44° CONVEGNO NAZIONALE di Studi di Medicina Trasfusionale
Rimini | Palacongressi, 3-5 maggio 2022
SIMTI

TROMBOCITOPENIA ALLOIMMUNE FETO-NEONATALE:

DIAGNOSI E GESTIONE CLINICA

Antonella Matteocci

A.O. S. Camillo – Forlanini

ROMA

naitbabies.org
neonatal alloimmune thrombocytopenia

La sottoscritta, **Antonella Matteocci** in qualità di Relatore

dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, ***NON È*** *in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.*

INTRODUCTION

Thrombocytopenia is a very common finding in the neonatal period, especially in critically ill and preterm newborn infants (NBIs). It is present in 1-5 % of babies at birth and in 20-50 % of critically ill newborns.

The current definition of thrombocytopenia, at any age, is a platelet count (PC) below 100 x 109 /L.
A PC below 50 x 109 /L is considered severe, which occurs in 0.1-0.5 % of cases.

There are three groups, based on the most common causes:

a) Intrauterine onset: immune thrombocytopenia, intrauterine infection , chromosomal abnormalities;
b) Early onset (less than 72 hours of life): placental insufficiency, perinatal asphyxia, perinatal infection, immune thrombocytopenia, disseminated intravascular coagulation;
c) Late onset (more than 72 hours of life): late-onset sepsis, necrotizing enterocolitis, amegakaryocytic thrombocytopenia, giant hemangioma.

Arch Argent Pediatr 2021

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

NAIT is uncommon, it is the primary cause of severe thrombocytopenia within 48 hours after delivery (<30.000/ul) and intracranial hemorrhage (ICH) in term newborns. It is reported in 40-50 % of first borns (75% at delivery).

The incidence of NAIT is 1 in every 1000-2000 live births.

Clinically significant intracerebral hemorrhage (ICH) occurs in 3 – 10 per 100 000 pregnancies within 96 hours after delivery.

The process of maternal IgG antibody transfer begins as early as 15 weeks' gestation targeting foreign HPA antigens that are paternally inherited, thereby eliciting platelet destruction in the fetus.

In some cases, a simultaneous suppression of megakaryocytopoiesis may also occur.

Infants with severe thrombocytopenia have a mortality rate of 10%, increasing to 33% with ICH.

Neonatal Alloimmune Thrombocytopenia, 2021

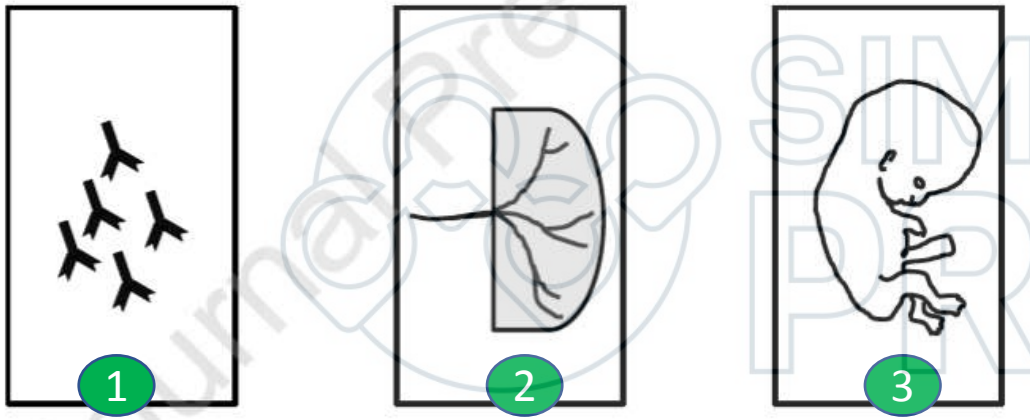
Prospects for risk stratification of anti-HPA-1a alloimmunized pregnant women

Transfusion and Apheresis Science, 31 December 2019

DOI: https://doi.org/10.1016/j.transci.2019.102709

Attributes of the maternal immune response, the feto-maternal interface and of the fetus that were correlated with the outcome (extent of thrombocytopenia or occurrence of intracranial hemorrhage) in anti-HPA-1a mediated fetal/neonatal alloimmune thrombocytopenia.

Figure 1

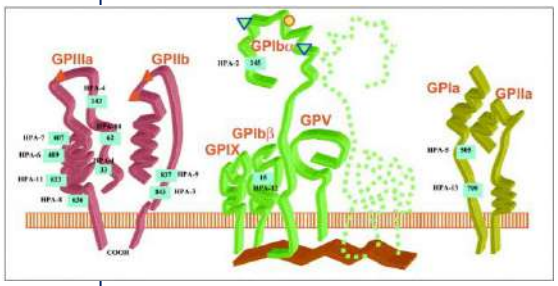


maternal
subtype
glycosylation
specificity
effector function: platelets
effector function: trophoblast
effector function: EC
antibody level

fetal-maternal interface
efficacy of transfer

intra-fetal
gender
C-reactive protein

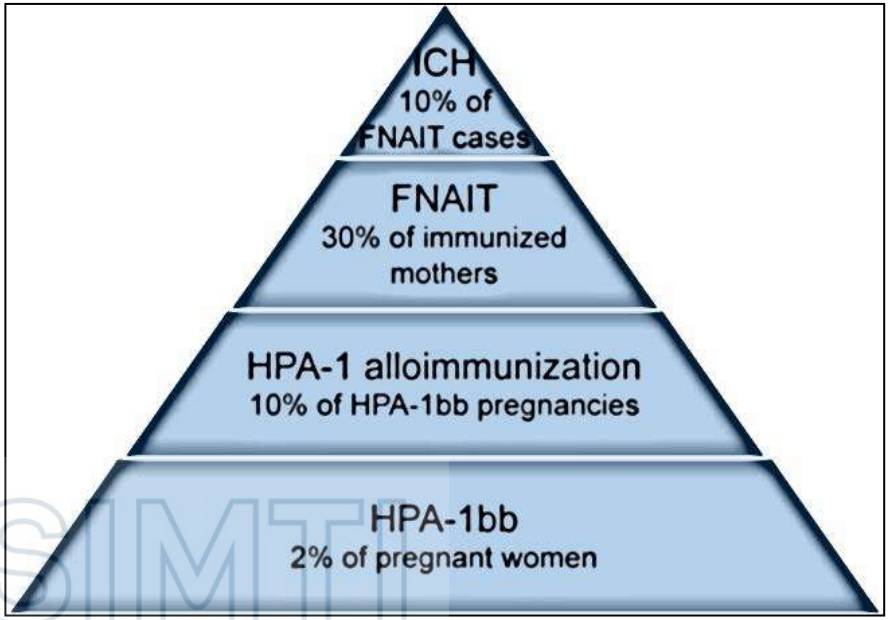
- 19 -



PATOGENESI DELLA FNAIT

Espressione antigeni piastrinici fetali :
***14-16 settimane* di gestazione**

Espressione su sinciziotrofoblasto:
I trimestre



HLA DRB3*01:01

- Alta affinità del peptide Leu33 sulla GP IIIa con il peptide del sito di presentazione di DRB3*0101

Fetal/neonatal alloimmune thrombocytopenia: a systematic review of impact of HLA-DRB3*01:01 on fetal/neonatal outcome

28 JULY 2020 • VOLUME 4, NUMBER 14 blood advances

HLA DRB3*01:01 Positive Predictive Value 17 – 35%
Negative Predictive Value 96-100%

Quadri severi di FNAIT in caso di ovodonazione
con neonato HPA 1 a/a
(procreazione medicalmente assistita)
Peterson et al, BJH 2013

Prospects for risk stratification of anti-HPA-1a alloimmunized pregnant women

Transfusion and Apheresis Science, 31 December 2019

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Anticorpi anti-HPA1a materni

No correlazione lineare tra piastrinopenia e ICH

QUANTITA'

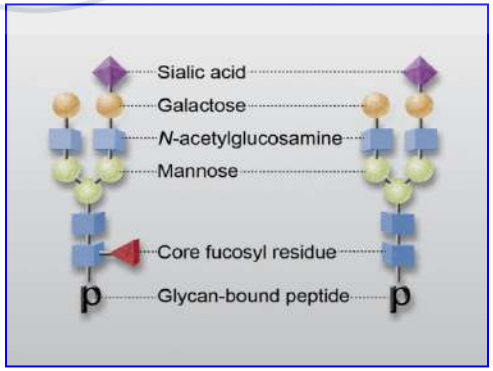
Concentrazione - Titolo

PPV 54%, NPV 95%

Non sempre correlazione tra titolo e piastrinopenia, tra titolo e ICH ??

QUALITA'

Sottotipo IgG:>IgG1
Grado fucosilazione
Specificità (aIIβ3, β3, av β3)
Tipi di legame con cellule(densità)
(piastrine feto-neonatali, trofoblasto, cellule endoteliali)



Anticorpi con piccole quantità di fucosio presentano un legame ad alta affinità con i recettori FcγRIIIa/b (aumentata fagocitosi e lisi). Correlano con maggiore severità della FNAIT e bassa conta piastrinica neonatale.

CLINICAL MANIFESTATIONS

Common clinical manifestations include ecchymosis, petechiae, and purpura, which are often identified on the infant's skin and mucous membranes postnatally.

Bleeding can occur in various locations throughout the body including the intracranial space, genitourinary system, gastrointestinal system, lungs, eyes, and spinal cord, and varies based on the severity of thrombocytopenia.

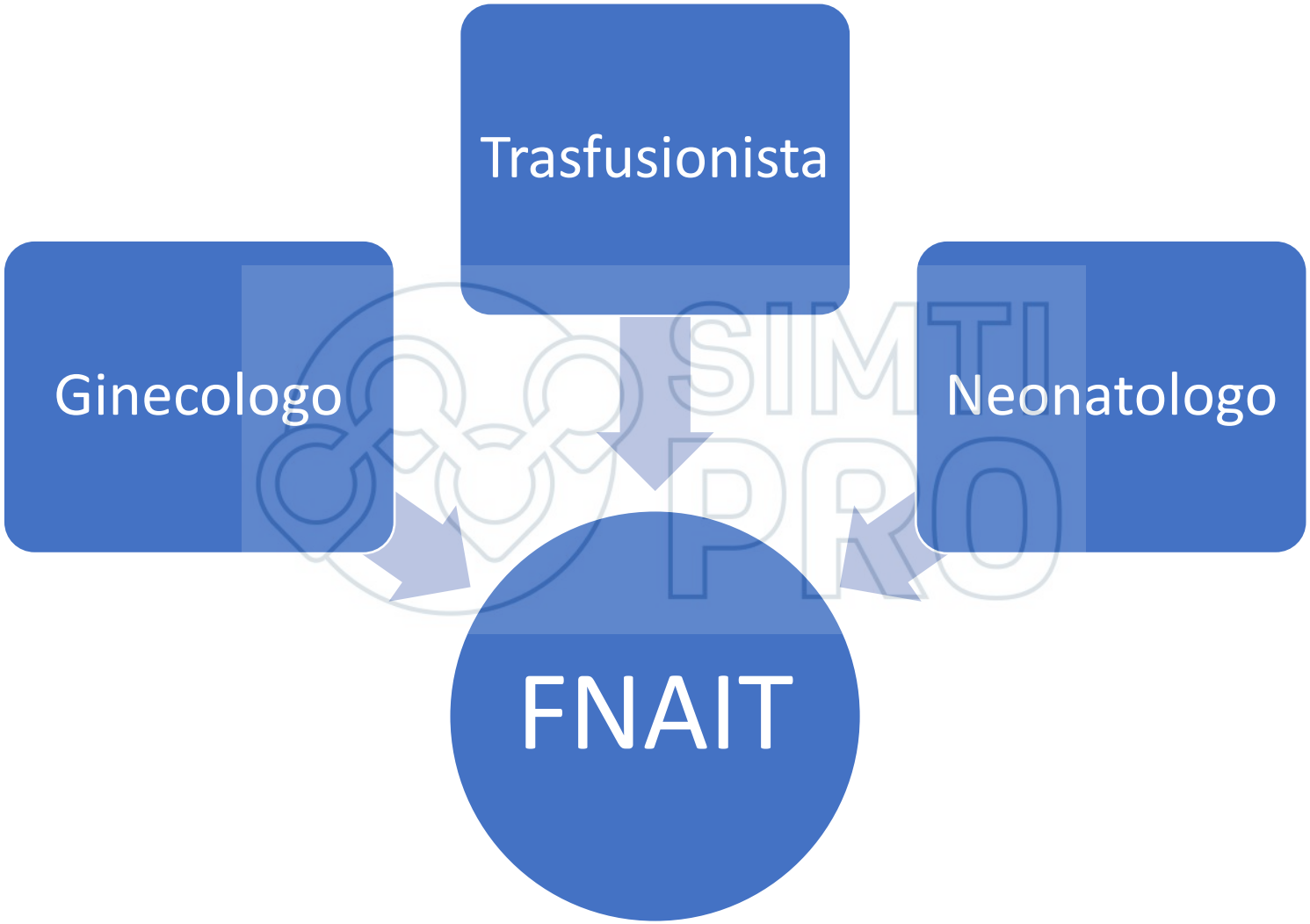
ICH is a serious complication that has been identified in utero as early as 20 weeks' gestation. It is estimated that 10% of infants who suffer from ICH as a result of NAIT will develop long-term neurological deficits and developmental delays.

It has been estimated that it develops in utero, which may sometimes lead to porencephaly or hydrocephalus.

Morbidity and mortality are high; the mortality rate has been reported to be 12-14 % without treatment.

Neonatal Alloimmune Thrombocytopenia, 2021

APPROCCIO MULTIDISCIPLINARE



Presently 37 HPAs have been identified on 6 platelet glycoprotein membrane surfaces as early as 14 weeks' gestation.

All races are susceptible to NAIT; HPA-1a, identified in 80% to 85% of diagnosed NAIT among Caucasians, is seldom identified in other races.

The second most commonly identified HPA associated with NAIT is HPA-5b, accounting for 10% to 15% of diagnosed NAIT among the African American population

Neonatal Alloimmune Thrombocytopenia, 2021

Laboratory Test	Results
CBC: *Supportive diagnosis*	
Infant[11]	Platelet count: $<30 \times 10^9$/L[6,11]
Maternal[6,11]	Platelet count: normal ($150\text{-}450 \times 10^9$/L)[6,11]
Platelet testing (MAIPA): *Definitive diagnosis*	
Maternal[3,11,14]	HPA-1a negative; antiplatelet antibodies present[3,11,14]
Paternal[3,11,14]	HPA-1a positive[3,11,14]
Paternal genotype[6,11,14]: *Definitive diagnosis*	100% recurrence rate to homozygous father (HPA-1a/1a)[6,14] 50% recurrence rate to heterozygous father (HPA-1a/1b)[6,14] with HPA-1a negative partner

Abbreviations: CBC, complete blood count; HPA, human platelet antigen; MAIPA, monoclonal antibody immobilization of platelet antigen.

[a]From Bertrand and Kaplan,[3] Akpan et al,[6] Sillers et al,[11] and Zdravic et al.[14]

>HPA-9b in Caucasici,FNAIT SEVERA+ICH

>HPA-6b e >HPA-21b in Asiatici con >HPA-4b

Associazione >HPA-1a con >HPA-25b

HPA-26b altera la funzione di GPIIb/IIIa e HPA-13b di GPIa/IIa con produzione anticorpi

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RUOLO DEL LABORATORIO NELLA FNAIT

Sospetta FNAIT in gravidanza
Neonato Piastrinopenico (<100x10^9/L)

Neonato: anticorpi/HPA

Madre

Cross-Match

Determinazione autoanticorpi sierici ed adesi

Determinazione alloanticorpi anti-HPA/HLA

Pos

NEG

Tipizzazione Molecolare HPA

Padre

Metodi diagnostici

Screening SPRCA → Identificazione ELISA → Identificazione Bead-based assay → Biologia Molecolare DNA Microarray → Cross-Match Piastrinici SPRCA

RUOLO DEL LABORATORIO NELLA FNAIT

Sospetta FNAIT in gravidanza
Neonato Piastrinopenico (<100x10⁹/L)

Neonato: anticorpi/HPA

Madre

Cross-Match

Determinazione autoanticorpi sierici ed adesi

Determinazione alloanticorpi anti-HPA/HLA

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NEG

Tipizza Molecola

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Metodi diagnostici

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Identificazione Bead-based assay

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Sospetta FNAIT in gravidanza
Neonato Piastrinopenico (<100x10⁹/L)

Neonato: anticorpi/HPA

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Cross-Match

Determinazione autoanticorpi sierici ed adesi

Determinazione alloanticorpi anti-HPA/HLA

Pos

NEG

Metodi diagnosti

Screening SPRCA

Identifica ELIS

4.3.8.2

Le tipologie di pazienti in cui va presa in considerazione ed eventualmente suggerita l'analisi molecolare dei sistemi HPA sono:

- donne in gravidanza con alloimmunizzazione HPA e storia pregressa di feti/neonati affetti da emorragia cerebrale ed i loro partner
- feti di madri con alloimmunizzazione HPA e storia pregressa di feti/neonati affetti da emorragia cerebrale, mediante metodo invasivo (villocentesi, amniocentesi) o non invasivo (DNA fetale libero nel plasma materno), se il padre è eterozigote per l'antigene nei confronti del quale la madre presenta l'anticorpo

Anti-HPA1a
75-90%

Anti-HPA5b
8-15%

Anti-HPA 15b ,
HPA 1b
4%

Anti-HPA 3a
anti-HPA 5a
2%

Anti-GP IV
Atg bassa
frequenza

Clinical characteristics of human platelet antigen (HPA)-1a and HPA-5b alloimmunised pregnancies and the association between platelet HPA-5b antibodies and symptomatic fetal neonatal alloimmune thrombocytopenia

British Journal of Haematology, 2021 Volume: 195, Issue: 4, Pages: 595-603,

Thijs W. de Vos,[1,2,3] Leendert Porcelijn,[4] Suzanne Hofstede-van Egmond,[4] Eva Pajkrt,[5] Dick Oepkes,[3] Enrico Lopriore,[1] C. Ellen van der Schoot,[6] Dian Winkelhorst[3,6] and Masja de Haas[2,3,7]

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Summary

Fetal neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal alloantibodies directed against the human platelet antigens (mostly HPA-1a or HPA-5b) of the (unborn) child and can lead to severe bleeding. Anti-HPA-1a-mediated FNAIT shows a severe clinical outcome more often than anti-HPA-5b-mediated FNAIT. Given the relatively high prevalence of anti-HPA-5b in pregnant women, the detection of anti-HPA-5b in FNAIT-suspected cases may in some cases be an incidental finding. Therefore we investigated the frequency of anti-HPA-5b-associated severe bleeding in FNAIT. We performed a retrospective nationwide cohort study in cases with clinical suspicion of FNAIT. HPA antibody screening was performed using monoclonal antibody-specific immobilisation of platelet antigens. Parents and neonates were typed for the cognate antigen. Clinical data were collected by a structured questionnaire. In 1 864 suspected FNAIT cases, 161 cases (8·6%) had anti-HPA-1a and 60 (3·2%) had anti-HPA-5b. The proportion of cases with severe bleeding did not differ between the cases with anti-HPA-1a (14/129; 11%) and anti-HPA-5b (4/40; 10%). In multigravida pregnant women with a FNAIT-suspected child, 100% (81/81) of anti-HPA-1a cases and 79% (38/48) of anti-HPA-5b cases were HPA-incompatible, whereas 86% and 52% respectively were expected, based on the HPA allele distribution. We conclude that anti-HPA-5b can be associated with severe neonatal bleeding symptoms. A prospective study is needed for true assessment of the natural history of anti-HPA-5b mediated FNAIT.

Keywords: alloimmune thrombocytopenia, neonatology, alloimmunisation during pregnancy, human platelet antigen.

Clinical characteristics of human platelet antigen (HPA)-1a and HPA-5b alloimmunised pregnancies and the association between platelet HPA-5b antibodies and symptomatic fetal neonatal alloimmune thrombocytopenia

January 2002 – January 2020
Suspected FNAIT 1864 cases

No anti-HPA antibodies detected 1602 cases

Anti-HPA antibodies detected 262 cases

Antigens	Allele frequency[a] Caucasian (%)	African (%)	Asian (%)	Glycoprotein / Amino acid change	Encoding gene / Nucleotide change	Immune platelet disorder reports
HPA-1a	72 a/a	90	100	GPIIIa / L33P	*ITGB3* / T196C	FNAIT, PTP, MPR
HPA-1b	26 a/b	10	0			
	2 b/b					
HPA-5a	88 a/a	82	98.6	GPIa / E505K	*ITGA2* / G1648A	FNAIT, PTP, MPR
HPA-5b	20 a/b	1 8	0.4			
	1 b/b					

Exclusion

More than one anti-HPA antibody		12
anti-HPA-1a + anti-HPA-3a	*n* = 1	
anti-HPA-1a + anti-HPA-5b	*n* = 6	
anti-HPA-3a + anti-HPA-5b	*n* = 3	
anti-HPA-1b + anti-HPA-5b	*n* = 1	
anti-HPA 2b + anti-HPA-5b	*n* = 1	
HPA specificity was not HPA-1a or HPA-5b		28 cases
No HPA-5b incompatibility		10 cases
No HPA-1b incompatibility		1 case

Newly detected FNAIT (eligible) 211 cases

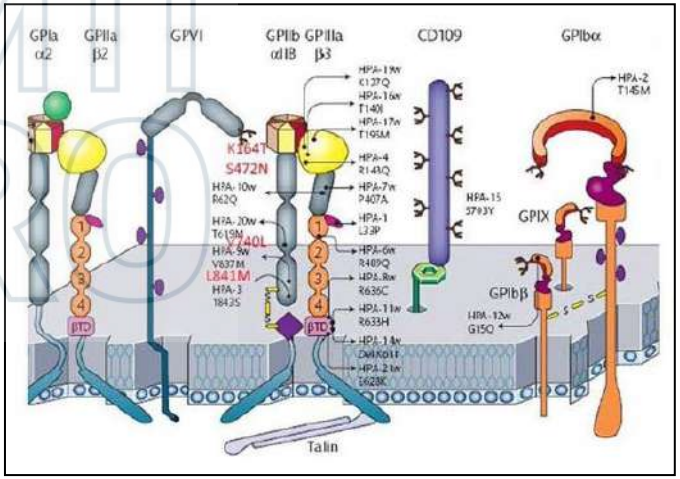
anti-HPA-1a	161 cases
anti-HPA-5b	50 cases

Exclusion

Lost to follow up anti-HPA-1a	32 cases
Lost to follow up anti-HPA-5b	10 cases

Newly detected FNAIT (included) 169 cases

anti-HPA-1a	129 cases
anti-HPA-5b	40 cases

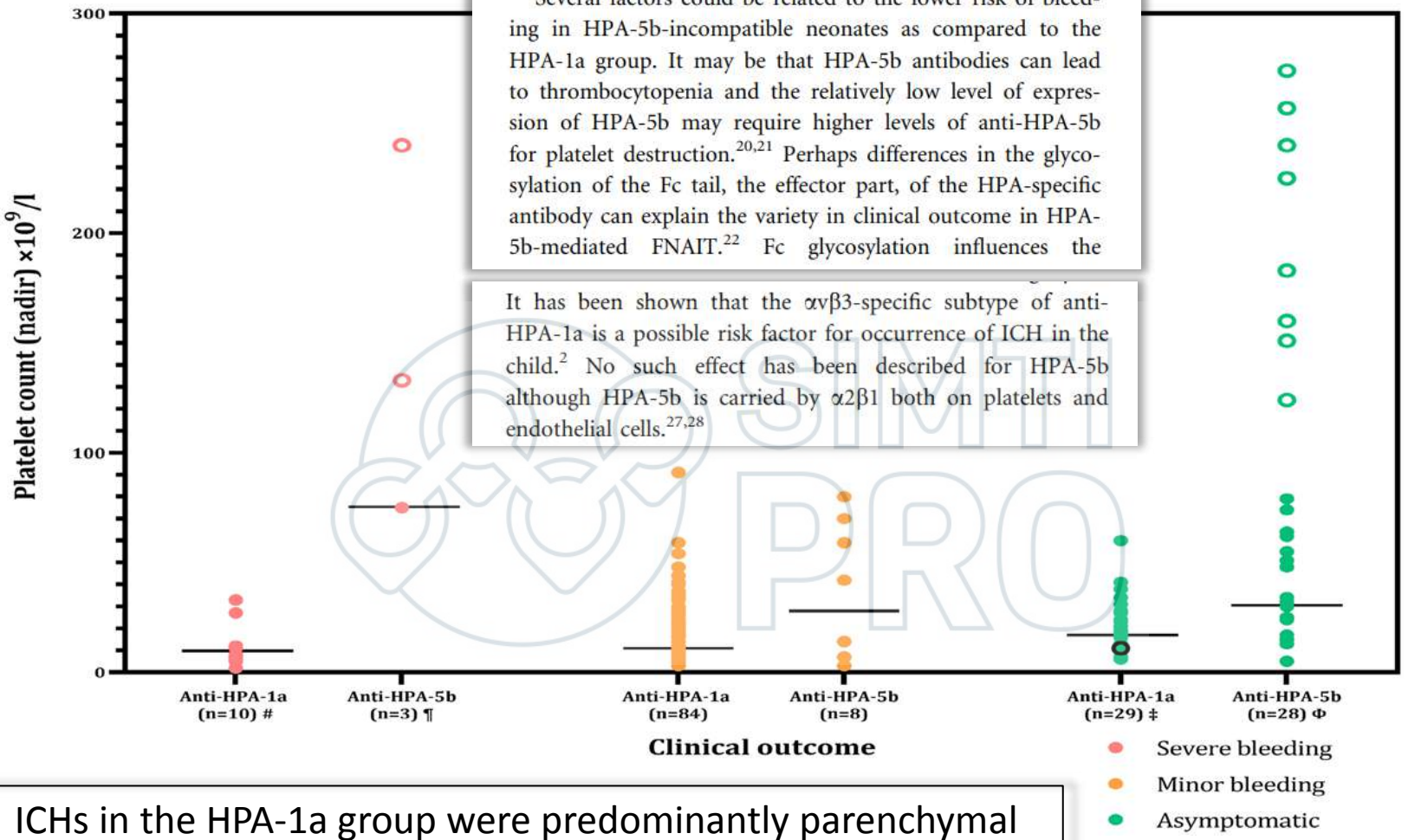


British Journal of Haematology, 2021 Volume: 195, Issue: 4, Pages: 595-603,

Clinical characteristics of human platelet antigen (HPA)-1a and HPA-5b alloimmunised pregnancies and the association between platelet HPA-5b antibodies and symptomatic fetal neonatal alloimmune thrombocytopenia

Several factors could be related to the lower risk of bleeding in HPA-5b-incompatible neonates as compared to the HPA-1a group. It may be that HPA-5b antibodies can lead to thrombocytopenia and the relatively low level of expression of HPA-5b may require higher levels of anti-HPA-5b for platelet destruction.[20,21] Perhaps differences in the glycosylation of the Fc tail, the effector part, of the HPA-specific antibody can explain the variety in clinical outcome in HPA-5b-mediated FNAIT.[22] Fc glycosylation influences the

It has been shown that the αvβ3-specific subtype of anti-HPA-1a is a possible risk factor for occurrence of ICH in the child.[2] No such effect has been described for HPA-5b although HPA-5b is carried by α2β1 both on platelets and endothelial cells.[27,28]



ICHs in the HPA-1a group were predominantly parenchymal and were mostly of intraventricular origin in the HPA-5b

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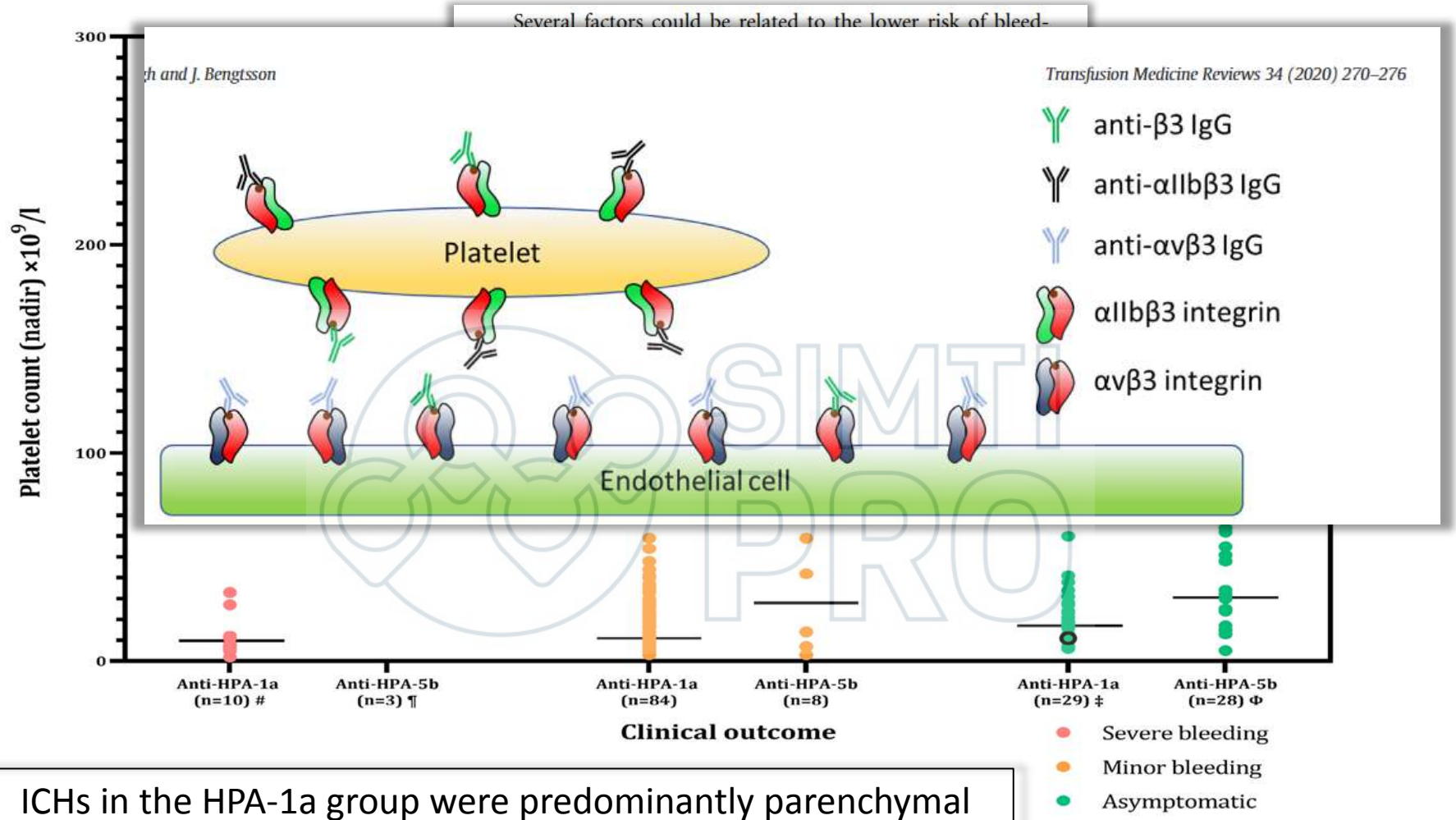

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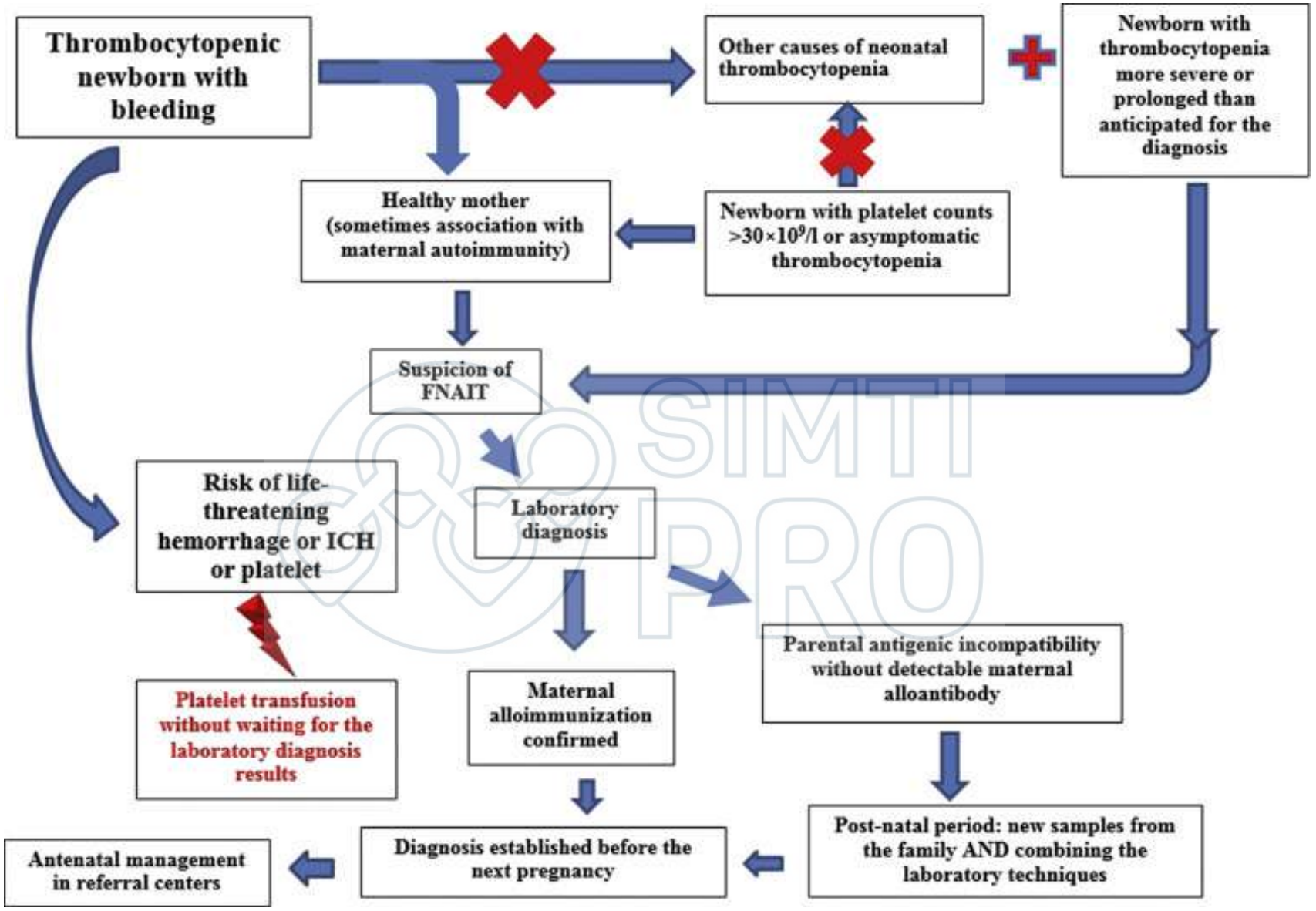
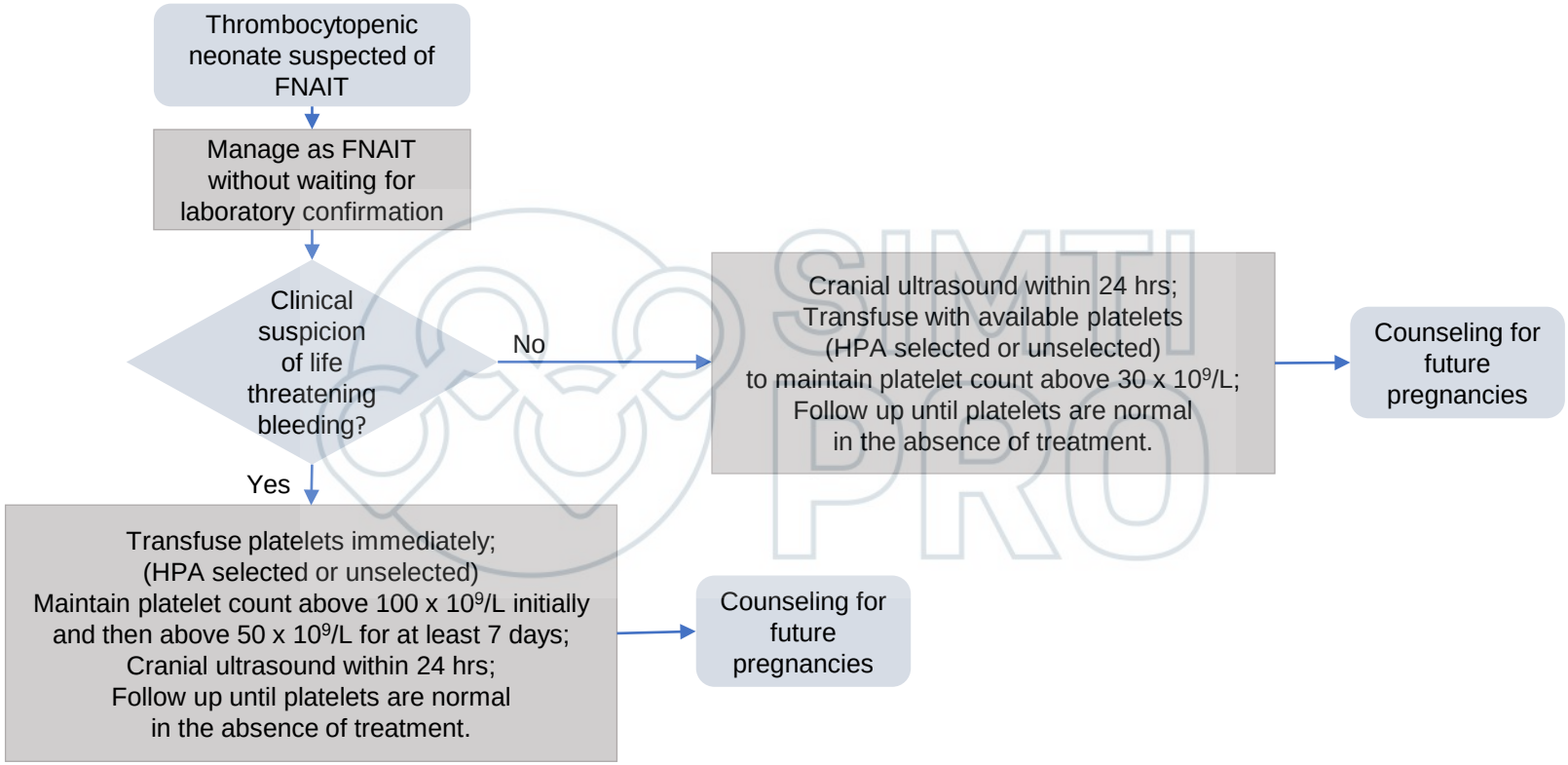

Thrombocytopenic newborn with bleeding
Other causes of neonatal thrombocytopenia
Newborn with thrombocytopenia more severe or prolonged than anticipated for the diagnosis
Healthy mother (sometimes association with maternal autoimmunity)
Newborn with platelet counts >30×10⁹/l or asymptomatic thrombocytopenia
Suspicion of FNAIT
Risk of life-threatening hemorrhage or ICH or platelet
Laboratory diagnosis
Platelet transfusion without waiting for the laboratory diagnosis results
Maternal alloimmunization confirmed
Parental antigenic incompatibility without detectable maternal alloantibody
Post-natal period: new samples from the family AND combining the laboratory techniques
Diagnosis established before the next pregnancy
Antenatal management in referral centers

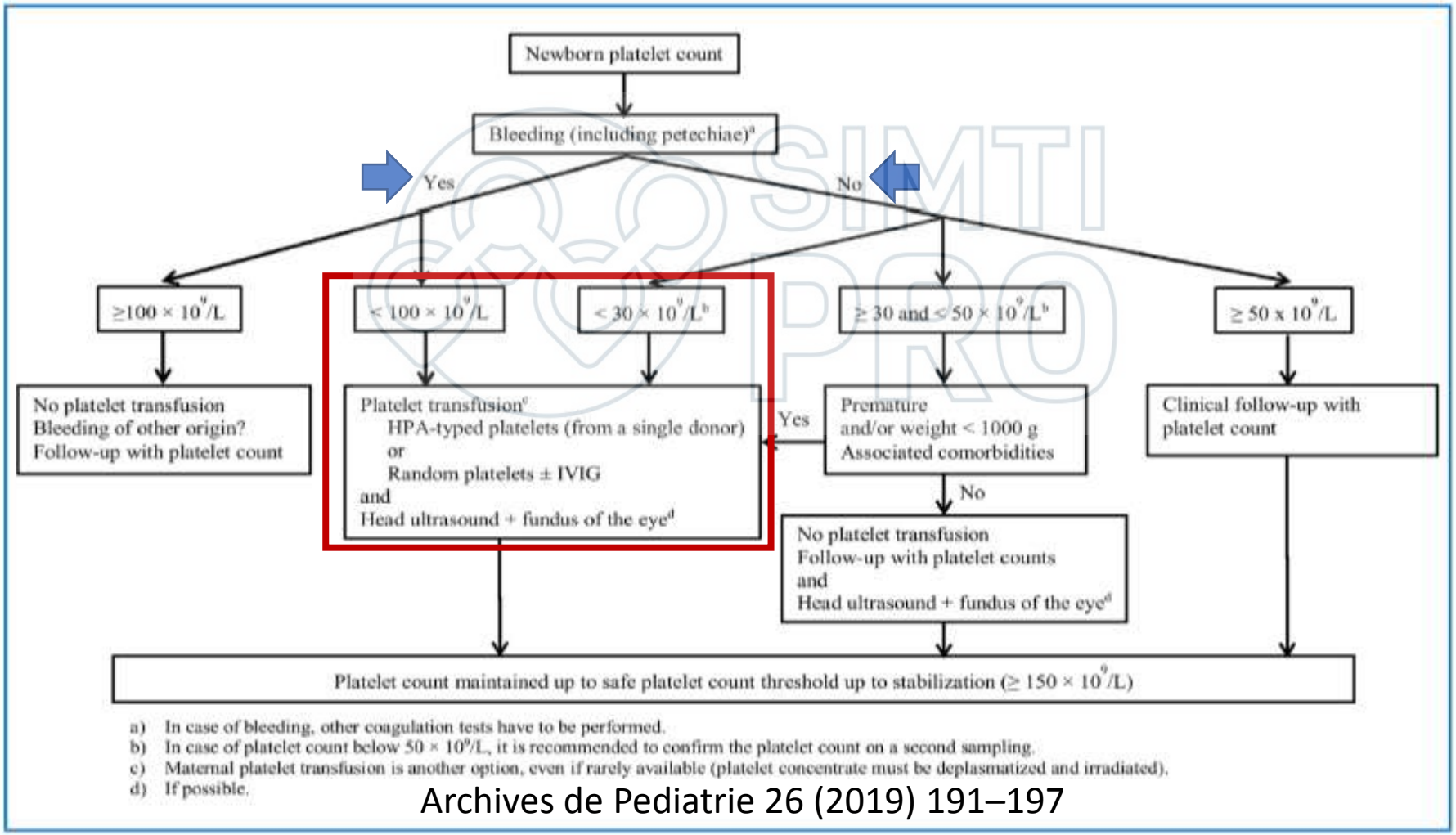
Postnatal algorithm



British Journal of Haematology, 2019, 185, 549–562

Algoritmo trattamento FNAIT (GFHT)

Management of neonatal thrombocytopenia in a context of maternal antiplatelet alloimmunization: Expert opinion of the French-speaking working group



a) In case of bleeding, other coagulation tests have to be performed.
b) In case of platelet count below 50 × 10⁹/L, it is recommended to confirm the platelet count on a second sampling.
c) Maternal platelet transfusion is another option, even if rarely available (platelet concentrate must be deplasmatized and irradiated).
d) If possible.

Archives de Pediatrie 26 (2019) 191–197

TRATTAMENTO NEONATALE

<30x10^9/L

- Trasfondere con CP ABO compatibile, HPA-compatibile, leucodepleto/CMV safe
- CP materno filtrato, lavato e irradiato o da *donatore ABO compatibile ma non HPA , leucodepleto/CMV safe*, IVIG 1gr/Kg per 2gg

>30x10^9/L

- In assenza di emorragie no trattamento ma monitoraggio conta PLT e ecografia/RMN cerebrale
- Nel pre-termine o in presenza di emorragia cerebrale trasfondere CP e IVIG 1gr/Kg per 2gg

Irradiare CE e CP nei seguenti casi:
-in seguito a TIU
-peso ≤1.500g e/o EG ≤30 sett.
-donazione parentale
-condizioni immunodeficienza
-trapianto CSE

Raccomandazioni SIMTI-SIN 2014

Management NAIT

EXPERT REVIEW OF HEMATOLOGY, 2017
VOL. 10, NO. 8, 729–737
https://doi.org/10.1080/17474086.2017.1346471

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REVIEW

OPEN ACCESS Check for updates

Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies

Dian Winkelhorst [a,b], Dick Oepkes[a] and Enrico Lopriore[c]

Table 1. Overview antenatal and postnatal management strategies in FNAIT.

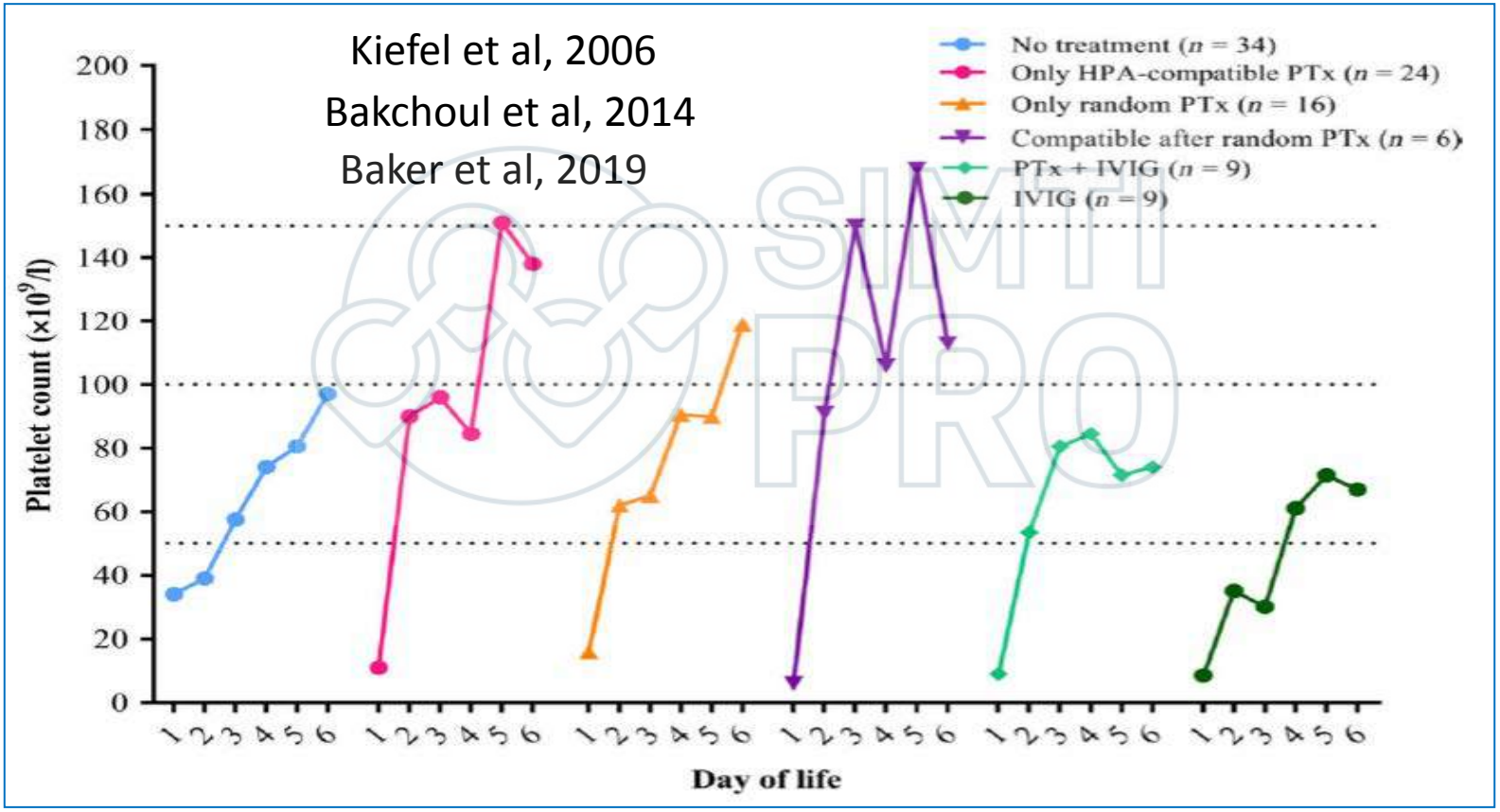
	Antenatal			Postnatal		
Treatment	Indication/Dose	Benefit	Risk	Indication/Dose	Benefit	Risk
Platelet transfusion	Various, from weekly to predelivery only	Treatment monitoring Prevents thrombocytopenia	High complication rate (fetal loss, emergency delivery)	First choice PLT < 20–30 prophylaxis PLT < 50–100 when bleeding	Direct effect on platelet count	Infections Allergic or febrile reactions
IVIG	First choice 0.5 g or 1 g/kg/wk	Noninvasive Prevents ICH	Blind administration Expensive	In addition to random PTx 1 g/kg/day for 2–5 days Not after antenatal IVIG	Prolongs and optimizes effect of random PTx	Delay in response
Corticosteroids	In addition to IVIG Prednisone 0.5 mg	Noninvasive, otherwise benefit unclear	Dose-related side effects Oligohydramnios	No indication Methylprednisone 1 mg iv every 8 h	Benefit unclear	No evidence

PLT: platelet count, $\times 10^9$/L; PTx: platelet transfusion; IVIG: intravenous immunoglobulins; ICH: intracranial hemorrhage.

Trattamento post-natale e outcome

Treatment and outcomes of fetal/neonatal alloimmune thrombocytopenia: a nationwide cohort study in newly detected cases

British Journal of Haematology, 2019, 184, 1011–1070

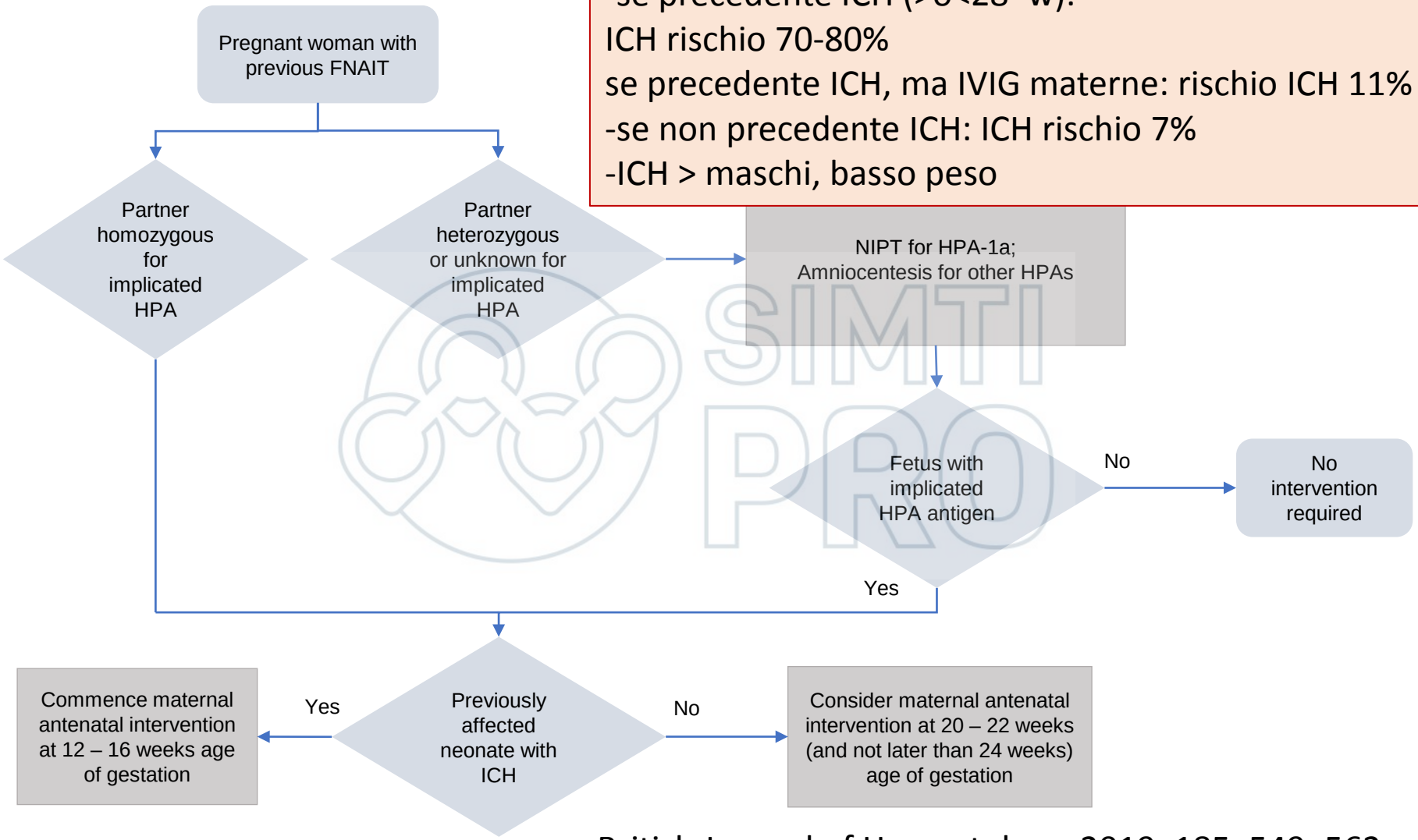


Postnatal intervention for the treatment of FNAIT: a systematic review *Journal of Perinatology (2019)*

….«Available studies do not clearly demonstrate a benefit for addition of IVIg to platelet transfusion»

Antenatal algorithm

Successive gravidanze:
-se precedente FNAIT: FNAIT rischio 100%
-se precedente ICH (>o<28^w):
ICH rischio 70-80%
se precedente ICH, ma IVIG materne: rischio ICH 11%
-se non precedente ICH: ICH rischio 7%
-ICH > maschi, basso peso



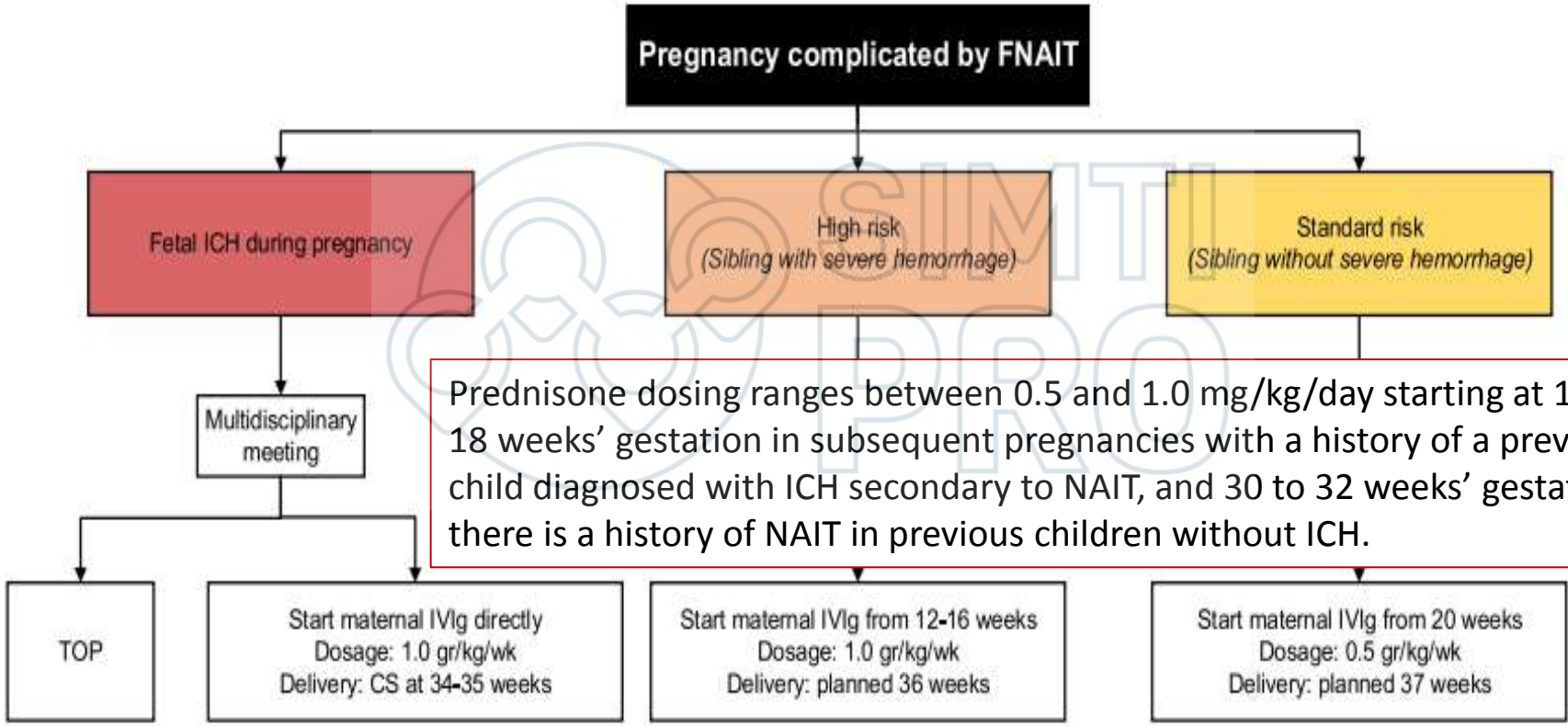
British Journal of Haematology, 2019, 185, 549–562

Epidemiology and management of fetal and neonatal alloimmune thrombocytopenia

PII: S1473-0502(19)30277-0

Transfusion and Apheresis Science, 31 December 2019

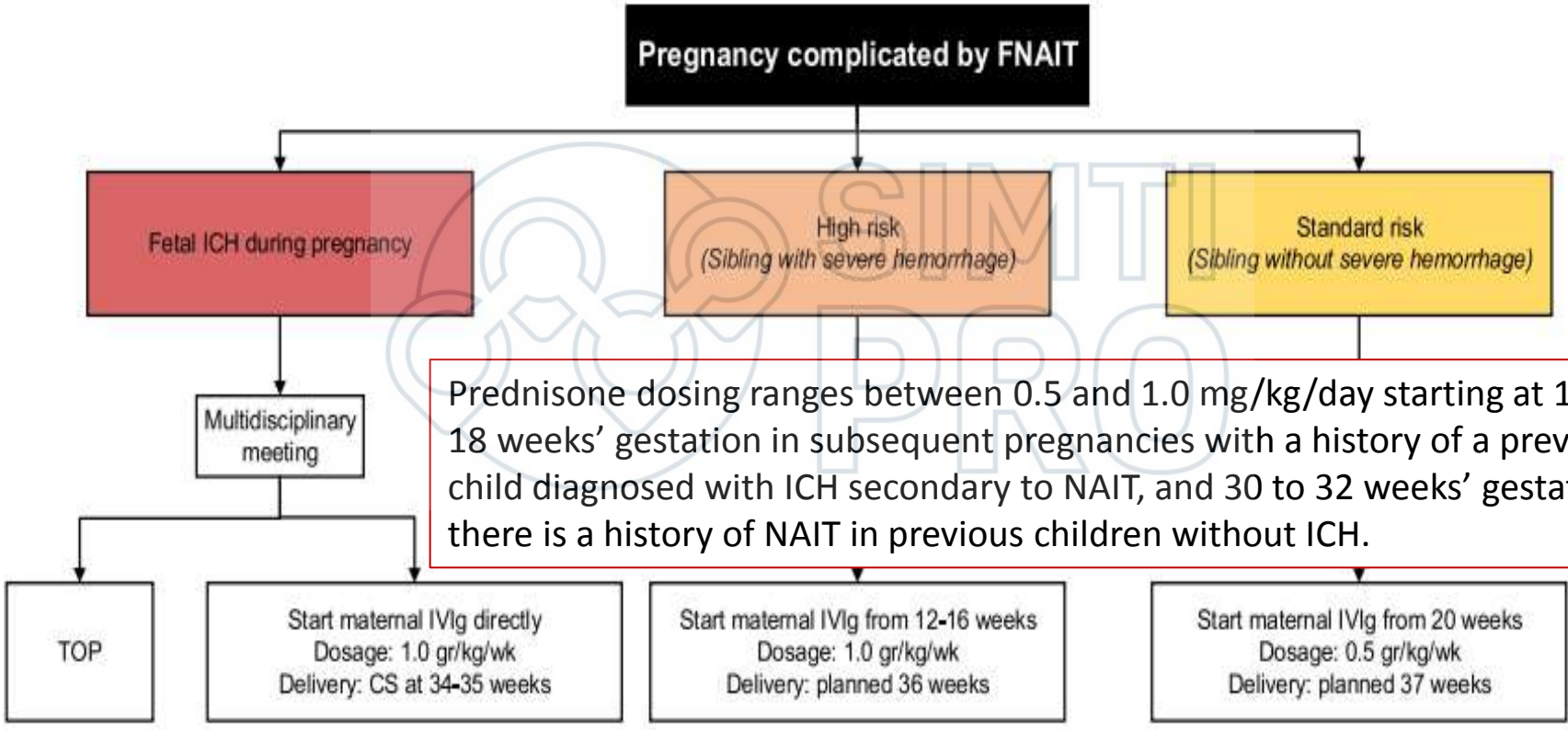
DOI: https://doi.org/10.1016/j.transci.2019.102704



Prednisone dosing ranges between 0.5 and 1.0 mg/kg/day starting at 16 to 18 weeks' gestation in subsequent pregnancies with a history of a previous child diagnosed with ICH secondary to NAIT, and 30 to 32 weeks' gestation if there is a history of NAIT in previous children without ICH.

To date, there are no trials of the most appropriate mode of delivery. Both modes of delivery continue to be used at different sites.

Adverse effects associated with IVIG therapy are rare but can include headache, rash, hemolytic anemia, renal failure, aseptic meningitis, and thrombosis in the mother. Despite these risks, no adverse effects from maternal treatment have been noted in the fetus.



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Management NAIT

EXPERT REVIEW OF HEMATOLOGY, 2017
VOL. 10, NO. 8, 729–737
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REVIEW

Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies

Dian Winkelhorst [a,b], Dick Oepkes[a] and Enrico Lopriore[c]

Table 1. Overview antenatal and postnatal management strategies in FNAIT.

	Antenatal			Postnatal		
Treatment	Indication/Dose	Benefit	Risk	Indication/Dose	Benefit	Risk
Platelet transfusion	Various, from weekly to predelivery only	Treatment monitoring Prevents thrombocytopenia	High complication rate (fetal loss, emergency delivery)	First choice PLT < 20–30 prophylaxis PLT < 50–100 when bleeding	Direct effect on platelet count	Infections Allergic or febrile reactions
IVIG	First choice 0.5 g or 1 g/kg/wk	Noninvasive Prevents ICH	Blind administration Expensive	In addition to random PTx 1 g/kg/day for 2–5 days Not after antenatal IVIG	Prolongs and optimizes effect of random PTx	Delay in response
Corticosteroids	In addition to IVIG Prednisone 0.5 mg	Noninvasive, otherwise benefit unclear	Dose-related side effects Oligohydramnios	No indication Methylprednisone 1 mg iv every 8 h	Benefit unclear	No evidence

PLT: platelet count, $\times 10^9$/L; PTx: platelet transfusion; IVIG: intravenous immunoglobulins; ICH: intracranial hemorrhage.

ANNO 2022

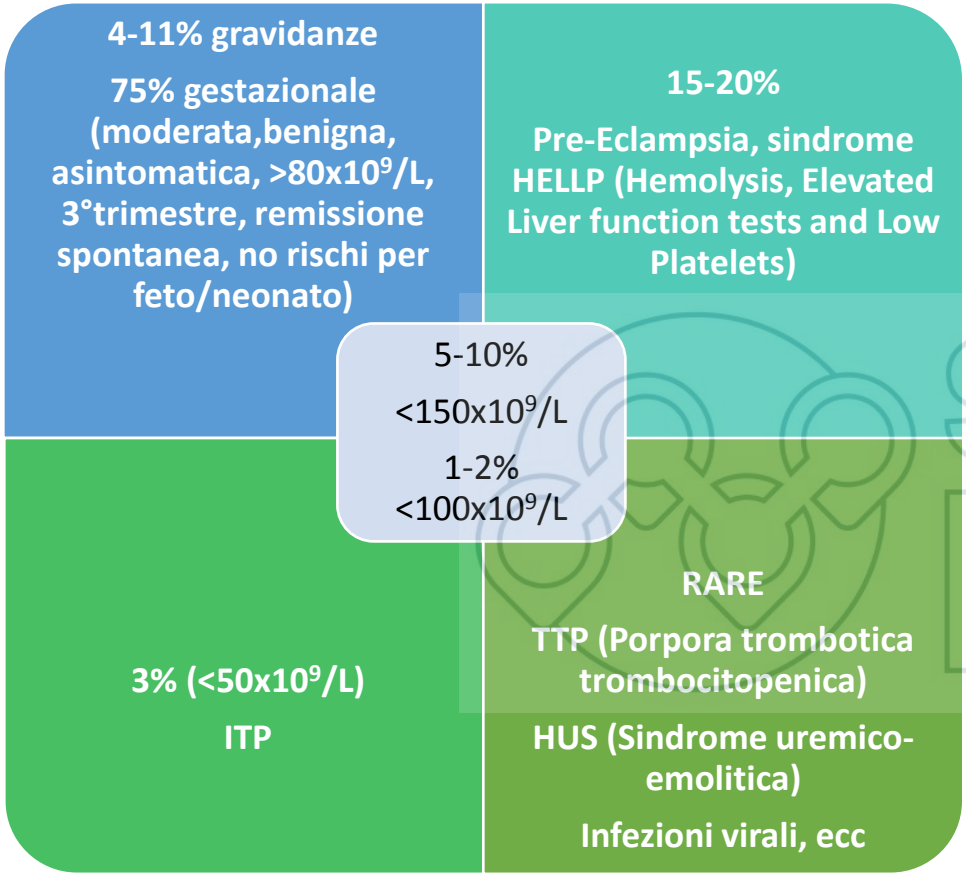
B) EMATOLOGIA

Trombocitopenia alloimmune fetale e neonatale

Trattamento per le madri in gravidanza: uso consentito, la dose massima non deve superare 1 g/kg/settimana.

Trattamento per i neonati: in caso di sanguinamento potenzialmente fatale o conta piastrinica inferiore a 30x109 /L, laddove non sia possibile una trasfusione di piastrine (selezionate per l'antigene piastrinico umano [HPA] o meno)

PIASTRINOPENIA IN GRAVIDANZA



Platelet count s during pregnancy.
N Engl J Med 2018

Neonatal Immune Thrombocytopenia (NITP)

- Passaggio transplacentare di autoanticorpi da madre con diagnosi di ITP (3%)
- 10-15% dei neonati: piastrinopenia transitoria <100x10^9/L
- 10% dei neonati: piastrinopenia <50x10^9/L
- 1-5 % dei neonati: piastrinopenia <20x10^9/L
- 5-15% richiede terapia
- 0-1% casi di emorragia cerebrale
- Mortalità neonatale <1%
- Trattamento con IVIG e CP se PLT<30x10$^{9/L}$
- Gli anticorpi possono persistere per 12 settimane

Thrombocytopenia in pregnancy

BLOOD, 23 NOVEMBER 2017 • VOLUME 130, NUMBER 21

LIFESPAN IMPLICATIONS

Clearance of maternal antibodies occurs over the first few weeks up to 3 months of life, without further implications on the newborn.

Infants diagnosed with ICH secondary to NAIT require medical treatment after thrombocytopenia has resolved, extending well into childhood or is lifelong depending on the severity of ICH.

Long-term implications from severe ICH include blindness, hydrocephalus, epilepsy, cerebral palsy, cognitive delays, and intellectual disability.

Developmental milestones should be closely monitored for the first 2 years of life in these children and genetic counseling offered to families.

Neonatal Alloimmune Thrombocytopenia, 2021

Fetal and Neonatal Alloimmune Thrombocytopenia: Management and Outcome of a Large International Retrospective Cohort

Objective: To evaluate the management and outcome of a large international cohort of cases of pregnancies complicated by fetal and neonatal alloimmune thrombocytopenia (FNAIT). ***Methods:*** This was an observational prospective and retrospective cohort study of all cases of FNAIT entered into the international multicentre No IntraCranial Haemorrhage (NOICH) registry during the period of 2001–2010. We evaluated human platelet antigen (HPA) specificity, the antenatal and postnatal interventions performed, and clinical outcome. ***Results:*** A total of 615 pregnancies complicated by FNAIT from 10 countries were included. Anti-HPA-1a was the most commonly implicated antibody. Antenatal treatment was administered in 273 pregnancies (44%), varying from intrauterine platelet transfusion to maternal administration of immunoglobulins, steroids, or a combination of those. Intracranial haemorrhage was diagnosed in 23 fetuses or neonates (3.7%). Overall perinatal mortality was 1.14% (n = 7). ***Conclusion:*** This study presents the largest cohort of cases of FNAIT published. Our data show that antenatal treatment for FNAIT results in favourable perinatal outcome. Over time, in most centres, treatment for FNAIT changed from an invasive to a complete non-invasive procedure.

Fetal Diagn Ther 2017;41:251–257
DOI: 10.1159/000448753

Table 1. HPA specifics

HPA type	Cases, n (%)	Mean PC ×10⁹/l	ICH
HPA-1a	544 (88)	105	19
HPA-5b	23 (3.6)	136	2
HPA-3a	7 (1.1)	147	
HPA-5a	4 (0.6)	184	
HPA-15a	5 (0.8)	200	
HPA-1a + -5b	18 (3)	94	2
HPA-1a + other	5 (0.8)		
Negative	2 (0.03)		
Unknown	7 (1.1)		
Total	615		

PC = Platelet count.

Perinatal Outcome and Long-Term Neurodevelopment after Intracranial Haemorrhage due to Fetal and Neonatal Alloimmune Thrombocytopenia

Abstract

Objectives: To evaluate the perinatal and long-term neurodevelopmental outcome in a cohort of children with intracranial haemorrhage (ICH) due to fetal and neonatal alloimmune thrombocytopenia (FNAIT) and to clearly outline the burden of this disease. ***Subjects and Methods:*** We performed an observational cohort study and included all consecutive cases of ICH caused by FNAIT from 1993 to 2015 at Leiden University Medical Centre. Neurological, motor, and cognitive development were assessed at a minimum age of 1 year. The primary outcome was adverse outcome, defined as perinatal death or severe neurodevelopmental impairment (NDI). Severe NDI was defined as any of the following: cerebral palsy (Gross Motor Function Classification System [GMFCS] level ≥II), bilateral deafness, blindness, or severe motor and/or cognitive developmental delay (<–2 SD). ***Results:*** In total, 21 cases of ICH due to FNAIT were included in the study. The perinatal mortality rate was 10/21 (48%). Long-term outcome was assessed in 10 children (*n* = 1 lost to follow-up). Severe and moderate NDI were diagnosed in 6/10 (60%) and 1/10 (10%) of the surviving children. The overall adverse outcome, including perinatal mortality or severe NDI, was 16/20 (80%). ***Conclusions:*** The risk of perinatal death or severe NDI in children with ICH due to FNAIT is high. Only screening and effective preventive treatment can avoid this burden.

Fetal Diagn Ther 2018
DOI: 10.1159/000488280

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Table 2. Intracranial haemorrhage characteristics and short-term outcome

Child No.	GA at birth	Antenatal IVIG	ICH location	Associated lesions	Mortality	Obstetric history	
1	33^{+4}	no	extensive subarachnoid and unilateral parenchymal frontal/temporal/occipital	–	yes, neonatal	G1P0	
2	35^{+0}	no	unilateral intraventricular and parenchymal	hydrocephalus	yes, neonatal	G2P1	healthy child
3	31^{+5}	no	bilateral parenchymal	–	yes, neonatal	G1P0	
4	36^{+5}	no	extensive bilateral parenchymal		yes, neonatal	G3P1	healthy child, miscarriage
5	38^{+1}	no	extensive bilateral parenchymal	hydrocephalus	yes, fetal	G2P0	miscarriage
6	22^{+0}	no	bilateral parenchymal	hydrocephalus	yes, TOP	G2P0	miscarriage
7	32^{+2}	no	extensive subarachnoid		yes, neonatal	G2P1	child with trisomy 21
8	30^{+0}	no	bilateral intraventricular and parenchymal	hydrocephalus	yes, neonatal	G3P0	miscarriage, one TOP
9	19^{+0}	no[1]	extensive bilateral parenchymal	–	yes, TOP	G4P3	two healthy children, one child with FNAIT
10	19^{+4}	no	unilateral parenchymal and intraventricular	–	yes, TOP	G3P1	healthy child, miscarriage

Fetal and Neonatal Alloimmune Thrombocytopenia: Management and Outcome of a Large International Retrospective Cohort

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Table 1. HPA specifics

Table 3. Intracranial haemorrhage and long-term outcome

Child No.	Associated lesions	Age at evaluation	Cerebral palsy	Developmental test	Total IQ	Long-term outcome	Severe NDI
11	none	8 years	–	WISC-III	86	attention deficit hyperactivity disorder	no
12	hydrocephalus, VPD	2, 8, and 14 years	spastic tetraplegia, GMFCS level V	Bayley-III, Reynell-Zinkin, KID-N	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
13	porencephalic cyst hydrocephalus, VPD	20 years	spastic tetraplegia, GMFCS level V	not tested due to severe impairment	49	bilateral blindness, severe cognitive and motor delay, epilepsy	yes
14	porencephalic cyst hydrocephalus, VPD	23 years	spastic tetraplegia, GMFCS level V	not tested due to severe impairment	49	bilateral blindness, hearing impairment, severe cognitive and motor delay	yes
15	bilateral porencephalic cyst, cerebellar destruction hydrocephalus, VPD	3 years	spastic diplegia, GMFCS level IV	SON	60	severe cognitive and motor delay	yes
16	none	5 years	–	WPPSI-III	110		no
17	bilateral porencephalic cyst hydrocephalus, VPD	1 year	spastic hemiplegia, GMFCS level IV	KID-N	49	visual impairment, severe cognitive and motor delay, epilepsy	yes
18	none	7 years	–	WISC-III	112		no
19	hydrocephalus, unilateral porencephalic cyst	5 years	spastic hemiplegia, GMFCS level II	WPPSI-III	85	problems with behaviour and attention regulation	no
20	hydrocephalus, bilateral porencephalic cysts	8 years	spastic diplegia, GMFCS level II	SON	50	severe cognitive and motor delay, epilepsy	yes
21	none	loss of contact information, no long-term follow-up available					

Bayley-III, Bayley Scales of Infant and Toddler Development third edition; GMFCS, Gross Motor Function Classification System; KID-N, Kent Infant Development Scale; NDI, neurodevelopmental impairment; SON, Snijders-Oomen Nonverbal Intelligence Test; VPD, ventriculoperitoneal drain; WISC-III, Wechsler Intelligence Scale for Children third edition; WPPSI-III, Wechsler Preschool Primary Scale of Intelligence third edition.

FUTURE DIRECTIONS IN THE TREATMENT OF NAIT

Promising research led to the development of the PROFNAIT project in 2011 in Europe.

The goal of this project is to develop prophylaxis treatment that can successfully and safely prevent NAIT in pregnancy.

The drug, NAITgam, is developed from plasma donated by women who are HPA1a-immunized and have given birth to a child with NAIT.

Anti-HPA-1a IgG is collected from the donated plasma and when administered to pregnant women who are positive for HPA-1a antibodies, eliciting an antibody-mediated immune response, thereby preventing NAIT in the newborn.

HPA-1a prophylaxis could be available, pending completion of clinical trials, within the next 5 years.

Despite the prevalence and negative sequelae associated with NAIT, no universal screening protocol for pregnant women exists.

Neonatal Alloimmune Thrombocytopenia, 2021

SCREENING

British Journal of Haematology, 2019, 185, 549–562

All pregnant women should probably be screened for HPA-1b1b in their first pregnancy if the cost effectiveness of detection is acceptable and a management scheme is in place (low evidence, weak recommendation).

Balance of harms and benefits: Screening may detect women at increased risk of adverse pregnancy outcomes. Screening may expose women to unnecessary antenatal intervention. The clinical and cost effectiveness has not been established.

Suggestions for practice: If HPA incompatibility is identified in pregnancies by screening, women should be directed to comprehensive care centres. HPA alloantibody determination and HLA haplotypes for HPA-1 incompatibility can be used antenatally to determine risk and guide antenatal intervention. If an HPA alloantibody is present, serial titres may be useful to determine risk, e.g. increasing titres are associated with a risk of FNAIT. If an HPA-1a alloantibody is not present, HLA haplotypes may be used determine risk of alloimmunization. The absence of HLA DRB3*01:01 is associated with very low risk of FNAIT. Alternatively, platelet products are made available on the day of delivery and neonatal platelet counts are determined immediately following delivery to determine if there is a need for platelet transfusion if antenatal intervention is not offered.

Open access Protocol

BMJ Open

HIP (HPA-screening in pregnancy) study: protocol of a nationwide, prospective and observational study to assess incidence and natural history of fetal/neonatal alloimmune thrombocytopenia and identifying pregnancies at risk

Dian Winkelhorst [1,2] Thijs W de Vos [2,3] Marije M Kamphuis,[4] Leendert Porcelijn,[5] Enrico Lopriore,[3] Dick Oepkes,[1] C Ellen van der Schoot,[2,6] Masja de Haas [7,8]

BMJ Open 2020;10:e034071.
doi:10.1136/bmjopen-2019-034071

CONCLUSION

Summary of Recommendations for Practice and Research	
What we know:	• NAIT is a platelet disorder caused by paternally inherited HPAs. • Affects first pregnancies. • Often undiagnosed prenatally due to lack of universal screening. • Can cause devastating effects on the neonate such as ICH from severely low platelet counts.
What needs to be studied:	• A universal screening protocol for all pregnant women using cell-free DNA should be implemented. • HPA-1a prophylax.is
What we can do today:	• Educate healthcare providers about the clinical manifestations and diagnosis of NAIT. • Include NAIT in differential diagnoses for thrombocytopenia, especially in a full-term, otherwise healthy infant. • Early diagnosis and treatment can minimize the severity of thrombocytopenia and deficits resulting from ICH. • With suspected NAIT, the treatment of choice is donor-matched, HPA-negative platelets and IVIG; however, treatment should not be delayed while awaiting a diagnosis and random donor platelets are often used at first.

Neonatal Alloimmune Thrombocytopenia, 2021

GRAZIE PER
L’ ATTENZIONE!

naitbabies.org
neonatal alloimmune thrombocytopenia