accelerated destruction of fetal platelets expressing the corresponding antigen. In this respect, it is similar to the more common condition of haemolytic disease of the newborn (HDN), which affects fetal red blood cells.

As fetal platelet antigens are expressed as early as the 16th week of gestation,[5] fetal thrombocytopenia and its consequent morbidity and mortality can occur early in pregnancy. In one case series, 46% of fetuses with NAIT who underwent fetal blood sampling (FBS) before 24 weeks gestation had an initial platelet count $<20 \times 10^9$/L.[6]

Almost all platelet antigens are inherited as paired alleles (ie one from each parent), although not all platelet antigens have as yet well-described corresponding antigens (see Table 1). Previously named eponymously, platelet-specific antigens are now classified numerically, according to the date of discovery, and in alphabetical pairs, in order of allele frequency ('a' for the high-frequency and 'b' for the low-frequency alleles).[7] These antigens are located on platelet membrane glycoproteins, and whilst called 'platelet-specific', some of these antigens are also expressed on other tissues, such as vascular endothelium.

Of the human platelet antigens (HPAs) so far described, a small number are responsible for the vast majority of clinically significant NAIT (see Table 2). Antibodies to platelet antigen HPA 1a are the most commonly implicated antibodies in Caucasians, although this is not the case for other ethnic groups.[8,9] In retrospective analyses of serologically confirmed cases of NAIT, the causative antibodies were directed against HPA 1a in 79%, HPA 5b in 9%, HPA 1b in 4% and HPA 3a in 2%.[10] In another

Table 1 Human platelet antigens

Antigens	Other names	Phenotypic frequency*	Glycoprotein location/amino acid change	Nucleotide substitution
HPA-1a (Pl^{A1})	Pl^A, Zw	72% a/a	GPIIIa/Leu ↔ Pro_{33}	T → C_{196}
HPA 1b (Pl^{A2})		26% a/b		
		2% b/b		
HPA-2a (Ko^b)	Ko, Sib	85% a/a	GPIb/Thr ↔ Met_{145}	C → T_{524}
HPA-2b (Ko^a)		14% a/b		
		1% b/b		
HPA-3a (Bak^a)	Bak, Lek	37% a/a	GPIIb/Ile:Ser_{843}	T → G_{622}
HPA-3b (Bak^b)		48% a/b		
		15% b/b		
HPA-4a (Pen^a)	Pen, Yuk	>99.9% a/a	GPIIIa/Arg:Gln_{143}	G → A_{526}
HPA-4b (Pen^b)		<0.1% a/b		
		<0.1% b/b		
HPA-5a (Br^b)	Br, Hc, Zav	80% a/a	GPIa/Glu:Lys_{505}	G → A_{648}
HPA-5b (Br^a)		19% a/b		
		1%b/b		
HPA-6bw	Ca^a, Tu	<1% b/b	GPIIIa/Arg ↔ Gln489	A → G_{1564}
HPA-7bw	Mo^b	<1% b/b	GPIIIa/Pro ↔ Ala_{407}	C → G_{1317}
HPA-8bw	Sr^a	<0.1% b/b	GPIIIa/Arg-Cys_{636}	T → C_{2004}
HPA-9bw	Max^a	<1% b/b	GPIIb/Val:Met_{837}	A → G_{2603}
HPA-10bw	La^a	1% b/b	GPIIIa/Arg:Gln_{62}	A → G_{281}
HPA-11bw	Gro^a	<0.5% b/b	GPIIIa/Arg:His_{633}	A → G_{1996}
HPA-12bw	ly^a	1% b/b	GPIb/Gly:Glu_{15}	A → G_{141}
HPA-13bw	Sit^a	<1% b/b	GPIa/Met:Thr_{799}	T → C_{2531}
HPA-14bw	Oe^a	1% b/b	GPIIIa/Del:Lys_{611}	A → $G_{1929\text{-}31}$
HPA-15a (Gov^b)	Gov	35% a/a	CD109/Tyr:Ser_{703}	A → C_{2108}
HPA-15b (Gov^a)		42% a/b		
		23% b/b		
HPA-16bw	Duv^a	<1%	GPIIIa/Thr:Ile_{140}	C → T_{517}
HPA-?	Va^a	<1%	GPIIIa/ND	ND
NA	Nak^a	99.8% (White)	CD36 (GPIV)	
		97% (Black)		T → G_{1264}
		96% (Asian)		C → T_{478}

*Phenotypic frequencies for the antigens shown are for white populations only.

Significant differences in gene frequencies may be found in black and Asian populations.

†There have been case reports of NAIT due to non-HPAs such as ABH and Class I HLA.[43]

ND, not determined; ?, antigen number not yet assigned; NA, not applicable; HPA, human platelet antigen; NAIT, neonatal alloimmune thrombocytopenia.

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Table 2 Anti-HPA specificities in reported case series of serologically confirmed NAIT

	Ghevaert *et al.*[22]	Davoren *et al.*[10]	Mueller-Eckhardt *et al.*[16]
Number of cases referred for suspected NAIT	1148	3743	348
Number of serologically confirmed NAIT	200	1162	118
Single antibody			
HPA 1a	75%	79%	90%
HPA 1b	0.5%	4%	<1%
HPA 2b		<1%	
HPA 3a	1%	2%	<1%
HPA 4a		<1%	
HPA 4b		<1%	
HPA 5a	0.5%	1%	
HPA 5b	15%	9%	8%
HPA 6b		<1%	
HPA 15b	4%		
GPIV (CD36)		<1%	
Multiple antibodies detected			
HPA 1a + 5b	3%	2%	<1%
HPA 1b + 3a		<1%	
HPA 1b + 5b		<1%	
HPA 5b + 15b	1%		
Others		<1%	

HPA, human platelet antigen; NAIT, neonatal alloimmune thrombocytopenia.

retrospective series, antibodies to HPA 1a were most commonly identified, followed by HPA 5b and less commonly HPA 1b, 3a, 3b and 15a. Where routine screening for HPA 1–5 was negative, further investigation identified antibodies to HPA 9b in eight women with NAIT, accounting for approximately 2% of all confirmed NAIT cases in this series.[11] Antibodies against HPA 9b were implicated in five (possibly six) cases from a total of 217 cases in another study investigating this rare alloantigen, suggesting that it might be more a common cause of NAIT despite its rarity in the general population.[12] Fetal thrombocytopenia has been reported to be more severe in cases of NAIT due to HPA 1a, HPA 3a and HPA 9b incompatibility.[6,11,13]

Prospective studies have demonstrated a frequency of HPA 1b homozygosity in pregnant women of 1.6–2.5% and an alloimmunisation rate of between 6 and 11.4% in these susceptible women.[3,4,14–16] It is not known why more women do not develop antibodies following exposure, sometimes repeatedly over multiple pregnancies. Alloimmunisation to HPA 1a is strongly associated with the HLA class II DRB3*0101 type.[4,15,17,18] HPA 1b homozygous women with this HLA class II type are more likely to develop anti-HPA 1a antibodies. Very few women without this HLA type develop anti-HPA antibodies, making the negative predictive value of this HLA type clinically useful.[4] In addition, babies born to immunised women without this HLA type are more likely to have only mild thrombocytopenia.[15]

Alloimmunisation can occur anytime during pregnancy, including delivery,[19] although the timing of sensitisation is currently not well known. Clinically significant NAIT can occur in the first pregnancy, unlike HDN.[4,15] Alloimmunisation does not necessarily result in fetal/neonatal thrombocytopenia.[3,4,14,15,20] The natural history of HPA 1a alloimmunisation has been investigated by antenatal screening for HPA 1a-negative women. It should be noted that antenatal screening studies include all pregnant women negative for HPA 1a and observe their subsequent development of anti-HPA 1a and neonatal thrombocytopenia. These studies are distinct from those that enrol women with a prior history of NAIT, known parental incompatibility or a previous neonate with thrombocytopenia. In one antenatal screening study, of HPA 1a-positive babies born to women with persistent antenatal anti-HPA 1a antibodies, approximately a third, had a normal platelet count at delivery and another third had a 'safe' platelet count of $50–150 \times 10^9$/L.[4]

The natural history of NAIT is variable. Some neonates are asymptomatic with thrombocytopenia only detected incidentally,[1] whilst others may present with petechiae and ecchymoses following delivery. At the other extreme, fetal death caused by haemorrhage can result from NAIT. Intracranial haemorrhage (ICH), one of the most serious bleeding complications, has been reported in up to 20% of affected neonates[16,21] and can occur in the antenatal, perinatal or neonatal period. In a prospective observational study that included 200 cases of NAIT, the rate of ICH was 13% overall, and 18% in the newly diagnosed alloimmunised pregnancies.[22] In another study of 111 NAIT cases with a rate of ICH of 11%, there was no significant difference among babies with HPA 1a incompatibility and neonatal thrombocytopenia in birth platelet count, incidence of other bleeding manifestations, mode of delivery, or birth weight in those infants with an ICH.[23] This demonstrates that the clinical diagnosis of ICH in NAIT is not straightforward, and all thrombocytopenic neonates ($<50 \times 10^9$/L), even if asymptomatic, should undergo radiological screening for ICH. In addition to the risk of mortality, ICH is associated with significant long-term neurological and developmental morbidity for the affected infants.[24,25]

Screening

As severe neonatal thrombocytopenia can occur in the first pregnancy, there has been interest in the utility of routine antenatal screening programmes for the anti-HPA 1a antibody. The largest trial to date was performed in Norway, where 100 448 pregnant women were typed for HPA 1, and these HPA 1a-negative women were screened for anti-HPA 1a. Immunised women were offered an intervention programme that consisted of early delivery by caesarean section with HPA 1a-negative platelets available for transfusion at the time of delivery. Compared with a

historical cohort, this screening programme seemed to reduce the number of severe NAIT-related complications from 10 of 51 to 3 of 57. However, 37 neonates required neonatal intensive care treatment for pulmonary maladaptation (in 28), hypoglycaemia, prematurity or because they were small for gestational age. None of the neonates suffered any long-term sequelae.[15] When compared with the screened population during the same time period, the detection rate for NAIT in the non-screened population was only 14% of the expected rate.[26] Screening programmes have not been widely adopted internationally, in part because of the lack of consensus about the optimal antenatal management of those identified as being at risk of NAIT, but without a history of an affected pregnancy, and the lack of standardisation for the testing of antibodies.[8] In addition, cost-benefit analyses of screening programmes have been limited by the lack of published data on long-term disability and fatalities for comparison with the screened population.[27,28]

Antenatal management

As the first pregnancy affected by NAIT is usually not detected until the delivery of a symptomatic child, there is usually no opportunity for antenatal therapy. However, for subsequent pregnancies at risk of NAIT, treatment can be given with the aim of maintaining a fetal platelet count to prevent serious bleeding. Treatment options include maternal intravenous immunoglobulin (IVIG), maternal corticosteroid treatment, FBS and intrauterine platelet transfusion (IUT) and early delivery.

Current antenatal management strategies focus on triaging risk on the basis of patient history (see Table 3). Unlike HDN, antibody levels are not widely used in clinical practice for predicting risk, as a correlation between antibody levels and clinical outcomes has not been established.[8]

Fetal blood sampling

Fetal blood sampling can be used to diagnose and determine the degree of thrombocytopenia, allow IUT, measure response to and direct therapy. However, there are significant risks associated with this procedure, including bleeding, premature delivery and death[29,30], and on the basis of recent published experience, the role of FBS in the management of NAIT has greatly diminished. It has been estimated that FBS has a fetal loss rate of 1.3% per procedure and 5.5% per affected pregnancy.[31] However, this is known to be highly variable among operators and centres. Fetuses with a low platelet count or a prior sibling with an antenatal ICH are more likely to suffer complications, including death.[32]

Table 3 Approach to risk assessment for women with a previous maternal history of NAIT

Clinical features	Risk of a baby with severe NAIT
Previous sibling with antenatal ICH Previous sibling FDIU	Very high risk
Previous sibling with perinatal ICH	High risk
No history of previous infant with ICH	Standard risk

ICH, intracranial haemorrhage; FDIU, fetal death *in utero*; NAIT, neonatal alloimmune thrombocytopenia.
Criteria for diagnosis include a clinical history consistent with NAIT.

The European Fetomaternal Alloimmune Thrombocytopenia Study Group reported the outcome of 55 pregnancies with NAIT due to HPA 1a alloimmunisation according to three antenatal treatment strategies, one of which was serial platelet IUT.[29] Success was considered a fetal platelet count of $>50 \times 10^9$/L for those receiving maternal IVIG therapy, and a pre-IUT fetal platelet count of $>20 \times 10^9$/L for those having regular IUTs. FBS was performed for each treatment group prior to the commencement of therapy. Thirty-three of the pregnancies were managed with serial platelet IUT with a success rate of 58%. These cases had a significantly lower pre-treatment platelet count than those who received maternal therapy. IUT was more likely to be successful if a post-IUT platelet count of $>200 \times 10^9$/L was achieved and repeat IUT was performed at intervals of seven days or less. In total, 18 of the pregnancies were managed with maternal therapy with a success rate of 67% (the majority of which received IVIG alone). Significant adverse events because of FBS occurred in seven of the 56 fetuses (12.5%), including two deaths and five deliveries before 32 weeks. Adverse events because of IVIG were negligible. Given the success of maternal therapy and the complications from FBS, the authors suggested that maternal therapy should be given for pregnancies considered high risk and commenced early (16 weeks).

Maternal therapy

With increasing concerns about the potential risks of FBS and IUT, there has been a gradual change recently to the use of IVIG-based treatment regimens for NAIT. Maternal IVIG has been shown in observational studies to be an effective therapy for at-risk pregnancies[31,33] and is now widely used in the antenatal management. The optimal dose (1 or 2 g/kg) and schedule (weekly, or more often), the time to initiate therapy, the addition of corticosteroids to treatment and the role of monitoring response with FBS are all yet to be determined. However, there are a number of studies that have examined these issues.

Berkowitz *et al.*[34] reported a parallel randomised trial of 'risk-based' therapy which included 78 women with 79 pregnancies. Women with a history of an antenatal ICH in a previous pregnancy were excluded from the study. Those with a history of a sibling with a peripartum ICH or with an initial fetal platelet count at 20 weeks $<20 \times 10^9$/L were included in the 'high-risk' arm and were randomised to IVIG 1 g/kg/week alone or with the addition of prednisolone 1 mg/kg/day. For this group, the combination of IVIG and prednisolone had a significantly higher response rate (89% compared with 35%) and a higher mean

platelet count than IVIG alone. The other women in the study were considered 'standard risk' (ie those with no history of a sibling with ICH and with the initial fetal platelet count of $>20 \times 10^9$/L) and were randomised to IVIG 1 g/kg/week or prednisolone 0.5 mg/kg/day. In this group, there was no significant difference in the response to treatment. These findings suggested that fetuses with severe thrombocytopenia require more intensive therapy. There were 11 serious complications of the 175 (6%) FBS performed and these resulted in the emergency delivery or death *in utero* of 11 (14%) of the neonates.

This was followed with another randomised study that compared a higher dose of IVIG (2 g/kg/week) with lower-dose IVIG (1 g/kg/week) plus prednisolone (0.5 mg/kg/day) from 20 weeks.[35] Seventy-three women with a history of NAIT were included and as with the previous study, those with a history of an antenatal ICH were excluded. A single FBS procedure was performed at 32 weeks (to avoid delivery at an earlier gestation because of a procedure-related complication) and salvage therapy instituted if the platelet count was $<30 \times 10^9$/L. There was no difference in patient outcomes, including platelet count at birth, platelet count at FBS and incidence of ICH, between the two groups. There were four complications from 79 (5%) FBS procedures with caesarean section delivery performed between 32 and 37 weeks. There were two ICH (one in each group) that occurred in the neonatal period and both had birth platelet counts $>100 \times 10^9$/L. The maternal side effects of treatment included moderate to severe fatigue and headache in those on high-dose IVIG, and an increase in gestational diabetes, fluid retention and mood swings in those patients on prednisolone.

Van den Akker *et al.*[36] in 2007 described a single-institution experience (in a series of 98 consecutive pregnancies in 85 women) according to the invasiveness of the management protocol used, with a trend over time to a less invasive approach. The first group included 13 pregnancies (none of which had a sibling with ICH) that were managed with FBS and IUT if the platelet count was $<100 \times 10^9$/L, without the use of IVIG. The second group included 33 pregnancies (11 with a sibling with ICH) treated with IVIG combined with FBS and IUT if required (if fetal platelet count $<50 \times 10^9$/L after 4 weeks of IVIG therapy). The IVIG commenced 4–6 weeks prior to the estimated time of occurrence of the sibling's ICH or at 32 weeks if no sibling history of ICH. The third group included 52 pregnancies (resulting in 53 neonates) managed entirely non-invasively with IVIG starting at 16 weeks if there was a sibling history of ICH (five pregnancies) and at 32 weeks in cases with no sibling history of ICH. This series had an overall perinatal survival rate of 99% and there were no neonatal ICH. Median gestation at birth was 37 weeks. Adverse events because of FBS occurred in 3% of the fetuses, including one fetal death. There were no deaths or ICH in the 52 pregnancies managed non-invasively.

Yinon *et al.*[37] reported on 30 pregnancies in 17 women at risk of NAIT but with no previous pregnancies affected by ICH. This series included 24 pregnancies that were treated with weekly IVIG 1 g/kg/week starting at 18–24 weeks until delivery. Only 8% of this group experienced treatment failure (defined as a platelet count $<30 \times 10^9$/L). There was no ICH or deaths. Of the women who had multiple pregnancies treated with IVIG, it was observed that a good response to treatment with IVIG in one pregnancy did not guarantee a response in subsequent pregnancies.

More recently, Bussel *et al.*[38] reported results of a stratified approach to antenatal management in 37 high-risk pregnancies in which a previous pregnancy was complicated by a fetal or perinatal ICH. The women were stratified according to the timing of the previous child's ICH. Women were considered extremely high risk if the ICH was <28 weeks and received IVIG 2 g/kg/week from mean gestation of 13 weeks. If the ICH was between 28 and 36 weeks, women were considered very high risk and received IVIG 1–2 g/kg/week from mean gestation of 12–14 weeks. Finally, high-risk women with an ICH in the perinatal period received either IVIG 1 g/kg/week ± prednisolone 1 mg/kg/day or IVIG 2 g/kg/week from a mean gestation of 16–25 weeks. There was a low rate of recurrent ICH (5 in 37 treated fetuses) with this stratified treatment strategy. Although there were only a small number of patients in each treatment group, the authors have made recommendations based on this large series of women with a history of fetal or perinatal ICH. For extremely high risk, they recommend commencing treatment at 12 weeks gestation with IVIG 2 g/kg/week with the empiric addition of prednisolone 1 mg/kg/day at 24–26 weeks to avoid FBS before 32 weeks gestation. For very high risk and high-risk pregnancies, they recommend IVIG 1 g/kg/week from 12 weeks gestation, with the addition of prednisolone 1 mg/kg/day or an increase in IVIG dose to 2 g/kg/week from 20 weeks. For all patients, FBS at 32 weeks was recommended to determine the need for further therapy and/or early delivery.

These studies demonstrate that successful antenatal management is possible with a less invasive approach. Clearly, treatment should be tailored according to the risk of severe NAIT, and based on current evidence, women with a sibling history of antenatal ICH are considered very high risk. Whilst an entirely non-invasive approach may be considered for standard-risk pregnancies (ie no sibling history of ICH), this is not the case for higher-risk pregnancies. However, the role of FBS in high-risk pregnancies remains uncertain, and clinicians must balance the risk of complications from FBS with the risk of missing a sub-optimal response or treatment failure with maternal therapy alone.

Delivery

There is no consensus on the most appropriate mode of delivery. A prospective study of 200 NAIT cases identified that all 17 post-natal ICH detected occurred within 24 h of delivery, which may suggest that the trauma of the delivery could have been a triggering factor.[22] As described earlier, the large screening study performed in Norway achieved

a lower rate of NAIT-related adverse events compared with historical controls with the use of early delivery by caesarean section and immediately available antigen-compatible platelets.[15] However, this was associated with a number of adverse events because of early delivery. Van den Akker *et al.*[39] described a series of 32 pregnancies in 29 women with NAIT managed with IVIG (with a median cord platelet count at birth of 145 [range 4–252]) and caesarean section for obstetric reasons only. In this series, vaginal delivery occurred in 23 (72%), including three who had infants with severe thrombocytopenia. There were no cases of ICH or death.

It is recommended that vaginal delivery only be allowed for those patients whose fetuses have a platelet count $>50 \times 10^9$/L at the time of delivery (or $>100 \times 10^9$/L at 32 weeks) as assessed by FBS,[31,35] but as discussed earlier, FBS is associated with considerable risk. For cases where the fetal platelet count is unknown, caesarean section before term is commonly recommended, although evidence supporting this recommendation is lacking.[31] Owing to the requirement for possible platelet transfusion, along with the risk of ICH and subsequent need for neuroimaging, the authors of this paper advise delivery in a tertiary centre with appropriate facilities, and with access to neonatologists, paediatricians and paediatric haematologists familiar with the management of this condition.

Post-natal management

As with antenatal management, many important questions remain about the post-natal management of NAIT. A recent systematic literature search failed to identify any randomised controlled trials or systematic reviews that compared different platelet thresholds for the transfusion of platelets for affected neonates and found that recommendations in the literature vary from a threshold of $30–100 \times 10^9$/L.[40] This paper also surveyed clinicians and identified significant variation in transfusion practice.

Intravenous immunoglobulin can be used in infants with thrombocytopenia due to NAIT. However, it may take one to three days before there is a rise in the platelet count. The usual dose varies from 1–2 g/kg.

HPA 1a- and HPA 5b-negative donor platelet concentrates are available on request from the Australian Red Cross Blood Service for IUT and for thrombocytopenic neonates suspected of having NAIT. As the confirmation of this diagnosis (and determination of the antibody specificity) may take some time, these platelets should be considered for neonates requiring platelet transfusion support (eg those with evidence of bleeding or significant thrombocytopenia) and in whom the diagnosis of NAIT is strongly suspected. Antigen-matched platelets have been shown to give larger platelet increments and a longer half-life than random donor platelets.[41] However, if these are not available, random (non-matched) donor platelets can be given as they may still achieve an adequate platelet count increment. This was demonstrated in a recent retrospective study where 24 of 27 newborns with NAIT achieved a platelet count above a threshold of 40×10^9/L with platelet transfusion from random donors.[42] Random donor platelets can also be given if there is any significant delay in accessing antigen-negative platelets, for example in the event a neonate is unexpectedly born with a low platelet count and especially if there is evidence of bleeding.

The mother is a potential source of antigen-negative platelets. She must be eligible to be a donor, the platelets must be plasma reduced (to remove antibodies, and this process can affect platelet recovery and function) and irradiated. However, maternal platelets are seldom used in Australia because there are often medical or practical reasons why platelets cannot be either collected or available for transfusion in a timely manner and random donor platelets are almost always more readily available.

Finally, as there have been reports of silent ICH in neonates with NAIT and as the clinical diagnosis of ICH is not straightforward,[23] all neonates with suspected NAIT and a platelet count $<50 \times 10^9$/L should have imaging performed to screen for an ICH.

The Australian NAIT registry

The national NAIT registry, recently established through collaboration between the Australian Red Cross Blood Service, Monash University Department of Epidemiology and Preventive Medicine and interested clinicians, aims to address some of the issues discussed previously. The low frequency of this condition makes research in individual institutions difficult, and the registry will provide the opportunity to more accurately define the incidence and clinical outcomes of NAIT, the range of treatment approaches used and explore clinical and laboratory factors that may influence outcome in Australia. The registry may also inform and inspire future hypothesis-driven research in this area.

The NAIT Registry will include all pregnant women who develop or have a history of NAIT and their children, both before and after birth. Following institutional ethics committee approval, clinicians from specialist units at participating hospitals may enter clinical data and diagnostic laboratories that perform the specialised testing will provide results for registered patients. Information is entered securely through an online database. The information collected will include maternal (patient demographics, prior history of NAIT and testing results) and paternal (demographics and testing results) details, antenatal management and fetal outcome, and neonatal details, including therapy and outcome.

To ensure that all eligible patients are captured, the clinical data in the registry will be cross-referenced with the four laboratories that perform diagnostic testing for NAIT across Australia. In addition, cases will be cross-referenced with the Blood Service, which provides specialist medical advice as well as blood products for affected patients (including IVIG and antigen-negative platelets). It is anticipated that approximately 20–30 patients will be identified each year across all participating hospitals. Registry staff will be

responsible for training clinicians to use the online database and for performing random audits on 5% of cases to ensure accurate extraction of data.

Conclusion

Neonatal alloimmune thrombocytopenia is a rare condition that can have significant and long-lasting consequences for those infants and their families who are affected. NAIT can occur during the first pregnancy and may not be diagnosed until the neonatal period. In Caucasians, the most commonly implicated platelet antigen is HPA 1a. The most useful predictor of severe disease is a history of a prior sibling with an antenatal ICH. For antenatal management of at-risk pregnancies, there is increasing experience with the successful use of IVIG with or without prednisolone, and consequently standard-risk pregnancies may be managed with a non-invasive approach. FBS (with or without IUT) can be used to direct and monitor response to therapy, and to inform decisions on mode and timing of delivery. However, FBS has significant risks, including fetal death, and is generally now reserved for high-risk pregnancies. For affected neonates, antigen-negative platelets, random donor platelets or IVIG may be used and the optimal treatment will depend upon product availability and clinical features.

As many aspects of the management of this important disease are in need of further study, and given the difficulty accruing patients for clinical trials and studies, we are pleased to announce the establishment of the national NAIT registry and extend an invitation to interested clinicians to contribute.

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