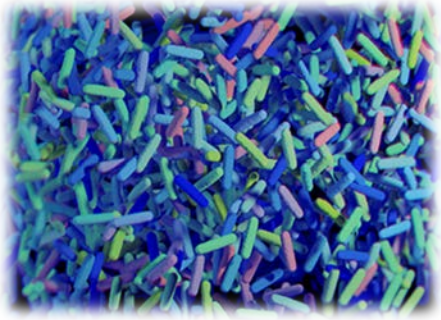
IMMUNOGLOBULINES POLYVALENTES ET MALADIE HÉMOLYTIQUE FŒTALE



4ème Journée « Yves Brossard » d'hémobiologie fœtale et néonatale

Paul Maurice

Centre National de Référence en Hémobiologie Périnatale

Service de Médecine Fœtale, Hôpital Armand Trousseau, AP-HP.Sorbonne Université

Immunoglobulines polyvalentes ?

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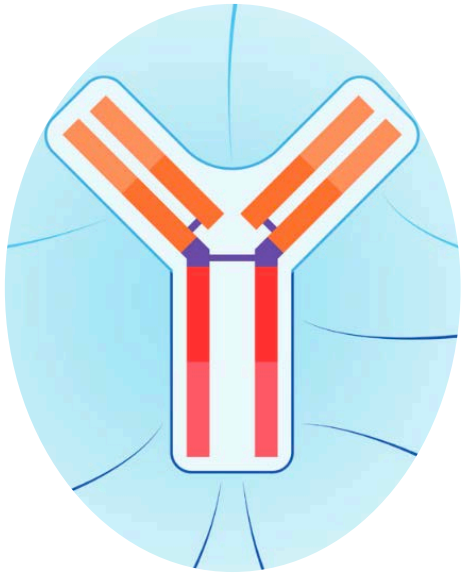
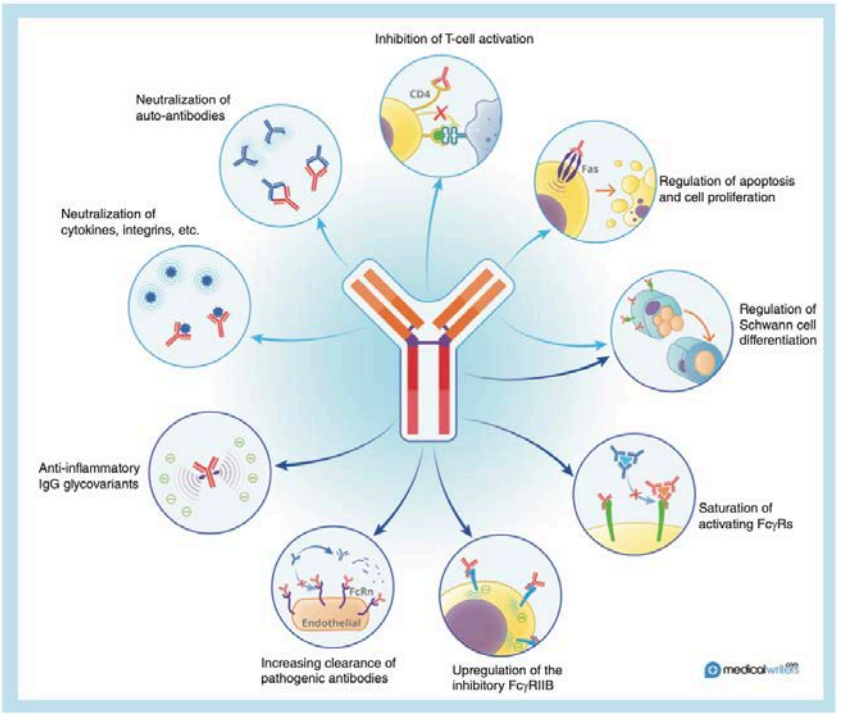


médicament dérivé du sang
pool de plasma ± 1000 dons
IgG
large spectre d'anticorps
répartition sous-classes proche du plasma humain natif

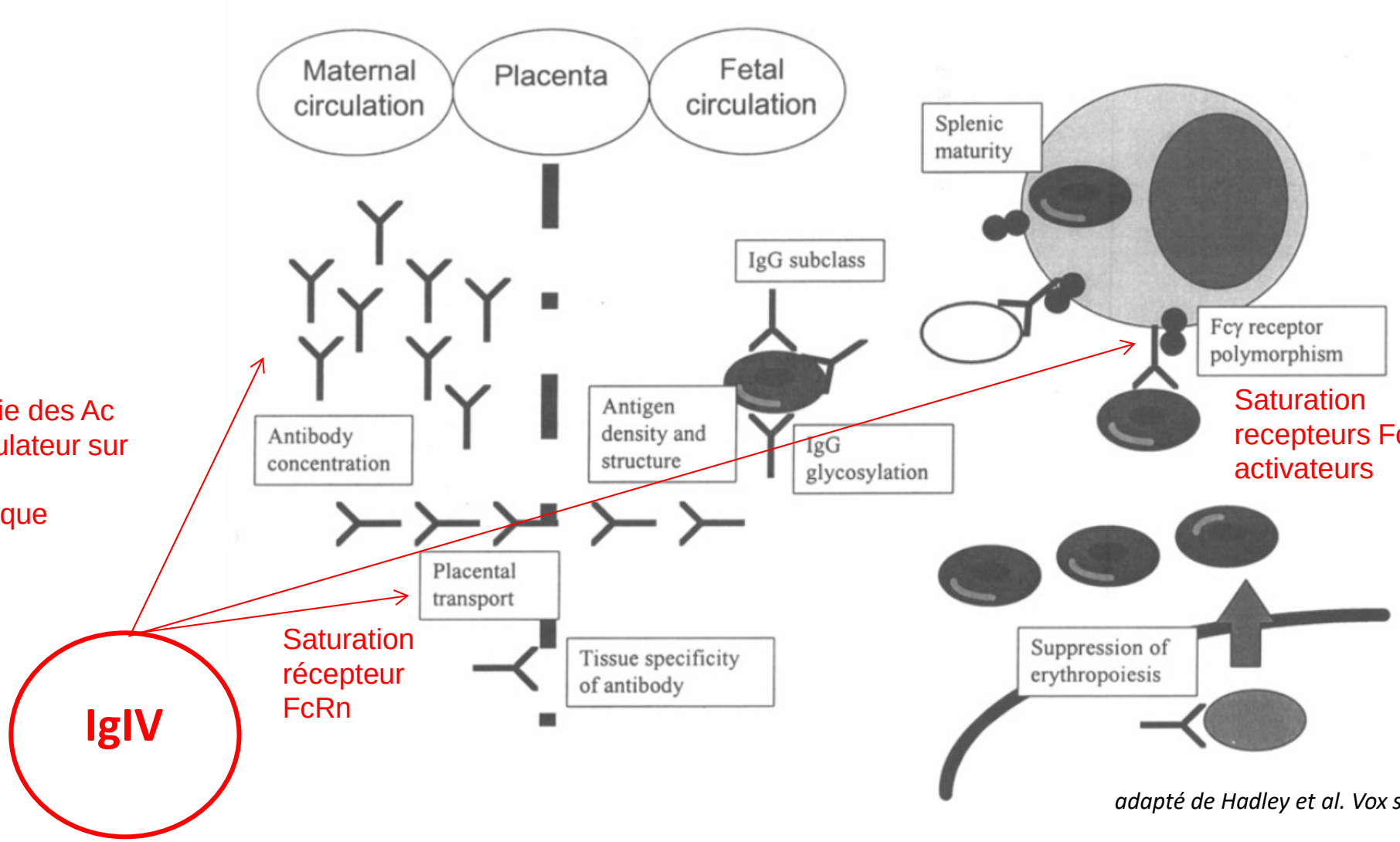
- ✓ Substitution
- ✓ **Immunomodulation**
  - ➢ mécanisme non totalement élucidé
  - ➢ multifactoriel
  - ➢ immunité humorale et cellulaire



Nikolov et al. Immunotherapy 2016

Action dans la maladie hémolytique

- Diminution demi-vie des Ac
- Effet immunomodulateur sur les Lymphocytes B
- Action anti-idiotypique



adapté de Hadley et al. Vox sang 1998

Berlin et al, Lancet , 1985

Allo-immunisation érythrocytaire sévère
Transfusion fœtale précoce

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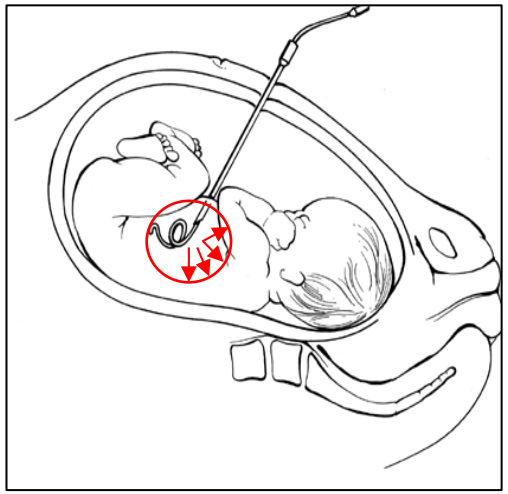
< 20 SA

3-6 % des transfusions
Survie globale 80-83 %
Risque de perte fœtale x 9
Transfusion intra-péritonéale



Canlorbe et al. Obstet Gynecol 2011
Lindenburg et al. BJOG 2013
Zwiers et al. UOG 2017

Efficacité ?

Antenatal immunoglobulin for fetal red blood cell alloimmunization (Review)

Cochrane Library
Cochrane Database of Systematic Reviews

Wong KS, Connan K, Rowlands S, Kornman LH, Savoia HF

2013

- ✓ Absence d'essai randomisé
- ✓ Séries de cas suggérant efficacité des IgIV pour retarder l'âge gestationnel à la 1re transfusion fœtale

Efficacité ?

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Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment; the PETIT study on severe hemolytic disease of the fetus and newborn

Carolien Zwiers, MD; Johanna G. van der Bom, MD, PhD; Inge L. van Kamp, MD, PhD; Nan van Geloven, PhD; Enrico Lopriore, MD, PhD; John Smoleniec, MD, PhD; Roland Devlieger, MD, PhD; Pauline E. Sim, BSc; Marie Anne Ledingham, MD, PhD; Eleonor Tiblad, MD, PhD; Kenneth J. Moise Jr, MD, PhD; Karl-Philip Gloning, MD, PhD; Mark D. Kilby, MD, PhD; Timothy G. Overton, MD; Ditte S. Jørgensen, MD; Katrine V. Schou, MD; Bettina Paek, MD; Martin Walker, MD; Emma Parry, MD; Dick Oepkes, MD, PhD; Masja de Haas, MD, PhD

SEPTEMBER 2018 **American Journal of Obstetrics & Gynecology**

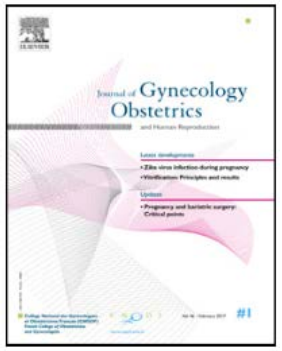
patientes avec atcd :
- décès périnatal lié à maladie hémolytique
ou
- transfusion fœtale < 24 SA

TABLE 2
Primary and secondary outcomes

	Unadjusted				Propensity analysis			
Outcome	IVIg group N = 24	Non-IVIg group N = 28	Effect size[a]	*P*	IVIg group[b] N = 24	Non-IVIg group[b] N = 26	Effect size[a]	*P*
Delta gestational age, d[c]	15 (0–31)	−9 (−19 to 1)	24 (6–43)	.011	0 (−11 to 11)	−4 (−13 to 5)	4 (−10 to +18)	.564
IUTs <20 wk	9 (38)	6 (21)	0.5 (0.1–1.5)	.207	6 (24)	6 (22)	1.1 (0.1–8.9)	.908

si début < 13 SA
1re transfusion
25 jours plus tard
en moyenne

Efficacité ?



Effect of intravenous immunoglobulins to postpone the gestational age of first intrauterine transfusion in very severe red blood cell alloimmunization: A case-control study

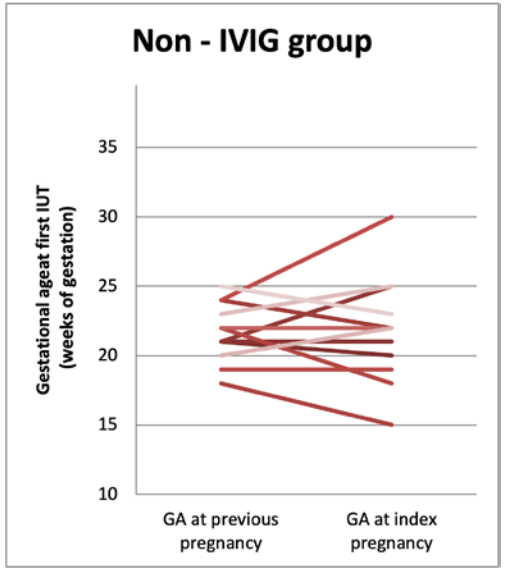
Emeline Maisonneuve[a,b,*], Anaïs Dugas[a], Stéphanie Friszer[a,b], Cécile Toly-Ndour[c], Laura Cariot[a], Ferdinand Dhombres[a,d], Anne Cortey[a,b], Agnès Mailloux[c], Bruno Carbonne[e], Jean-Marie Jouannic[a,b,d]

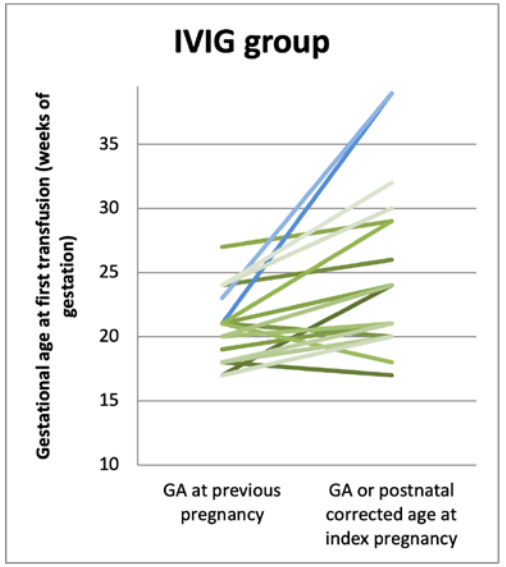
20 cas – 21 témoins

- 1re transfusion ≥ 2 semaines plus tard par rapport à grossesse précédente et naissance vivante > 28 SA
  2/11 (18%) versus 10/16 (63%), p = 0.03

- 1re transfusion > 20 SA
  18/20 (90%) vs 15/21 (71%), p = 0.24

- Terme grossesse cas index - Terme grossesse précédente (jours)
  + 22 [+11 ; +49] versus -2 [-17 ; +12], p = 0.02





Efficacité ?

Centre National de Référence en Hémobiologie Périnatale

Intravenous immunoglobulin for the treatment of severe maternal alloimmunization: individual patient data meta-analysis

Hiba J. Mustafa, MD; Enaja V. Sambatur, MD; Giorgio Pagani, MD; Francesco D'Antonio, MD; Emeline Maisonneuve, MD; Paul Maurice, MD; Carolien Zwiers, MD; Joanne E. J. T. Verweij, MD; Anna Flood, BS; Alireza A. Shamshirsaz, MD; Jean-Marie Jouannic, MD; Asma Khalil, MD

OCTOBER 2024 **American Journal of Obstetrics & Gynecology**

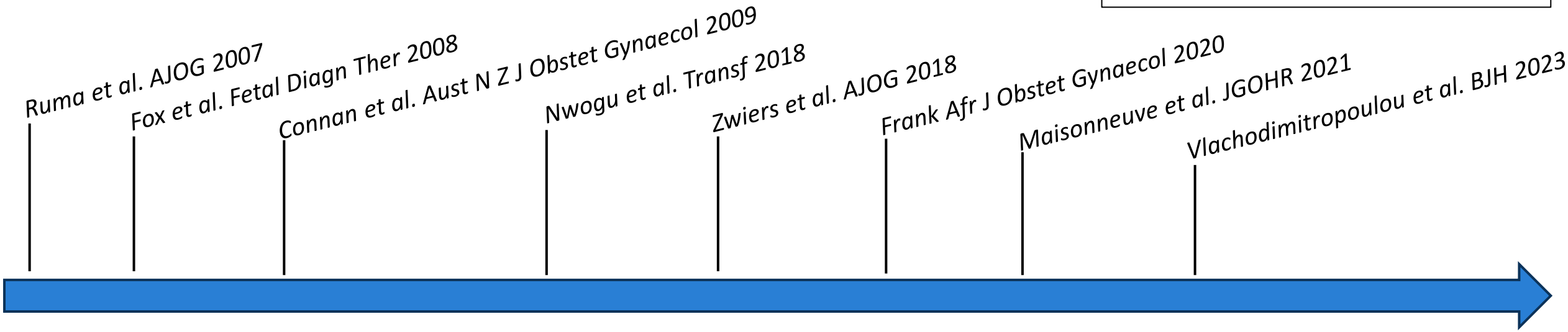
Etudes portant sur cas d'allo-immunisation sévère défini comme :

- décès périnatal lié à maladie hémolytique

ou

- transfusion fœtale < 24 SA

méta-analyse des données individuelles de chaque cas



Efficacité ?

Centre National de Référence en Hémobiologie Périnatale

TABLE 3
Outcomes between the groups of the included 8 studies in the meta-analysis

	IVIG			Non-IVIG			
Outcome	No. of studies	N or n/N	Raw mean (SD)	No. of studies	N or n/N	Raw mean (SD)	IRR or MD (95% CrI)
Delta GA at the first IUT (GA of current pregnancy − GA at previous pregnancy) in weeks[a]	6	61	2.30 (5.21)	2	40	−0.92 (3.90)	3.19 (1.28−5.05)
GA at the first IUT in weeks[a]	8	96	23.3 (4.16)	7	75	22.0 (3.63)	1.32 (0.08−2.50)
Number of IUT[a]	8	89	4.29 (2.08)	6	65	3.88 (2.00)	0.41 (−0.26 to 1.06)
Postponing first IUT ≥2 wk compared with previous pregnancy	6	34/61 (55.7%)	—	2	8/40 (20.0%)	—	2.94 (1.36−7.02)
IUT<20 wk	8	18/97 (18.6%)	—	6	22/97 (22.7%)	—	0.81 (0.43−1.51)
Hydrops at time of first IUT	7	6/62 (9.7%)	—	5	31/67 (46.3%)	—	0.19 (0.07−0.45)
Hb level at the time of first IUT (g/dL)	7	79	6.39 (3.05)	6	53	4.29 (2.28)	2.09 (1.12−3.05)
Fetal demise	7	8/73 (11%)	—	6	40/86 (46.5%)	—	0.23 (0.10−0.47)
Live birth at ≥28 wk of gestation	8	82/97 (84.5%)	—	7	44/97 (45.4%)	—	1.88 (1.31−2.69)
Live birth at ≥32 wk of gestation	8	79/97 (81.4%)	—	7	41/97 (42.3%)	—	1.93 (1.32−2.83)
Survival at birth	8	84/97 (86.6%)	—	7	46/97 (47.4%)	—	1.82 (1.30−2.61)
GA at delivery in weeks[a]	8	91	34.3 (4.67)	7	83	29.3 (7.21)	4.99 (3.26−6.81)
GA at delivery for live births in weeks[a]	8	84	35.1 (4.43)	6	46	34.8 (2.94)	0.33 (−1.04 to 1.78)
Hb level at time of delivery (g/dL)[a]	2	22	11.9 (2.83)	2	23	11.4 (2.40)	0.48 (−1.07 to 0.8)
Bilirubin level at the time of delivery (μmol/L)[a]	2	20	121 (78.8)	2	24	138.0 (74.6)	−17.14 (−65.96 to 0.78)
Survival at hospital discharge	7	66/67 (98.5%)	—	6	43/49 (87.7%)	—	1.15 (0.78−1.74)

CrI, credible interval; *GA*, gestational age; *Hb*, hemoglobin; *IUT*, intrauterine transfusion; *IVIG*, intravenous immunoglobulin; *IRR*, incidence rate ratio; *MD*, mean difference; *PI*, prediction interval; *SD*, standard deviation.

[a] Denotes continuous variables in which provided effect measure is MD and raw mean (SD) data are provided.

Mustafa. Intravenous immunoglobulin for maternal alloimmunization. Am J Obstet Gynecol 2024.

Avis Experts

Monitoring and management of hemolytic disease of the fetus and newborn based on an international expert Delphi consensus

HDFN Delphi Working Group

American Journal of Obstetrics & Gynecology MONTH 2024

TABLE 3
Prenatal management with intravenous immunoglobulins

Items assessed in Delphi questionnaires	Round in which item was included: 1 (N=77)	2
For eligible pregnancies, IVIg should be considered	54/77 (70.0)[a]	
Indications in fetal anemia		
Prior fetal or neonatal death due to HDFN	38/53 (71.7)	
History of IUT at <24 wk in the previous pregnancy	37/53 (70.0)	
Current MCA Dopplers >1.5 MoM at <16–18 wk regardless of obstetric history	11/53 (20.8)	
Current critical antibody titers at <16–18 wk+confirmed Current fetal genotype at risk, regardless of obstetric history	7/53 (13.2)	
History of IUT at any GA in the previous pregnancy	7/53 (13.2)	
GA at initiation of IVIg		
6–10 wk	3/53 (5.7)	
10–14 wk	41/53 (77.4)	
14–18 wk or >18 wk	9/53 (17.0)	
Maximal GA at which IVIg should not be offered		
>14 wk	3/53 (5.7)	
>16 wk	6/53 (11.3)	
>17 wk	1/53 (1.9)	
>18 wk	6/53 (11.3)	
>20 wk	19/53 (35.8)	
No GA limit	18/53 (33.9)	
GA at which IVIg should be stopped, given no signs of fetal anemia		
Up to 24 wk	9/53 (17.0)	
Up to 26 wk	2/53 (3.8)	
Up to 28 wk	1/53 (1.9)	
Up to 32 wk	9/53 (17.0)	
Up to 35 wk	13/53 (24.5)	
Up to 37 wk	7/53 (13.2)	
Until delivery occurs regardless of GA	12/53 (22.6)	
IVIg Dosing		
No loading dose+1 g/kg/week	40/53 (75.5)	
2 g/kg loading dose+1 g/kg/week every week after	5/53 (9.4)	
No loading dose+2 g/kg every 3 wk administered as 1 g/kg/day over 2 d	4/53 (7.5)	
No loading dose+0.5 g/kg/week	4/53 (7.5)	
MCA Doppler monitoring once every week while on IVIg	49/53 (92.5)	
If suggestive of fetal anemia, IVIG should be stopped and IUT started	49/53 (92.5)	

All percentages are presented in parentheses ().

CS, Caesarean section; *GA*, gestational age; *IUT*, intrauterine transfusion; *IVIg*, intravascular immunoglobulins; *MoM*, multiple of the median.

[a] Dark gray shading represents consensus (defined as ≥70% agreement), light gray represents significant agreement (of 60%–69%), and white represents no agreement (<60%). A '-' in a cell means that the issue was not addressed in that round.

Pratique

Variations in antenatal management and outcomes in haemolytic disease of the fetus and newborn: an international, retrospective, observational cohort study

*Derek P de Winter, Enrico Lopriore, Emilie Thorup, Olav Bjørn Petersen, Morten H Dziegiel, Karin Sundberg, Roland Devlieger, Luc de Catte, Liesbeth Lewi, Anne Debeer, Véronique Houfflin-Debarge, Louise Ghesquiere, Charles Garabedian, Kévin Le Duc, Eugenia Antolin, Nieves Mendez, James Castleman, Wing Ting Tse, Jean-Marie Jouannic, Paul Maurice, Jane Currie, Emma Mullen, Lut Geerts, Kerry Rademan, Asma Khalil, Borna Poljak, Smriti Prasad, Eleonor Tiblad, Kajsa Bohlin, Annegret Geipel, Johanna Rath, Fergal Malone, David Mackin, Yoav Yinon, Stav Cohen, Greg Ryan, Evangelia Vlachodimitropoulou, Karl-Philipp Gloning, Stefan Verlohren, Beate Mayer, Mariano Lanna, Stefano Faiola, Tanja Premru Sršen, Lilijana Kornhauser Cerar, Saul Snowise, Luming Sun, Lucas Otaño, César Hernan Meller, Ngina K Connors, Matthew Saxonhouse, Aline Wolter, Ivonne Bedei, Philipp Klaritsch, Sarah Jauch, Eduardo Teixeira da Silva Ribeiro, Fernando Maia Peixoto Filho, Raigam Jafet Martinez-Portilla, Alexandra Matias, Obdulia Alejos Abad, Juan Parra Roca, Ángel Guillermo Alcázar Grisi, Edgar Juan José Chávez Navarro, Johanna G van der Bom, Masja de Haas, EJT (Joanne) Verweij, for the DIONYSUS investigators**

Lancet Haematol 2024

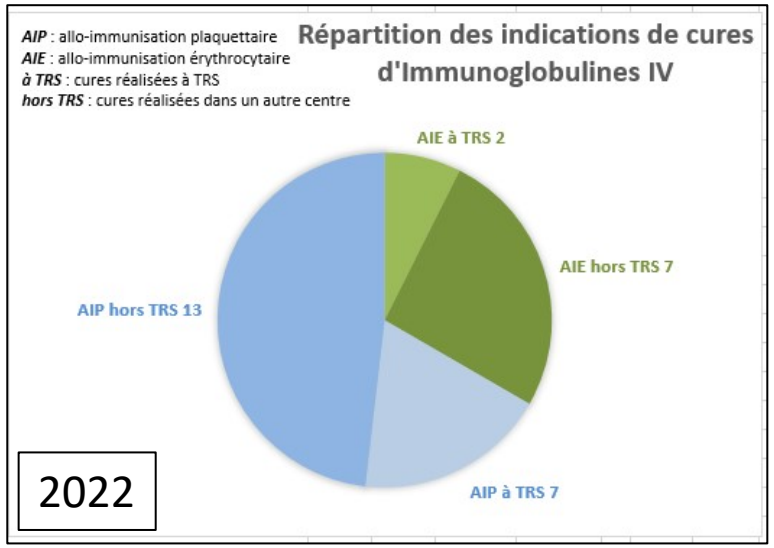
	Liveborn, with any form of antenatal treatment (n=1349)
Intravenous immunoglobulin only	11 (0·8%)
Intrauterine transfusion + intravenous immunoglobulin	60 (4·4%)
Intravenous immunoglobulin + plasmapheresis	2 (0·1%)
Intrauterine transfusion + intravenous immunoglobulin + plasmapheresis	17 (1·3%)

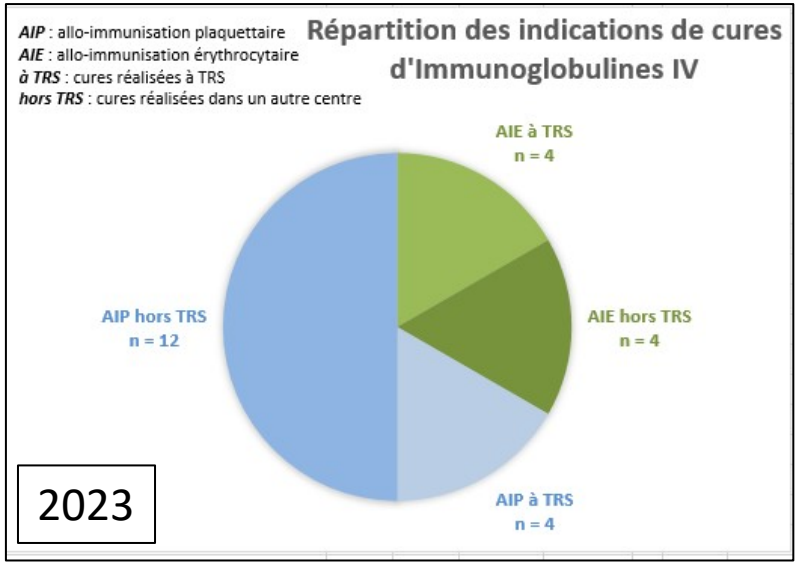
Début âge gestationnel médian 15 SA [12,8 – 16,6]

médiane 8 doses [5-11]

54 patientes traitées sans ATCD

au CNRHP





utilisation depuis 2012

Allo-immunisation très sévère avec :
- décès péri-partum

et/ou

- TIU < 24 SA

→ **décaler terme 1re TIU grossesse suivante**

Indication décidée en RCP

début entre 11 et 13 SA
(parfois avant résultat génotypage fœtal *RHD*)
jusqu'à la naissance ou la 1re TIU

Clairyg® Gamunex® Privigen®

Contraintes

PUBLIÉ LE 14/10/2021 - MIS À JOUR LE 22/12/2021

Tensions d'approvisionnement en immunoglobulines humaines : rappel de la hiérarchisation des indications

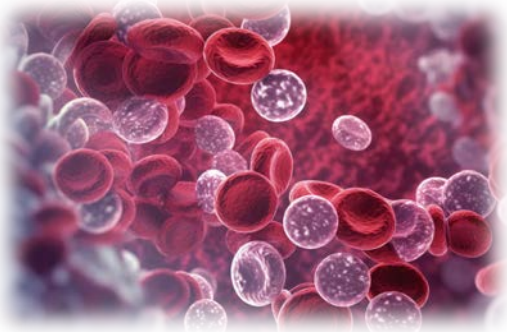
A+ A-

ansm
Agence nationale de sécurité du médicament et des produits de santé

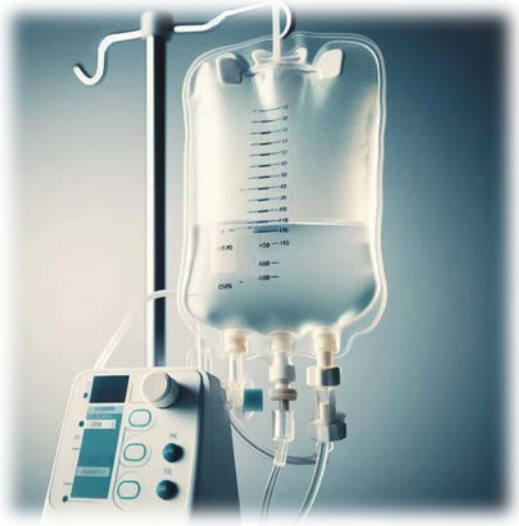
Cure –> entre 3000 et 5000 euros

Hors AMM

Médicament dérivé du sang



- ✓ Administration hospitalière > 24h
- ✓ Hebdomadaire
- ✓ fin T1 -> 1re transfusion ou naissance
- ✓ Effets secondaires fréquents
  céphalées, hyperthermie,
  frissons, tachycardie, hypotension
  …..



Conclusion

- ✓ Mécanismes d'action non élucidés
- ✓ Allo-immunisation érythrocytaire très sévère
- ✓ Faible niveau de preuve – Efficacité non nulle – Décaler la 1re transfusion *in utero*
- ✓ Relatif consensus sur indication, dose et âge gestationnel de début
- ✓ Contraintes majeures
- ✓ Alternative ?