

Antenatal Management in Neonatal Alloimmune Thrombocytopenia

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Abstract

Background: Neonatal alloimmune thrombocytopenia (NAIT) is a blood-related disorder that affects expectant mothers and their babies. NAIT is triggered by maternal antibodies raised against alloantigens carried on fetal platelets. NAIT can be a substantial cause of morbidity and mortality in newborns and is the furthestmost communal cause of intracranial haemorrhage in full-term infants. Numerous strategies were proven to successfully manage NAIT in subsequent pregnancies such as serial fetal blood sampling (FBS), intrauterine platelet transfusions (IUPT) and weekly maternal IV immunoglobulin infusion (IVIg) whether alone or accompanied with a complementary corticosteroid therapy yet optimal management has not been determined.

Aim of the Work: was to assess evaluate the effect of antenatal treatment options on neonatal outcomes, including neonatal PLT count, ICH, and mortality.

Methods: A review of the scientific literature was conducted to cover relative literature published between 1940 and 2017. Scientific database included were Pubmed, Embase, CENTRAL and SCOPUS Cochrane Library. Articles were screened according to the inclusion and exclusion criteria according to Prisma guidelines. Methods: A review of the scientific literature was conducted to cover relative literature published between 1940 and 2017. Scientific database included were Pubmed, Embase, CENTRAL and SCOPUS Cochrane Library. Articles were screened according to the inclusion and exclusion criteria according to Prisma guidelines.

Results: 13 studies have met the eligibility criteria and thus included in the present systematic review noting that Pooling of results was not feasible due to the considerable heterogeneity. A relatively high complication rate of FBS and IUPT was a clear observation (manifested mainly of preterm emergency cesarean section); 11% per treated pregnancy in all studies combined. There was a comparable outcome regarding the occurrence of intracranial hemorrhage, regardless of the antenatal management strategy applied; FBS, IUPT, or IVIg with or without corticosteroids. There is no consistent evidence for the value of adding steroids to IVIg.

Conclusion: We suggest first-line antenatal management for women carrying a fetus at risk of recurrent NAIT which should be administered as a weekly IVIG with or without the addition of corticosteroids. Acclaimed that Preventive antenatal strategies should be based upon the risk of disease severity.

Keywords: Neonatal Thrombocytopenia; Fetal Therapy; Intracranial Hemorrhage; Intravenous Immunoglobulin; Alloimmunization; Antenatal; Prenatal Management of NAIT/FNAIT

Introduction

Neonatal alloimmune thrombocytopenia (NAIT) is the commonest cause of early onset isolated thrombocytopenia in an otherwise healthy neonate [1].

NAIT is a disorder in which fetal platelets contain an antigen inherited from the father that the mother lacks, most commonly human platelet antigen (HPA)-1a incompatibility. The mother then develops antibodies against this paternal antigen and these antibodies cross the placenta and bind to the fetal platelets. Clearance of the antibody-coated platelets results in fetal/neonatal thrombocytopenia; platelet function remains relatively normal. In contrast to Rh(D) alloimmunization, NAIT often affects a first pregnancy [2].

Two plausible mechanisms have been proposed to explain the occurrence of maternal alloimmunization in NAIT. One mechanism involves maternal exposure to HPA on fetal platelets due to fetomaternal bleeding related to obstetrical complications, trauma, or delivery. The other mechanism is maternal exposure to integrin beta-3 on placental syncytiotrophoblast cells during pregnancy [3].

Incidence of NAIT

The incidence of NAIT is reported to be between 1:800 and 1:1000 live births by the unselected Caucasian population by prospective studies [4]. In clinically presenting cases, the rate of intracranial hemorrhage is ~20% followed by death in 10% and neurological sequelae in 20% of these newborns [5]. The most serious complication is intracranial hemorrhage (ICH) in the case of severe thrombocytopenia. The morbidity has been estimated to be 20% of the reported cases and mortality up to 15% [6]. Alloimmune thrombocytopenia can be diagnosed during pregnancy or at birth.

In contrast to maternal immunization against fetal red cell antigens, it is common for immunization against platelet alloantigens to occur during a first pregnancy and for a firstborn infant to be affected by NAIT. However, most instances of maternal immunization may be triggered by exposure to fetal blood at the time of delivery, setting the stage for an infant to be born subsequently with thrombocytopenia [7].

Clinical Manifestations of NAIT

It's important to mention that NAIT is the leading cause of severe thrombocytopenia in the fetus and neonate [8] which can substantially trigger serious bleeding, intracranial haemorrhage and death [9], and is the leading cause of intracranial haemorrhage in full term infants [10]. A severely affected infant will present with florid petechial haemorrhages and purpura and a profoundly low platelet count.

It has been shown in several studies that up to 7% - 20% of fetuses/neonates affected by NAIT will suffer from ICH with as many as 75% of these cases occurring antenatally, diagnosed as early as the mid-second trimester [11].

Depending on the severity of thrombocytopenia (mild, moderate, or severe), NAIT may present as a spectrum of disease findings. A platelet count of $< 150,000/\mu\text{L}$ has been used to define thrombocytopenia because this is the threshold used in adults and represents the lower fifth percentile. Approximately 0.5% - 0.9% of neonates will have thrombocytopenia, and this can be further classified as mild, moderate, or severe [12].

The commonest mode of presentation is the well neonate with bruises or petechiae, but the spectrum of disease ranges from sub-clinical moderate thrombocytopenia to catastrophic intracranial haemorrhage and death. A high index of suspicion is essential in all cases of active bleeding, but also in asymptomatic laboratory diagnosed thrombocytopenia. A history of thrombocytopenia in a previous sibling makes the diagnosis almost certain.

The most serious complication of NAIT is intracranial haemorrhage, which occurs in 10 - 20% of symptomatic infants [13]. Up to 80% of these bleeds occur prenatally [14]. After delivery, the greatest risk of bleeding is in the first 96h of life [13,14]. Untreated, the thrombocytopenia in the neonate typically resolves within the first two weeks of life. For reasons not well understood, a low count sometimes persists for longer periods of time, occasionally for several months.

Management of NAIT

In the absence of screening programs, the diagnosis is almost always established after birth of a symptomatic child.

Therefore, in order to prevent recurrence of NAIT in a subsequent pregnancy, several interventions have been used. At first, serial fetal blood sampling (FBS) with often weekly platelet transfusions were used, however, after the empirical observation by Bussel, *et al.* [15] in 1988 that antenatal maternal treatment with high-dose intravenous immunoglobulins (IVIG) seemed to prevent ICH in high-risk pregnancies, IVIG became the cornerstone of NAIT treatment. Several centres in both Europe and the USA advocate the use of FBS for verification of fetal platelet count before and during maternal treatment. Controversy exists whether FBS, with its inherent risks of bleeding, boosting of antibody levels, emergency (preterm) caesarean section and fetal loss, should remain part of the management of NAIT [16].

In the present review, we aim to assess antenatal treatment strategies for FNAIT.

Materials and Methods

Data Sources

We carried out a systematic review of RCTs, prospective and retrospective studies of operated from 1940 to December 2017. This review was performed according to the PRISMA guidelines [17].

Data Sources: Literature searches of Pubmed, Embase, CENTRAL and SCOPUS Cochrane Library between 1940 and 2017 were performed. The search terms were used in combinations and together with the Boolean operators OR and AND; Search terms used were: "neonatal thrombocytopenia", "platelet antigens", "alloimmune thrombocytopenia", "NAIT", "FNAIT".

Study Selection and Criteria

Search results were screened by scanning abstracts for the following

Inclusion Criteria:

1. ≥ 5 pregnant women with pregnancies at risk for FNAIT or fetuses/neonates diagnosed with NAIT.
2. Patients treated with either IVIG, steroids, or IUPT
3. Included any of the outcomes: intracranial hemorrhage and fetal/neonatal PLT count;
4. Articles published in the English language.

Exclusion Criteria:

1. Literature published in languages other than the English language.
2. Articles that didn't meet the endpoint or desired outcomes.
3. Studies with the same cohort and same NAIT population with either fewer population or most complete data extraction.

Disagreements for inclusion were resolved by consensus.

Data Extraction

Studies abstracted data were reviewed independently and resolved disagreements by consensus. Reference lists were also cross-checked for relevant citations.

Studies were evaluated for quality and a review protocol was followed throughout.

Results

Searches identified 3247 publications in addition to another 54 publications that were found through manual research. After removal of duplicates, abstracts and titles 1143 publications were assessed as identified from title and abstract, and 935 papers were excluded. In a second round of screening for eligibility, further 195 were excluded since 36 papers full text could not be retrieved and another 76 papers with the same cohort. There were also 74 papers excluded because they did not match the study outcome. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] guidelines in reporting the results (Figure 1).

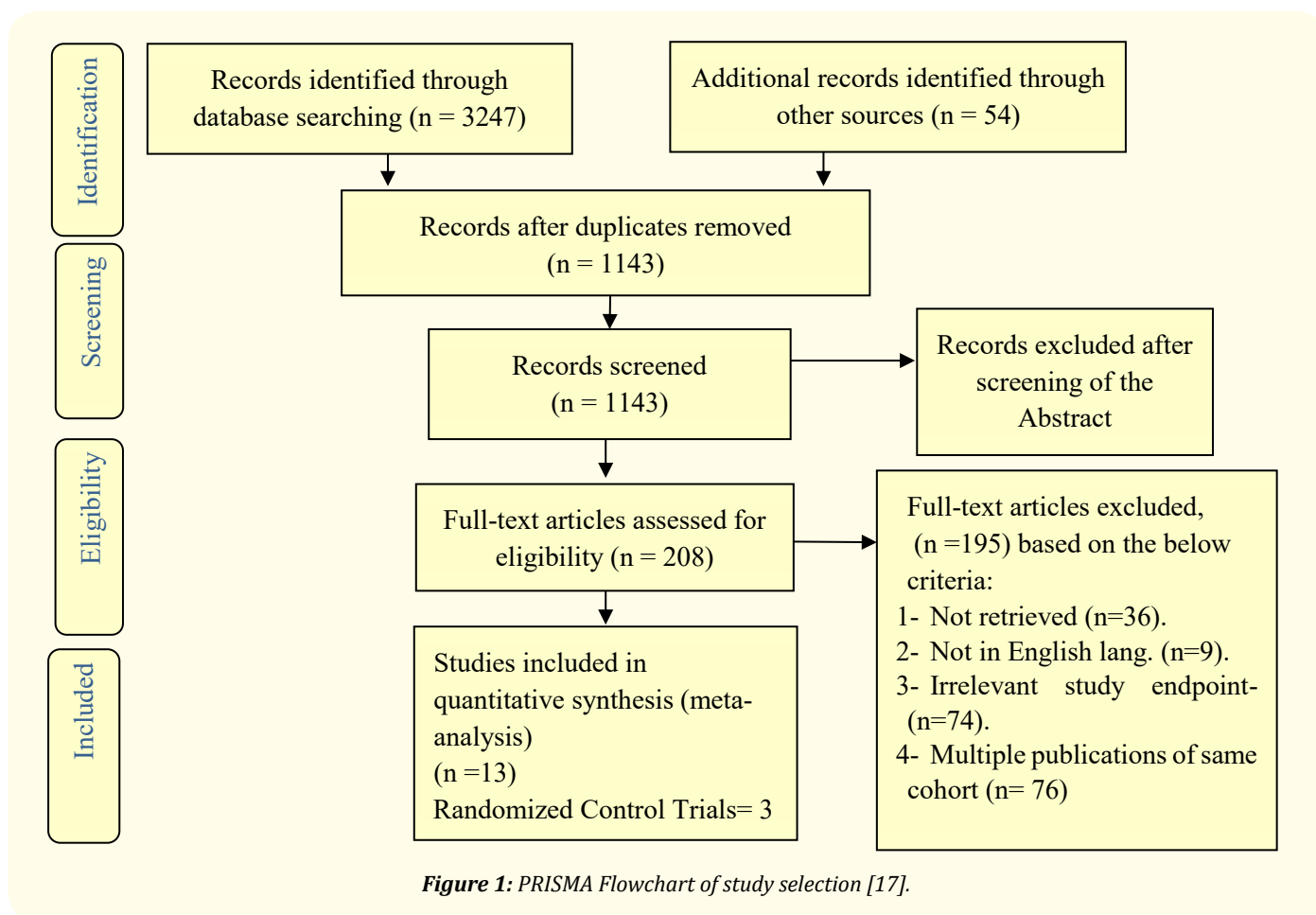


Figure 1: PRISMA Flowchart of study selection [17].

Finally, 13 [18-30] studies were included; 3 RCTs, 3 Prospective, and 7 retrospective studies.

Most studies included pregnancies at risk for FNAIT based on a history of FNAIT, additionally specified as with ICH, PLT count < 100 × 109/L, PLT count < 50 × 109/L, or with signs of bleeding, or based on another female family member with NAIT or recurrent spontaneous

miscarriages. It was observed that the earliest that fetal blood was sampled was in gestational week 16 but most commonly, sampling began in weeks 20 or 22. Of the 16 studies performing IUPT, 8 reported a fetal PLT count threshold to infuse PLTs. HPA-1a was the predominant cause of FNAIT in all articles, ranging from 72% to 100% of reported patients.

Characteristics of each individual study, intervention and outcomes (Antenatal management" IVIG and corticosteroids and FBS/IUPT" Perinatal outcome "ICH, Neonatal PLT count and mortality", are detailed in Table 1 whilst Treatment-related complications are interpreted in Table 2.

Study Design	Authors	N	Study Arms (risk group in case of stratification)	ICH in sibling, n (%)	FBS, n (%)	IUPT, n (%)	FBS/IUPT-related AE, n (%)	Duration IVIG, wk, mean (range)	SE IVIG/steroids, n (%)	ICH, n (%)	Mean PLTs × 10 ⁹ /L	PLT < 50 × 10 ⁹ /L, n (%)	Mortality, n (%)
Randomized controlled trials	Bussel JB., <i>et al</i> [18], 1996	28	IVIG*	6 (21)	All	0	5 (9)	10	0	0	96	<30 6 (21)	5 (9)
		26	IVIG +steroids	4 (15)	All	0		11	2 (8)	0	110	<30 5 (19)	
	Berkowitz RL., <i>et al.</i> [19], 2006	40	IVIG (all)	4 (10)	All	0	11 (14)	NR	NR	3	104	NR	4 (5)
		19	IVIG +Steroids (high)	3 (16)	All	0		NR	NR		99	NR	
		20	Steroids (standard)	0	All	0		NA	NR		108	NR	
	Berkowitz RL., <i>et al.</i> [20], 2007	37	IVIG 2 g	0	All	0	2 (5)	16 (11-20)	12 (32)	1	169	5 (14)	0
36		IVIG 1 g + steroids	0	All	0	2 (6)	16 (12-19)	13 (33)	1	134	4 (11)	0	
Prospective studies	Lynch L., <i>et al.</i> [21], 1992	9	IVIG	5 (56)	All	1 (11)	NR	NR	NR	0	57	4 (44)	NR
		9	IVIG + steroids	3 (33)	8 89)	0	NR	NR	5 (56)	0	64	3 (33)	NR
	Silver RM., <i>et al.</i> [22], 2000	8	IVIG	3 (30)	All	NR	2 (20)	12 (3-16)	NR	0	NR	1 (13)	0
		2	Fetal IVIG		All	NR		2 (1-2)	NR	0	NR	2 (100)	0
	Radder CM., <i>et al.</i> [23], 2004	37	IVIG ± IUPT	8 (19)	26(70)	26(70)	0	5 (2-15)	NR	0	67	17 (46)	0
13		FBS ± IUPT	All		9 (69)	2 (22)	NA	NA	0	32	7 (54)	1 (8)	
Retrospective Studies	Murphy MF., <i>et al.</i> [24], 1994	8	IVIG + IUPT ± steroids	6 (75)	All	6 (100)	1 (13)	9 (4-17)	NR	1	340	0	2 (25)
		7	IUPT ± steroids	5 (71)	All	7 (100)	0	NA	NR	2	305	0	1 (14)
	Kornfeld I., <i>et al.</i> [25], 1996	4	IVIG + IUPT	1 (25)	All	4 (100)	1 (25)	NR	0	0	182	0	1 (25)
		6	IVIG	1 (17)	All	0	1 (17)	NR	0	0	98	2 (33)	1 (17)
	Sainio S., <i>et al.</i> [26], 1999	11	IVIG ± IUPT*	1 (9)	All	9 (82)	2 (18)	6 (1-12)	1 (9)	0	109	5 (45)	0
		4	IUPT	0	All	4 (100)	2 (50)	NA	NA	0	76	2 (50)	0
	Birchall JE., <i>et al</i> [27], 2003	18	IVIG ± IUPT*	6 (60)	All	6 (33)	3 (17)	9 (1-19)	1 (6)	1§	81	6 (33)	0
		31	IUPT weekly	11 (42)	All	31 (100)	10 (30)	NA	NA	2§	NR	NR	3 (10)
		7	FBS ± single IUPT	0	All	5 (71)	2 (29)	NA	NA	0	NR	NR	0
	van den Akker ES., <i>et al.</i> [28], 2007]	53	IVIG (all)	5 (9)	0	0	NA	8 (2-24)	NR	0	125	10 (19)	0
		33	FBS + IVIG (all)	11 (33)	All	NR	3 (7)	6 (2-21)	NR	0	174	0	1 (3)
		13	FBS + IUPT (standard)	0	All	13 (100)	0	NA	NA	0	145	3 (23)	0
	Bussel JB., <i>et al.</i> [29], 2010	5	IVIG 1 g (high + very high)	5 (100)	All	1 (17)	3 (8)	15 (7-25)	NR	1	165	0	0
		19	IVIG 1 g + steroids (all)	19 (100)	All	0		12 (5-25)	NR	3	85	6 (40)	2 (11)
4		IVIG 2 g (all)	4 (100)	All	0	22 (18-25)		NR	0	112	0	0	
9		IVIG 2 g + steroids (all)	9 (100)	All	0	23 (18-27)		NR	1	135	0	0	
Mechoulan A., <i>et al.</i> [30], 2011	17	IVIG	5 (29)	9	0	1 (11)	12	NR	0	68	10 (59)	0	
	6	IVIG + steroids	0	0	0	NA	7	NR	0	78	4 (67)	0	

Table 1: Summary of the key outcomes of the included studies.

Authors+ Year of Publication	AEs in FBS/IUPT n/N (%)*	Complications after FBS or IUPT (n)	SEs in IVIG n/N (%)*	Reported SEs in IVIG treatment (n)	SEs in steroids n/N (%)*	Reported SEs in steroid treatment (n)
Bussel JB., <i>et al.</i> [18], 1996	5/59 (9)‡	Fetal or neonatal death after exsanguination (5)‡	0/54	None	2/26 (8)	Oligohydramnios (2) dexamethasone 1.5 mg - dexamethasone 4.5 mg
Berkowitz RL., <i>et al.</i> [19], 2006	11/79 (14)	Fetal death (1); neonatal death (1); emergency CS or delivery (10); <34 wk (NR); due to fetal distress (8); streaming (1); PROM (1)	NR	NR	NR	NR
Berkowitz RL., <i>et al.</i> [20], 2007	4/74 (5)	Emergency CS (4); <34 wk (3); due to fetal distress (2); PROM (2)	NR	Rash (1) discontinued IVIG, headache, fatigue†	NR	Gestational diabetes (7), insomnia, mood swings†
Lynch L., <i>et al.</i> [21], 1992	NR	NR	NR	NR	5/9 (56)	Oligohydramnios (4) dexamethasone 5 mg
Silver RM., <i>et al.</i> [22], 2000	2/10 (20)	Emergency CS due to insertion bleeding (2), <34 wk (1)	NR	NR	NA	NA
Radder CM., <i>et al.</i> [23], 2004	2/40 (5)	Neonatal death after fetal distress (1); emergency CS due to exsanguination (1)	NR	NR	NR	NR
Murphy MF., <i>et al.</i> [24], 1994	1/15 (7)	fetal death due to cord hematoma (1)	NR	NR	NR	NR
Kornfeld I., <i>et al.</i> [25], 1996	2/10 (20)	Pregnancy loss at 16 wk's gestation (1); neonatal death due to chorioamnionitis at 25 wk (1);	0/10	None	NA	NA
Sainio S., <i>et al.</i> [26], 1999	4/15 (27)	Emergency CS or delivery (4); <34 wk (1); due to fetal distress (3); acute amnionitis after ROM (1)	1/11 (9)	Headache and tachycardia (1), continued IVIG	NR	NR
Birchall JE., <i>et al.</i> [27], 2003	15/38 (39)	Fetal death (2); after exsanguination (1); emergency CS/delivery (13); <34 wk (6); due to fetal distress (6), infection (1), technical difficulties (3), cord spasm or thrombosis (2), placental artery bleeding (1)	1/18 (6)	Headache and tachycardia (1), continued IVIG	NR	NR
van den Akker ES., <i>et al.</i> [28], 2007	3/99 (3)	Perinatal death (1); emergency CS due to fetal distress (3); <34 wk (0)	NR	NR	NA	NA
Bussel JB., <i>et al.</i> [29], 2010	4/37 (11)	Emergency CS or delivery (4); <34 wk (NR); due to fetal distress (3); insertion bleeding (1)	NR	NR	NR	NR
Mechoulan A., <i>et al.</i> [30], 2011	1/9 (11)	Emergency CS due to fetal distress (1); <34 wk (0)	NR	NR	NR	NR

Table 2: Complications of antenatal treatment.

Key Outcome measures and abbreviations:

- PLT count: Platelets Count ($<100 \times 10^9/L$ and PLT count $<50 \times 10^9/L$)
- FBS: Fetal Blood Sampling
- ICH: Intracranial Hemorrhage
- IVIG: Intravenous Immunoglobulin
- IUPT: Intrauterine Platelet Transfusions

Discussion

This review suggests that noninvasive treatment strategies such as IVIG are a safe and effective option for the antenatal management of pregnancies complicated by NAIT, with a lower complications rate in comparison to FBS and/or IUPT. Nevertheless, the gestational age at which antenatal IVIG treatment should begin in FNAIT has not been well defined yet it was observed that an earlier start of IVIG treatment will not necessarily result in a linear increase in the amount of immunoglobulin G (IgG) transported to the fetus [31]. The amount of IgG that traverses the placenta depends on gestational age (with the greatest placental transport taking place in the third trimester), the IgG subclass, maternal IgG levels, and placental integrity [31].

The severity of the disease in previous pregnancies can be a key determinant before making treatment decisions.

In cohort analyses performed by Bussel, *et al.* [29] and Van der Lugt, *et al.* [32], pregnancies were divided into risk groups based on the only established risk factor for recurrent ICHs [33]:

1. High risk: siblings have ICH
2. Standard risk: siblings have no ICH
3. High risk, very high risk, and extremely high risk: and when the ICH occurred in pregnancy.

The onset of initiation of IVIG treatment was dependent on the abovementioned classification, and the dosage used banked on the presumption that ICH recurred in 79% of subsequent pregnancies [23]. However, one study [34] of 43 cases of ICH suggested that suggested that in order to reduce the risk of recurrent ICHs in subsequent pregnancies, IVIG should be initiated before 20 weeks' gestation.

IVIG recommended dosage

It's not clear if the commonly used dose of 1 g/kg per week is the best treatment for all FNAIT pregnancies, or this could be reduced or increased in certain subgroups.

Data from an RCT conducted by Paridaans NP, *et al.* [35] and retrospective data provided by Van Der Lugt, *et al.* [32] showed that the lower dose of 0.5 g/kg per week appeared not to be inferior to the 1 g/kg per week IVIG in standard risk (i.e. a previous sibling that did not have an ICH) populations. Given the dose-related side effects and costs, a dose of 0.5 g/kg per week could be regarded as suitable for these women. A limited number of patients were treated with the lower dose, and therefore more data are probably required to change practice.

Conversely, higher doses (i.e. 2 g/kg per week) have also been used, but the studies analyzed were limited by adequately comparable treatment arms [29].

The use of IVIG in pregnancies at risk for FNAIT is still off-label, and the possible immunostimulative or immunosuppressive effect of exposing the maturing fetal immune system to IVIG has not been adequately addressed. One cohort study by Radder, *et al.* [36] attempted to address this by examining the neurodevelopmental outcome of 50 children at a median age of 5 years, of which 37 were exposed to IVIG during fetal life. A higher incidence of otorhinolaryngological and hearing disability in the group that did not receive IVIG was found.

IgG, IgG subclass, IgA, and IgM levels were comparable between groups. A trend was found between high plasma IgE levels and in utero IVIG exposure; nonetheless, no difference in eczema or allergies was observed between the 2 groups. Although, based on this small cohort study, in utero exposure to IVIG seems to have no clinically apparent adverse effects in early childhood, further immunological research with a larger group of patients is needed to fully answer this question.

The benefit of adding corticosteroids to IVIG is unclear. One study found improvement in PLT counts (defined as a PLT count $>25 \times 10^9/L$ at second sampling, an increase by $>10 \times 10^9/L$ compared with the first sampling, or a PLT count $>40 \times 10^9/L$ that was not decreased by $>10 \times 10^9/L$) [16]. The remaining studies that compared treatment with IVIG to IVIG with steroids did not show significant differences in the PLT count, ICH, or mortality [18-21,29]. However, more data from RCTs comparing IVIG to IVIG with steroids that include a sufficient control group that are needed to reach any well-founded conclusions.

Bottom-line, in order to establish a significant improvement in the treatment and prevention of NAIT, physicians need to manage to prevent index cases, a strategy that was proven to be highly successful in hemolytic disease of the fetus and newborn, caused by the red blood cell counterpart of FNAIT. For that to happen, population-based screening programs are needed so as to identify first pregnancies at risk in time to start effective antenatal prophylaxis or treatment.

The result and conclusion of the present review are concurrent with a systematic review performed by Winkelhorst D, *et al* [16].

Conclusion

There is a strong body of evidence suggesting that the optimal approach for management of NAIT is indeed a noninvasive approach, involving a weekly administration of IVIG, whether alone or accompanied with corticosteroids.

Nevertheless, the optimal dose and start of the treatment, there are insufficient data to recommend a specific gestational age or a specific dose. However, available data supports:

- Very High risk: a higher dose of IVIG (i.e. 2 g/kg per week) with or without corticosteroids, depending upon severity.
- High-risk pregnancies (sibling suffered from an ICH) with a dose of 1 g/kg per week of IVIG, started between 12 and 20 weeks' gestation.
- Standard risk pregnancies (sibling didn't suffer from an ICH), the data supports starting treatment between 20 and 24 weeks' gestation and the use of IVIG at a dose of 1 g/kg per week with or without steroids.
- Lower risk: might allow the use of a lower dose of IVIG (i.e. 0.5 g/kg per week).

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