PTI vs allo-immunisation plaquettaire materno-fœtale : quelles différences pour le nouveau-né

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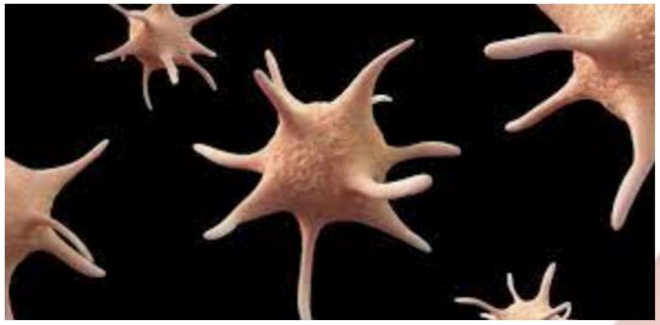
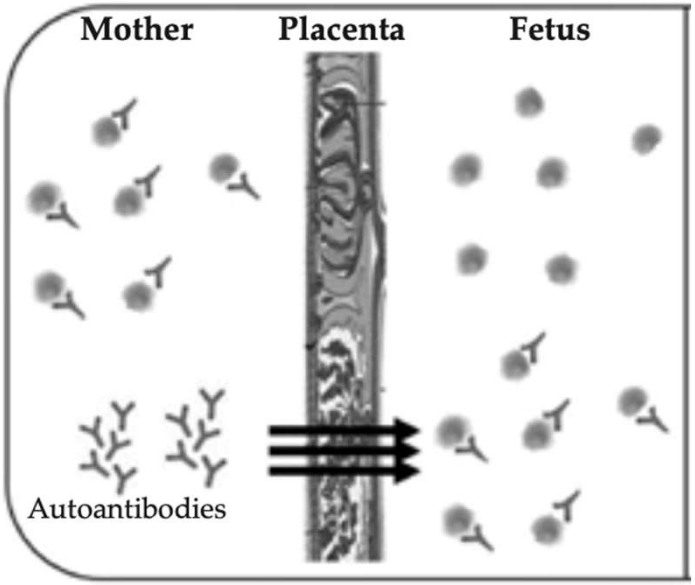
PTI



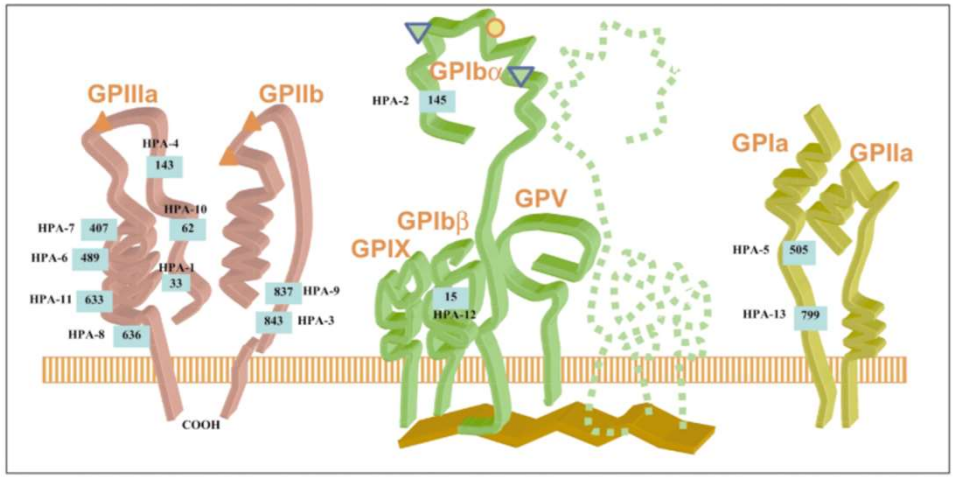
Physiopathologie



Passage transplacentaire d'auto-Ac anti-plaquettaires

cibles : GPIIbIIIa et GPIbIX

Destruction par phagocytes mononucléés



PTI : 1/1000 à 1/10 000 grossesses

Cines D. B. Levine L. D. Blood 2017

Khaspekova S. G. et al. Platelets 2018
Michel M. Lousteau V. Hématologie 2017
Donato H. Arch Argent Pediatr 2021

Thrombopénie néonatale - Histoire naturelle

Variable dans la littérature : 15 → 50%

Thrombopénie sévère (< 50 G/l) : 8 → 10%

Michel M. Lousteau V. Hématologie 2017
Donato H. Arch Argent Pediatr 2021

Manifestations hémorragiques rares chez le nouveau-né

Table 4. Neonatal outcomes for 108 infants (106 livebirths) of 105 women* with severe maternal ITP

	No Rx (*n* = 22)	Steroids (*n* = 39)	IVIG (*n* = 19)	Steroids + IVIG (*n* = 28)	Total (*n* = 108)
Platelet nadir					
<20 × 10^9/L	0	0	0	0	0
20–50 × 10^9/L	0	0	0	3 (11)	3 (3)
51–100 × 10^9/L	4 (18)	2 (5)	1 (5)	2 (7)	9 (8)
150–100 × 10^9/L	2 (9)	5 (13)	1 (5)	3 (11)	11 (10)
Intracranial Haemorrhage, *n* (%)	0	0	0	0	0
Death, *n* (%)	0	0	0	0	0

Care A. et al. BJOG 2017

Thrombopénie néonatale - Histoire naturelle

Risque d'hémorragie intra-crânienne < 1 %

Donato H. Arch Argent Pediatr 2021

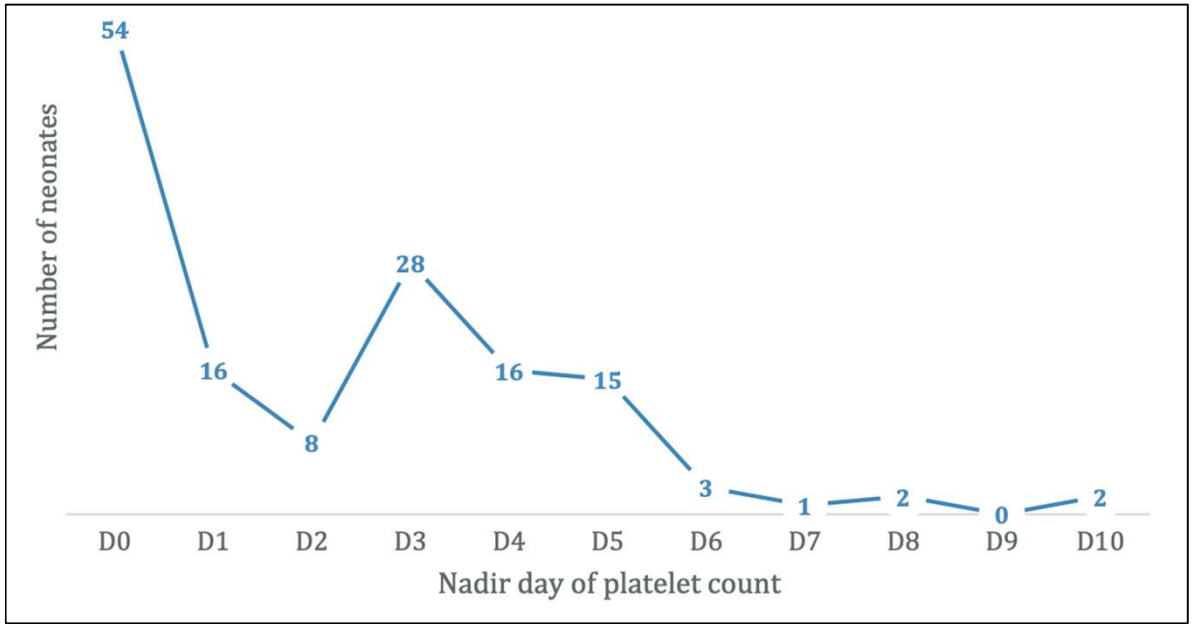
Table 2. Immune thrombocytopenia (ITP) and pregnancy outcome for 171 women with pre-existing ITP and their neonates

	Total (n = 171)*
Neonate outcome	
Newborn weight, g, median (IQR) (n = 154)	3167.5 (2850-3470)
Neonatal thrombocytopenia (<100 × 10^9/L) (n = 136)	37 (27.2)
<50 × 10^9/L	19 (14.0)
<30 × 10^9/L	13 (9.6)
Hemorrhage complication	2 (1.2)
If yes, platelet count, median × 10^9/L (IQR)	6.5 (6-7)

Guillet S. et al. Blood 2023

Thrombopénie néonatale - Histoire naturelle

Thrombopénie J0 – J10/J15



Point F. et al. Acta Paediatrica 2022

Table 2 Postnatal outcome and management in 67 neonates born after maternal ITP

Age at platelet nadir (days)[a]	3 (1–7)

Van Der Lugt N. M. Vox Sang 2013

Thrombopénie néonatale – Traitement

Centre National de Référence en Hémobiologie Périnatale

HAS

Recommandations HAS 2015

AE	• NP < 20 G.L^{-1} ou hémorragie : transfusion de CPA associée à un traitement par immunoglobulines IV en dose unique de 1 g/kg. • NP > 20 G.L^{-1} : pas de transfusion plaquettaire en l'absence d'hémorragie documentée.

Echographie transfontanellaire
si NP < 50 G/l

Table 2 (continued)

	Total (n = 171)*
IVIg treatment	18 (10.5)
If yes, platelet count, median × 10^9/L (IQR)	25.5 (15-35)
Platelet transfusion	8 (4.7)
If yes, platelet count, median × 10^9/L (IQR)	15 (12-31)

Guillet S. et al. Blood 2023

3.1.4 | Neonatal treatment

Special treatment for thrombocytopenia was initiated in 30 (21%) neonates. The treatments were only intravenous immunoglobulins in 16 cases (11%), isolated platelet transfusion in 1 case (0.7%) and intravenous immunoglobulin combined with platelet transfusion in 13 cases (9%).

Point F. et al. Acta Paediatrica 2022

Thrombopénie néonatale – Traitement

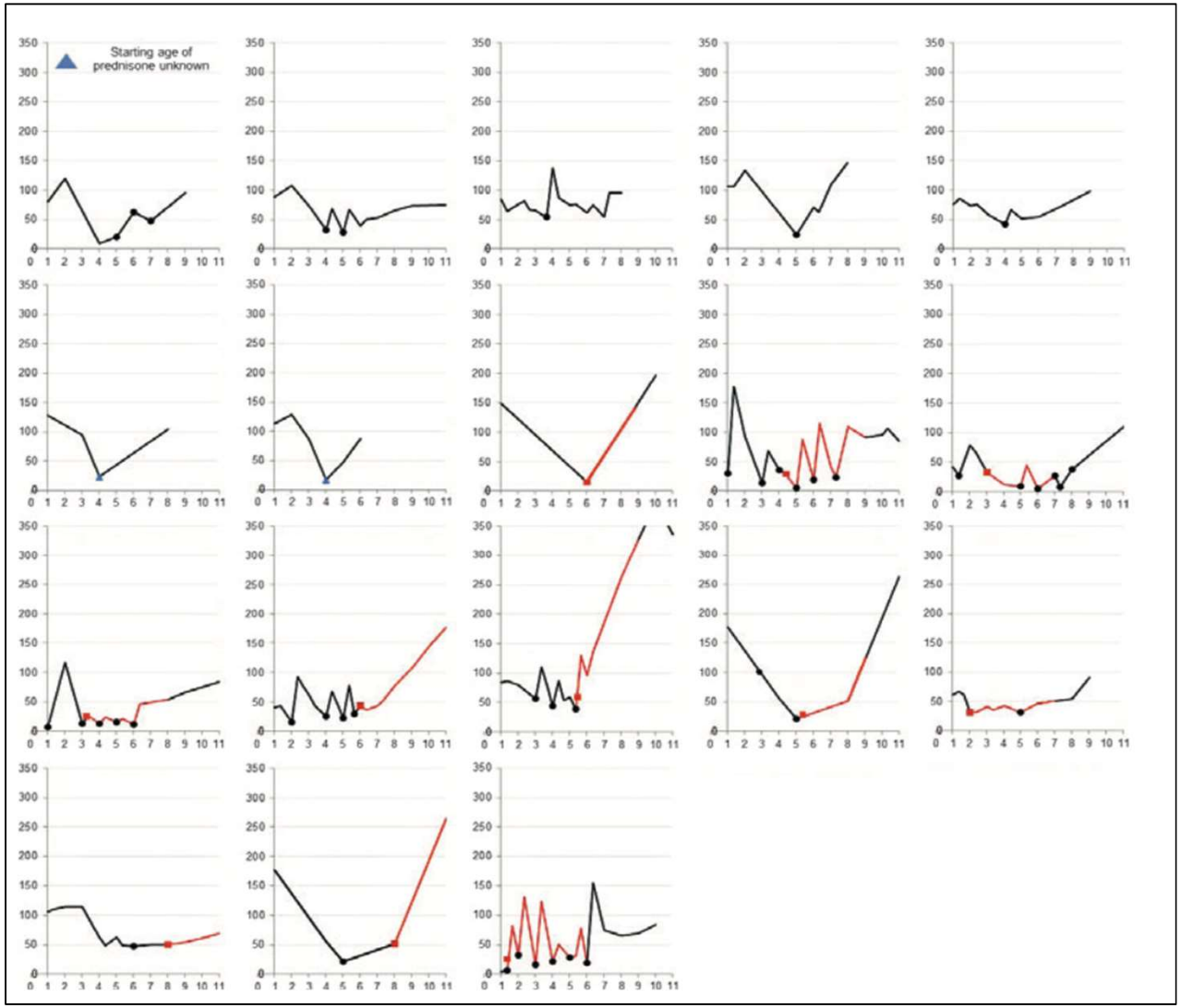


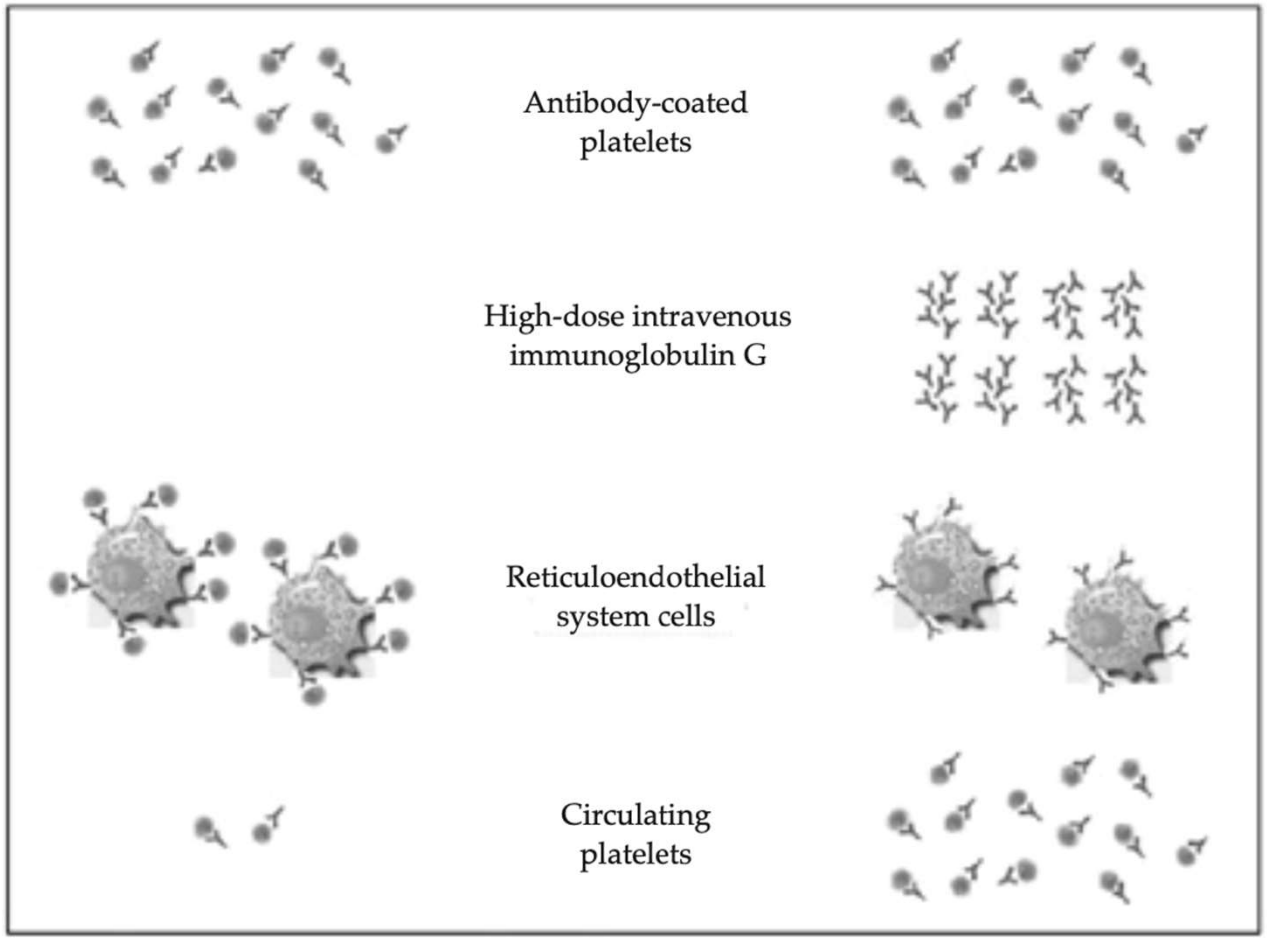
Table 3 Characteristics of neonates treated with platelet transfusions and/or intravenous immunoglobulin (IVIG; $n = 16$)

Number of platelet transfusions a neonate[a]		3 (1–6)
Fall of platelet count after platelet transfusion, n (%)[b]	1st	9/15 (60·0)
	2nd	8/9 (88·9)
	3rd	6/8 (75·0)
	4th	5/6 (83·3)
	5th	2/5 (40·0)
	6th	0/3 (0·0)
Increment after first platelet transfusion × 10^9/l[a]		52 (3–147)
Decline of platelet count <24 h after platelet transfusion × 10^9/l[a]		66 (15–163)
Interval of start IVIG, after first platelet count <50 × 10^9/l (days)[a]		3 (1–14)
Duration until platelets count >50 × 10^9/l and increasing after start IVIG (days)[a]		1 (0–8)

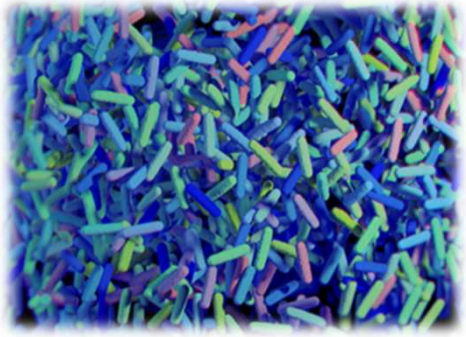
IVIG, intravenous immunoglobulin.
[a]Median (range).
[b]Fall of platelet count to <50 × 10^9/l after platelet transfusion.

Van Der Lugt N. M. Vox Sang 2013

Thrombopénie néonatale – Traitement



Immunoglobulines polyvalentes



Donato H. Arch Argent Pediatr 2021

Accouchement

d'une rachianesthésie en toute sécurité. L'accouchement a lieu par voie basse sauf si l'obstétricien juge qu'il existe des raisons obstétricales indépendantes du PTI justifiant la réalisation d'une césarienne. Les extractions instrumentales par forceps et surtout par ventouses ou spatules doivent être évitées. Une thrombopénie néonatale toujours transitoire devra être systématiquement recherchée chez le nouveau-né à la naissance.

CNRHP
Centre National de Référence en Hémobiologie Périnatale

Mai 2017

Protocole national de diagnostic et de soins (PNDS)

Purpura thrombopénique immunologique de l'enfant et de l'adulte

Prédire la thrombopénie

Possible même si PTI résolutif

Traitement maternel -> sans action chez le NN

Michel M. Lousteau V. Hématologie 2017
Donato H. Arch Argent Pediatr 2021

TABLE 3 Risk factors for severe nTP at nadir

	Severe nTP at nadir ($N = 32$)	No severe nTP at nadir ($N = 113$)	Odds ratio	*p*-value
History of previous neonate with severe nTP *N* (%)[a]	12/17 (70.6)	4/74 (5.4)	42.0 [9.8–179.1]	<0.001
History of splenectomy *N* (%)	11 (34.4)	24 (21.2)	1.9 [0.8–4.6]	0.13
New onset ITP *N* (%)	16 (14.2)	5 (15.6)	1.1 [0.3–3.3]	0.78
Maternal treatment during pregnancy *N* (%)	15 (46.9)	30 (26.8)	2.4 [1.1–5.4]	0.03
Maternal nadir platelets during pregnancy Median (Q1; Q3)	35.5×10^9/L (14; 64.5)	71×10^9/L (35; 128)	0.5[c] [0.2–1.2]	0.005
Years since ITP diagnosis Median (Q1; Q3)[b]	7.0 (4.0; 14.0)	8.0 (4.0; 10.0)	1.0 [0.9–1.1]	0.75
First trimester maternal platelet count Median (Q1;Q3)	103×10^9/L (65; 186)	115×10^9/L (85.5; 185)	0.9[c] [0.7–1.1]	0.26
Maternal platelet count at birth Median (Q1; Q3)	75×10^9/L (50.5; 155)	122×10^9/L (76; 170)	0.7[c] [0.56–0.98]	0.024

Abbreviations: ITP, immune thrombocytopenia; nTP, neonatal thrombocytopenia.

[a]Of the 91 multiparous patients.

[b]Of the 124 patients with ITP diagnosed before pregnancy.

[c]Difference of 50×10^9/L.

Point F. et al. Acta Paediatrica 2022

Prédire la thrombopénie

Centre National de Référence en Hémobiologie Périnatale

Table 3. Factors associated with neonatal thrombocytopenia <50 × 10^9/L in 171 newborns

	Neonatal thrombocytopenia (platelet count <50 × 10^9/L)			Univariable analysis		Multivariable analysis	
	Total (n = 136)	No (n = 117)	Yes (n = 19)	Unadjusted odds ratio [95% CI]	*P* value*	Adjusted odds ratio [95% CI]	*P* value†
Maternal platelet count at delivery < 50 × 10^9/L (n=127/109/18)	8 (6.3)	6 (5.5)	2 (11.1)	2.15 [0.40-11.57]	.37		
Maternal platelet count < 50 × 10^9/L within 3 months before delivery	44 (32.4)	33 (28.2)	11 (57.9)	3.5 [1.29-9.47]	.01	4.07 [1.41-11.73]	.009
Disease status at pregnancy diagnosis					.14		
CR	62 (45.6)	57 (48.7)	5 (26.3)	1 (ref)			
R	59 (43.4)	49 (41.9)	10 (52.6)	2.33 [0.74-7.27]			
NR	15 (11.0)	11 (9.4)	4 (21.1)	4.15 [0.96-17.93]			
Disease status worsening between M0 and M9	65 (47.8)	52 (44.4)	13 (68.4)	2.71 [0.96-7.61]	.06		
Previous history of neonatal thrombocytopenia	20 (14.7)	13 (11.1)	7 (36.8)	4.67 [1.56-13.96]	.006	5.55 [1.72-17.89]	.004
Previous splenectomy	16 (11.8)	13 (11.1)	3 (15.8)	1.50 [0.38-5.85]	.56		
Treatment to prepare delivery IVIg and/or CT	58 (42.7)	47 (40.2)	11 (57.9)	2.05 [0.77-5.47]	.15		

The results are given as number of events (%).

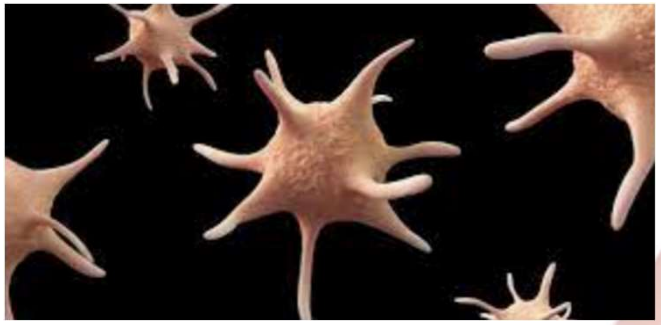
CI, confidence interval; CR, complete response; CT, corticosteroids; IVIg, intravenous immunoglobulin; NR, nonresponse; R, response; ref, reference category.

*Wald test from univariable logistic regression.

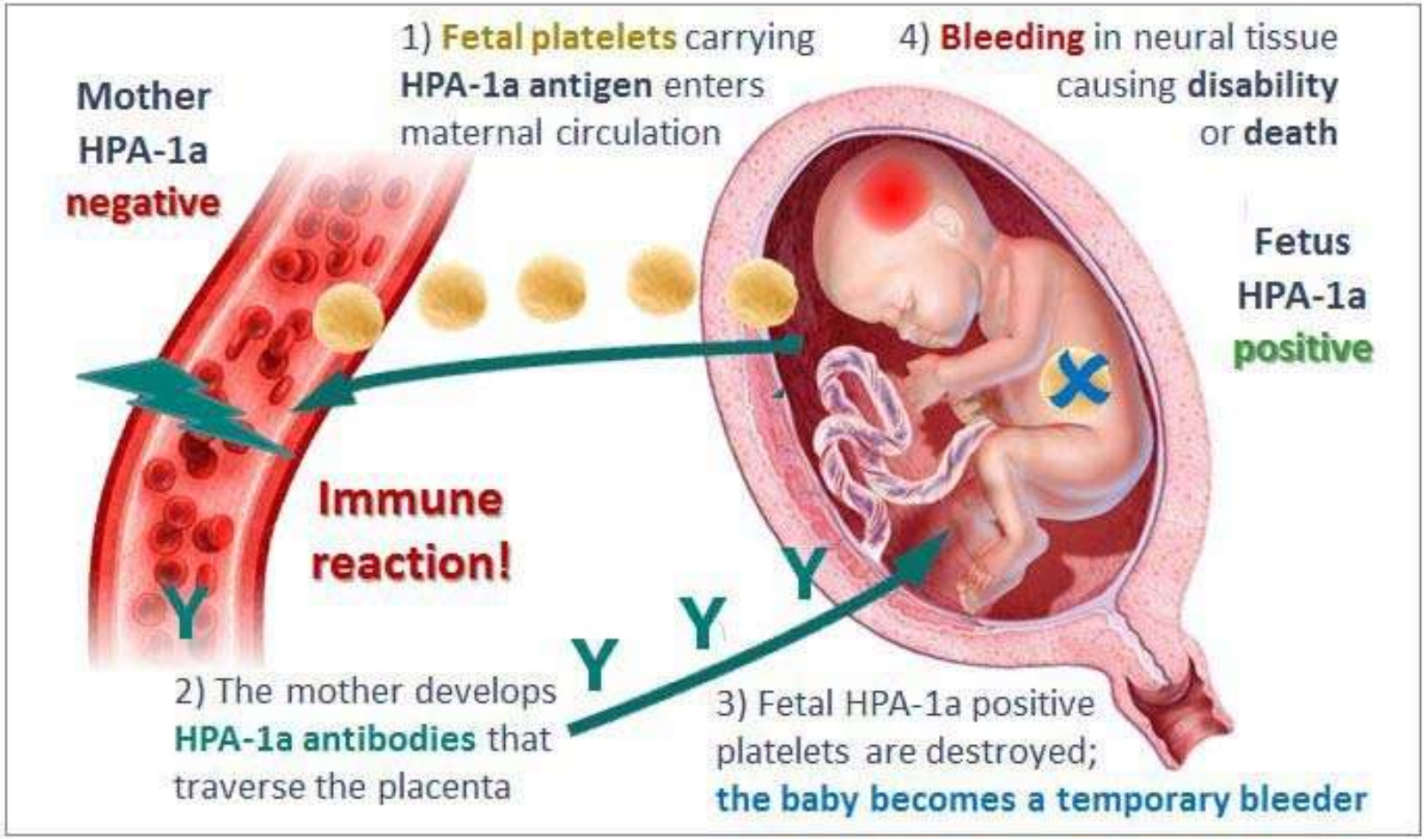
†Multivariable logistic regression model, adjusted for maternal platelet count and previous history of neonatal thrombocytopenia.

Guillet S. et al. Blood 2023

Allo-immunisation plaquettaire materno-fœtale



FNAIT: Fetal/neonatal alloimmune thrombocytopenia



Bussel AJOG 2021

FNAIT

- 1/1000 naissances vivantes
- dès 1ère grossesse
- Passage transplacentaire des IgG maternelles anti-plaquettaire **dès 14 SA**
- Expression des antigènes plaquettaires **dès 18 SA**

- **Cause la plus fréquente de thrombopénie sévère et d'hémorragie intra-crânienne (nouveau-né / fœtus)**

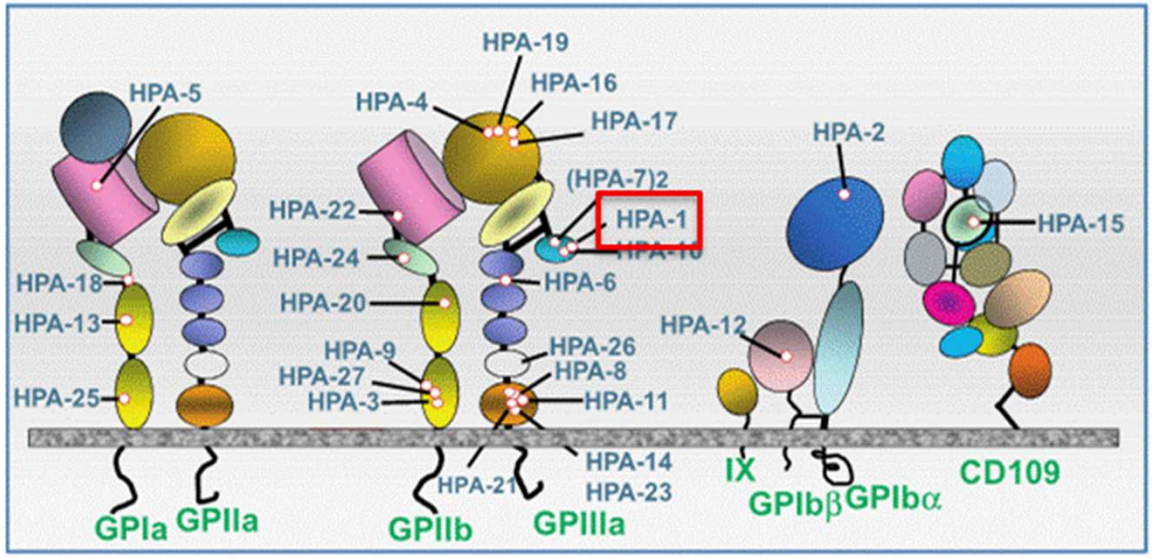
Petermann, Transfusion Clinique et Biologique, 2017
Kamphuis, Pediatrics, 2014
Bussel, 2001
Durand-Zaleski I, American Journal of Perinatology, 1996

Antigènes HPA

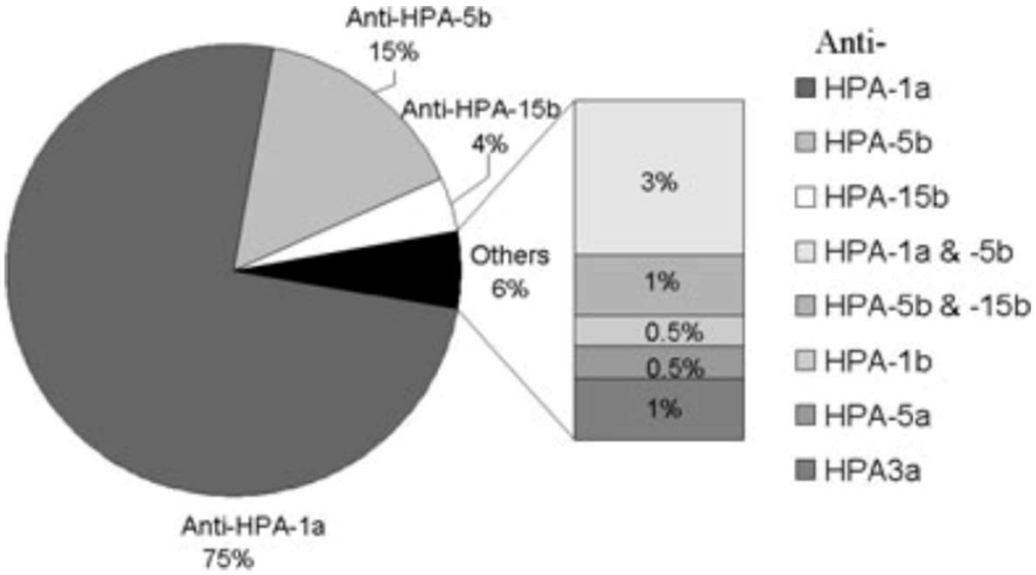
- Antigènes HPA exprimés par **glycoprotéines plaquettaires**

- **GPIaIIa - GPIIbIIIa – GPIbIX – CD109**
- Support des systèmes HPA : **HPA-1** / HPA-3 / HPA-5 / HPA-15 / …

- **Systèmes HPA**
  - Système bi-allélique
    - Allèle « a »
    - Allèle « b »



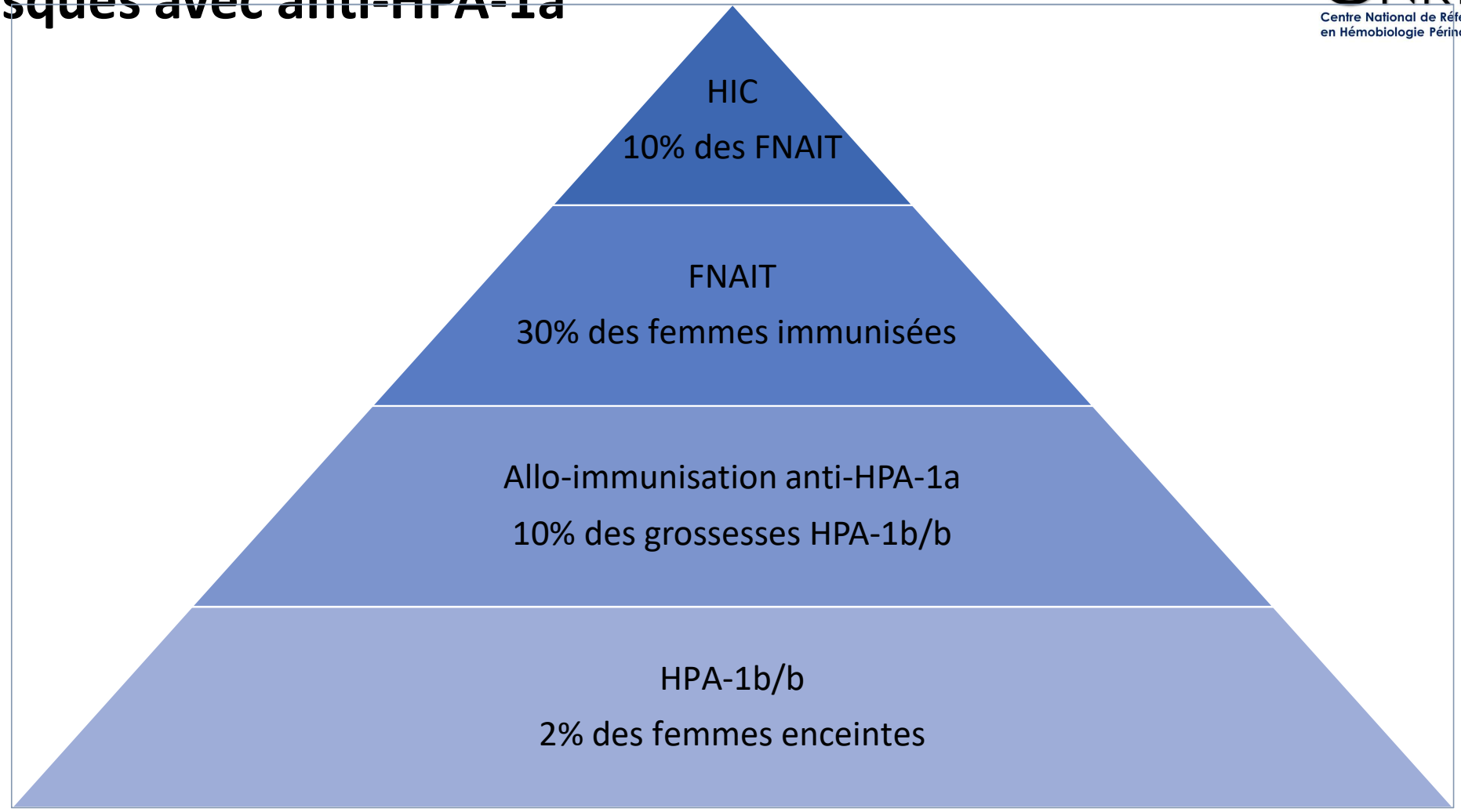
Antigènes HPA



	Antibody				
	HPA-1	HPA-2	HPA-3	HPA-5	HPA-15
Genotype					
aa	72.5	86	40	84	23.5
ab	22	12	47	15.5	47
bb	5.5	2	13	7.5	28.5
Alleles					
a	83 (85)	92 (92)	63 (62)	92 (91)	48 (46)
b	17 (15)	8 (8)	37 (38)	8 (9)	52 (54)

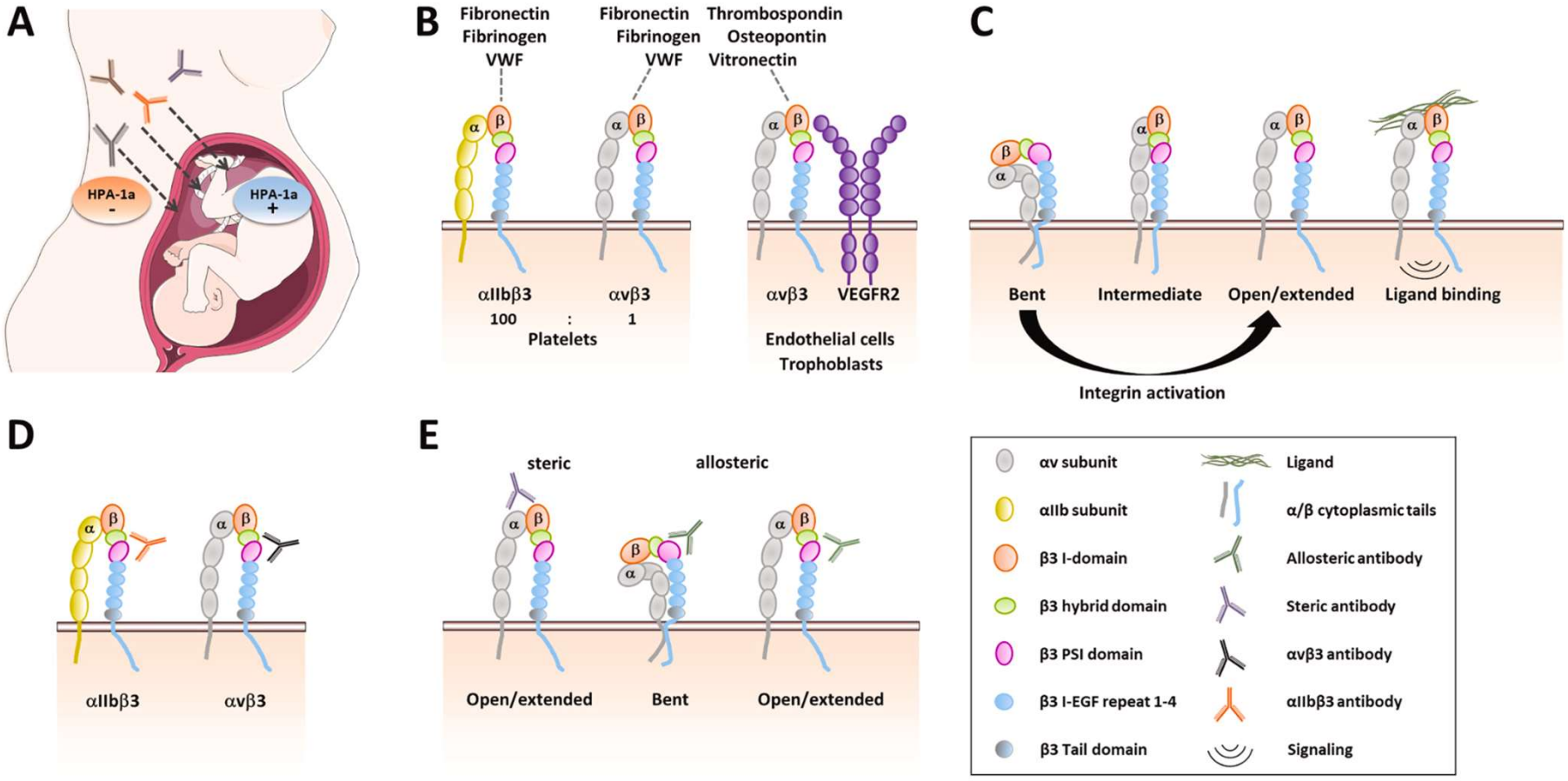
Ghevaert Transfusion 2007

Risques avec anti-HPA-1a



Kamphuis et al. Pediatrics 201

Cibles – Anti-HPA-1



Stam Blood Reviews 2022

Hémorragie intra-crânienne

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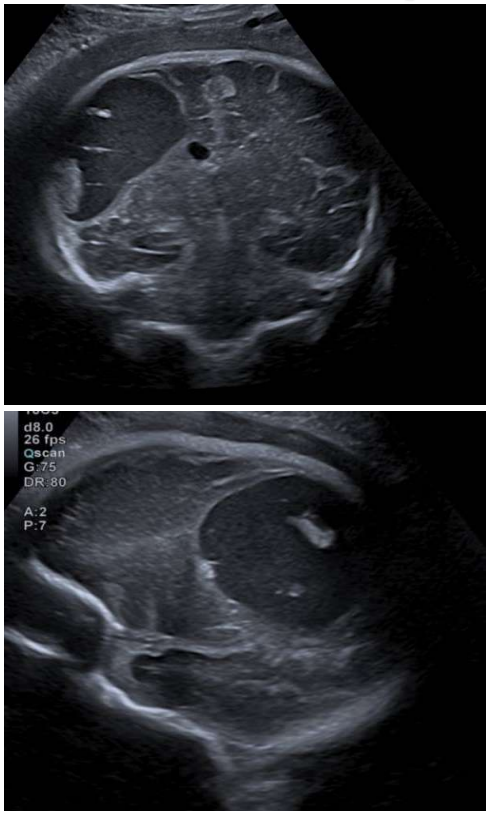


- ✓Possible dès 18 SA
- ✓**Majoritairement *in utero***
- ✓**2e moitié T2 - T3 ++**
- ✓10% HIC = Décès / 20% = Séquelles neurologiques
- ✓Récurrence
  - 72% (95% CI 46-98)
  - 79% (95% CI 61-97) avec MFIU

Tiller H, International Journal of Women's Health, 2017
Radder Vox Sanguinis 2003
Sainio S, Br J Haematol 2017
Bertrand Blood 2011

devant HIC -> Ponction de sang fœtal en cas d'IMG
Si pas de thrombopénie -> Exclusion FNAIT

Thrombopénie néonatale

dans les 48 premières heures de vie

Lieberman L. et al. BJH 2019

Issues néonatales - anti-HPA-1a

Numération plaquettaire naissance (G/l)	48 [9 ; 149]
Nadir plaquettes (G/l)	47 [9 ; 133]
Thrombopénie (≤ 150 G/L)	17 (77,3)
Thrombopénie sévère (< 50 G/L)	12 (54,6)
Transfusion de concentrés de plaquettes	10 (45,5)
Ig IV	11 (50)

Série CNRHP

Bilan Immunologie plaquettaire

- Mise en évidence d'un allo-anticorps maternel spécifiquement anti-plaquettaire

- MAIPA : Monoclonal Antibody-specific Immobilization of Platelet Antigens

- Génotypage plaquettaire (parents ou mère + enfant)

  → incompatibilité antigénique cohérente

	HPA-1	HPA-3	HPA-5	HPA-15
mère	HPA-1 b/b	HPA-3 b/b	HPA-5 a/a	HPA-15 b/b
père	HPA-1 a/a	HPA-3 a/b	HPA-5 a/b	HPA-15 a/a

Bilan Immunologie plaquettaire

Centre National de Référence en Hémobiologie Périnatale

Recherche Allo-Ac anti-plaquettaire chez la mère (MAIPA)

RECHERCHE D'ANTICORPS SERIQUES ANTI-PLAQUETTAIRES

Vis-à-vis des plaquettes de donneurs

MAIPA indirect GPIa-IIa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

MAIPA indirect GPIIb-IIIa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

MAIPA indirect GPIb-IX
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

IDENTIFICATION DES ANTICORPS SERIQUES ANTI-PLAQUETTAIRES

MAIPA indirect identification HPA-1aa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

MAIPA indirect identification HPA-1bb
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

MAIPA indirect identification HPA-3aa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

MAIPA indirect identification HPA-3bb
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

Cross match mère – père

Crossmatch GPIa-IIa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

Crossmatch GPIIb-IIIa
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

Crossmatch GPIb-IX
MAIPA INDIRECT (Technique immuno-enzymatique, Trousse ApDia) - INFINITE

Génotypage plaquettaire

HPA-1 a/a
HPA-3 b/b
HPA-5 a/a
Technique PCR Multiplexe (HPA Beadchip Kit BioArray IMMUCOR)

Prise en charge d'une grossesses à risque

CNRHP
Centre National de Référence en Hémobiologie Périnatale

1/ Incompatibilité ?

si père hétérozygote ou inconnu → **Génotypage fœtal plaquettaire non invasif sur sang maternel**

2/ Traitement anténatal

3/ Organisation naissance

Traitement anténatal

- **Prévenir récidive HIC -> Immunoglobulines polyvalentes (Ig IV)**

Efficacité 99%

	Antenatal		
Treatment	Indication/Dose	Benefit	Risk
Platelet transfusion	Various, from weekly to predelivery only	Treatment monitoring Prevents thrombocytopenia	High complication rate (fetal loss, emergency delivery)
IVIG	First choice 0.5 g or 1 g/kg/wk	Noninvasive Prevents ICH	Blind administration Expensive
Corticosteroids	In addition to IVIG Prednisone 0.5 mg	Noninvasive, otherwise benefit unclear	Dose-related side effects Oligohydramnios

Winkelhorst Expert Review of Hematology 2017

❑ **Efficacité du traitement -> Surveillance échographique mensuelle**

Naissance

- 37 - 38 SA -> rapport bénéfice/risque prématurité vs FNAIT

- Risque de la voie basse ?

« In this study, all 17 postnatal ICHs were discovered within the first 24 hours after birth, suggesting that the trauma of the delivery might be the main triggering factor. »

Ghevaert Transfusion 2007

« There were no confirmed cases of ICH occurring intra-partum in this study, and only two bleedings occurred after delivery.»
23 AVB – cohorte rétrospective – 43 cas d'HIC

Tiller BMJ Open 2013

Table 2. Data on delivery, neonatal outcome and treatment

	Spontaneous vaginal delivery (*n* = 23)	**Caesarean section (*n* = 9)**
ICH, *n*	0	0
Median platelet count (range)	146 × 10^9/l (12–252)	144 × 10^9/l (4–231)
Platelet count < 50 × 10^9/l, *n*	3	1
Neonatal treatment	6	3
IVIG only, *n*	3	0
Platelet transfusion only, *n*	0	3
Combination of IVIG and donor platelet transfusion, *n*	3	0

There were no significant differences between the two groups for all parameters.

Van Den Akker BJOG 2006

Naissance

- Atcd HIC -> césarienne élective pour beaucoup de centres
- Ponction de sang fœtal -> voie basse si plaquettes fœtales > 100 ?

If the fetal platelet count is unknown, a planned delivery should be performed (very low evidence, strong recommendation).

If the fetal platelet count is unknown, assisted delivery and invasive procedures on the fetus during delivery should be avoided, including forceps, vacuum-assisted delivery, scalp blood sampling and scalp electrodes (very low evidence, strong recommendation).

A cord blood sample should be sent for platelet count determination immediately after delivery (low evidence, strong recommendation).

HPA-selected platelets should be available at the time of delivery (low evidence, strong recommendation).

bjh research paper

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

Lieberman L. et al. BJH 2019

Prise en charge nouveau-né

Centre National de Référence en Hémobiologie Périnatale

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

bjh research paper

If a platelet transfusion is indicated, HPA-selected platelets should be used if immediately available (moderate evidence, strong recommendation).

If HPA-selected platelets are not immediately available, HPA unselected platelets should be transfused (moderate evidence, strong recommendation).

In the rare circumstance where either HPA unselected or HPA selected platelets are not available; infuse the neonate with IVIG 1 g/kg.

Platelets should be transfused immediately if life-threatening bleeding is present

Lieberman L. et al. BJH 2019

Prise en charge nouveau-né

Centre National de Référence en Hémobiologie Périnatale

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

bjh research paper

In the presence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain platelet counts initially above 100 × 10^9/l and then above 50 × 10^9/l for at least 7 days (very low evidence, strong recommendation).

In the absence of life-threatening bleeding in a neonate, such as intracranial or gastrointestinal bleeding, platelets should be transfused to maintain a platelet count above 30 × 10^9/l (very low evidence, strong recommendation).

A cranial ultrasound should be performed to screen for ICH in all neonates suspected of FNAIT within 24 h of delivery (very low evidence, strong recommendation).

Lieberman L. et al. BJH 2019

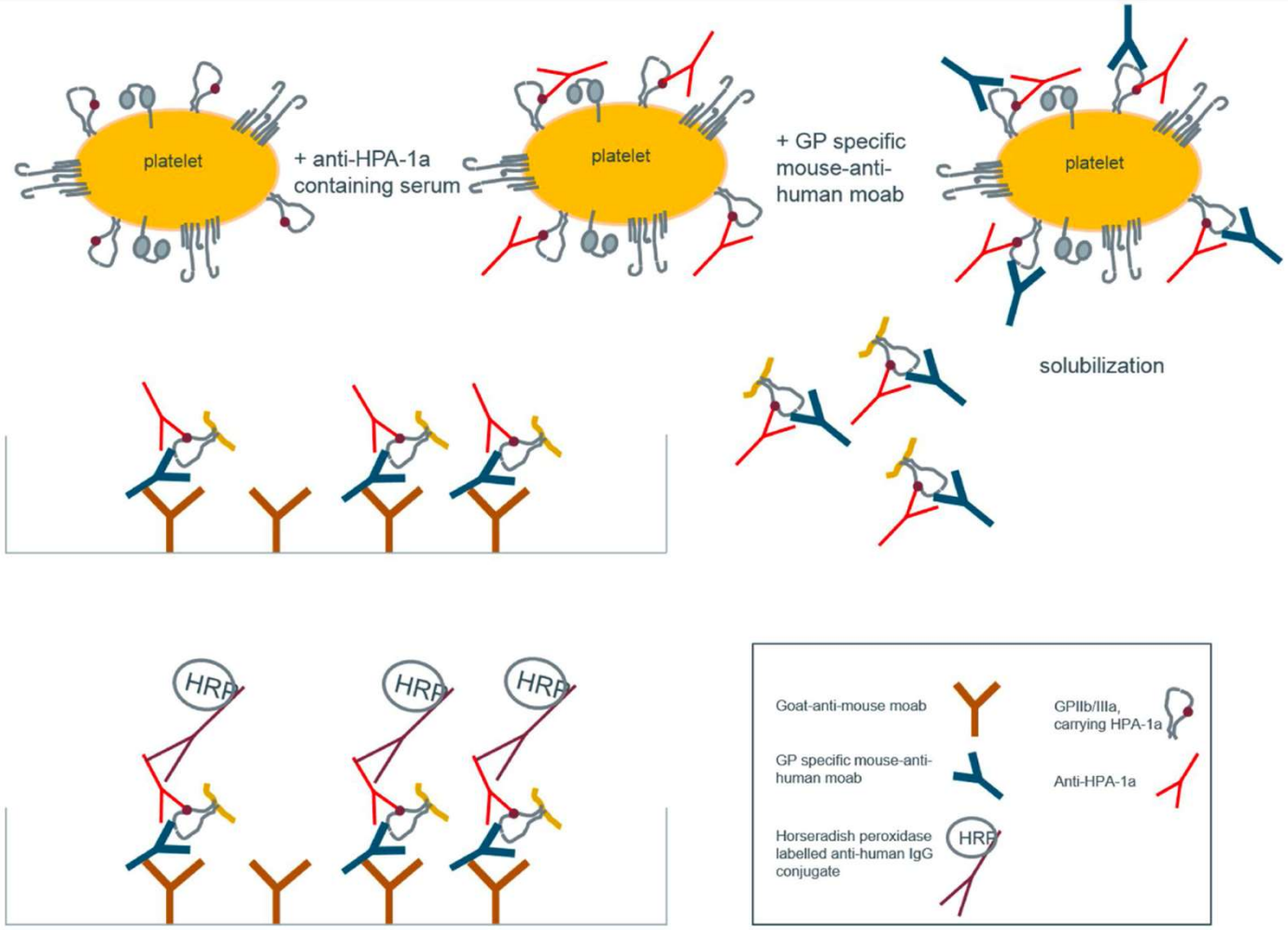
Allo-immunisation plaquettaire

- ✓ ATCD -> Risque
- ✓ hémorragie intra-crânienne et thrombopénie néonatale plus sévère et plus fréquente
- ✓ Immunoglobulines anténatales à visée fœtale ou néonatale
- ✓ césarienne ?
- ✓ 48 premières heures -> J7
- ✓ concentré de plaquettes phénotypées

PTI

- ✓ ATCD -> Risque
- ✓ thrombopénie néonatale moins sévère et moins fréquente - complication hémorragique sévère rare
- ✓ pas de traitement anténatal à visée fœtale ou néonatale
- ✓ voie basse
- ✓ J3/J5 -> J10/J15 (parfois plus)

Immunologie plaquettaire - MAIPA



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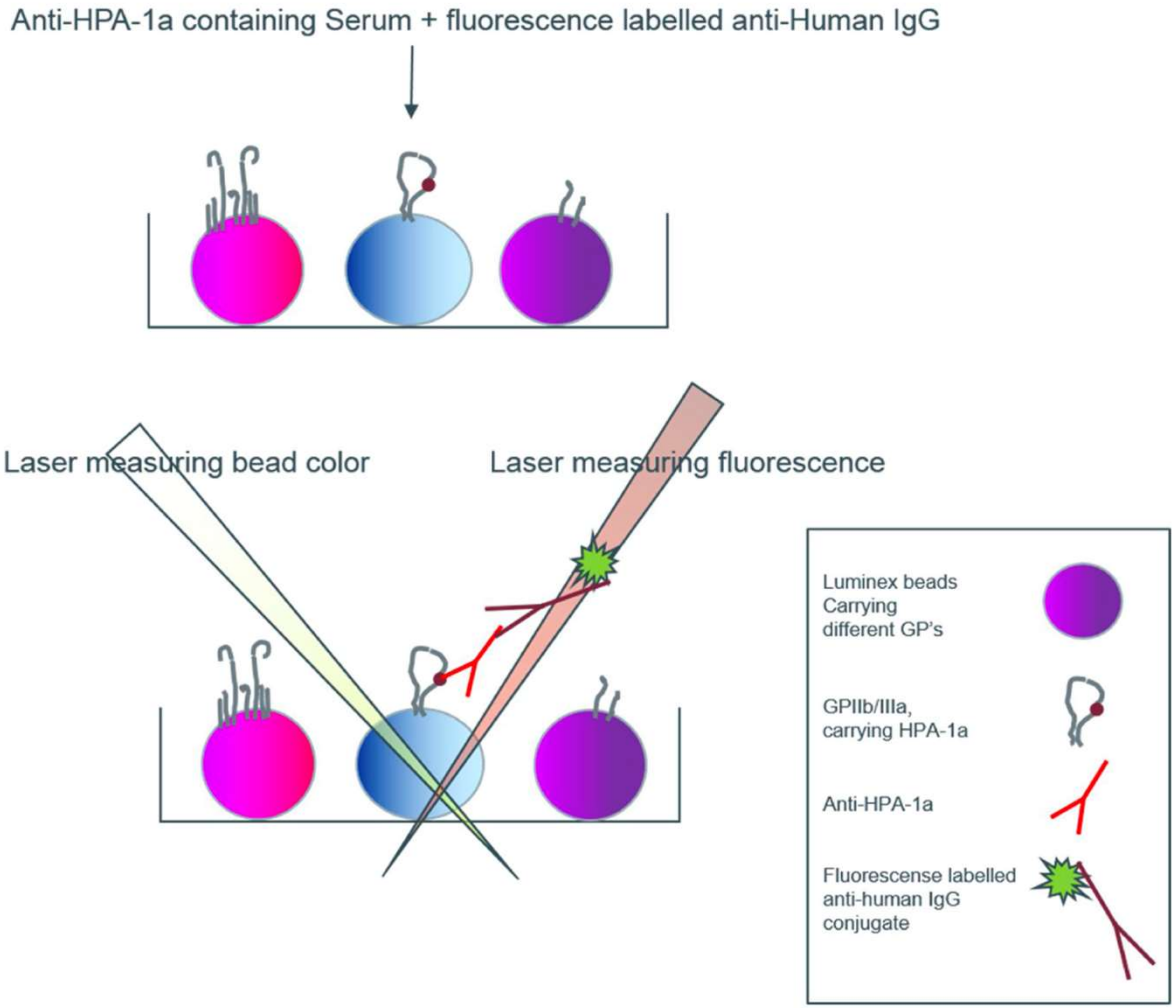
Immunologie plaquettaire - Luminex



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