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Fetal and Neonatal Alloimmune Thrombocytopenia: evidence based screening

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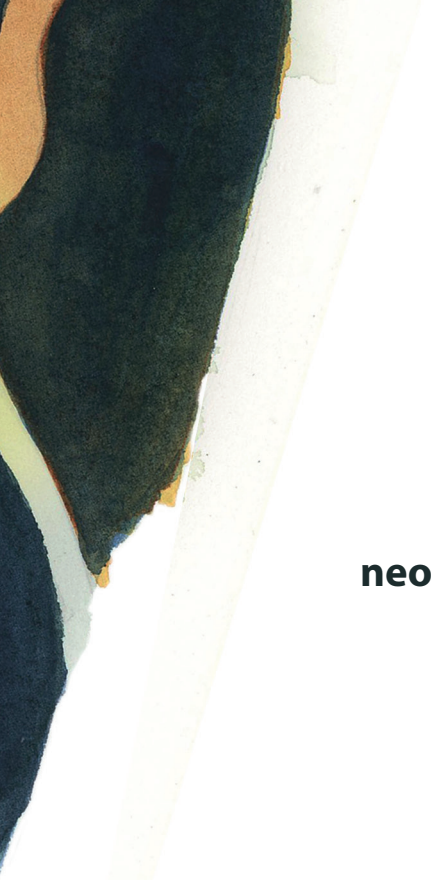

Chapter 5

Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review

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Abstract

Several strategies can be used to manage fetal or neonatal alloimmune thrombocytopenia (FNAIT) in subsequent pregnancies. Serial fetal blood sampling (FBS) and intrauterine platelet transfusions (IUPT), as well as weekly maternal IV immunoglobulin infusion (IVIg), with or without additional corticosteroid therapy, are common options, but the optimal management has not been determined. The aim of this systematic review was to assess antenatal treatment strategies for FNAIT. Four randomized controlled trials and 22 nonrandomized studies were included. Pooling of results was not possible due to considerable heterogeneity. Most studies found comparable outcomes 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. FBS or IUPT resulted in a relatively high complication rate (consisting mainly of preterm emergency cesarean section) of 11% per treated pregnancy in all studies combined. Overall, noninvasive management in pregnant mothers who have had a previous neonate with FNAIT is effective without the relatively high rate of adverse outcomes seen with invasive strategies. This systematic review suggests that first line antenatal management in FNAIT is weekly IVIg administration, with or without the addition of corticosteroids.

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) may lead to severe bleeding complications such as intracranial hemorrhage (ICH), in the fetus or newborn. Thrombocytopenia is caused by maternal alloantibodies against human platelet (PLT) antigens (HPAs) resulting from maternal alloimmunization after exposure to paternally derived antigens on fetal PLTs. The most commonly involved are HPA-1a alloantibodies, which are responsible for approximately 80% of FNAIT cases.[1,2] Not only do these maternal alloantibodies cause destruction and inhibit the production of fetal PLTs, they are also thought to affect vascular integrity and angiogenesis, resulting in an increased risk of intracranial and extracranial bleeding complications in fetuses and neonates and potentially intrauterine and perinatal death.[3-6]

In the absence of population-based screening programs, the diagnosis of FNAIT is usually made after an incidental finding of neonatal thrombocytopenia or because of bleeding complications ranging from bruising or petechiae to intracranial hemorrhage in the fetus or newborn.

Consequently, with an estimated recurrence rate of 79% of severe bleeding complications, the current challenge is to determine the best management strategy of subsequent pregnancies in women with a history of FNAIT with the goal of preventing these complications and avoiding maternal toxicities.[7] To avoid unnecessary interventions and anxiety, paternal genotyping should always be performed for the HPA involved in the preceding FNAIT. In case of paternal heterozygosity, maternal-fetal incompatibility should be determined either using amniocentesis or assessing cell-free fetal DNA, when HPA-1a is involved.

One of the first prenatal treatment strategies was ultrasound-guided fetal blood sampling (FBS) and intrauterine platelet transfusion (IUPT).[8] This technique, used for the treatment of fetal anemia, was applied to fetuses with thrombocytopenia and involved the transfusion of PLTs. Cordocentesis in the presence of thrombocytopenia may, however, lead to fetal bradycardia, tamponade of the cord and bleeding complications in the fetus including exsanguination. In addition, given the short life span of transfused PLTs, transfusions are needed regularly, increasing the overall risk of fetal loss.[9] The first non-invasive treatment, maternal infusion of intravenous immunoglobulin (IVIg) was reported in 1988, after which IVIg rapidly gained ground as a standard antenatal treatment strategy for FNAIT as have corticosteroids.[10] Prolonged use of IVIg and corticosteroids during pregnancy are associated with adverse effects as well. Although the side effects of IVIg are usually mild, hemolytic anemia, renal failure, aseptic meningitis and thrombotic complications may occur.[11,12] Corticosteroids are associated with hypertension and diabetes. Both agents can affect the quality of life of patients.[12]

No international consensus on the optimal antenatal management of FNAIT exists, and numerous strategies, non-invasive as well as invasive, are applied in different centers that specialize in antenatal therapy. Because FNAIT is a rare disease, systematically reviewing the literature to determine the evidence to support antenatal treatment options can inform practice. Hence, we performed a systematic review of all available literature on antenatal management strategies, to inform and assist in the development of guidelines.

Methods

Data Sources

This review was performed according to the PRISMA guidelines.[13] With the assistance of a medical research library specialist, an electronic search strategy was developed, and applied to databases Medline, EMBASE and Cochrane Library from 1946 to December 2015 (supplemental Appendix, available on the Blood Web site). Reference lists were cross-checked for relevant citations.

Study Selection and data extraction

Citations were reviewed by 2 reviewers to identify studies that met the following inclusion criteria: (1) original study; (2) included ≥5 pregnant women with pregnancies at risk for FNAIT or fetuses/neonates diagnosed with FNAIT; (3) treated with either IVIg, steroids or IUPT; (4) included any of the outcomes: intracranial hemorrhage and fetal/neonatal PLT count; and (5) published in the English language. When there was a disagreement, the full report was retrieved and independent assessment was repeated. Disagreements for inclusion were resolved by consensus. For articles that were published more than once and contained the same FNAIT population, only the study with the largest number of women and the most complete data extraction was included. Data extraction was performed by 2 authors according to a predetermined standardized format of study characteristics, outcome data and complications of interventions (Table 5.1).

Risk of bias was assessed according to The Cochrane Collaboration's tool.[14] for randomized studies, and Newcastle-Ottawa Scale (NOS)[15] for nonrandomized studies. The Newcastle-Ottawa Scale is based on 3 parameters: selection, comparability, and outcome (Table 5.2). For the parameter selection, we assessed whether the exposed cohort was representable for the FNAIT population (defined as HPA incompatible pregnancies), if the patient enrollment was consecutive, and if ICH was absent at start of the treatment. The parameter comparability was met if cohorts had a comparable proportion of siblings with ICH. For the parameter outcome of the Newcastle-Ottawa Scale, we assessed if the outcome of ICH was assessed by cranial ultrasound, if the follow-up was adequate (neonatal instead of fetal PLT count) and lastly, if neonatal PLT count and ICH data were available for all subjects.

Data Analysis

Due to considerable methodological heterogeneity of the studies, a descriptive review of all included studies was performed rather than a meta-analysis. In 2011, a Cochrane review of part of the included RCTs was performed by Rayment et al,[16] who also did not pool data.

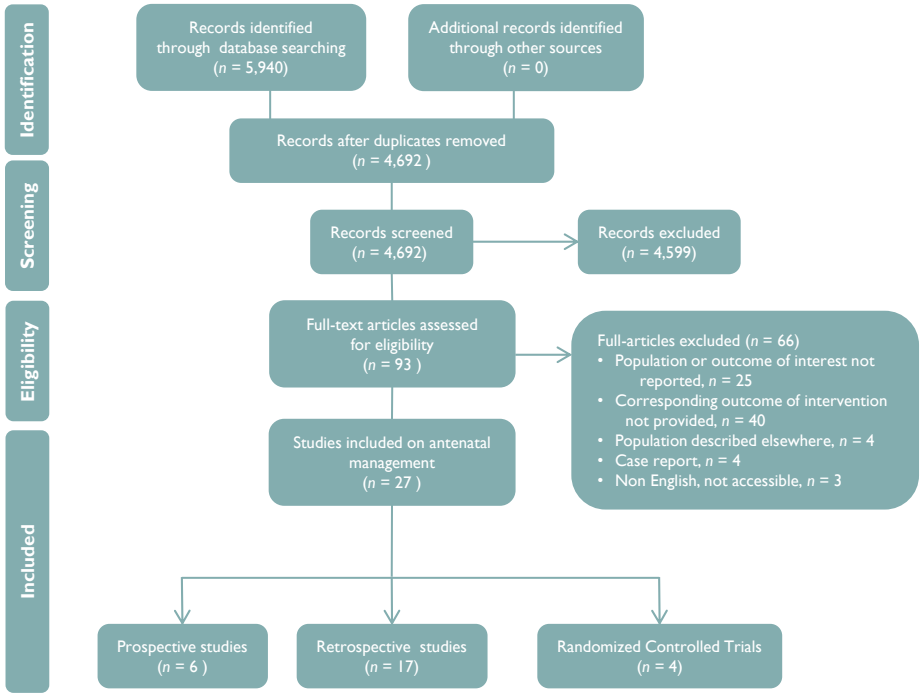


Figure 5.1 – Flowchart of search strategy

Table 5.1 – Study Outcomes

First author, year	**Study arms** (risk group in case of stratification)	***n***	**ICH in sibling** *n* (%)	**FBS** *n* (%)	**IUPT** *n* (%)
Randomized Controlled Trials					
Paridaans, 2015[30]	IVIG 0.5g	12	0	0	0
	IVIG 1g	11	0	0	0
Berkowitz, 2007[37]	IVIG 2g	37	0	All	0
	IVIG 1g + steroids	36	0	All	0
Berkowitz, 2006[35]	IVIG (all)	40	4 (10)	All	0
	IVIG + steroids (high)	19	3 (16)	All	0
	Steroids (standard)	20	0	All	0
Bussel, 1996[20]	IVIG§	28	6 (21)	All	0
	IVIG + steroids	26	4 (15)	All	0
Prospective Studies					
Kanhai, 2006[17]	IVIG ± IUPT	7	7 (100)	3 (43)	3 (43)
Bertrand, 2006[39]	IUPT pre-delivery	2	0	All	2 (100)
	IVIG ± IUPT	4	0	2 (50)	2 (50)
	IVIG + steroids	13	2 (15)	1 (8)	1 (8)
Radder, 2004[18]	IVIG ± IUPT	37	8 (19)	26 (70)	26 (70)
	FBS ± IUPT	13		All	9 (69)
Silver, 2000[23]	IVIG	8	3 (30)	All	NR
	Fetal IVIG	2		All	NR
Lynch, 1992[22]	IVIG	9	5 (56)	All	1 (11)
	IVIG + steroids	9	3 (33)	8 (89)	0
Retrospective Studies					
van der Lugt, 2015[31]	IVIG 1g (all)	5	2 (40)	0	0
	IVIG 0.5g (standard)	17	0	0	0
Bertrand, 2011[32]	IVIG	27		0	0
	IVIG + steroids	54	9 (14)	0	0
	Steroids	11		0	0
Mechoulan, 2011[24]	IVIG	17	5 (29)	9	0
	IVIG + steroids	6	0	0	0
Bussel, 2010[19]	IVIG 1g (high, very high)	5	5 (100)	All	1 (17)
	IVIG 1g + steroids (all)	19	19 (100)	All	0
	IVIG 2g (all)	4	4 (100)	All	0
	IVIG 2g + steroids (all)	9	9 (100)	All	0
Giers, 2010[21]	Fetal IVIG + IUPT	10	NR	All	10 (100)

	FBS/IUPT Related AE *n* (%)	**Duration IVIG in wks** mean (range)	**SE IVIG/ steroids** *n* (%)	**ICH** *n* (%)	**Mean PLTs** $\times 10^9$/L	**PLT <50 $\times 10^9$/L** *n* (%)	**Mortality** *n* (%)
	NA	10 (7-11)	0	0	81	3 (25)	0
	NA	11 (7-12)	0	0	110	4 (36)	0
	2 (5)	16 (11-20)	12 (32)	1	169	5 (14)	0
	2 (6)	16 (12-19)	13 (33)	1	134	4 (11)	0
		NR	NR		104	NR	
	11 (14)	NR	NR	3	99	NR	4 (5)
		NA	NR		108	NR	
	5 (9)	10	0	0	96	<30 6 (21)	5 (9)¶
		11	2 (8)	0	110	<30 5 (19)	
	NR	17 (8-21)	NR	0	28‡	7 (100)‡	0
	NR	NA	NA	0	210	0	0
	NR	17 (15-19)	NR	0	204	0	0
	NR	12 (5-20)	NR	0	118	4 (31)	0
	0	5 (2-15)	NR	0	67	17 (46)	0
	2 (22)	NA	NA	0	32	7 (54)	1 (8)
	2 (20)	12 (3-16)	NR	0	NR	1 (13)	0
		2 (1-2)	NR	0	NR	2 (100)	0
	NR	NR	NR	0	57	4 (44)	NR
	NR	NR	5 (56)	0	64	3 (33)	NR
	NA	NR	0	1*	63	8 (67)	0
	NA	NR	0	0	104	4 (33)	0
	NA	14	NR	0	89	12 (44)	0
	NA	14	NR	0	135	13 (27)	0
	NA	NA	NR	0	46	8 (73)	0
	1 (11)	12	NR	0	68	10 (59)	0
	NA	7	NR	0	78	4 (67)	0
		15 (7-25)	NR	1	165	0	0
	3 (8)	12 (5-25)	NR	3	85	6 (40)	2 (11)
		22 (18-25)	NR	0	112	0	0
		23 (18-27)	NR	1	135	0	0
	0	10 (6-14)	NR	0	189†	0	0

Table 5.1 – Continued

First author, year	Study arms (risk group in case of stratification)	*n*	ICH in sibling *n* (%)	FBS *n* (%)	IUPT *n* (%)
te Pas, 2007[25]	IVIG	13	5 (38)	NR	2 (15)
van den Akker, 2007[34]	IVIG (all)	53	5 (9)	0	0
	FBS + IVIG (all)	33	11 (33)	All	NR
	FBS + IUPT (standard)	13	0	All	13 (100)
Ghevaert, 2007[41]	IUPT ± IVIG ± steroids	40	NR	All	40 (100)
	IVIG and/or steroids	7	NR	NR	0
	No treatment	8	NR	NA	NA
Yinon, 2006[38]	IVIG	24	0	4 (17)	0
	No treatment	6	0	NA	NA
Tiblad, 2003[27]	IVIG §	9	5 (56)	0	0
	IUPT	3	0	All	3 (100)
	No treatment	6	2 (34)	0	0
Birchall, 2003[28]	IVIG ± IUPT§	18	6 (60)	All	6 (33)
	IUPT weekly	31	11 (42)	All	31 (100)
	FBS ± single IUPT	7	0	All	5 (71)
Sainio, 1999[42]	IVIG ± IUPT§	11	1 (9)	All	9 (82)
	IUPT	4	0	All	4 (100)
Kaplan, 1998[29]	IVIG	27	7 (26)	All	1 (4)
	Steroids	10	NR	All	NR
Kornfeld, 1996[33]	IVIG + IUPT	4	1 (25)	All	4 (100)
	IVIG	6	1 (17)	All	0
Murphy, 1994[40]	IVIG + IUPT ± steroids	8	6 (75)	All	6 (100)
	IUPT ± steroids	7	5 (71)	All	7 (100)
Wenstrom, 1992[36]	IVIG	2	NR	All	0
	IVIG + steroids	4	NR	All	0
Kaplan, 1988[25]	IUPT	4	1 (20)	All	5 (100)
	IVIG (5days) + IUPT	1	0	All	1 (100)

*** ICH occurred before start therapy; † Platelet count after IUPT; ‡ Platelet count before pre-delivery IUPT; § One or two patients also received steroids (supplementary table S5.1); ¶ Five fetuses exsanguinated and were excluded from analysis.**

FBS/IUPT Related AE *n* (%)	Duration IVIG in wks mean (range)	SE IVIG/ steroids *n* (%)	ICH *n* (%)	Mean PLTs $\times 10^9$/L	PLT <50 $\times 10^9$/L *n* (%)	Mortality *n* (%)
NR	NR	NR	0	83	6 (46)	0
NA	8 (2-24)	NR	0	125	10 (19)	0
3 (7)	6 (2-21)	NR	0	174	0	1 (3)
0	NA	NA	0	145	3 (23)	0
3 (8)	NR	NR	4	107	NR	6 (15)
1 (14)	NR	NR	0	7-219	NR	1 (14)
NA	NA	NA	0	6-84	NR	0
NR	15 (9-19)	NR	0	118	<30 2 (8)	0
NA	NA	NA	0	24	<30 4 (67)	0
NA	NR	NR	0	90	4 (44)	0
3 (100)	NA	NA	0	47	2 (100)	1 (33)
NA	NA	NA	1	9	4 (80)	1 (17)
3 (17)	9 (1-19)	1 (6)	1*	81	6 (33)	0
10 (30)	NA	NA	2*	NR	NR	3 (10)
2 (29)	NA	NA	0	NR	NR	0
2 (18)	6 (1-12)	1 (9)	0	109	5 (45)	0
2 (50)	NA	NA	0	76	2 (50)	0
NR	7 (2-15)	NR	2	69	13 (48)	2 (7)
NR	NA	NR	NR	NR	6 (60)	NR
1 (25)	NR	0	0	182	0	1 (25)
1 (17)	NR	0	0	98	2 (33)	1 (17)
1 (13)	9 (4-17)	NR	1*	340†	0†	2 (25)
0	NA	NR	2*	305†	0†	1 (14)
NR	14 (13-14)	0	0	60	1 (50)	0
NR	11 (5-20)	0	0	146	0	0
0	NA	NA	0	200	0	0
0	5	0	0	107	0	0

AE, adverse events; FBS, fetal blood sampling; ICH, intracranial hemorrhage; IVIG, intravenous immunoglobulins; IUPT, intrauterine platelet transfusion; NA, not applicable; NR, not reported; PLT, neonatal platelet count; SE, side effects.

Results

Study selection and characteristics

Our search strategy retrieved a total of 4692 single records that were screened for title and abstract, resulting in 93 full-text articles to be assessed for eligibility. Of those, 26 studies describing antenatal interventions in FNAIT were included (Figure 5.1), consisting of 4 RCTs, 5 prospective and 17 retrospective studies (Table 5.1; supplementary table S5.1).

Most studies included pregnancies at risk for FNAIT based on a history of FNAIT, additionally specified as with ICH,[17-19] PLT < 100×10^9/L,[20,21] PLT < 50×10^9/L[17,22] or signs of bleeding,[21,23,24] or based on another female family member with FNAIT[25] (1) or recurrent spontaneous miscarriages.[21] One study identified postnatal FNAIT patients from a population of thrombocytopenic neonates.[26] Five studies did not report testing for incompatibility between pregnant women and fetus as a condition for inclusion in their study.[21,22,27-29] FBS was performed in all but 3 studies.[30-32] The earliest that fetal blood was sampled was in gestational week 16,[33] but most commonly began in weeks 20 or 22. Of the 16 studies performing IUPT, 8 reported a fetal PLT count threshold to infuse PLTs.[17-19,21-23,28,34] HPA-1a was the predominant cause of FNAIT in all articles, ranging from 72 to 100% of reported patients.

The overall quality of the RCTs was considered adequate, with the lack of blinding presenting the highest risk of bias (Table 5.2). Comparing or pooling data from the nonrandomized cohort studies included in this review was hampered by differences in patient selection, in particular HPA type and severity of disease in the previous affected siblings.[21,24] In addition, relevant data were lacking in several studies, such as exclusion of ICH by ultrasound before starting treatment[35] and outcome data for all treatment arms (Table 5.2).

Antenatal management

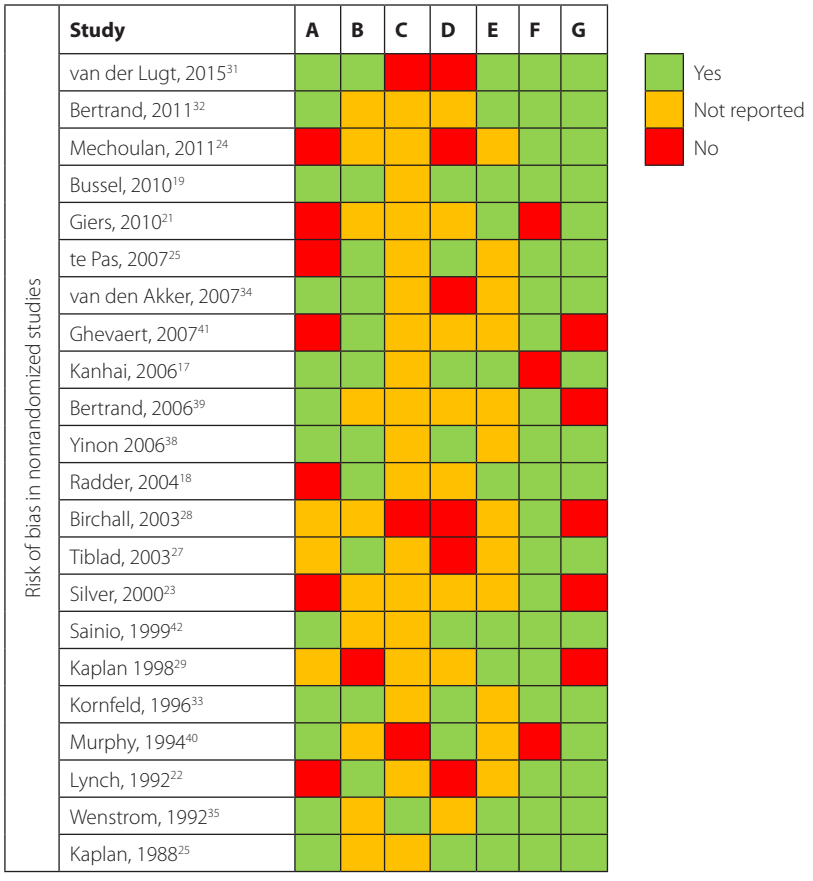
IVIg and corticosteroids

Of the 26 studies, 17 had a treatment arm with IVIg alone,[19,20,22-24,26,27,29-38] 3 studies with corticosteroids alone[29,35] and 11 had a study arm that combined IVIg and corticosteroid treatment.[19,20,22,24,32,35-37,39-41] There were 2 studies comparing all 3 arms.[35,39] In most studies, IVIg was administered at dose 1 g/kg/week.

Doses other than 1 g/kg/week in one or more cases were reported in 9 studies; 0.4 g/kg/day for 5 days,[25,40] 0.5 g/kg/week,[22,30,31] 0.8 g/kg/week,[28] 1g/kg/2weeks[24,32] and 2g/kg/week.[19,37] Two studies did not report the IVIg dose.[39,41] IVIg administration commenced as early as 10 weeks' gestation[19] and as late as 32 weeks gestation.[18] Two studies administered IVIg directly to the fetus.[21,23] Prednisone was used mainly at a dose of 0.5 mg/kg/day and dexamethasone at a dose of 1.5 mg/day. Specific dosages can be found in supplementary table S5.1.

Table 5.2 – Quality assessment of all 26 included studies

A. Random sequence generation (selection bias); **B.** Allocation concealment (selection bias); **C.** Blinding of participants and personnel (performance bias); **D.** Blinding of outcome assessment (detection bias); **E.** Incomplete outcome data (attrition bias); **F.** Selective reporting (reporting bias); **G.** Other bias.



A. Representative exposed cohort; **B.** Consecutive patient enrolment; **C.** Outcome absent at start study; **D.** Comparable proportion ICH in siblings; **E.** Outcome assessment; **F.** Adequate duration follow-up; **G.** Complete outcome data for all subjects.

FBS / IUPT

FBS was employed in 24 of the 26 studies. In 16 of these studies, FBS was combined with IUPTs. Five studies included a study arm with IUPT as sole treatment.[25,27,28,38,42] IUPT in combination with IVIg was used in three studies.[21,33,40] The remainder of IUPTs were performed in addition to a maternal therapy strategy of IVIg and/or steroids.[17-19,21,25,28,29,39,42] One study reported FBS and PLT transfusion in all fetuses prior to delivery.[21] Three studies did not report the number of IUPTs performed for their study groups.[22,29,34]

Risk stratification

Four studies stratified by risk group and altered interventions based on risk.[19,31,34,35] The stratification was either based on whether a sibling suffered an ICH[31,34,35], (high-risk), or on the timing of the ICH in the sibling (e.g. antenatal or postnatal) (supplementary table S5.1).[19]

Perinatal outcome

ICH

All but 1 study described the occurrence of ICH for all study arms.[29] In the 25 studies in which ICH was described, of the 839 pregnancies, a total of 24 ICHs were observed (3%). Seven of these occurred before treatment was started and 1 occurred in a group where no treatment was provided. Four ICHs were described by Ghevaert et al[41] as part of a large retrospective analysis of patients with suspected FNAIT investigated at a reference laboratory. Unfortunately, no additional information on previously affected pregnancies or on the patients themselves was provided. Of the remaining 12 patients, 5 were described by Bussel et al,[19] who reported different strategies of IVIg treatment in a high risk population (all siblings suffered from ICH). Three ICHs (2 grade III-IV hemorrhages resulting in fetal demise and 1 grade I hemorrhage) occurred after receiving 1 g/kg/week IVIg and 1 mg/kg/day prednisone, the fourth one was a grade II-III perinatal hemorrhage after delivery at 24 weeks' gestation and the last one was a grade I hemorrhage, both after a combination of 2 g/kg/week IVIg with 1 mg/kg/day prednisone. Furthermore, Berkowitz et al[35] described 2 neonates with ICHs that occurred in a low-risk population where none of the siblings suffered an ICH. Both ICHs were grade I subependymal hemorrhages, detected postnatally with normal neonatal PLT counts at birth (133 and 197 $\times$ 10^9/L) after treatment with 2 g/kg/week IVIg and 1g/kg/week IVIg with 1 mg/kg/day prednisone (treatment started at 20 weeks). Kaplan et al[29] described 27 pregnancies treated with 1 g/kg/week of IVIg, in which 2 fetuses had ICHs (one resulting in death and one resulting in neurological sequela), both in the group of nine patients with persistent low PLTs despite treatment. Lastly, Berkowitz et al[35] reported 3 ICHs, 2 grade I hemorrhages and 1 grade III ICH in a neonate that was delivered at 28 weeks' gestation because of persisting fetal bradycardia after FBS. Overall, no remarkable or significant differences could be identified in the occurrence of ICHs between various study arms.

Mortality

Two studies did not report mortality rates.[22,29] In the 24 remaining studies there was an overall mortality rate of 4% (30/821); of these, 17 were related to a FBS/IUPT (53%) and seven were due to ICH (22%). In 6 fetuses/neonates the cause could not be determined. Ghevaert et al[41] described a fetal loss due to acute amnionitis at 16 weeks gestation (not related to treatment) and Murphy et al[40] report a fetal loss after a severe fall of the mother on icy pavement.

Neonatal PLT Count

Twenty studies reported neonatal PLT counts. Of the other 6 studies, 1 study reported the fetal PLT counts before pre-delivery IUPT,[17] 2 studies reported fetal PLT counts after pre-delivery IUPT[21,40] and 3 studies did not provide the neonatal PLT counts for all study arms.[23,28,29] The mean neonatal PLT counts ($\times 10^9$/L), as well as the proportion of neonates with PLT counts below 50×10^9/L, varied widely between the studies ranging from 0% to 100%, regardless of the intervention.

Three studies compared IVIg treatment alone to corticosteroids alone.[29,32,35] Kaplan et al[29] found a higher proportion of neonates with a PLT count $<50 \times 10^9$/L in the group treated with steroids compared with IVIg only (60% vs 48%) as did Bertrand et al[32] (73% vs 44%). Berkowitz et al[35] found comparable mean PLT counts between those groups in patients; 104×10^9/L with IVIg only versus 108×10^9/L in the steroids only arm.

Three studies compared a non-invasive strategy (IVIg or IVIg and corticosteroids without FBS) to a strategy that included FBS and IUPT.[27,33,34] Kornfeld et al[33] showed that IVIg treatment alone improved neonatal PLT counts in 4 of 6 patients, however, only 1 pregnancy was high risk. Tiblad et al[27] reported a higher median PLT count of 90×10^9/L in the group treated with IVIg and a lower proportion of neonates with PLT counts below 50×10^9/L, 44% versus 100% in patients treated with IUPT. In addition, in the group treated with IVIg, 56% of the pregnancies were high risk, compared to 0% in the group treated with IUPT. Most recently, Van den Akker et al[34] compared 53 women treated with IVIg only to 13 women treated with IUPT only; median neonatal PLT counts were 125×10^9/L and 145×10^9/L, respectively.

Table 5.3 – Complications of antenatal treatment

First author, year	AE in FBS/IUPT *n*/N (%)*	Complications after FBS or IUPT (*n*)
Mechoulan, 2011[24]	1/9 (11)	Emergency CS due to fetal distress (1), <34 weeks (0)
Bussel, 2010[19]	4/37 (11)	Emergency CS or delivery (4), <34 weeks (NR) due to fetal distress (3), insertion bleeding (1)
van den Akker, 2007[34]	3/99 (3)	Perinatal death (1) Emergency CS due to fetal distress (3), <34 weeks (0)
Berkowitz, 2007[37]	4/74 (5)	Emergency CS (4), <34 weeks (3) due to fetal distress (2), ROM (2)
Berkowitz, 2006[35]	11/79 (14)	Fetal death (1). Neonatal death (1) Emergency CS or delivery (10), <34 weeks (NR) due to fetal distress (8), streaming (1), PROM (1)
Radder, 2004[18]	2/40 (5)	Neonatal death after fetal distress (1) Emergency CS due to exsanguination (1)
Birchall, 2003[28]	15/38 (39)	Fetal death (2), after exsanguination (1) Emergency CS/delivery (13), <34 weeks (6) due to fetal distress (6), infection (1), technical difficulties (3), cord spasm or thrombosis (2), placental artery bleeding (10)
Silver, 2000[23]	2/10 (20)	Emergency CS due to insertion bleeding (2), <34 weeks (1)
Sainio, 1999[42]	4/15 (27)	Emergency CS or delivery (4), <34 weeks (1) due to fetal distress (3) acute amnionitis after ROM (1)
Bussel, 1996[20]	5/59 (9) ‡	Fetal or neonatal death after exsanguination (5) ‡
Kornfeld, 1996[33]	2/10 (20)	Pregnancy loss at 16 weeks gestation (1) Neonatal death due to chorioamnionitis at 25 weeks (1)
Murphy, 1994[40]	1/15 (7)	Fetal death due to cord hematoma (1)
Lynch, 1992[22]	NR	NR

AE, adverse events; CS, cesarean section; CTG, cardiotocogram; FBS, fetal blood sampling; IVIg, intravenous immunoglobulins; IUPT, intrauterine platelet transfusion; SE, side effects; PROM, rupture of membranes.

	SE in IVIg *n*/N (%)*	**Reported side effects in IVIg treatment** (*n*)	**SE in steroids** *n*/N (%)*	**Reported side effects in steroid treatment** (*n*)
	NR	NR	NR	NR
	NR	NR	NR	NR
	NR	NR	NA	NA
	NR	Rash (1) discontinued IVIG Headache, fatigue	NR	Gestational diabetes (7) Insomnia, mood swings
	NR	NR	NR	NR
	NR	NR	NR	NR
	1/18 (6)	Headache and tachycardia (1), continued IVIG	NR	NR
	NR	NR	NA	NA
	1/11 (9)	Headache and tachycardia (1), continued IVIG	NR	NR
	0/54	None	2/26 (8)	Oligohydramnios (2) in - Dexamethasone 1.5mg - Dexamethasone 4.5mg
	0/10	None	NA	NA
	NR	NR	NR	NR
	NR	NR	5/9 (56)	Oligohydramnios (4) in - Dexamethasone 5mg

*** number of reported complications (*n*) versus the total number of patients treated with this specific strategy (N); † Number of side effects reported, the total number of patients that reported a side effect is unclear; ‡ The complications occurring during this study were reported in detail elsewhere[40].**

Of the 8 studies comparing IVIg only with IVIg and corticosteroids, Berkowitz et al[35] identified comparable platelet counts between groups treated with IVIg only and IVIg with steroids (104×10^9/L and 99×10^9/L respectively). The same group of investigators[19] described management in 37 high-risk pregnancies. Four regimens, based on the timing of a ICH occurring in a previous pregnancy, were compared (Table 5.1 and supplementary table S5.1). No differences in neonatal PLT count between the treatment groups were identified (Table 5.1). Although Bertrand et al[32] reported a significant difference in the number of neonates that needed postnatal treatment (26% in the group treated with IVIg and steroids versus 59% in the group treated with IVIg only [$p = 0.01$]), no significant differences in mean neonatal PLT count or severe thrombocytopenia were observed. The remaining 5 studies reported comparable neonatal PLT counts in women treated with IVIg only and IVIg combined with corticosteroids as well.[20,22,24,36,37]

Of the 4 studies that compared different IVIg regimens, 2 found comparable neonatal PLT counts with doses of 0.5 g/kg/week, 1 g/kg/week and 2 g/kg/week.[19,30] Van Der Lugt et al[31] reported a non-significant, lower mean PLT count in five women treated with 1 g/kg/week (63×10^9/L) compared to 17 women treated with 0.5 g/kg/week (104×10^9/L).

Treatment-related complications

Of 24 studies in which FBS was performed with or without IUPT, 2 studies reported no procedure-related complications and 12 studies reported a total of 53 complications with a frequency ranging from 3% to 39% per treated pregnancy (Table 5.3). One study reported complications in more detail elsewhere.[20,43]

Overall, the proportion of treated cases with complications due to either FBS or IUPT was 11% (54 complications in 497 treated pregnancies). The most frequently described complication was the performance of an emergency cesarean section, mainly due to fetal distress (persisting bradycardia or fetal decelerations), of which approximately half resulted in a delivery before 34 weeks' gestation. Fourteen of the 54 complications resulted in a fetal or neonatal death (26%).

Of the 26 studies that used either IVIg or corticosteroids, 11 reported the side effects of the treatment. The most commonly reported side effect of dexamethasone treatment was the occurrence of oligohydramnios. Headache and rash were the most frequently reported side effects of IVIg treatment, leading to discontinuing of the treatment in only 1 patient.[37]

Discussion

Main findings

A non-invasive management approach in pregnancies complicated by FNAIT was found to be equally effective as compared with IUPT in preventing fetal and neonatal bleeding due to thrombocytopenia. Our analysis revealed a relatively high complication rate of antenatal management by FBS and IUPT of 11%, with 1 in 3 of these leading to fetal or neonatal loss. The most common non-invasive treatment administered to pregnant women was IVIg, primarily in a weekly dose of 1 g/kg. IVIg only had a 98.7% success rate for preventing ICH (4 ICHs occurred in 315 pregnancies).[16,17,19-24,26-32,34,35] This is consistent with the 97.3% found in the Cochrane analysis reported by Rayment et al[16], which included 37 pregnancies treated with IVIg only. However, none of the studies were powered to detect a significant difference in bleeding outcomes.

Strengths and limitations

Besides the obvious lack of randomized studies with an adequate control group (placebo or no treatment), the main limitation of our review is the heterogeneity of the extracted data from the primary studies. Although neonatal outcomes are generally well reported and appear quite homogenous, the crux of the heterogeneity is the diversity of study designs. First, there is an extensive variation in treatment strategies used, especially in different combinations. For example, Sainio et al[42] described 15 women treated with 6 different strategies (IVIG only, IVIg and steroids, IVIg and IUPT, IVIg and steroids and IUPT, as well as weekly IUPT or FBS only). Secondly, the dosage of specific treatments differed considerably (eg, prednisone was prescribed as 0.5 to 1 mg/kg/day as well as 10 mg, 20 mg, 30 mg and 60 mg per day). The interval and duration of therapeutic strategies also differed considerably between studies. For example, mean duration of IVIg treatment varied from 2 weeks[18,23] to 22 weeks.[19] Additionally, in 3 of the 4 RCTs, treatment intensification was applied to increase fetal PLT counts, which could have led to underestimation of the difference between treatment arms when comparing neonatal PLT counts.[20,35,37] Lastly, there was great variability in the risk of ICH when determined by the proportion of siblings with ICH not only between studies, but also between study arms.

The 2 most commonly used endpoints for studies are ICH and neonatal PLT counts. Whereas antenatal strategies target the prevention of bleeding complications in fetuses and neonates, preferably mortality and long-term neurodevelopmental impairment should be the gold standard outcomes. Because these outcomes are rare, most studies are not powered to detect significant differences between treatment strategies and must resort to using PLT counts as surrogate outcome measurements.

In this regard, there appears to be a correlation between PLT count and risk of bleeding, but this does not appear to be a linear relationship.[41] Although the neonatal PLT count appears to be a logical and best available surrogate outcome in evaluating antenatal treatment strategies, this parameter has limitations. Comparing treatment modalities based on mean or median PLT counts may therefore show some effect, but may not be meaningful clinically.[44] In addition, very low PLT counts were often found in fetuses or neonates without any bleeding. Although it is unclear to what extent animal studies can be used for understanding pathophysiology in humans, there is increasing evidence suggesting impairment of angiogenesis and endothelial integrity as a possible cause of increased bleeding tendency, leading to the assumption that thrombocytopenia is not the sole cause of bleeding complications in FNAIT.[3,45,46]

Our systematic review was designed to evaluate the effect of antenatal treatment options on neonatal outcome including neonatal PLT count, ICH and mortality, but it did not facilitate any conclusions on the need for centralized care, the optimal timing or mode of delivery; nor whether pre-delivery FBS should be performed to determine mode of delivery, neonatal brain imaging or the need for matched PLTs.

Ultimately, to our knowledge, this is the first systematically performed review that considers all available evidence, including randomized as well as nonrandomized studies. Despite the size and heterogeneity of the studies limiting the strength of this evidence, we used predefined outcome measures of all available evidence on antenatal management in pregnancies complicated by FNAIT.

Interpretation

This review suggests that non-invasive treatment strategies are safe and effective options for the antenatal management of pregnancies complicated by FNAIT, with a lower risk of severe complications compared with FBS and/or IUPT. The gestational age at which to start antenatal IVIg treatment in FNAIT has, however, not been well defined. It is reasonable to consider the severity of the disease in previous pregnancies when making treatment decisions. An earlier start of IVIg treatment will not necessarily result in a linear increase in the amount of IgG transported to the fetus.[47] 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.[47]

In cohort analyses performed by Bussel et al[19] and Van der Lugt et al[31], pregnancies were divided into risk groups based on the only established risk factor for recurrent ICH, whether the sibling had (high risk) or did not have (standard risk) an ICH and when the ICH occurred in pregnancy (high risk, very high risk, and extremely high risk).[48,49] The time of initiation of IVIg treatment was based on this stratification, and the dosage used relied on the presumption that ICH recurred

in 79% of subsequent pregnancies.[7] An analysis of 43 cases of ICH performed by Tiller et al[44] suggested that in order to reduce the risk of recurrent ICHs in subsequent pregnancies, IVIg should be initiated before 20 weeks gestation.

Whether the commonly used dose of 1 g/kg/week is the best treatment for all FNAIT pregnancies, or whether this could be reduced or increased in certain subgroups remains unclear. Data from the previously described RCT and retrospective data provided by Van Der Lugt et al[31] showed that the lower dose of 0.5 g/kg/week appeared not to be inferior to the 1 g/kg/week IVIG in standard risk (ie, 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/week could be regarded 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 (ie, 2 g/kg/week) have also been used but the studies analysed were limited by adequately comparable treatment arms.[19,37]

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,[18] 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 > 25×10^9L at second sampling, an increase by > 10×10^9L compared to the first sampling, or PLT > 40×10^9L that was not decreased by > 10×10^9L).[16,35] The remaining 8 studies comparing treatment with IVIg to IVIg with steroids did not show significant differences in the PLT count, ICH or mortality.[19,20,22,24,32,35-37] More data from randomized studies comparing IVIg to IVIg with steroids that include an adequate control group are needed to reach any firm conclusions.

To achieve a major improvement in the treatment and prevention of FNAIT, physicians need to be able 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 cell counterpart of FNAIT. In order to do so, population-based screening programs are needed to identify first pregnancies at risk in time to start effective antenatal prophylaxis or treatment.

In conclusion, this article represents a systematic review on the effectiveness of different antenatal treatment strategies in pregnancies complicated by FNAIT, aiming to prevent ICH and bleeding-related fetal/neonatal losses. Our summary provides the best available evidence that suggests that the optimal approach is a non-invasive approach, involving weekly administration of IVIg, with or without the addition corticosteroids. Regarding the optimal dose and start of the treatment, there are insufficient data to recommend a specific gestational age or specific dose. However, the data support the treatment of high-risk pregnancies (ie, sibling suffered from an ICH) with 1 g/kg/week IVIg, started between 12 and 20 weeks gestation. For standard risk pregnancies (ie, no sibling suffered from an ICH) the data support starting treatment between 20 and 24 weeks gestation, and to use IVIg 1 g/kg/week with or without steroids. Additional data, especially a reliable biomarker of severity in a patient known to be affected, might allow the use of a lower dose IVIg (ie, 0.5 g/kg/week) or, alternatively, a higher dose IVIg (ie, 2 g/kg/week) with or without corticosteroids, depending upon severity.

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Supplemental material

Supplementary table S5.1 – Study characteristics

First author, year, country, center	*n*	ICH sibling (%)	Identification of cases	HPA-1a *n*/N	GA first FBS
Randomized Controlled Trials					
Padriaans, 2015[27] Netherlands, MC	23	0/23	Previous FNAIT without ICH and incompatible fetus	22/23	None
Berkowitz, 2007[34] USA/ Canada, MC	74	0/74	Previous FNAIT and incompatible fetus	NR	32
Berkowitz, 2006[33] USA, MC	79	7/79 (9)	Previous FNAIT and incompatible fetus	74/79	20
Bussel, 1996[17] USA, MC	54	10/54 (19)	Previous FNAIT with fetal PLT < 100 and incompatible fetus	52/54	26
Prospective Studies					
Kanhai, 2006[14] Netherlands, SC	7	7/7 (100)	Previous FNAIT with ICH and incompatible fetus	7/7	Pre-delivery
Bertrand, 2006[36] France, SC	19	2/19 (11)	Previous FNAIT and incompatible fetus	19/19	24
Radder, 2004[15] Netherlands, SC	50	8/42 (19)	Previous FNAIT with PLT<50 or with ICH and incompatible fetus	37/42	29
Silver, 2000[20] USA, SC	10	3/10 (30)	Previous FNAIT with signs of bleeding and incompatible fetus	10/10	22-28
Lynch, 1992[19] USA, MC	18	10/18 (56)	Previous FNAIT with PLT<40	17/18	26
Retrospective Studies					
Lugt, 2015[28] Netherlands, SC	22	2/22 (9)	Previous FNAIT and incompatible fetus	19/22	None
Bertrand, 2011[29] France, MC	92	9/66 (14)	Previous FNAIT and incompatible fetus	92/92	None
Mechoulan, 2011[21] France, MC	23	7/21 (33)	Previous FNAIT with bleeding and incompatible fetus	23/23	22
Bussel, 2010[16] USA, MC	37	37/37 (100)	Previous FNAIT with ICH and incompatible fetus	35/37	20-24

	Indication IUPT	GA start IVIg	Dose IVIg (cases treated)	Corticosteroid dose (cases treated)	Risk stratification for outcome (cases treated)
	None	28	0.5g/kg/wk (12) 1g/kg/wk (11)	None	None
	None	20	1g/kg/wk (37) 2g/kg/wk (37)	Prednisone 0.5mg/kg/day (37)	None
	None	24	1g/kg/wk (79)	Prednisone 1mg/kg/day (39)	Standard: fetal PLT>20 (39) High: fetal PLT<20 or sibling ICH (40)
	None	26	1g/kg/wk (54)	Dexamethasone 1.5mg/day (26), 5 changed to: Prednisone 60mg/day (4)	None
	PLT<100	16	1g/kg/wk (7)	None	None
	NR	23	NR	13/19, not otherwise specified	None
	PLT<100 or PLT<50 IVIG	32	1g/kg/wk (37)	Prednisone 60mg/day for 3wks (1)	None
	PLT<150	NR	1g/kg/wk (8) Fetal 1g/kg (2)	None	None
	PLT<100	26	1g/kg/wk (17) 0.5g/kg/wk (1)	Dexamethasone 5mg/day (3), 3mg/day (2), 1.5mg/day (2) Prednisone 10mg/day (2)	None
	None	16 or 28	0.5g/kg/wk (17) 1g/kg/wk (5)	None	Standard: sibling no ICH (20) High: sibling ICH (2)
	None	NR	1g/kg/wk (81) 1g/kg/2wk (1)	Prednisone 0.5mg/kg/day (65)	None
	None	24	1g/kg/wk (22) 1g/kg/2wk (1)	6/23, not otherwise specified	None
	PLT<50	13, 16 or 20	1g/kg/wk (24) 2g/kg/wk (13)	Prednisone 1mg/kg/day (5)	Based on GA of ICH sibling High: perinatal (12) Very high: 28-36 wks (17) Extremely high: <28 wks (8)

Supplementary table S5.1 – Continued

First author, year, country, center		ICH sibling	Identification of cases	HPA-1a	GA first FBS
	n	(%)		*n*/N	
Giers, 2010[18] Germany, SC	10	NR	Previous FNAIT with PLT<100 and skin bleeding or miscarriage with high anti-HPA-1a titre	9/10	20
te Pas, 2007[23] Netherlands, SC	13	5/13 (38)	Thrombocytopenic neonates due to FNAIT	12/13	NR
vd Akker, 2007[31] Netherlands, SC	99	16/99 (16)	Previous FNAIT and incompatible fetus	76/85	NR
Gheveart, 2007[38] UK, SC	55	NR	Previous FNAIT and incompatible fetus	49/55	NR
Yinon, 2006[35] Israel, SC	30	0/30	Previous FNAIT and incompatible fetus	21/30	Pre-delivery
Tilblad, 2003[24] Sweden, SC	18	1/18 (1)	Previous FNAIT	17/18	NR
Birchall, 2003[25] UK, MC	56	12/49 (24)	Previous FNAIT due to anti-HPA-1a	55/55	25
Sainio 1999[39] Finland, SC	15	2/15 (13)	Previous FNAIT or anti-HPA-1a and incompatible fetus	13/15	25
Kaplan, 1998[26] Europe, MC	37	4/27 (15)	Previous FNAIT	37/37	22-28
Kornfeld, 1996[30] Canada, SC	10	2/10 (20)	Previous FNAIT and incompatible fetus	9/10	16-24
Murphy, 1994[37] UK, SC	12	11/12 (92)	Previous FNAIT and incompatible fetus	12/12	26
Wenstrom, 1992[32] USA, SC	6	NR	Previous FNAIT and incompatible fetus	5/6	20-32
Kaplan, 1988[22] France, SC	9	1/9 (11)	Previous FNAIT or sister with FNAIT and incompatible fetus	9/9	20-22

FBS, fetal blood sampling; FNAIT, fetal/neonatal alloimmune thrombocytopenia; GA, gestational age (weeks); HPA, human platelet antigen; ICH, intracranial hemorrhage; IUFD, intrauterine fetal demise; IUPT, intrauterine platelet transfusion; IVIg, intravenous immunoglobulins; MC, multi center; NR, not reported; PLT, platelet count; SC, single center.

	Indication IUPT	GA start IVIg	Dose IVIg (cases treated)	Corticosteroid dose (cases treated)	Risk stratification for outcome (cases treated)
	Pre delivery	20	Fetal 1g/kg/wk (10)	None	None
	NR	NR	1g/kg/wk (19)	None	None
	PLT<100 or PLT<50 IVIG	18	1g/kg/wk (86)	None	Standard: sibling no ICH (83) High: sibling ICH (16)
	NR	NR	NR	16/51, not otherwise specified	None
	None	18-24	1g/kg/wk (24)	None	None
	NR	15-28	1g/kg/wk (9)	Prednisone, dose not specified (1)	None
	PLT<20 or PLT<40	26	0.8g/kg/wk (18) 1g/kg/wk (1)	Prednisone 0.5mg/kg/day (2)	None
	NR	NR	1g/kg/wk (11)	Prednisone 20-30 mg/day (2)	None
	NR	NR	1g/kg/wk (27)	0,5mg/kg/day, not further specified (10)	None
	NR	NR	1g/kg/wk (10)	None	None
	NR	20	1g/kg/wk (7) 0.4g/kg 5days (1)	Prednisone 20mg/day (5)	None
	None	NR	1g/kg/wk (6)	Dexamethasone 1,5mg/ day (3), one switch to Prednisone 60mg/day (1)	None
	NR	35	0,4g/kg/day for 5 days (1)	None	None