Piastrinopenia alloimmune feto-neonatale: marker predittivi e trattamento

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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 mie funzioni al fine di trarne vantaggio.

Antonella Matteocci

INTRODUZIONE

- La piastrinopenia alloimmune feto-neonatale (FNAIT) è una patologia rara (sottostimata) associata ad elevata morbidità e mortalità.
- Causa emorragie severe, in particolare a livello intracranico (ICH).
- Richiede una diagnosi tempestiva e trattamento appropriato.
- Sono necessari algoritmi condivisi per standardizzare i test diagnostici ed identificare le gravidanze ad alto rischio.
- Sono state pubblicate recentemente le raccomandazioni dell'International Collaboration for Transfusion Medicine Guidelines (ICTMG)

FNAIT: Prevenzione e Trattamento

Fetal/Neonatal Alloimmune Thrombocytopenia: Pathogenesis, Diagnostics and Prevention

Table 2 Characteristics of HDN and FNAIT; strategies for prevention and treatment

	HDFN/HDN	FNAIT
Pathogenesis	Alloantibodies to erythrocyte antigens	Alloantibodies to platelet antigens
Clinical symptoms	Hemolytic disease Most severe: hydrops fetalis	Petechiae, hematomas, melena, hemoptysis, retinal bleeding or hematuria Most severe: ICH in fetus or newborn
Immunization	>95 % cases during delivery; HDN risk in the next pregnancy	75 % of cases during delivery; 25 % of cases during pregnancy
Most frequent and most severe: others	Anti-D; risk in RhD negative women (15 % in Caucasian population) Anti-Rhc; E; K; others	Anti-HPA-1a; risk in HPA-1a negative women (2 % in Caucasian population) Anti-HPA-5a; other HPAs
Antigen characteristics	Rh proteins only on erythrocytes	HPA-1a present on integrin β3 on platelets and vascular endothelial cells
HLA restriction	Unknown	HLA DRB3*01:01
Frequency	1/1000–2000 (in the era of immunoprophylaxis)	1/1000–2000
Screening methods	RhD phenotyping in all pregnant women; anti-RhD examination 3× during pregnancy plus antibodies to other RBC antigens tested 2× during pregnancy[a]	Not performed
Doppler USG	Effective in detecting fetal anemia; therapeutic intervention can prevent hydrops fetalis	ICH can be detected but therapeutic intervention which minimize its effect are limited
Treatment	Effective; standardized	Effective; individualized
Immunoprophylaxis	Available for anti-D; not available for others	Under development for HPA-1a

HDFN hemolytic disease of the fetus and newborn

[a] Total number of tests in Poland 400,000 pregnancies × 5 = 2,000,000

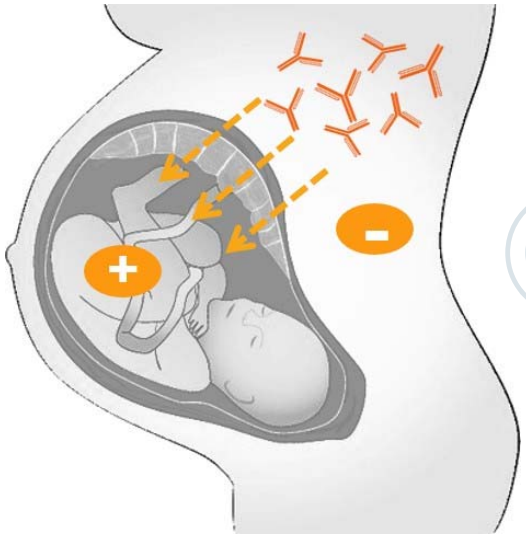
Arch. Immunol. Ther. Exp. (2016) 64:279–290

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Foetal and neonatal alloimmune thrombocytopenia—A rare, potentially serious and often underdiagnosed bleeding condition



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 nascita
-ICH antenatale 80% (II trim)
-ICH entro 96h dal parto
-Mortalità ICH: 9-48%

……Although FNAIT is considered as the platelet counterpart of HDFN there are still aspects of the disease pathogenesis that are not fully understood…..

FNAIT: INCIDENZA

1:1.000-2.000

- Refsum et al, 2018

Prima causa di piastrinopenia in neonati sani a termine

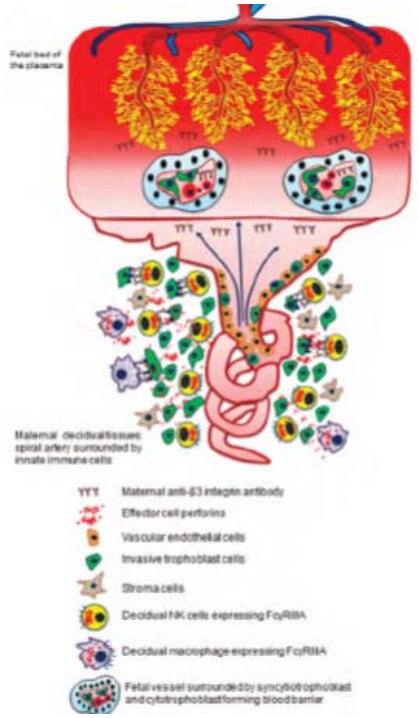
- Winkelhorst et al, 2017

3% piastrinopenie

27% piastrinopenie severe

Emorragia intracranica (ICH): 1:10.000

- Kjeldsen-Kragh et al, 2019



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

Epidemiology and management of fetal and neonatal alloimmune thrombocytopenia

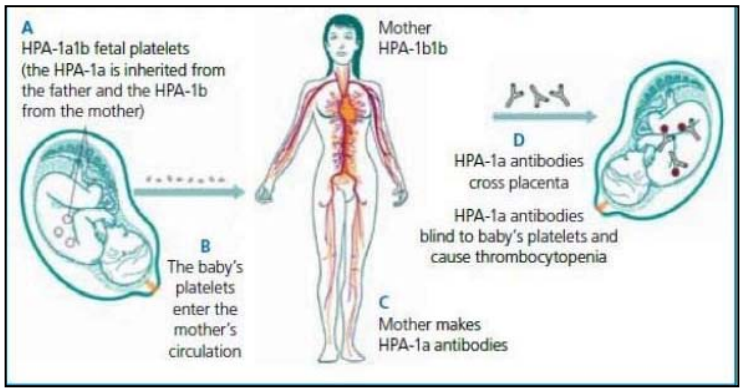
PII: S1473-0502(19)30277-0

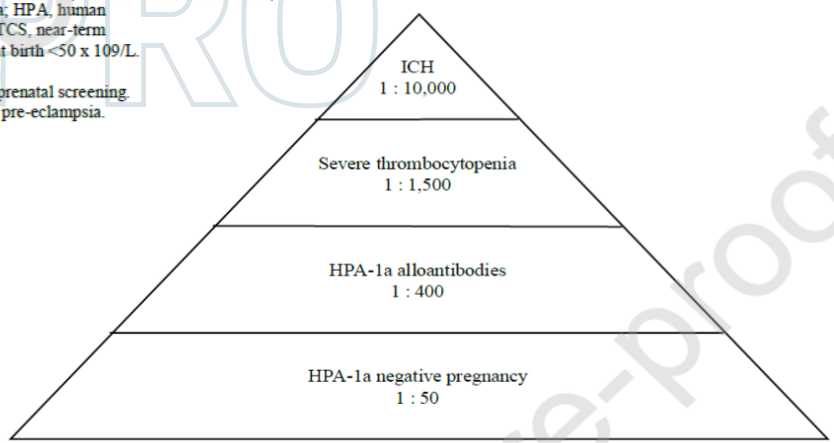
Transfusion and Apheresis Science, 31 December 2019

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

Author, year	HPA-1a negative	Antenatal anti-HPA-1a	PLT < 50 × 10⁹/l	Mild bleeding	Severe bleeding	Intervention
Mueller-Eckhardt, 1985 [36]	26/1,211 (2.1)	2/26 (7.7)	0	0	0	None
Reznikoff-Etievant, 1988 [37]	27/860 (3.1)	0/27 (0)	0	0	0	None
Blanchette 1990 [38]	81/5,000 (1.6)	3/50 (6.0)	1	0	1	NTCS, PP
Doughty, 1995 [42]	74/3,473 (3.2)	1/71 (1.4)	0*	0*	0	FBS/IUPT, IVIg, PP
Durand-Zaleski, 1996 [40]	52/2,066 (2.5)	4/45 (8.9)	1	0	0	FBS, IVIg, CTS
Williamson, 1998 [41]	618/24,417 (2.5)	37/385 (9.6)**	8	7	1	PP
Davoren, 2003 [42]	54/4,090 (1.3)	2/34 (5.9)	1	1	0	FBS, IUPT, PP
Maslanka, 2003 [43]	144/8,013 (1.8)	12/122 (9.8)	3	1	0	IUPT, IVIg
Turner, 2005 [44]	546/26,506 (2.1)	25/318 (7.9)	5	3	0	PP
Kjeldsen-Kragh, 2007 [45]	2,111/100,448 (2.1)	144/1,990 (7.2)	48	NR	2	NTSC, PP
Debska, 2018 [46]	373/15,204 (2.5)	22/373 (5.9)	3	NR	NR	IUPT, IVIg

Numbers are n/N (%). CST, antenatal corticosteroids; FBS, fetal blood sampling; FNAIT, fetal and neonatal alloimmune thrombocytopenia; HPA, human platelet antigen; IUPT, intrauterine platelet transfusion; IVIg, antenatal intravenous immunoglobulins; NR, not reported; NT, not tested; NTCS, near-term cesarean section; PLT, platelet count; PP, postnatal platelets available for transfusion. Severe FNAIT is defined as neonatal platelet count at birth <50 x 109/L. Mild bleeding is defined as only skin or mucosal bleeding. Severe bleeding is defined as internal organ hemorrhage or ICH.
*One HPA-1a negative women delivered two severely affected twin children, anti-HPA-1a antibodies detected after birth, not detected by prenatal screening.
** Two pregnancies ended in loss of the baby, one at 15 weeks, another as neonatal death from immaturity after CS at 25 weeks for severe pre-eclampsia.





HPA: Human platelet antigen, FNAIT: Fetal and neonatal alloimmune thrombocytopenia, ICH: intracranial haemorrhage, Severe thrombocytopenia is defined as a platelet count below 50 × 10⁹/L.

FNAIT: Meccanismo patogenetico

IgG materne attraversano la placenta

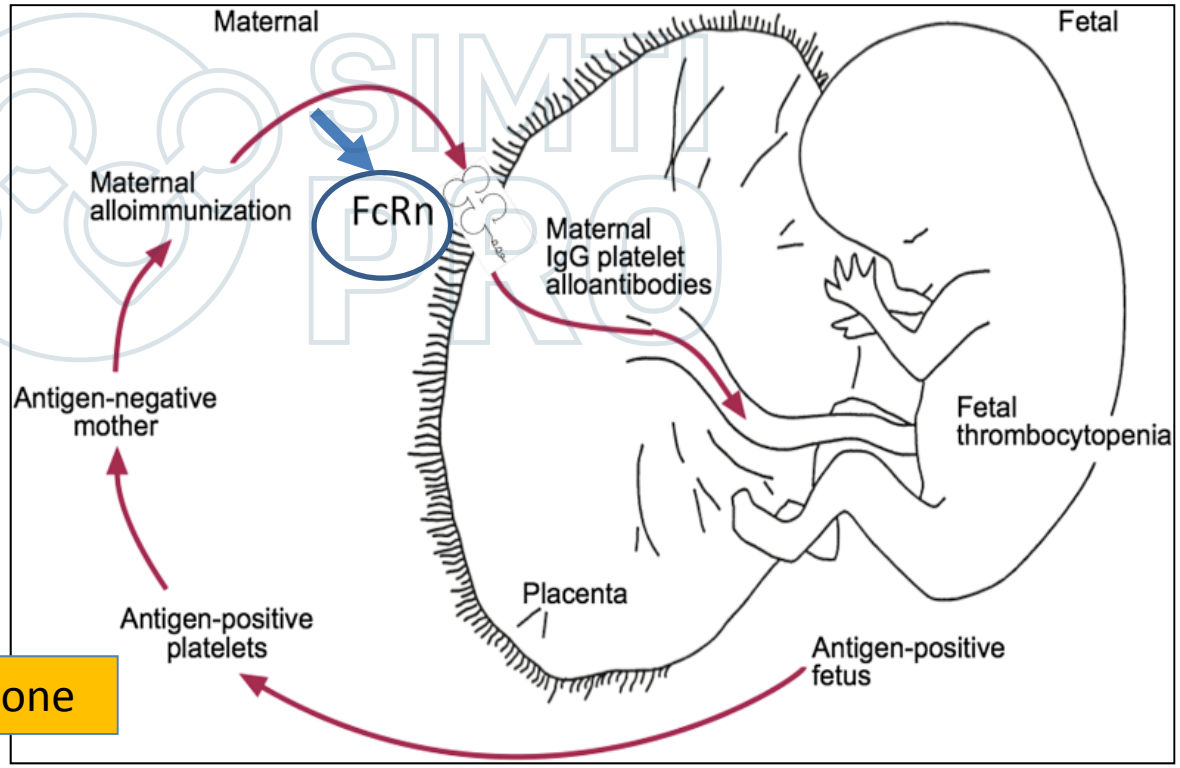
Distruzione piastrine fetali

Inibizione megacariopoiesi fetale

Anticorpi materni diretti verso antigeni ereditati dal padre

Può manifestarsi anche in prima gravidanza

16^ settimana di gestazione



Brojer et al, 2016
Liu et al, 2015

FNAIT: Quadro clinico

Table 1 Classification of fetal and neonatal thrombocytopenias

	Condition
Fetal	**Alloimmune** **Congenital infection** (e.g. CMV, toxoplasma, rubella, HIV) **Aneuploidy** (e.g. trisomies 18, 13, 21, or triploidy) **Autoimmune** (e.g. ITP, SLE) Severe Rh haemolytic disease Congenital/inherited (e.g. Wiskott-Aldrich syndrome)
Early onset neonatal (<72 hours)	**Placental insufficiency** (e.g. PET, IUGR, diabetes) **Perinatal asphyxia** **Perinatal infection** (e.g. *E coli*, GBS, *Haemophilus influenzae*) **DIC** **Alloimmune** **Autoimmune** (e.g. ITP, SLE) Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Thrombosis (e.g. aortic, renal vein) Bone marrow replacement (e.g. congenital leukaemia) Kasabach-Merritt syndrome Metabolic disease (e.g. proprionic and methylmalonic acidaemia) Congenital/inherited (e.g. TAR, CAMT)
Late onset neonatal (>72 hours)	**Late onset sepsis** **NEC** Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g. proprionic and methylmalonic acidaemia) Congenital/nherited (e.g. TAR, CAMT)

Piastrinopenia isolata senza altre cause cliniche (nadir entro 48h)

(Diagnosi differenziale)

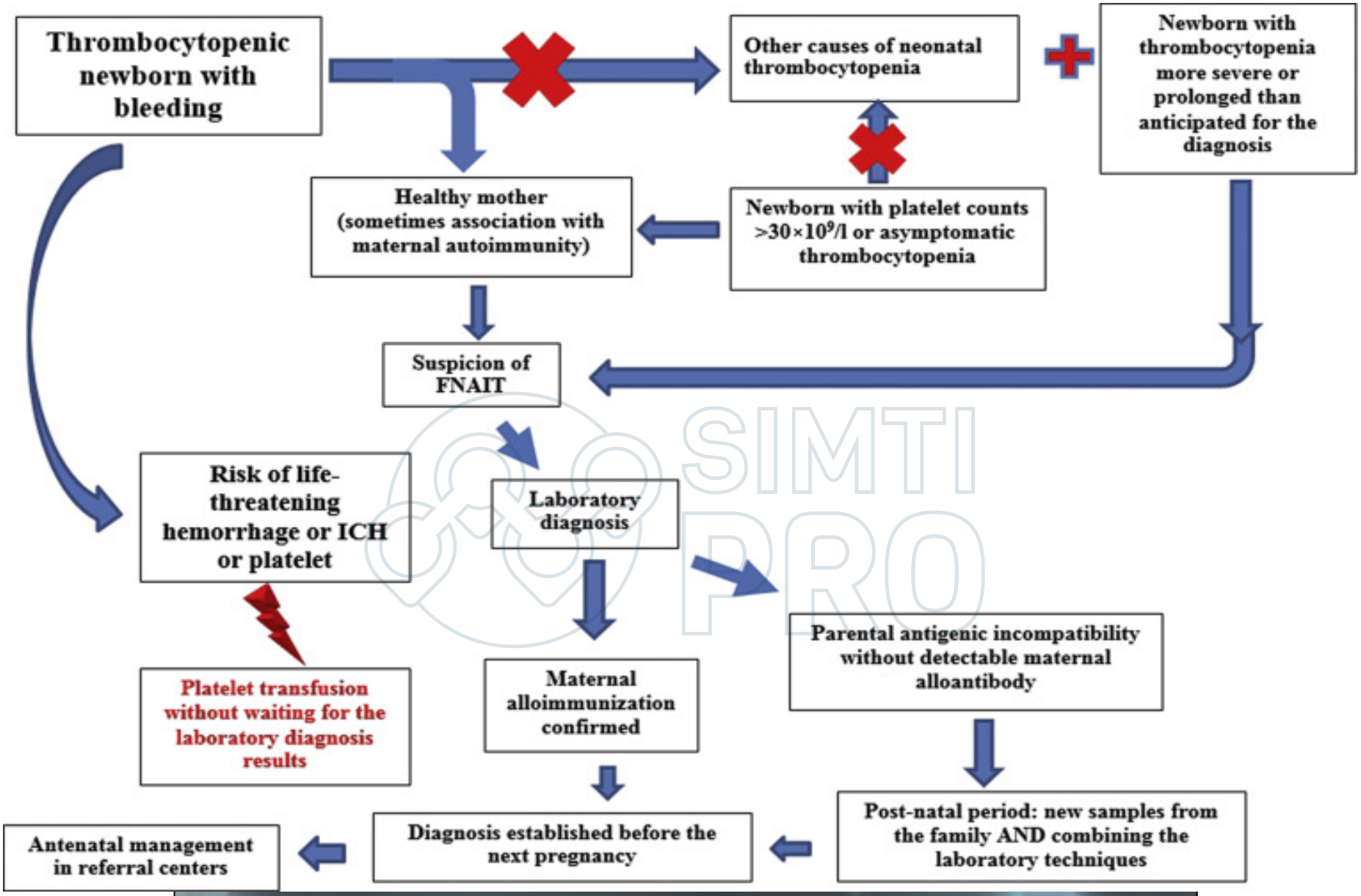
Nei casi lievi o moderati il quadro si risolve entro 1-5 settimane

Asintomatico, petecchie, porpora, ematomi, emorragie retiniche, polmonari o gastrointestinali, **ICH**

Quadri severi rari, conseguenze cliniche severe per il feto/neonato, spese sanitarie molto costose

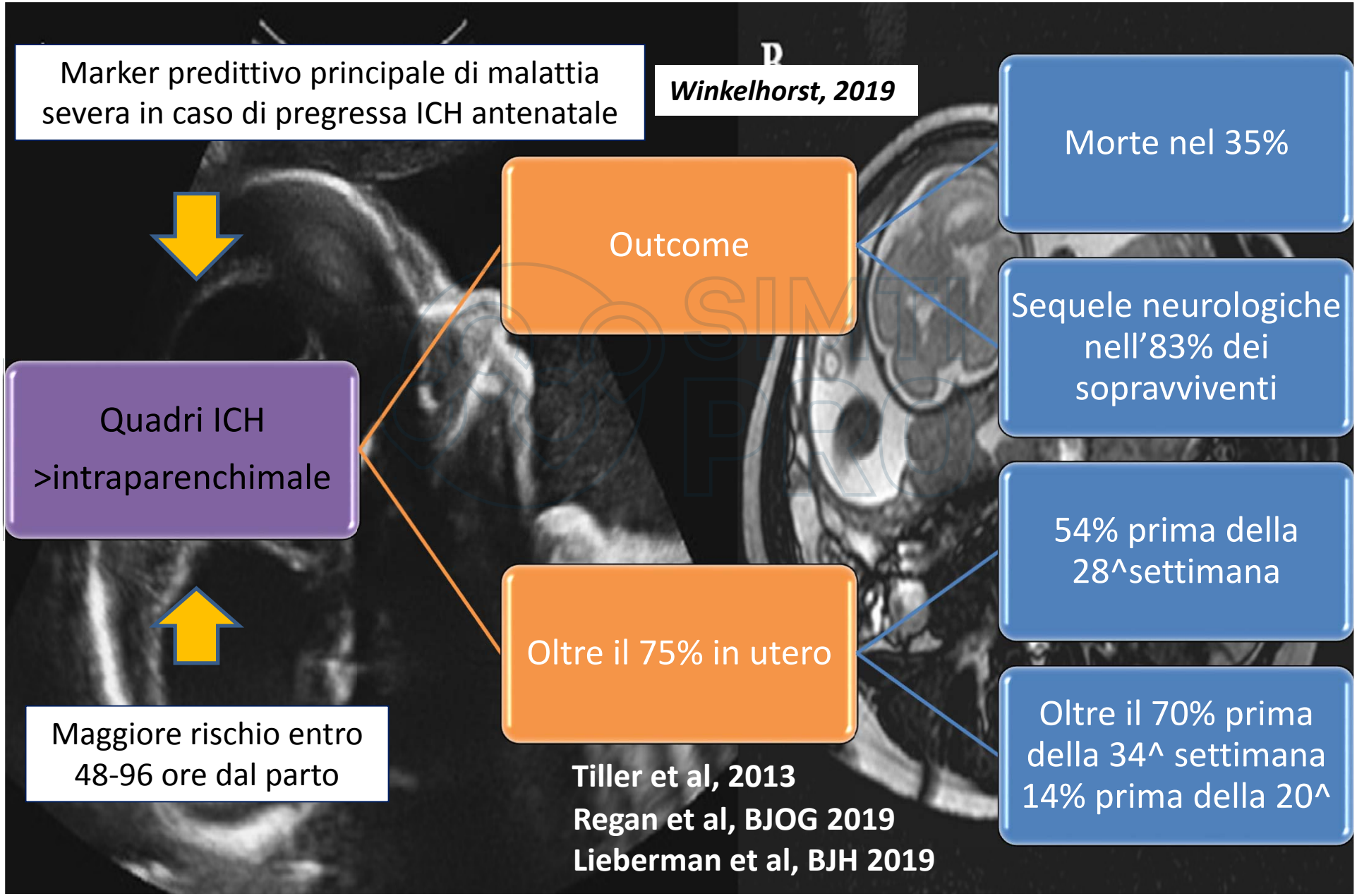
Piastrinopenia $<50x10^9/l$, severa: $<25x10^9/l$

Regan et al, BJOG 2019
Lieberman et al, BJH 2019



Platelet 2019, https://doi.org/10.1016/B978-0-12-813456-6.00045-X

Emorragia intracranica



Antigeni Piastrinici

- *Antigeni in comune con eritrociti (ABO, I,P,Le)*
- *Antigeni in comune con leucociti(HLA -A,B,C)*
- *Antigeni piastrino-specifici (HPA)*

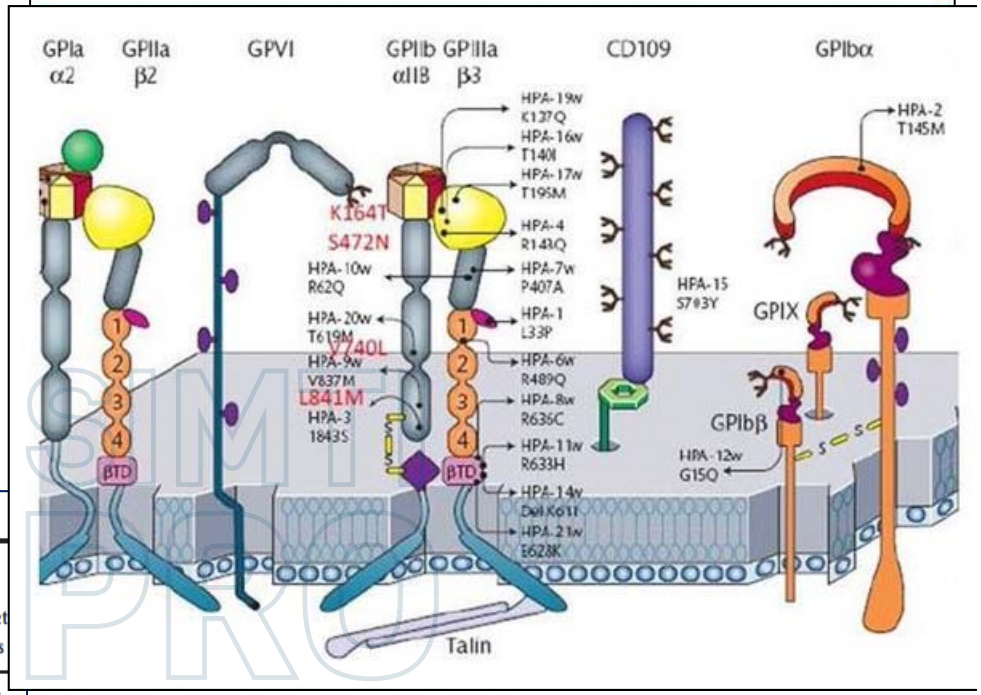


Table 1 Human platelet allo-antigens **www.ebi.ac.uk/ipd/hpa/**

Biallelic HPA	Allele frequency[a]					
Antigens	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-2a	85 a/a	71	95	GPIbα / T145M	*GPIBA* / C524T	FNAIT, PTP, MPR
HPA-2b	14 a/b	29	5			
	1 b/b					
HPA-3a	37 a/a	68	59.5	GPIIb / I843S	*ITGA2B* / T2621G	FNAIT, PTP, MPR
HPA-3b	48 a/b	32	40.5			
	15 b/b					
HPA-4a	>99.9 a/a	100	99.5	GPIIIa / R143Q	*ITGB3* / G526A	FNAIT, PTP, MPR
HPA-4b	< 0.1 a/b	0	0.5			
	< 0.1 a/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					
HPA-15a	35 a/a	65	53	CD109 / Y703S	*CD109* / A2108C	FNAIT, PTP, MPR
HPA-15b	42 a/b	35	47			
	23 b/b					

Glicoproteina IIb/IIIa

GPIIb(CD41) e GPIIIa(CD61), geni su cromosoma 17 , circa 80.000 molecole/piastrina

Presenti 24/37 HPA

Assenza complesso IIb/IIIa: Tromboastenia di Glanzmann

Specificità anticorpali e limiti diagnostici

Anti-HPA1a	Anti-HPA5b	Anti-HPA15b	Anti-HPA1b	Anti-HPA3a, Anti-HPA5a
75-90%	8-15%	4%	1-4%	1-2%

British Journal of Haematology, 2015, 171, 671–682

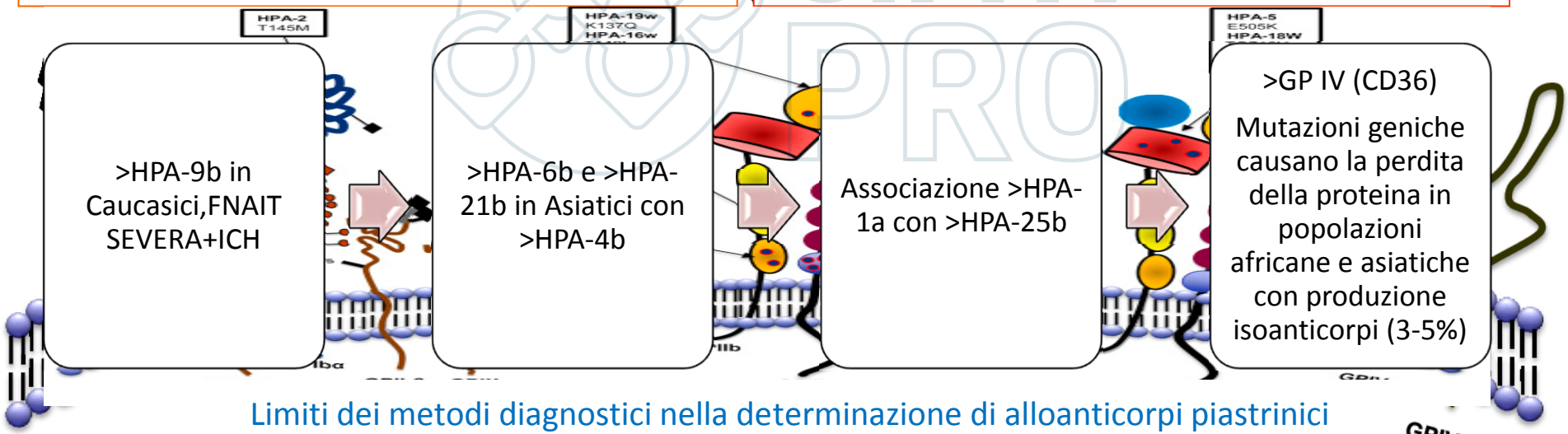
FNAIT DA ANTICORPI ANTI-HPA A BASSA FREQUENZA

Transfusion. 2014 May ; 54(5): 1286–1293. doi:10.1111/trf.12450.

LOW FREQUENCY HUMAN PLATELET ANTIGENS (HPA) AS TRIGGERS FOR NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)

Transfusion. 2010 February ; 50(2): 324–333. doi:10.1111/j.1537-2995.2009.02438.x.

New low-frequency platelet glycoprotein polymorphisms associated with neonatal alloimmune thrombocytopenia



Limiti dei metodi diagnostici nella determinazione di alloanticorpi piastrinici

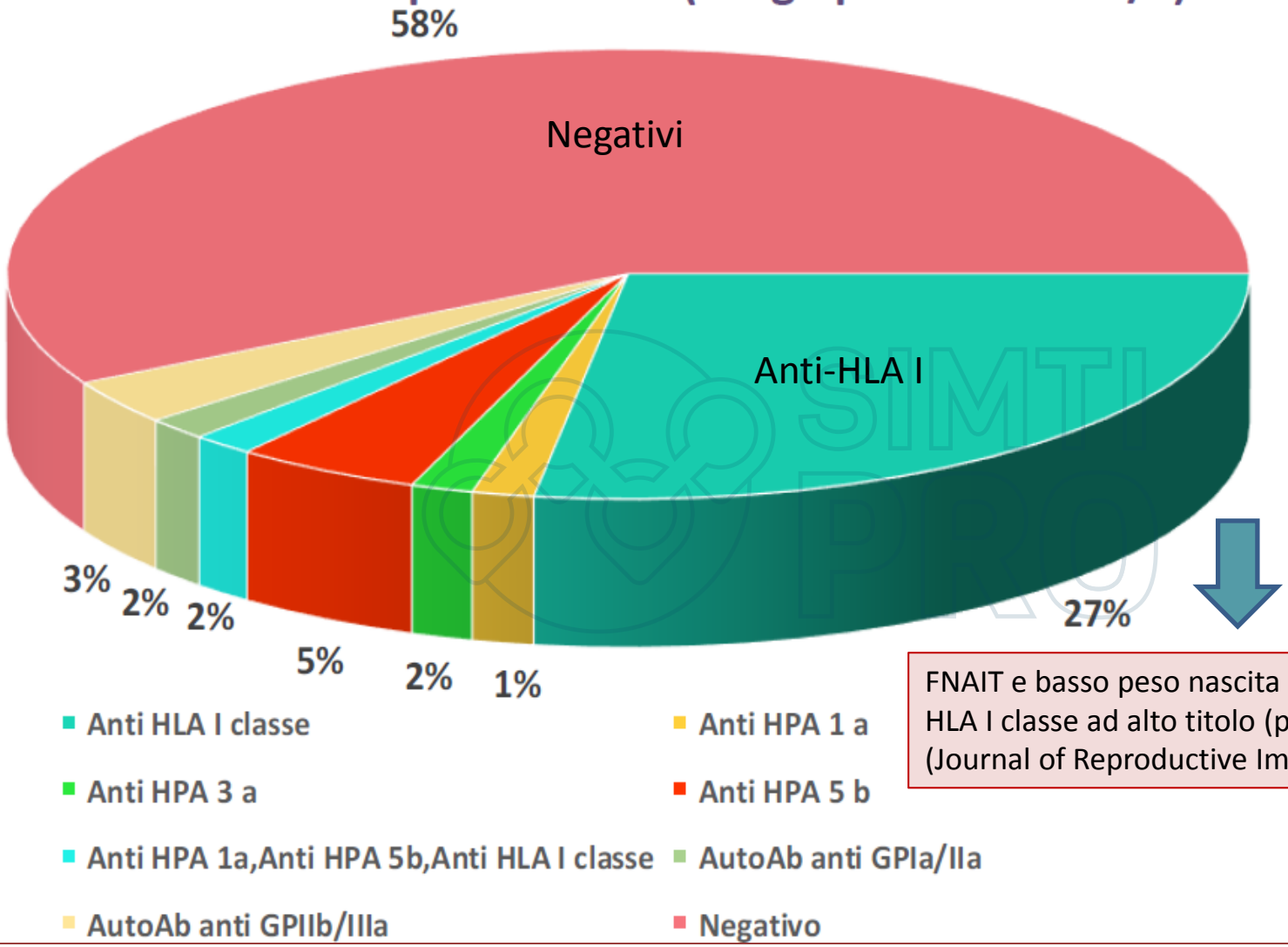
2/3 dei casi di sospetta NAIT rimangono irrisolti (anti-HLA)
BJH, 2013

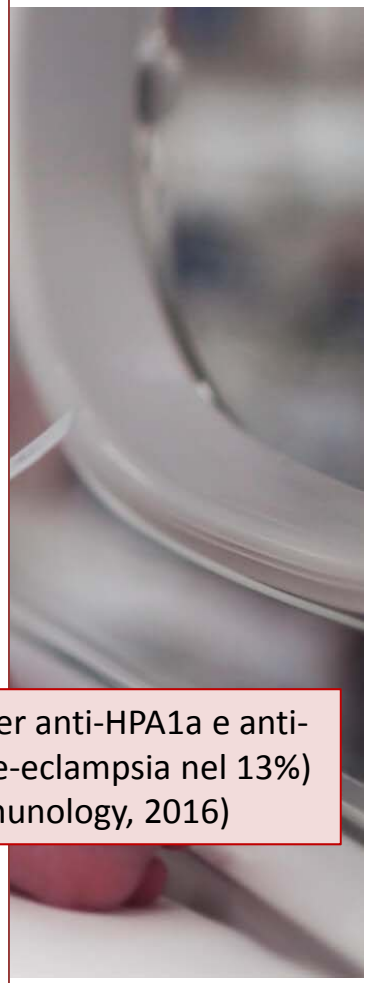
HPA-3
labilità epitopi

HPA-15
1.000 siti

Falsi Negativi: basso titolo, IVIG, antigeni non presenti nei kit

Ospedale S. Camillo (anni 2010-2019)
62 casi di sospetta FNAIT (range plt 11-60x10^9/L)





FNAIT e basso peso nascita per anti-HPA1a e anti-HLA I classe ad alto titolo (pre-eclampsia nel 13%) (Journal of Reproductive Immunology, 2016)

FNAIT: Sistemi diagnostici

- SPRCA (fase solida)
- ELISA: MACE, MAIPA
- Citofluorimetria
- Bead-Based Assay
- PCR SSP, Microarray fase solida e liquida

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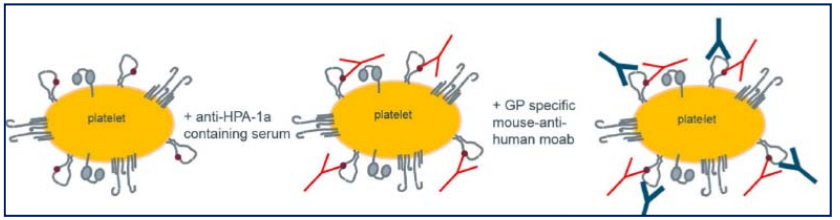
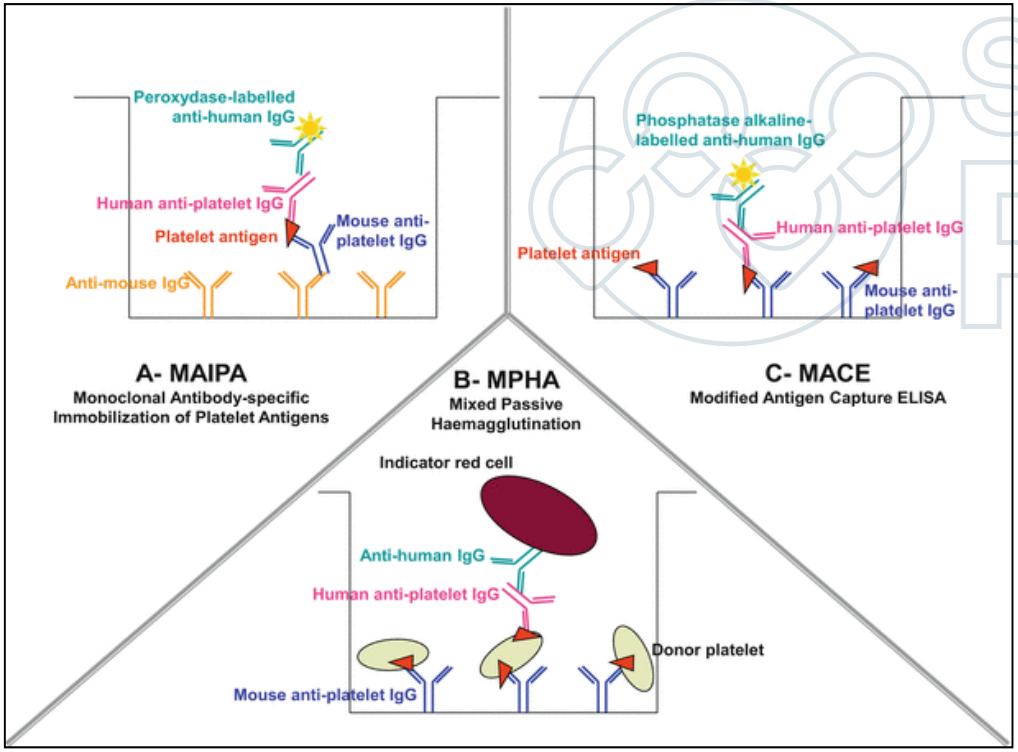
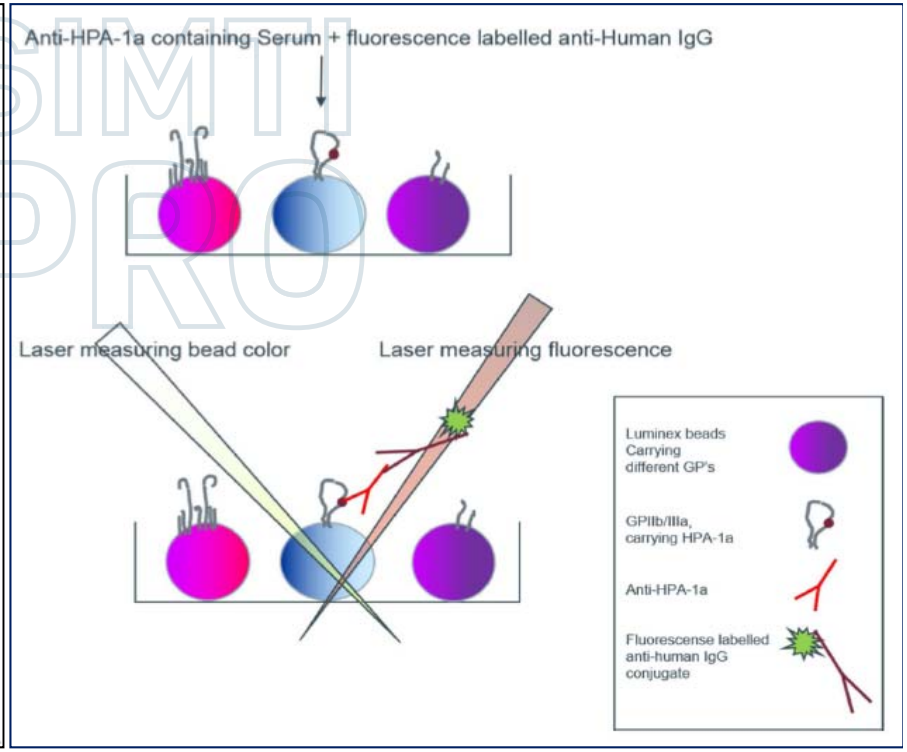
Progress and development of platelet antibody detection







FNAIT: Algoritmo Diagnostico

Sospetta FNAIT in gravidanza: Neonato Piastrinopenico (<50x10^9/L)

Ricerca anticorpi >HPA, >HLA I (SPRCA, ELISA)

NEG

Cross-match (SPRCA)

POS

Padre

Tipizzazione HPA

Raccomandazioni per l'impiego delle metodiche molecolari

Madre

Si suggerisce di avviare all'analisi molecolare dei sistemi HPA-1, 3, 4, 5, 15 donne in gravidanza con alloimmunizzazione HPA e con storia pregressa di feti/neonati con emorragia cerebrale e i loro partner, feti di donne nella suddetta condizione se il padre è eterozigote per l'antigene piastrinico coinvolto,

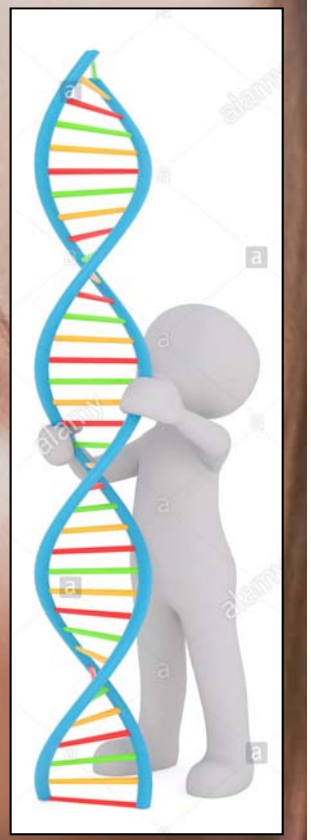
Se eterozigote genotipizzazione HPA fetale

Tipizzazione HPA (Microarray, PCR-SSP)

Neonato

Ricerca anticorpi >HPA, HLA I

Tipizzazione HPA



D. Winkelhorst, D. Oepkes / Best Practice & Research Clinical Obstetrics and Gynaecology, 2019

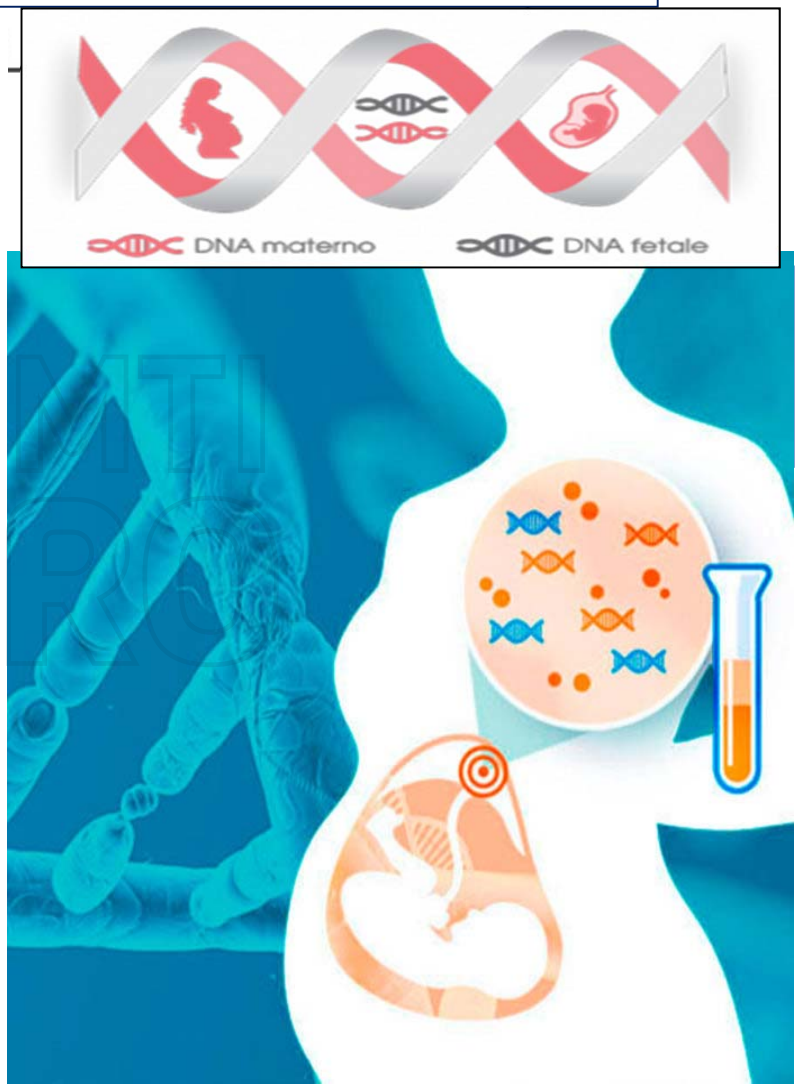
Recent advances in non-invasive fetal HPA-1a typing

Transfusion and Apheresis Science, 31 December 2019
DOI: https://doi.org/10.1016/j.transci.2019.102708

Table 1. Overview of currently applied fetal HPA-1a genotyping methods

Method	Requirements	Earliest time	Advantages	Disadvantages
Real-time PCR post-MspI digestion	Real-time instrument	2nd trimester 18 weeks	Sequence-specific restriction enzyme digestion of HPA-1b allele minimizes unspecific amplification	Requires pre-PCR processing with increased sample manipulation False positive results due to incomplete digestion
Allele-specific Real-time PCR	Real-time instrument	2nd trimester 18 weeks	Simple PCR assay Straightforward approach	Sufficient allele specificity difficult to achieve No internal control for fetal DNA
PCR HRM	Real-time instrument with melting curve analysis software	2nd trimester 15 weeks	Simple PCR assay Low cost Unique intercalating dye No need for labelled probes	No internal control for fetal DNA
COLD-PCR	Real-time instrument	1st trimester* 12 weeks	Simple PCR assay Increased sensitivity compared to conventional real-time PCR assays	No internal control for fetal DNA
Targeted Massive Parallel Sequencing	Expensive NGS platforms	1st trimester* 13 weeks	Unbiased amplification of mother and fetal sequences Deep coverage Internal controls for presence of fetal DNA	High cost per sample Bioinformatics skills needed for analysis of the results
Digital PCR	Expensive microfluidic PCR device	1st trimester* 8 weeks	Low volume of reagents Partitioning minimizes maternal allele competition High sensitivity High accuracy	Poor signal threshold may lead to false positives Droplet volume variability affects accurate quantification

*Earliest time for its application only evaluated in a small number of samples. Further studies with a larger number of 1st trimester samples are required.



FNAIT: Immunizzazione anti-HPA1a

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

Incidenza

- 2% sono HPA1bb
- 30% madri con feto HPA-1a positivo e 10% forma anticorpi
- 20-30% neonati presenta NAIT severa

HLA DRB3*01:01

- Presente nel 30% della popolazione
- Aumentato rischio di immunizzazione anti HPA-1a (>90% delle donne con DRB3*01:01 producono l'anticorpo)

Basi molecolari

- Sostituzione Leu33in HPA-1a e Pro33 in HPA-1b
- Alta affinità del peptide Leu33 sulla GP IIIa con il peptide del sito di presentazione di DRB3*01:01

Kjeldsen-Kragh et al, Blood Avances 2019
Kjeldsen-Kragh et al, Transfusion 2019

FNAIT: Rischio Immunizzazione anti-HPA1a - 1

Risk of HPA-1a–immunization in HPA-1a–negative women after giving birth to an HPA-1a–positive child

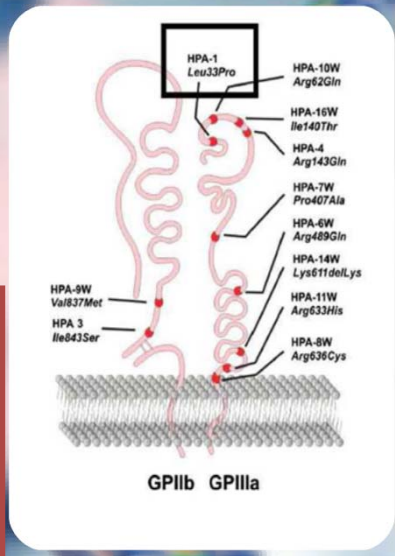
TRANSFUSION 2019

HLA-DRB3*01:01 positive

HPA-1a negative

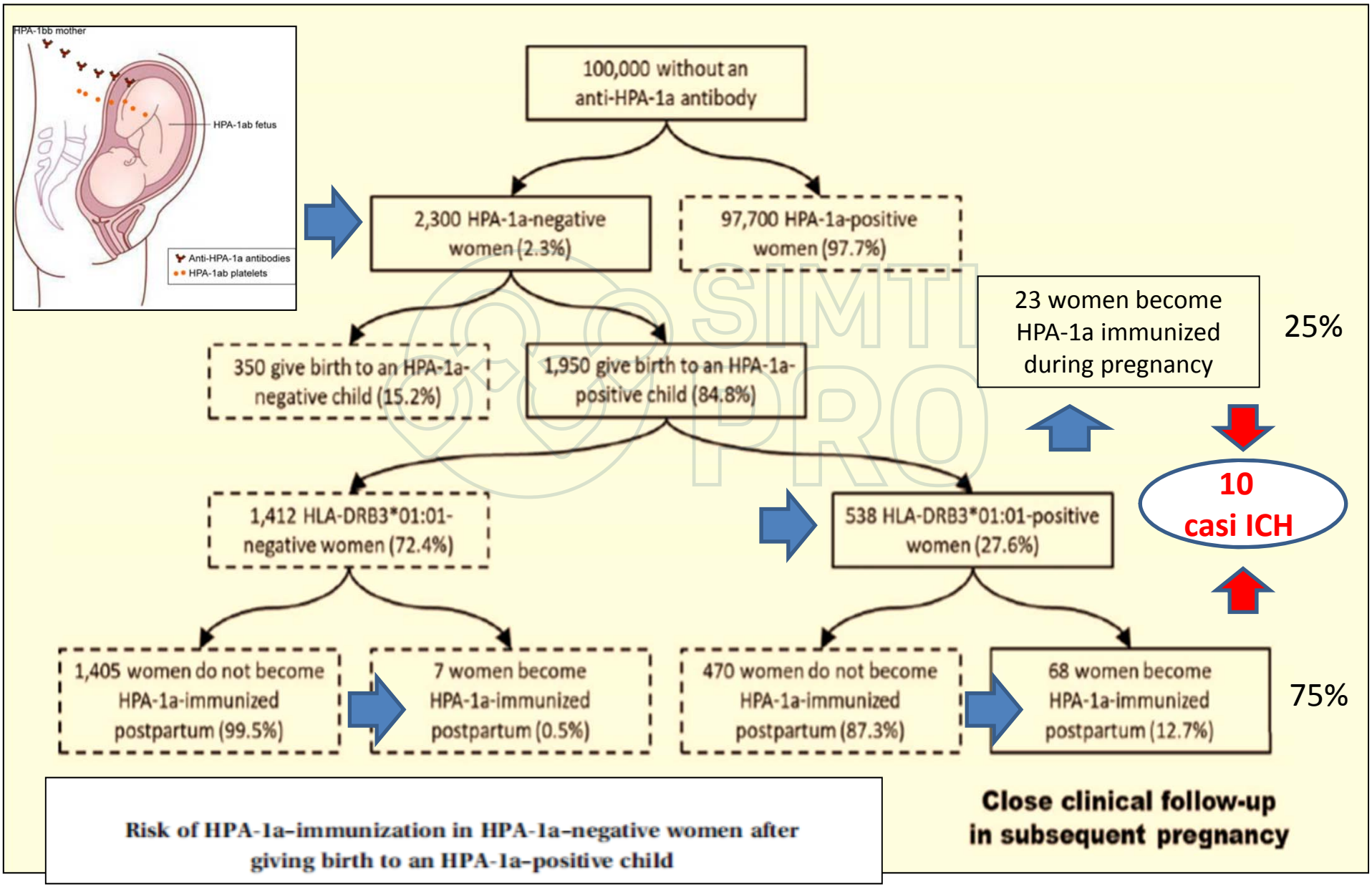
Rischio di immunizzazione dopo il parto	Rischio di immunizzazione dopo il parto
12,7%	0,5%
(25 volte più elevato)	

HLA-DRB3*01:01 negative



Non è stata valutata la correlazione tra nullipare e multipare e la zigosità dell'allele.

FNAIT: Rischio Immunizzazione anti-HPA1a - 2



FNAIT: Ruolo dell'allele HLA DRB3*01:01

HLA-DRB3*01:01 exhibits a dose-dependent impact on HPA-1a antibody levels in HPA-1a–immunized women

9 APRIL 2019 · VOLUME 3, NUMBER 7 blood advances

Key Points

- HLA-DRB3*01:01 has a dose-dependent impact on HPA-1a antibody levels in HPA-1a–immunized women giving birth to an HPA-1a–positive child.
- HLA-DRB3*01:01 has a dose-dependent impact on the neonatal platelet counts in HPA-1a–positive children born of HPA-1a–immunized women.

N.130 HPA-1a–immunized women were divided into 3 groups

	Group 1	Group 2	Group 3
HLA-DRB3*01:01	HLA-DRB3*01:01 negative	HLA-DRB3*01:01 heterozygous	HLA-DRB3*01:01 homozygous
Anti-HPA-1a levels	1.5 IU/mL (0.0-19.0 IU/mL)	21.1 IU/mL (0.0-1967 IU/mL)	43.7 IU/mL (1.0-980 IU/mL)
Neonatal platelet counts	241 x 109/L (59 x 109/L to 393 x 109/L)	107 x 109/L (4 x 109/L to 387 x 109/L)	32 x 109/L (4 x 109/L to 352 x 109/L)

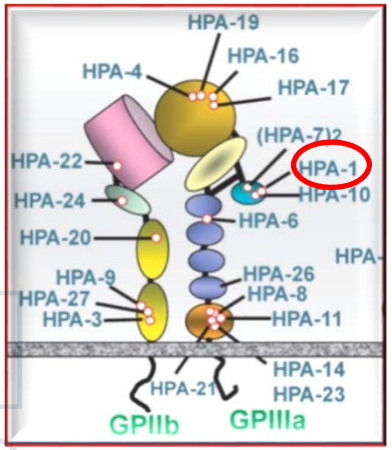
Foetal and neonatal alloimmune thrombocytopenia – The role of the HLA-DRB3*01:01 allele for HPA-1a-immunisation and foetal/neonatal outcome

Transfusion and Apheresis Science, 31 December 2019
DOI: https://doi.org/10.1016/j.transci.2019.102707

Table 2: Association between foetal/neonatal outcome and maternal HLA-DRB3*01:01 carrier status in HPA-1a-immunised women – pooled data from 4 prospective FNAIT studies [19-21, 25]*

Neonatal platelet counts	# of HLA-DRB3*01:01 positive	# of HLA-DRB3*01:01 negative
# of children with ≥ 50 × 10^9/L	125	18
# of children with < 50 × 10^9/L (# of children with ICH)	66 (3)	0
Total	191	18

P = 0.001 (Fisher's exact test).



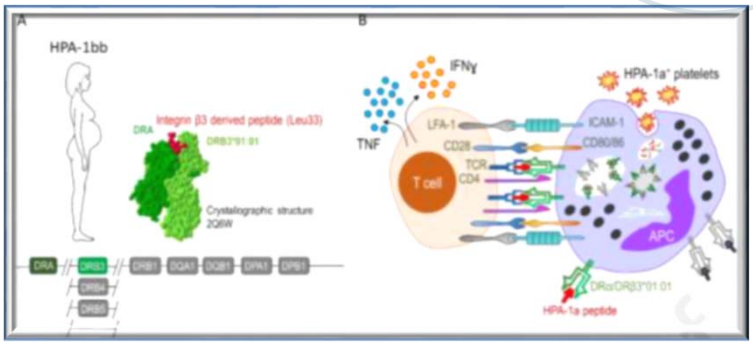


Table 3: Association between foetal/neonatal outcome and maternal HLA-DRB3*01:01 carrier status irrespective of HPA-1a-immunisation status – pooled data from 3 prospective FNAIT studies [19-21]*

Neonatal platelet counts	# of HLA-DRB3*01:01 positive	# of HLA-DRB3*01:01 negative
# of children with ≥ 50 × 10^9/L	253	470
# of children with < 50 × 10^9/L	18	0
Total	271	470

Although not reported, it is assumed that none of the HLA-DRB3*01:01 negative non-immunised women in the control groups gave birth to severely thrombocytopenic children.

P = 0.00001 (Fisher's exact test).

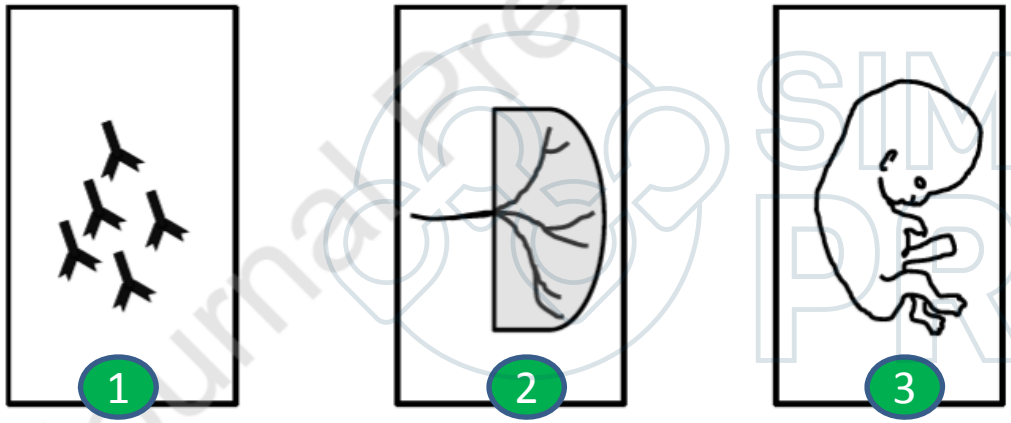
Prospects for risk stratification of anti-HPA-1a alloimmunized pregnant women

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

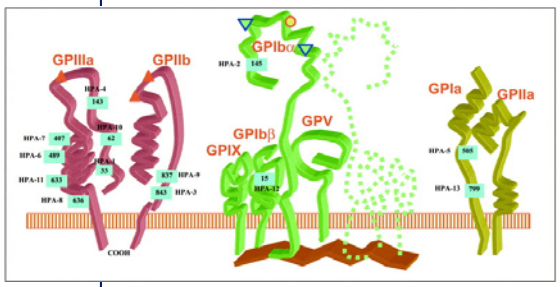


maternal
subtype
glycosylation
specificity
effector function: platelets
effector function: trophoblast
effector function: EC
antibody level

fetal-maternal interface
efficacy of transfer

intra-fetal
gender
C-reactive protein

- 19 -



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

Anticorpi anti-HPA1a materni

QUANTITA'

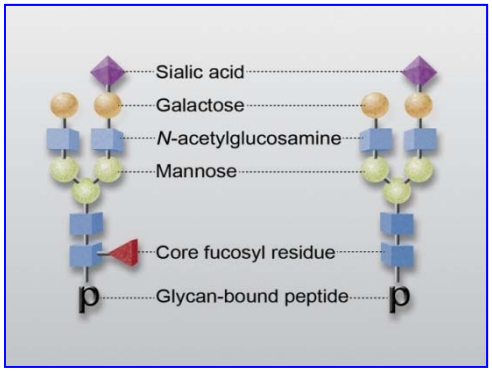
No correlazione lineare tra piastrinopenia e ICH

QUALITA'

Concentrazione - Titolo

PPV 54%, NPV 95%

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



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.

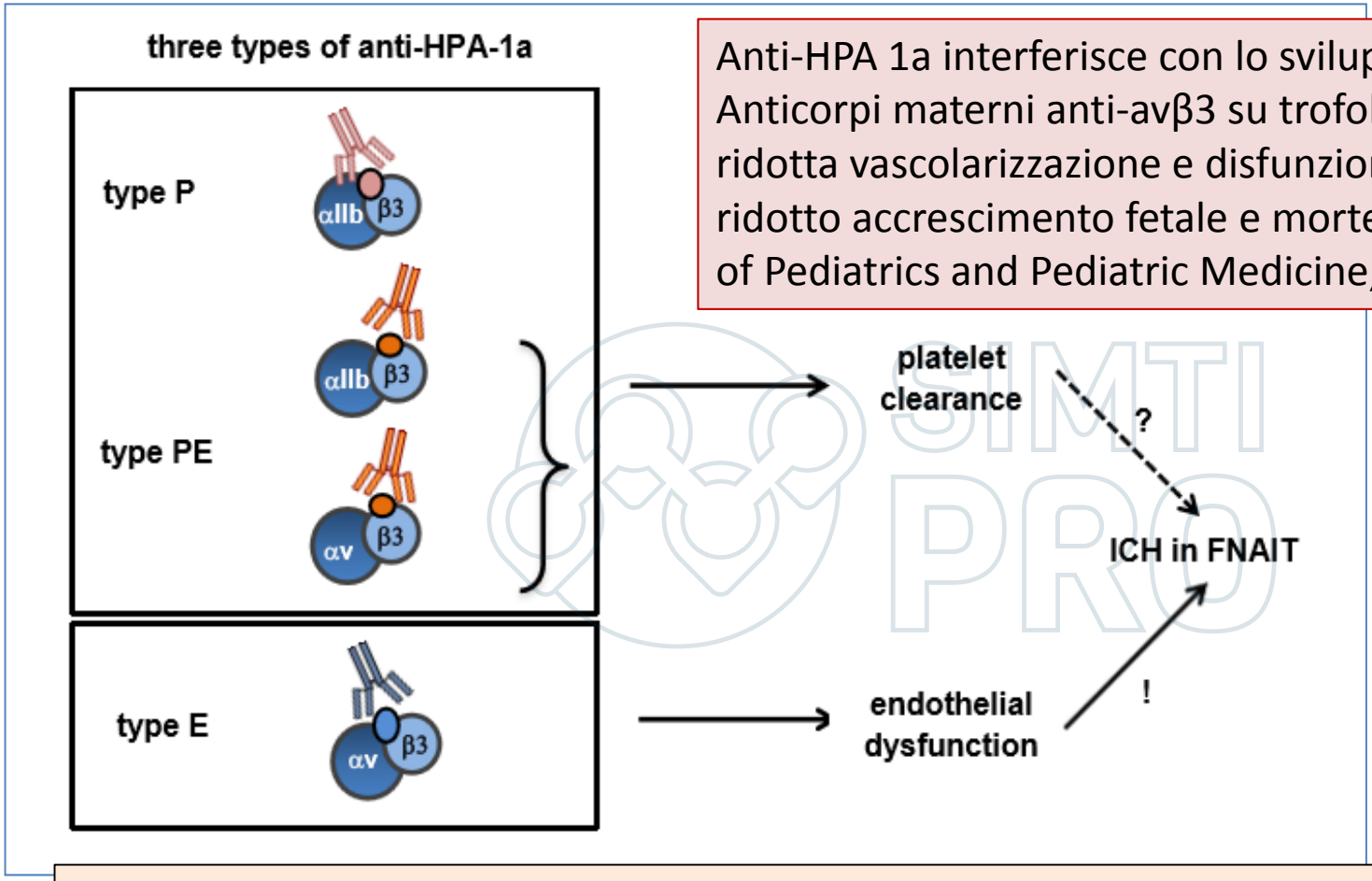
Ruolo del titolo anticorpale

Risk stratification in HPA-1a immunized pregnant women https://doi.org/10.1016/j.transci.2019.102709

Factor	Evidence of risk modulation		Test feasibility	Potential for risk stratification	Consider in further studies?	References
	experimental (case series > 20)	clinical (prospective study)				
	yes/no	*yes/no*	*easy/advanced/difficult*	*none/low/intermediate/high*	*yes/no*	
Anti-HPA-1a isotype	no	no	easy	low	yes	[11-13]
Anti-HPA-1a core fucosylation	yes	no	difficult	intermediate (no decision level)	yes	[1819]
Functional capacity of anti-HPA-1a:platelets	yes	no	advanced	intermediate (too few reports)	yes	[26]
Functional capacity of anti-HPA-1a:endothelial cells	yes	no	difficult	high	yes	[25]
Functional capacity of anti-HPA-1a: placenta	yes	no	easy	none*	yes	[29,30]
Anti-HPA-1a antibody level	yes	yes	easy	intermediate (NPV:95% CI: 86 – 98%)	yes	[36]
Placenta function: FcRn	no	no	easy	none	no	[47]
Fetal gender	yes	yes	easy	low	yes	[4]
Fetal CRP	yes	no	easy	none*	yes	[49]

*results are not available during pregnancy (only after delivery) and are therefore considered to have no potential for risk stratification in a HPA-1a immunized pregnant woman.

Tre specificità anticorpali e ICH

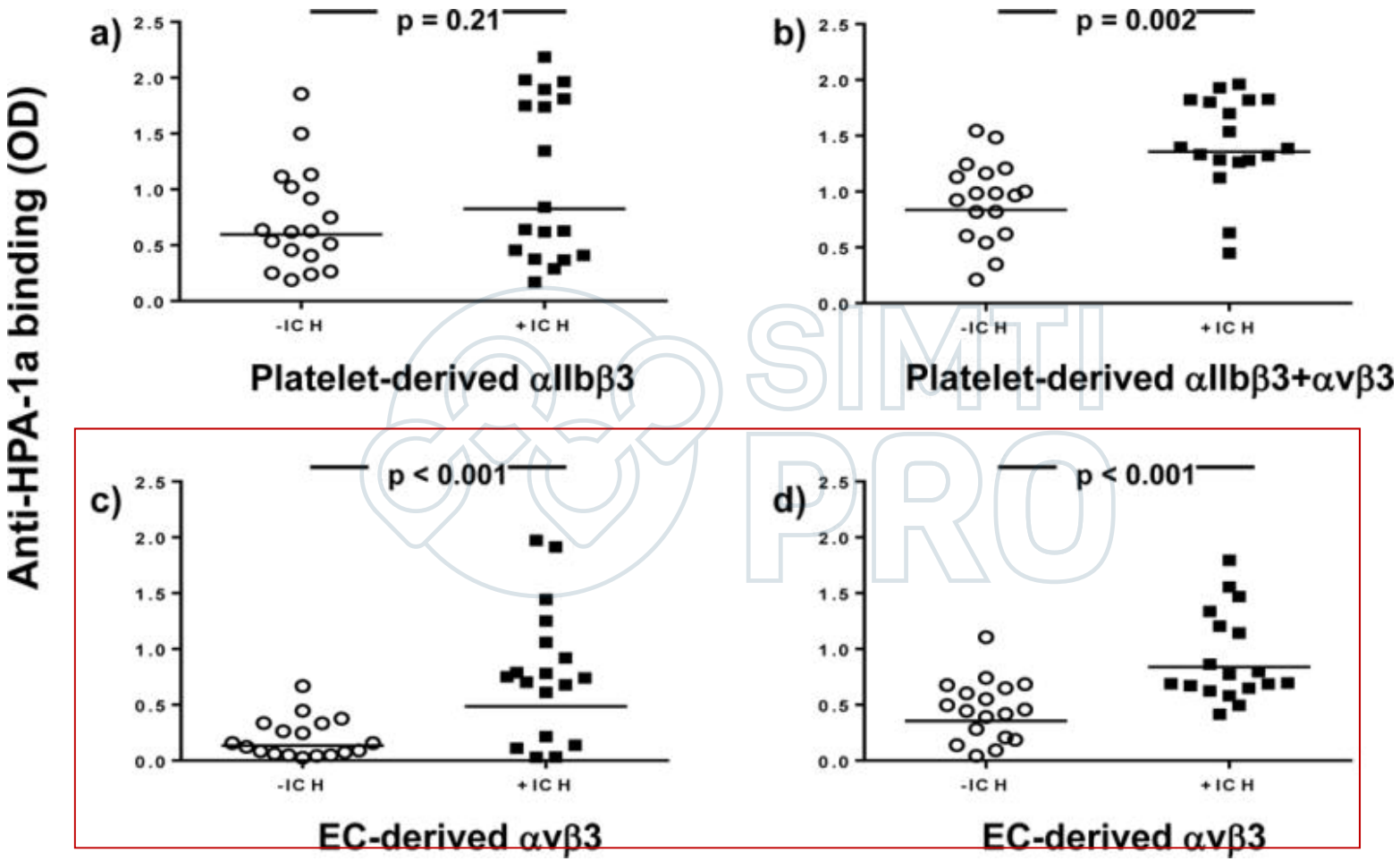


Anti-HPA 1a interferisce con lo sviluppo placentare
Anticorpi materni anti-avβ3 su trofoblasto causano ridotta vascolarizzazione e disfunzione placentare, ridotto accrescimento fetale e morte in FNAIT (Journal of Pediatrics and Pediatric Medicine, 2018)

anti-HPA-1a is not a single antibody entity: anti-β3, anti-aIIbβ3, and anti-avβ3 (ICH+)

Analysis of anti–HPA-1a antibodies of the anti–αvβ3 subtype in maternal serum has potential in the diagnostic prediction of ICH development and may allow for modification of prophylactic treatment in fetal/neonatal alloimmune thrombocytopenia

Dati clinici e diagnostici in ICH- e ICH+



Antiendothelial αvβ3 Antibodies Are a Major Cause of Intracranial Bleeding in Fetal/Neonatal Alloimmune Thrombocytopenia

Arterioscler Thromb Vasc Biol. 2016;36:1517-1524

Raccomandazioni ICTMG

Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach

British Journal of Haematology, 2019

Lani Lieberman,[1,2] Andreas Greinacher,[3] Michael F. Murphy,[4] James Bussel,[5] Tamam Bakchoul,[6] Stacy Corke,[7] Mette Kjaer,[8,9] Jens Kjeldsen-Kragh,[9,10] Gerald Bertrand,[11] Dick Oepkes,[12] Jillian M. Baker,[13] Heather Hume,[14] Edwin Massey,[15] Cécile Kaplan,[16] Donald M. Arnold,[17] Shoma Baidya,[18] Greg Ryan,[1,19] Helen Savoia,[20] Denise Landry,[21] Nadine Shehata[1,19,22] and for the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

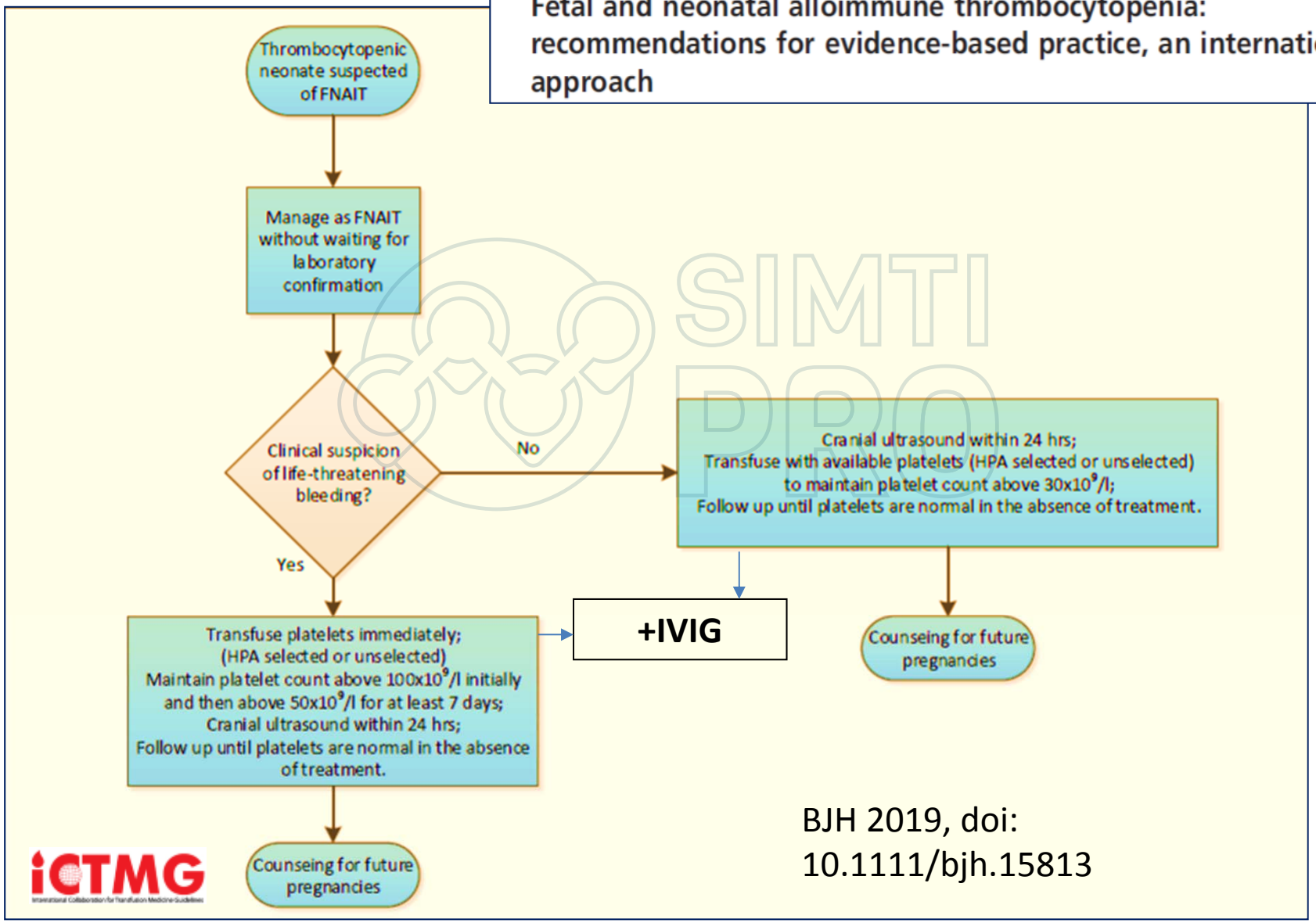
Table I. References used for guidance on FNAIT.

Guideline topics	Number of citations included: Randomized studies	Number of citations included: Nonrandomized studies
Postnatal management	0	13
Antenatal management	5	24
Economic Studies for Screening	0	3
HPA alloimmunization	0	15
HLA DRB3*0101 as risk factor for alloimmunization	0	13
Non-invasive prenatal testing	0	3

FNAIT, fetal and neonatal alloimmune thrombocytopenia; HLA, human leucocyte antigen; HPA, human platelet antigen.

Algoritmo ICTMG post-natale

Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach



BJH 2019, doi: 10.1111/bjh.15813

Management ante e post-natale

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

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.

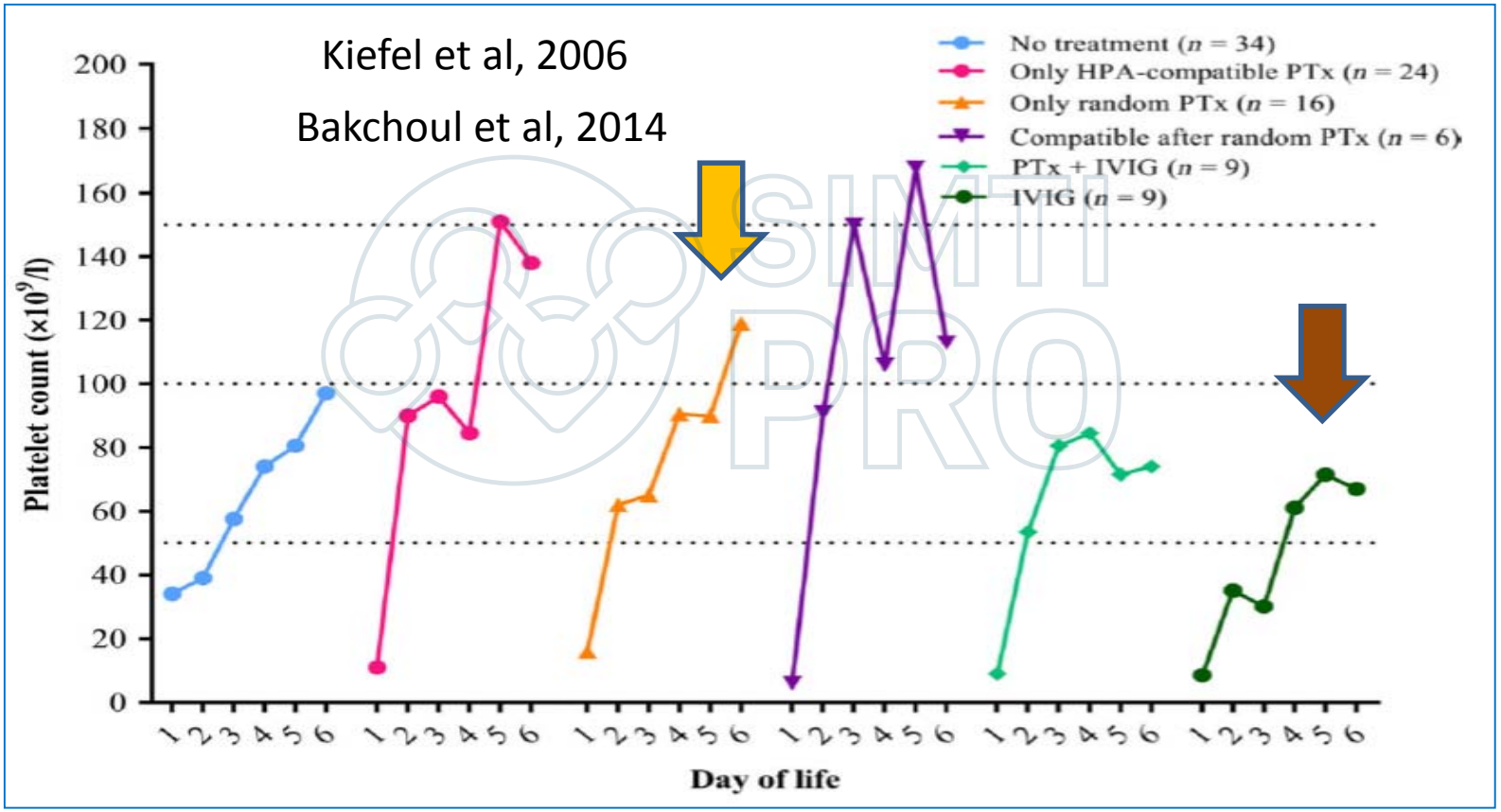
	Antenatal			Postnatal		
Treatment	Indication/Dose	Benefit	Risk	Indication/Dose	Benefit	Risk
Platelet transfusion	Various, from weekly to predelivery only	Treatment monitoring Prevents thrombocytopenia	High complication rate (fetal loss, emergency delivery)	First choice PLT < 20–30 prophylaxis PLT < 50–100 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.

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



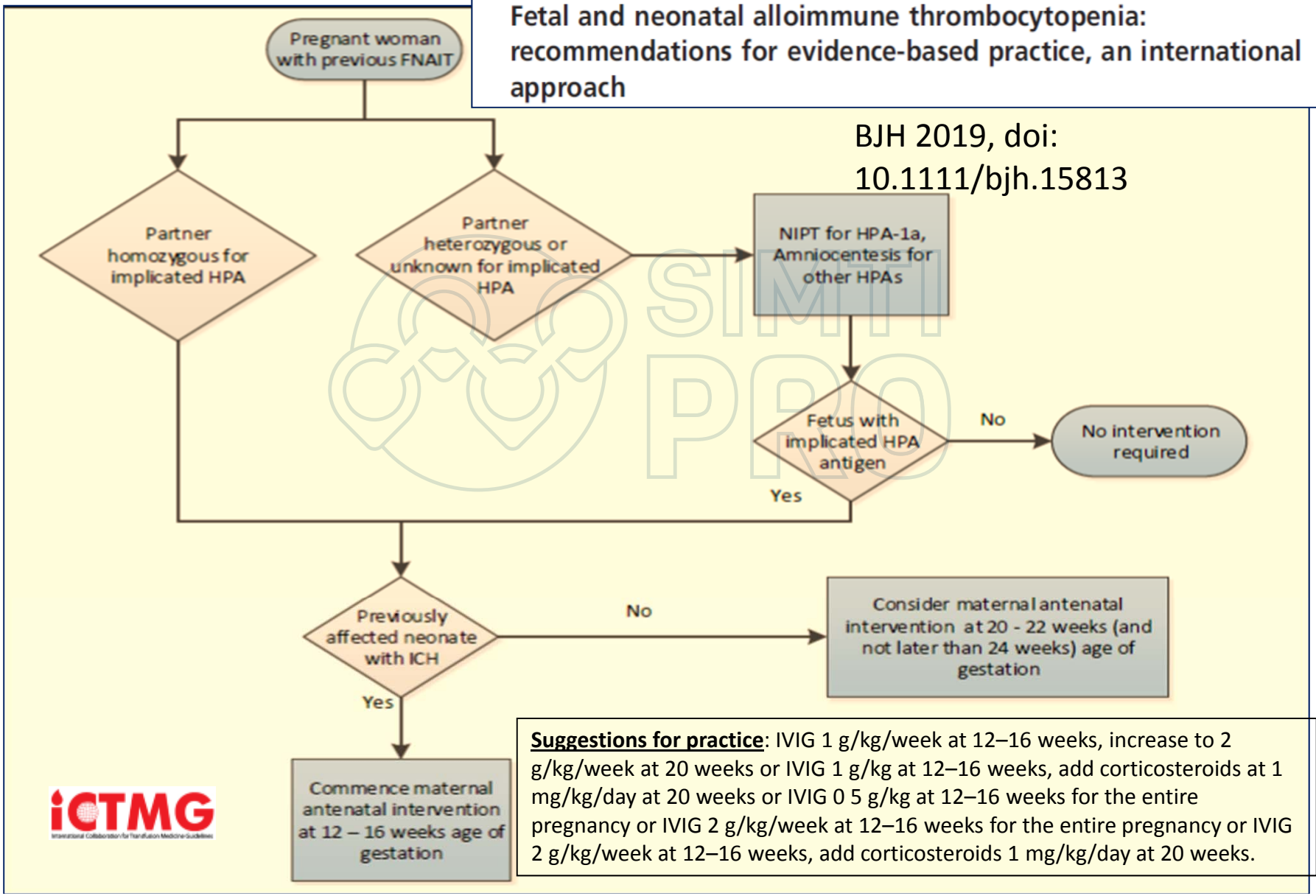
Postnatal intervention for the treatment of FNAIT: a systematic review *Journal of Perinatology (2019)*

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

Algoritmo ICTMG ante-natale

Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach

BJH 2019, doi: 10.1111/bjh.15813

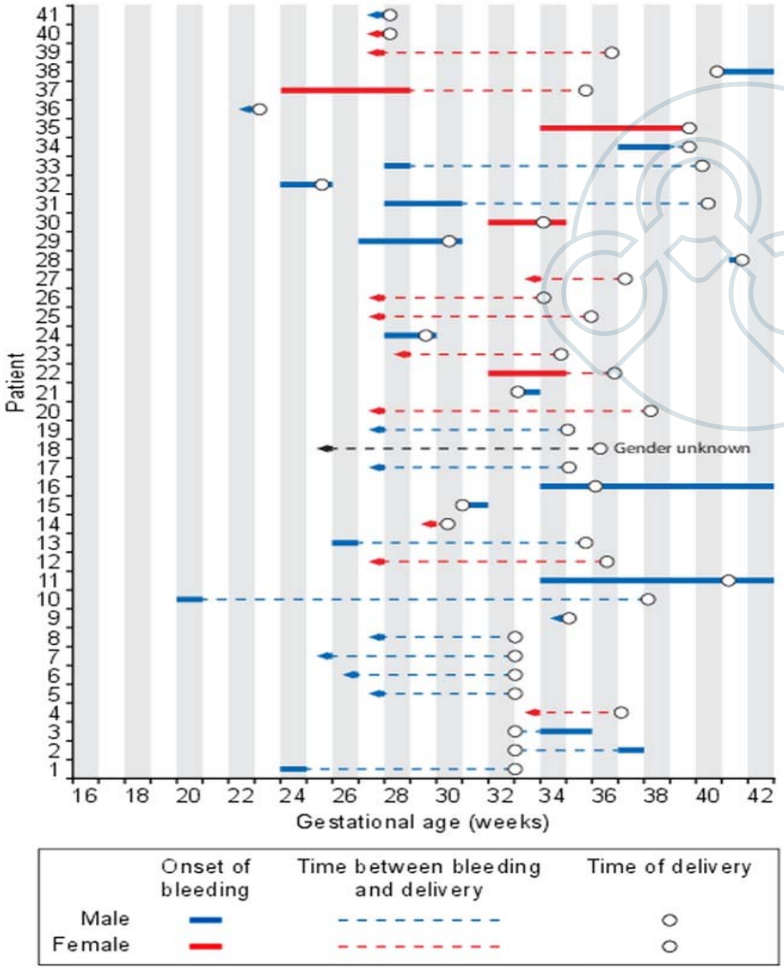


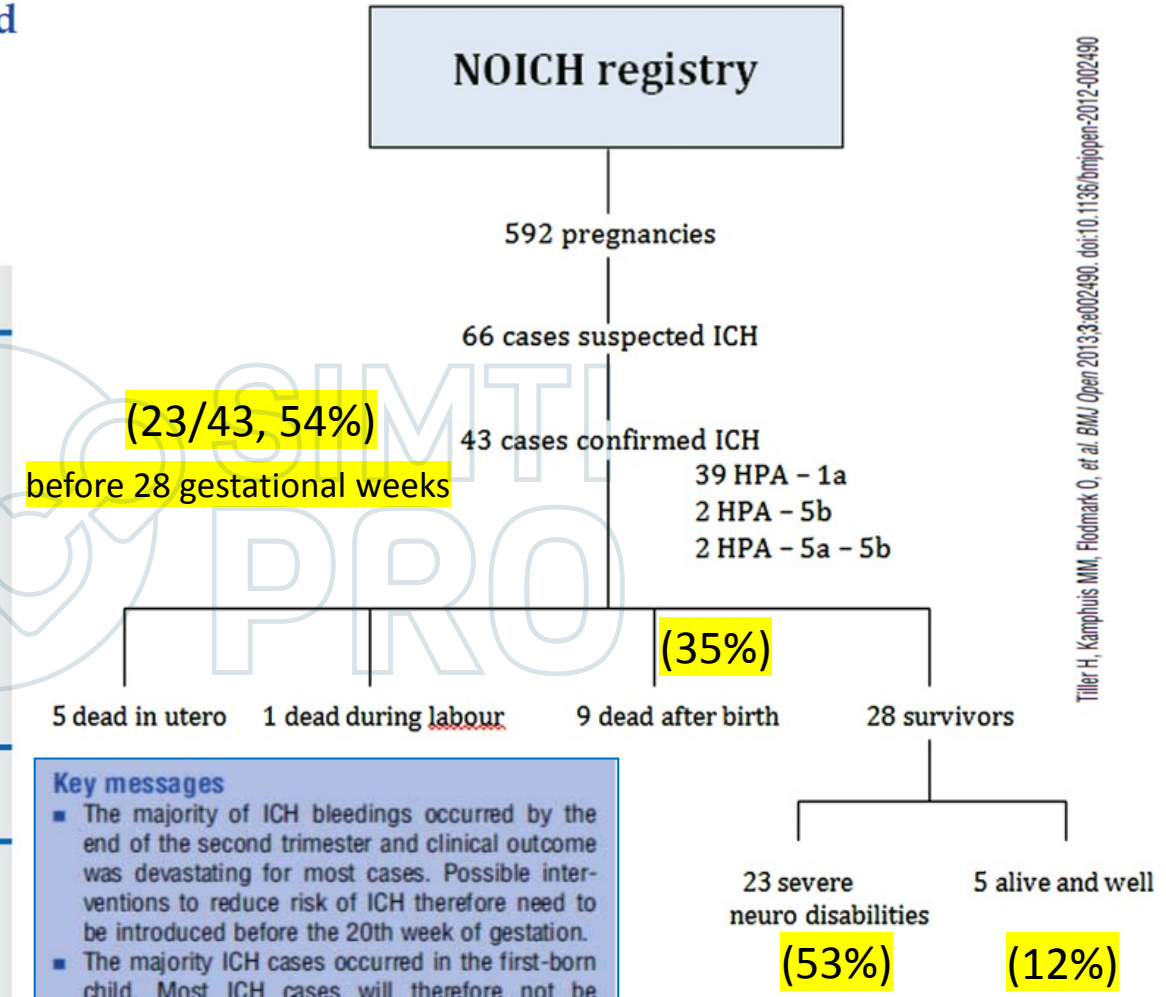
Suggestions for practice: IVIG 1 g/kg/week at 12–16 weeks, increase to 2 g/kg/week at 20 weeks or IVIG 1 g/kg at 12–16 weeks, add corticosteroids at 1 mg/kg/day at 20 weeks or IVIG 0 5 g/kg at 12–16 weeks for the entire pregnancy or IVIG 2 g/kg/week at 12–16 weeks for the entire pregnancy or IVIG 2 g/kg/week at 12–16 weeks, add corticosteroids 1 mg/kg/day at 20 weeks.

No Intracranial Hemorrhage Registry 2013

Time of Bleeding onset

Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry





Key messages

- The majority of ICH bleedings occurred by the end of the second trimester and clinical outcome was devastating for most cases. Possible interventions to reduce risk of ICH therefore need to be introduced before the 20th week of gestation.
- The majority ICH cases occurred in the first-born child. Most ICH cases will therefore not be recognised in time for treatment if we do not identify pregnancies at risk before the first child is born.
- IVIG treatment during the subsequent pregnancy seemed to be protective with regard to ICH in most cases, reducing the ICH recurrence risk from 79% as previously reported, to 11%.

63% first pregnancy
91% without IVIG
Median ab level 105UI/ml

ICH E OUTCOME A BREVE TERMINE

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 Diagn Ther 2018
DOI: 10.1159/000488280

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

ICH E OUTCOME A LUNGO TERMINE

Fetal Diagn Ther 2018
DOI: 10.1159/000488280

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.

Cerebral palsy, bilateral deafness or blindness, severe motor and /or cognitive development delay

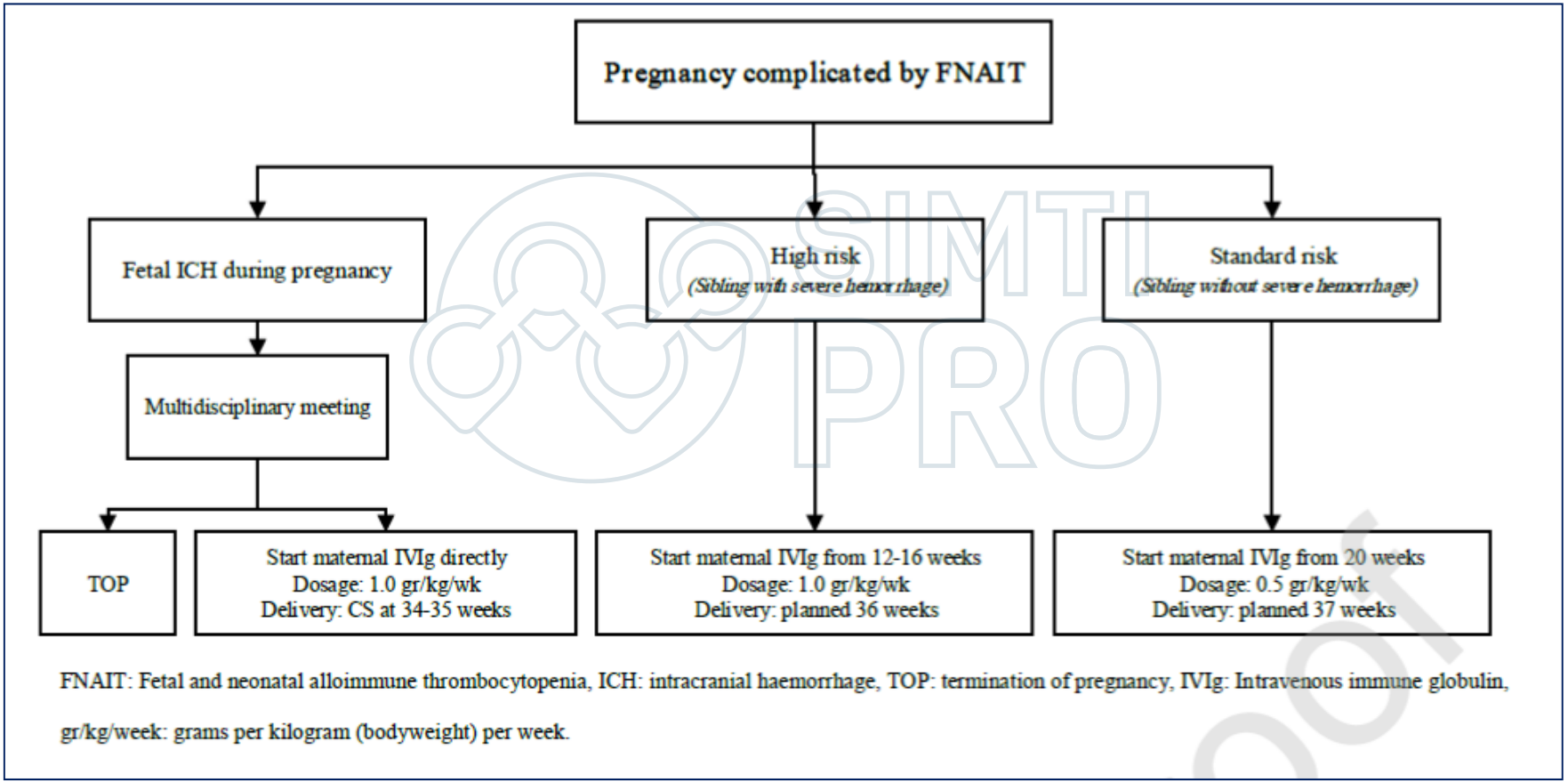
Perinatal Outcome and Long-Term Neurodevelopment after Intracranial Haemorrhage due to Fetal and Neonatal Alloimmune Thrombocytopenia

Epidemiology and management of fetal and neonatal alloimmune thrombocytopenia

PII: S1473-0502(19)30277-0

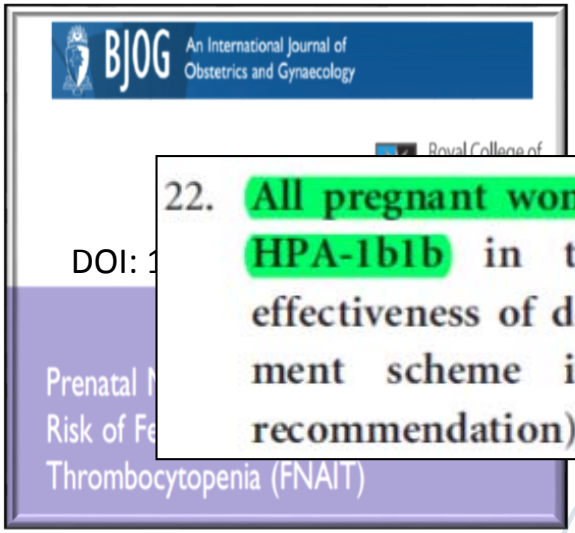
Transfusion and Apheresis Science, 31 December 2019

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



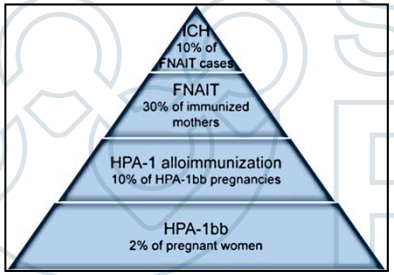
FNAIT: Fetal and neonatal alloimmune thrombocytopenia, ICH: intracranial haemorrhage, TOP: termination of pregnancy, IVIg: Intravenous immune globulin, gr/kg/week: grams per kilogram (bodyweight) per week.

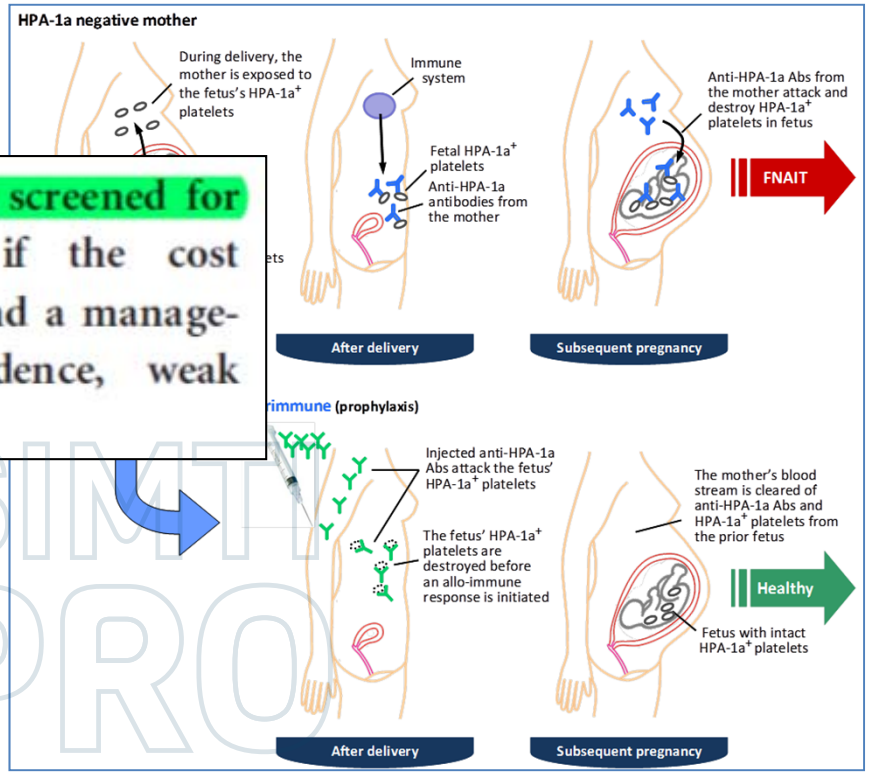
Raccomandazioni ICTMG e BJOG per lo screening



BJH 2019, doi: 10.1111/bjh.15813

22. 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).





7. Future prophylaxis

7.1 PROFNAIT

7.2 Recombinant anti-HPA-1a

7.3 Anti-FcRn therapy

La storia ostetrica ha una sensibilità diagnostica soltanto del 13% e la maggior parte dei casi di FNAIT non viene identificata fino al parto.

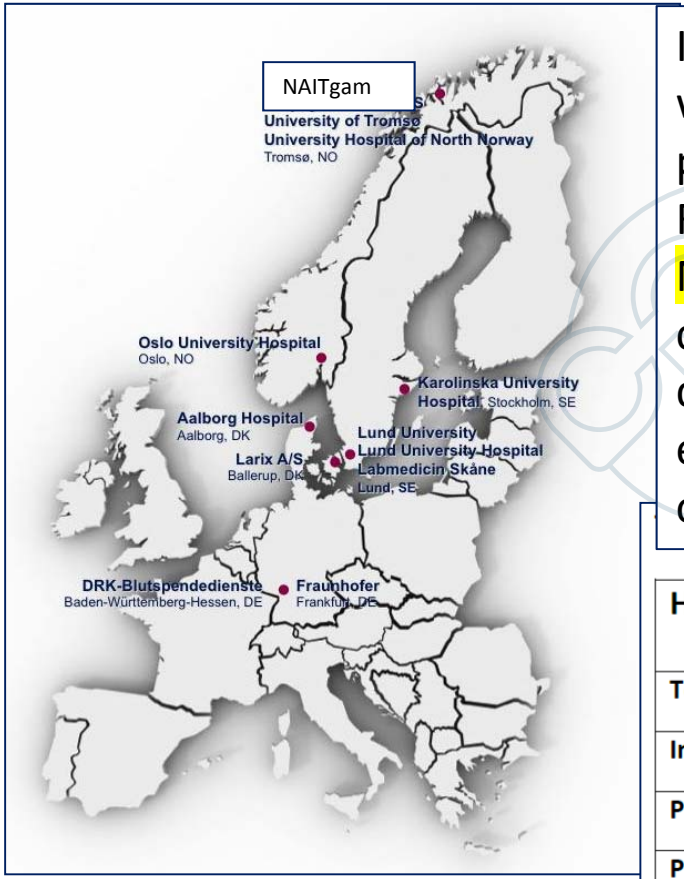
7.1 PROFNAIT

In the same way that anti-D prophylaxis is given to RhD-negative pregnant women to prevent the formation of immune anti-D antibodies during pregnancy with an RhD-positive fetus, research is underway on a product to prevent women forming immune anti-HPA-1a.[42] The PROFNAIT project[43] is a consortium of 11 Northern European hospitals, universities, blood services and companies with expertise in FNAIT, supported by European Union funding from 2012–18, to develop an anti-HPA-1a immunoglobulin for prophylaxis. PROFNAIT received orphan drug status from the European Medicines Agency in 2011 and the Food and Drug Administration in 2013. Phase I and II studies have been completed but have not yet reported and a phase III trial is awaited.

Strategies to develop a prophylaxis for the prevention of HPA-1a immunization and fetal and neonatal alloimmune thrombocytopenia

Transfusion and Apheresis Science, 31 December 2019

DOI: https://doi.org/10.1016/j.transci.2019.102712



In 2012 the EU-funded PROFNAIT project was established with the aim of developing a hyperimmune anti-HPA-1a IgG prophylaxis for prevention of HPA-1a-immunization and FNAIT. The PROFNAIT consortium consisted of eleven Northern European hospitals and USA, blood banks and companies with experience and key expertise in FNAIT and drug development. In addition, strong collaboration was entered with NAITbabies (www.NAITbabies.com), a patient organization run by families affected by FNAIT.

Hyperimmune plasma for NAITgam production	
Total Volume, (L)	84 (EU), 515 (US)
Individual anti-HPA-1a antibody level, range (IU/ml)	2-143
Percentage of fucosylated total IgG (n=81), mean % (SEM)	84 (9)
Percentage of fucosylated anti-HPA-1a IgG (n=81), mean % (SEM)	37 (4)

TOWARDS ROUTINE HPA-SCREENING IN PREGNANCY TO PREVENT FNAIT (HIP)

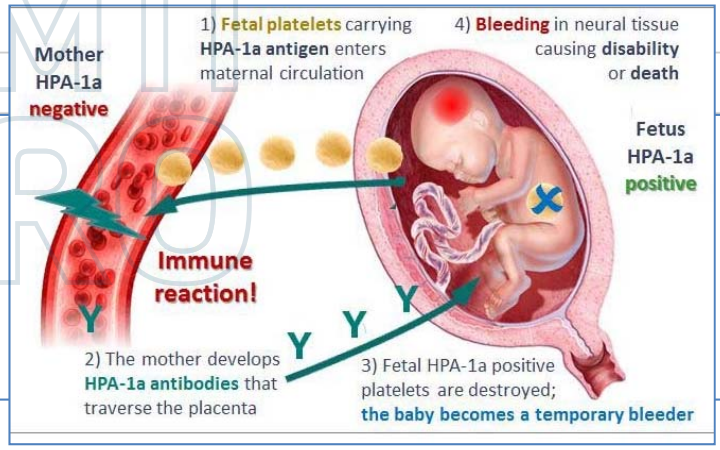
https://clinicaltrials.gov/ct2/show/NCT04067375

Study Sponsor	Leiden University Medical Center		
Collaborators	• Sanquin Research & Blood Bank Divisions • Landsteiner Foundation for Blood Transfusion		
Investigators	Study Director:	Dick Oepkes, Prof MD PhD	Department of Obstetrics, Leiden University Medical Centre, Leiden
	Study Director:	Masja de Haas, Prof MD PhD	Department of Immunohematology Diagnostics, Sanquin Diagnostics, Amsterdam
	Study Director:	Ellen vd Schoot, Prof MD PhD	Department of Experimental Immunohematology, Sanquin Reseach, Amsterdam
PRS Account	Leiden University Medical Center		
Verification Date	August 2019		

U.S. National Library of Medicine
ClinicalTrials.gov

Estimated Primary Date : April 1, 2020

Estimated Study : April 1, 2021



Objectives:

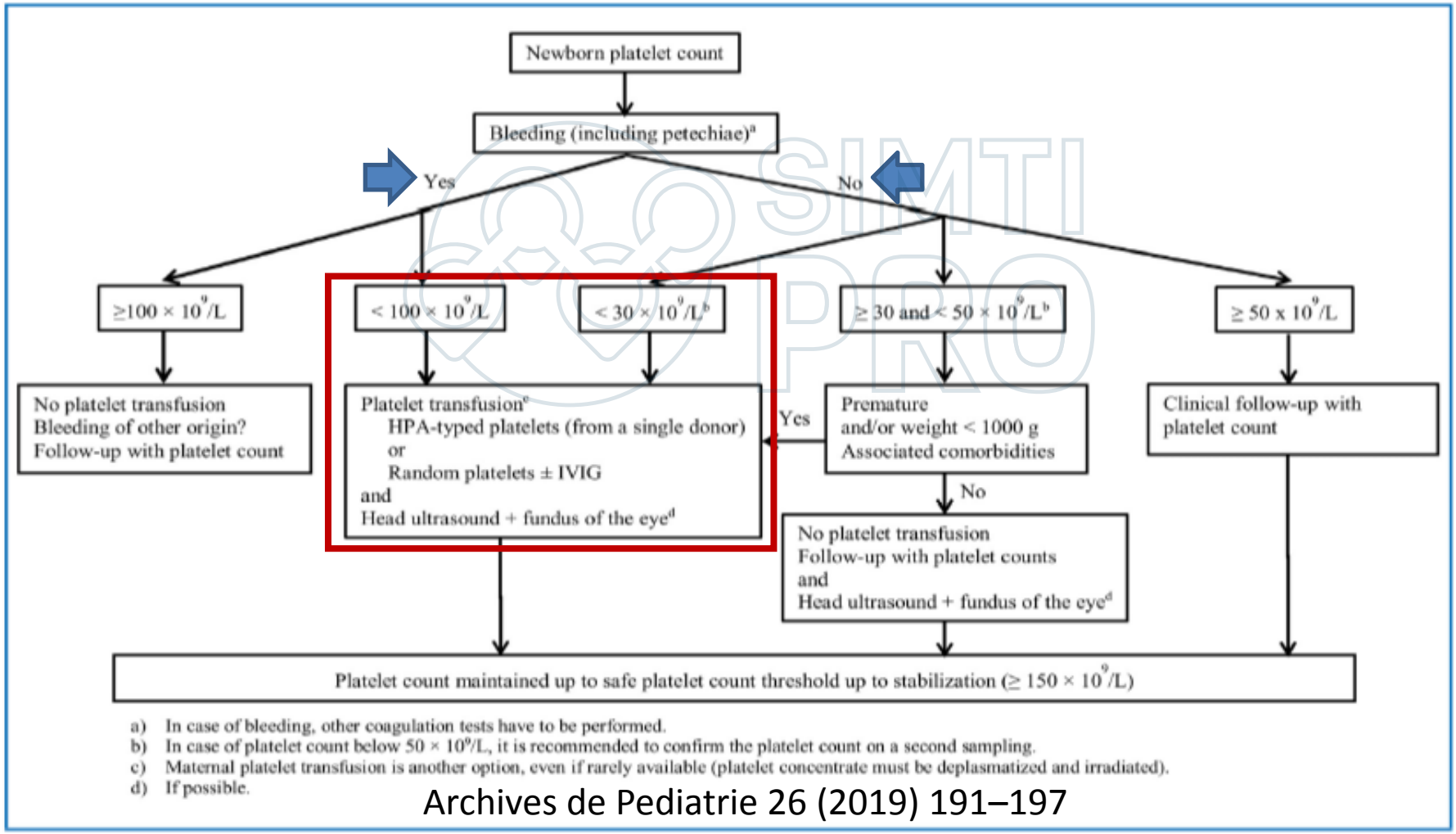
1. The main objective of this study is to assess the incidence and severity of FNAIT and bleeding complications (including ICH) among neonates.
2. To develop a screening platform, including diagnostic assay(s) to identify fetuses at high risk for bleeding complications due to FNAIT.

Study design: Prospective observational cohort

Study population: Pregnant women

Algoritmo trattamento FNAIT (GFHT)

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



Archives de Pediatrie 26 (2019) 191–197

Conclusion

There continues to be a pressing need for **additional collaborative research** and recommendations for FNAIT.

Development of **risk stratification algorithms** to guide managements and standardize laboratory testing **to identify high risk pregnancies** are needed

Antenatal and **postnatal strategies** need further optimization.

The use of **HPA-1a antibody concentration** and **biomarkers** to guide antenatal management needs continued exploration.

Morbidity resulting from the psychological stress of families at risk for FNAIT has yet to be addressed in any study.

Reducing the morbidity and mortality of FNAIT and its treatments remains a priority, as does the development of screening algorithms to prevent occurrence of FNAIT.

BJH 2019, doi: 10.1111/bjh.15813

Contents lists available at ScienceDirect

Transfusion and Apheresis Science 2019

journal homepage: www.elsevier.com/locate/transci

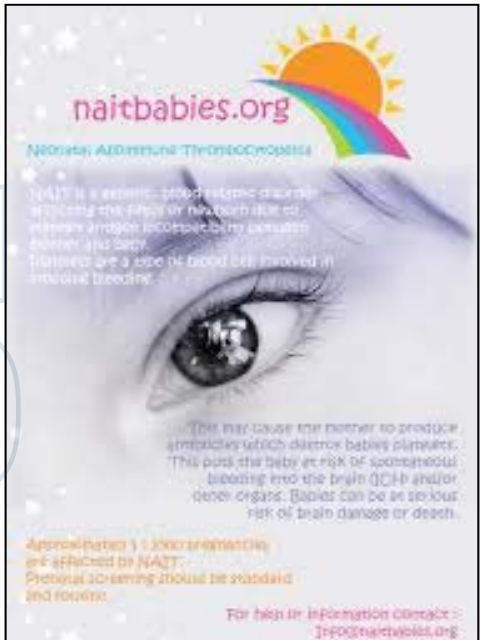
Naitbabies – A patient organisation for families affected by foetal and neonatal alloimmune thrombocytopenia – FNAIT

Thea Palmer

13 Redfield Terrace, Penzance, Cornwall, TR18 4HR, England, UK

Fig. 2. FNAIT children with complex disabilities due to ICH.

Fig. 1. Naitbabies Support Group Members - FNAIT 30-year celebration at Weill Cornell University, New York.



Naitbabies is a small Charitable Incorporated Organisation (CIO) (Foundation) registered in England, United Kingdom and run by families who have been diagnosed with foetal and neonatal alloimmune thrombocytopenia (FNAIT). FNAIT is a rare, life threatening bleeding disorder caused by the maternal immune response against fetal platelet antigens. Clinical research shows that approximately 1:1000 babies are affected by this disorder; of those 5–10 % will suffer internal bleeding, most particularly intracranial haemorrhage. As the only patient organisation for FNAIT, we advocate for parents worldwide; as of July 8th 2019 our Parents Support Group numbered 1250 members. We support research into FNAIT, its causes, treatment and prevention. Since 2012 we have been collaborating with scientists who have been engaged on a programme to develop a prophylactic treatment to prevent FNAIT in HPA-1a negative women. Our aim is to see routine prenatal screening for FNAIT for all pregnant women.

GRAZIE PER L'ATTENZIONE!