



The University of Texas at Austin  
Dell Medical School

# Red Cell Alloimmunization 2025: Now and the Future

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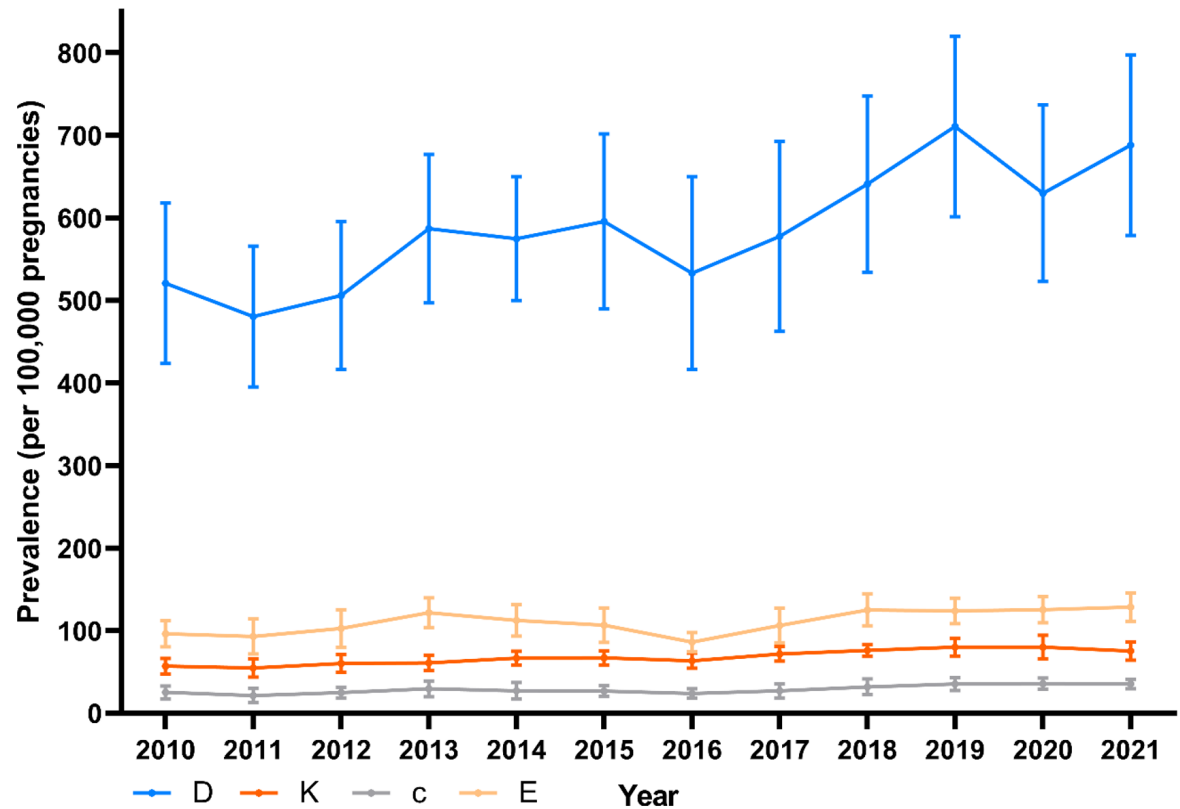
Comprehensive Fetal Care Center

# Conflicts of Interest

NAME	TASK	FUNDING
Johnson and Johnson, Inc	Research	Fees paid to UT-Austin on behalf of Moise
Johnson and Johnson, Inc	Advisory board phase 2 & 3 clinical trials on Nipocalimab for HDFN	No fees paid
Johnson and Johnson, Inc	Immunologic advisory Board regarding Nipocalimab uses in pregnancy	No fees paid
BillionToOne, Inc.	Consultant	Fees paid directly to Moise
UpToDate, Inc.	Royalties for authored chapters	Fees paid directly to Moise
Health Management Associates, Inc.	Consulting for formation of fetal care centers	Fees paid to UT-Austin on behalf of Moise

# Incidence of Antibodies in a US Population

- Commercial lab
- Prenatal panels
- 2010 - 2021
- 9.9 million pregnancies
- 1.5% w/ pos antibody
  - ✓ D: 586/100,000 D: 21
  - ✓ E: 110/100,000 E: 8
  - ✓ K: 68/100,000 K: 46
  - ✓ c: 29/100,000 c: 1.9



*Sugrue et al. Blood Adv 2024;8:4311-9*

## Screening for Antibodies

### Step 1

- Antibody screen and identification at 6 – 9 months after exposure to O pos low titer red cells in individuals at risk for severe HDFN (patient can develop other anti-red cell antibodies associated with HDFN)
- If positive, consider pre-conceptual counseling
- If negative, repeat antibody screening early in next pregnancy

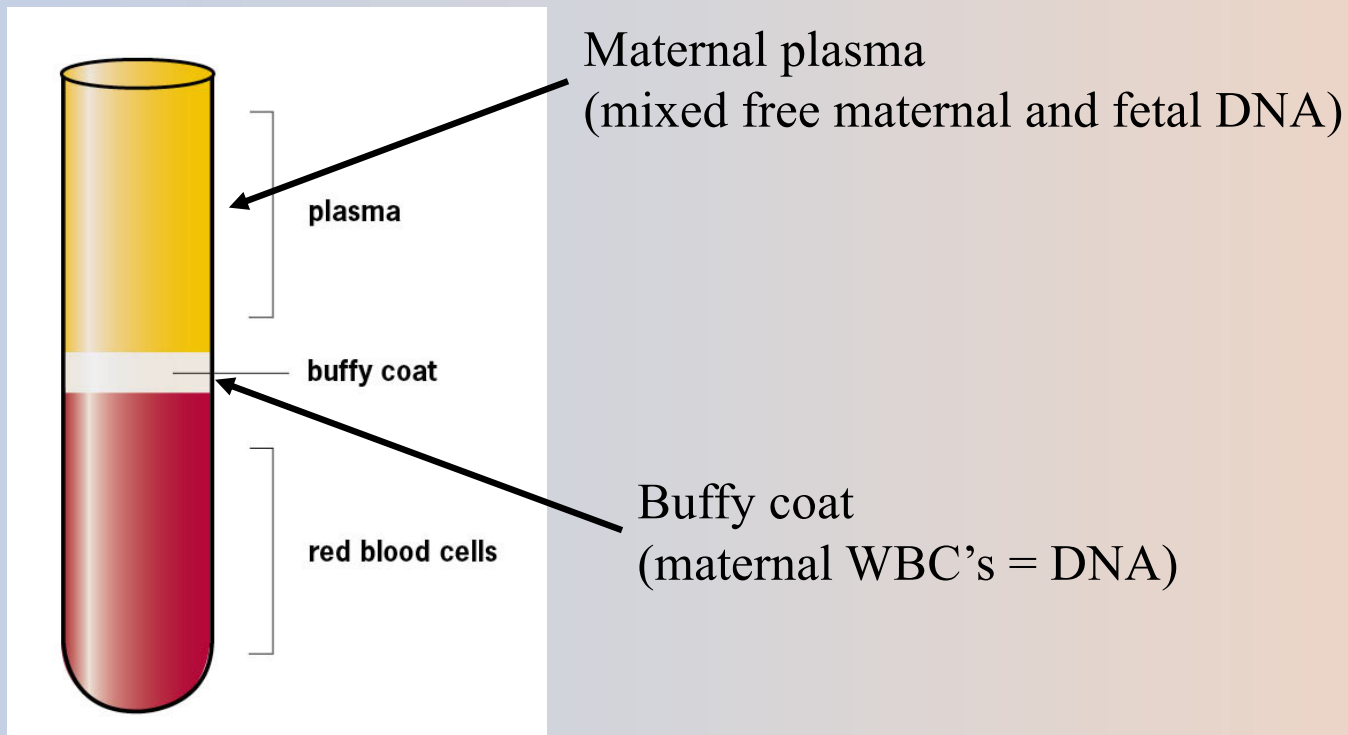
## Screening for Antibodies

### Step 2

- If positive antibody screen – perform titer
- Critical titer for most antibodies: 16
- Critical titer for anti-c and anti-Kell: 4
- In general, higher titers are associated with more severe HDFN

# RED CELL ALLOIMMUNIZATION

## DNA-based Red Cell Typing



## Free Fetal DNA for RhD Fetal Antigen Determination

<b>BillionToOne Assay (UNITY®)</b>						
No of samples/ patients	<i>RHD pos</i> NIPT	<i>RHD neg</i> NIPT	Rh <i>pos</i> result	Rh <i>neg</i> result	Sensitivity (95% CI)	Specificity (95% CI)
<sup>1</sup> 456	254	191	454	192	100% (98.6 – 100)	100% (98.1 – 100)
<sup>2</sup> 401	261	140	261	140	100% (98.6 – 100)	100% 97.4 – 100)
<b>Natera Assay (Panorama®)</b>						
<sup>3</sup> 110	70	40	70	40	100% (94.9 – 100)	100% (91.2 – 100)
<sup>4</sup> 655	358 <sup>\$</sup>	295	356	297	100% (98.9 – 100)	99.3% (97.6 – 99.8)

\$ 2 false positive cases

<sup>1</sup> Rego et al. *Obstet Gynecol* 2024;144:436-43.

<sup>2</sup> Julio et al. *Obstet Gynecol* (in press)

<sup>3</sup> Wang et al. *American Society of Human Genetics Annual Meeting* 2023

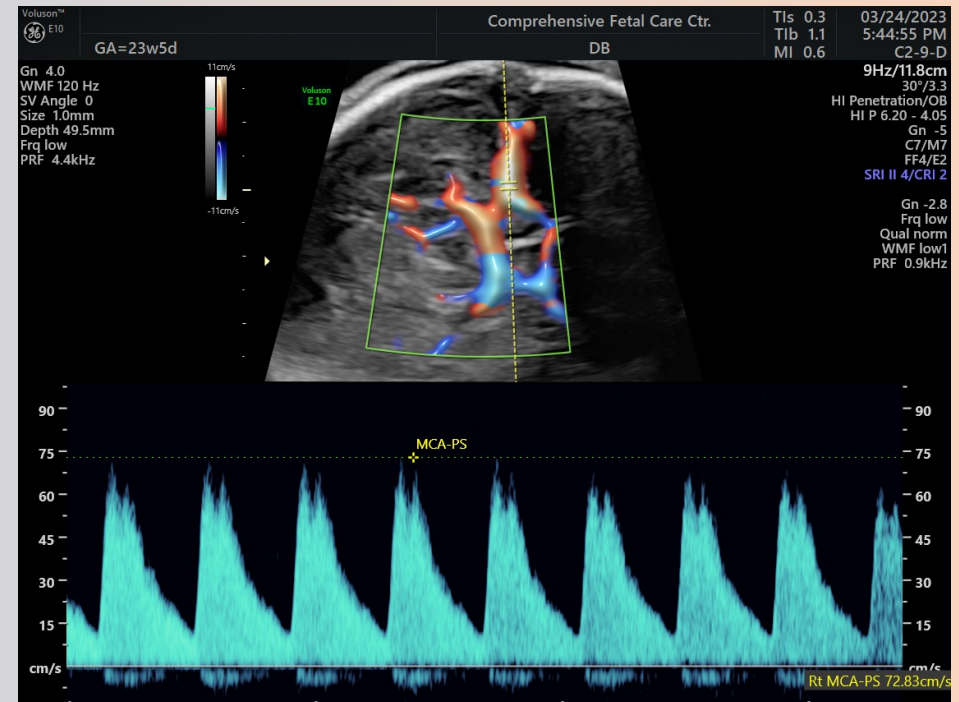
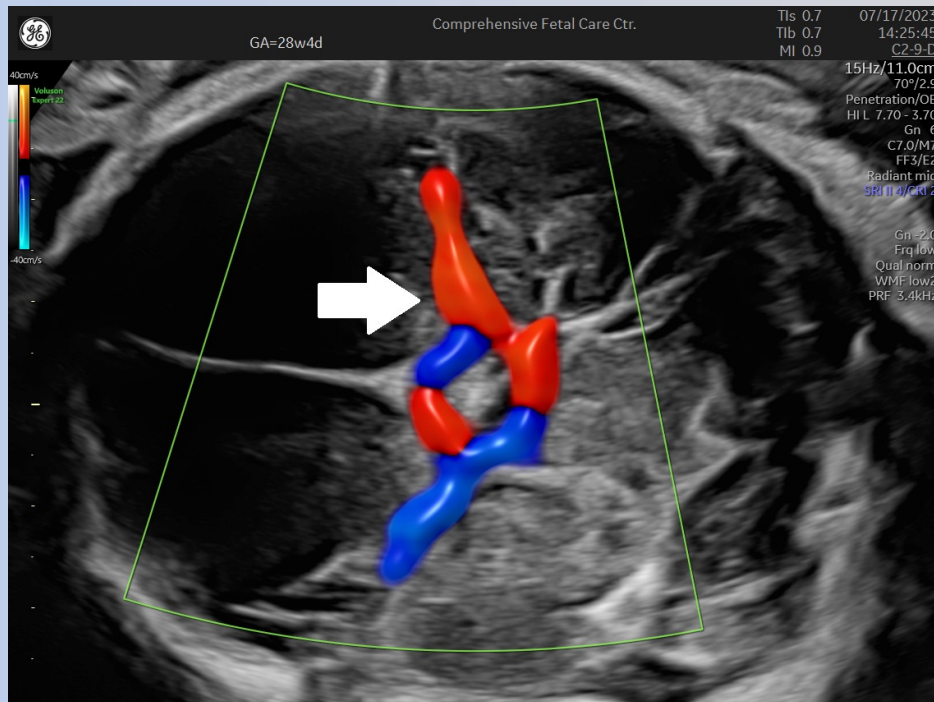
<sup>4</sup> Thompson et al. *Obstet Gynecol* 2025; 145: 211-6.

## MCA-PSV Doppler



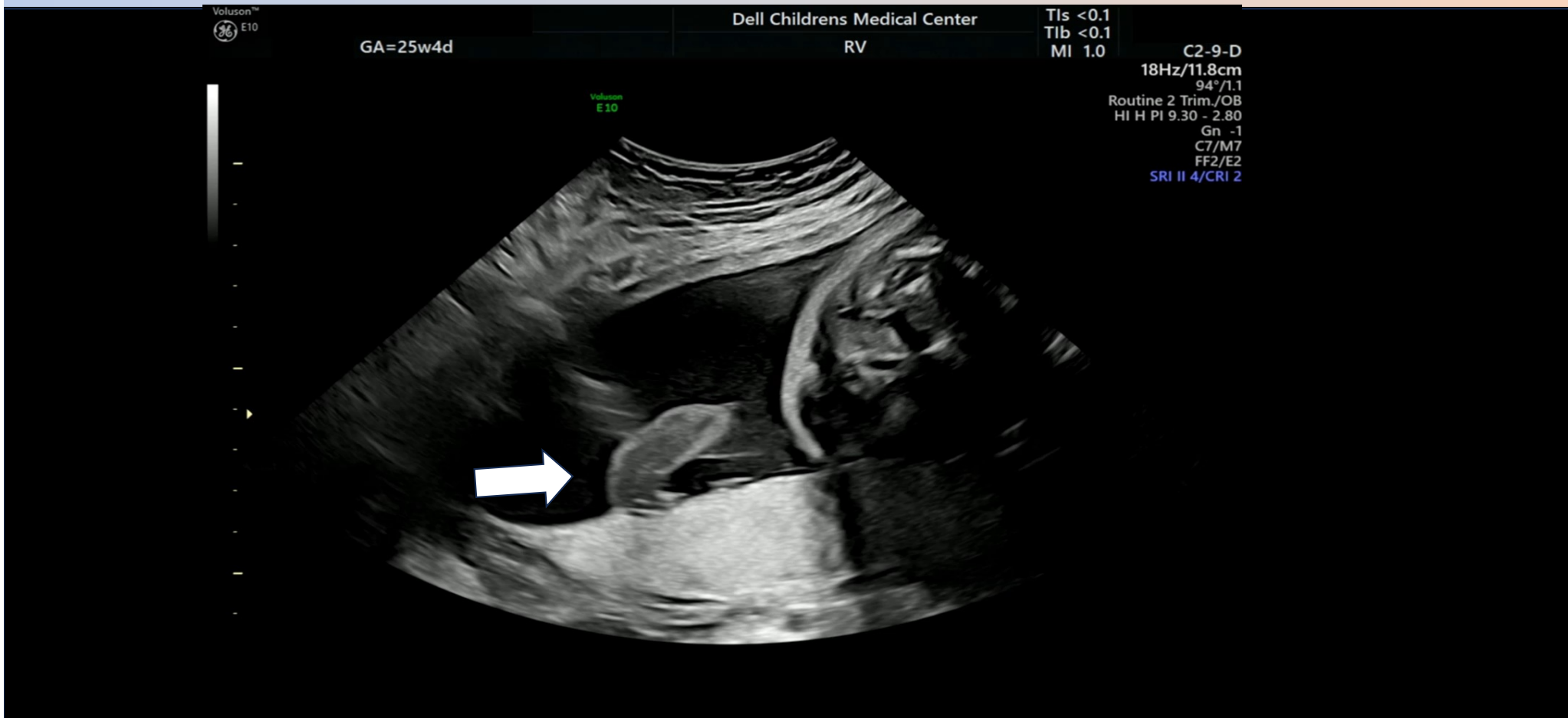


# Middle Cerebral Artery Doppler

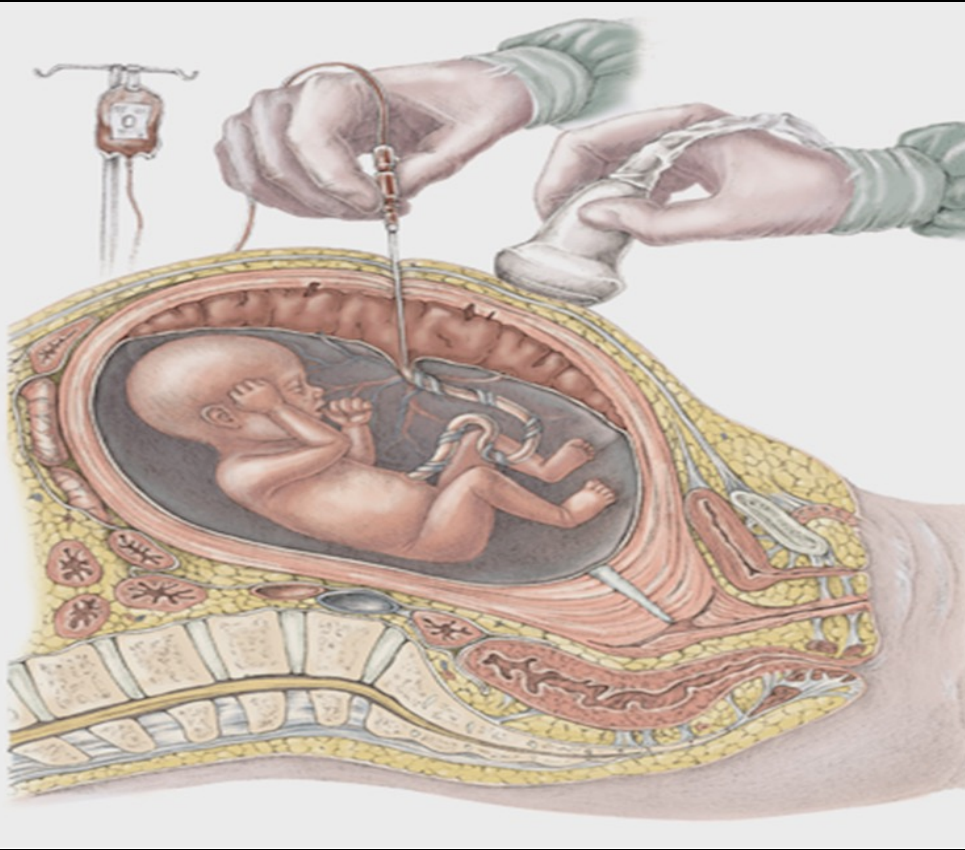


$\text{MCA-PSV} > 1.5 \text{ MoM for gestational age} = \text{moderate/severe fetal anemia}$

## Intrauterine Transfusions (video)



# Intrauterine Transfusions



- Performed between 15 – 35 weeks gestation
- Donor blood - Rh neg, CMV neg, irradiated
- Amount based on initial fetal hct and fetal weight by ultrasound
- Repeated every 2 – 4 weeks
- Average number: 4
- Perinatal loss @ < 20 weeks = 20%
- Perinatal loss > 20 weeks = 3-5%

# Immunotherapy

# Early Onset HDFN

- Gestational age of 20 – 22 weeks at onset of fetal disease
- Fetal death
- Hydrops
- Fetal anemia requiring intrauterine transfusions

# Intravenous Immune Globulin

- Start at 10 – 12 weeks gestation
- 2 gr/kg loading dose then 1 gr/kg weekly
- Very expensive
- Complications: severe headache, aseptic meningitis

## Intravenous Immune Globulin Meta-analysis

- 8 studies: 97 cases w/IVIG/ 97 cases without IVIG
- Outcomes compared to previous pregnancy

Outcome	Risk (95% CI)
↑ Change in gest age at first IUT (wks)	3.9 (1.28 – 5.05)
↑ Incidence of 2 week gain before 1 <sup>st</sup> IUT	2.94 (1.36 – 7.02)
↑ Hemoglobin at 1 <sup>st</sup> IUT (gr/dl)	2.09 (1.12 – 3.05)
↓ Risk of fetal hydrops	0.19 (0.07 – 0.45)
↓ Fetal demise	0.23 (0.10 – 0.47)
↑ Overall rate of survival	1.82 (1.30 – 2.61)
↑ Live birth > 28 weeks gestation	1.88 (1.31 – 2.69)
↑ Livebirth > 32 weeks gestation	1.82 (1.30 – 2.61)

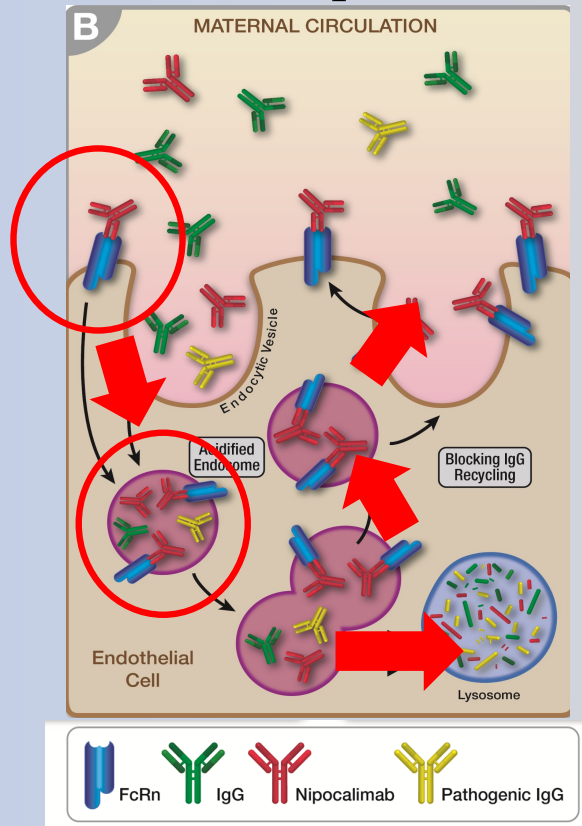
*Mustafa et al. Am J Obstet Gynecol 2024; 231:417-429*

# Nipocalimab

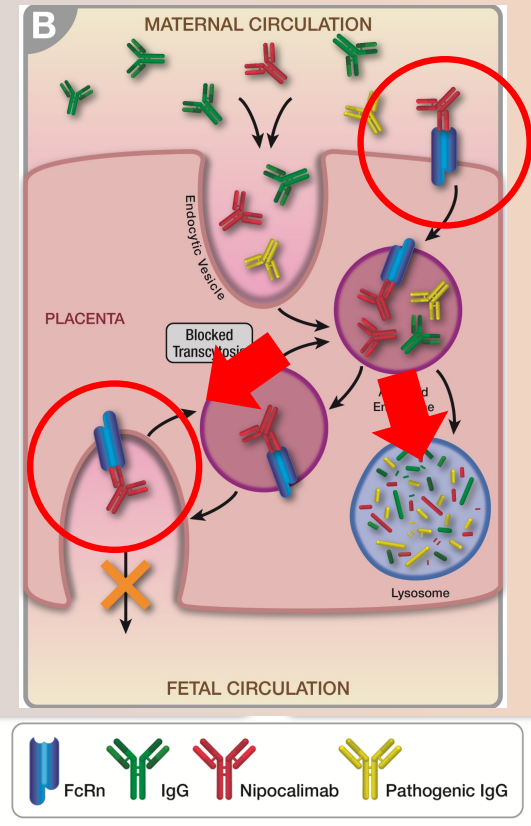


# Mechanism of FcRn blockade

## FcRN Peripheral Blockade



## FcRN Placental Blockade



*The* NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

# Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn

K.J. Moise, Jr., L.E. Ling, D. Oepkes, E. Tiblad, E.J.T.J. Verweij, E. Lopriore, J. Smoleniec, U.J. Sachs, G. Bein, M.D. Kilby, R.S. Miller, R. Devlieger, F. Audibert, S.P. Emery, K. Markham, M.E. Norton, O. Ocón-Hernández, P. Pandya, L. Pereira, R.M. Silver, R. Windrim, J.B. Streisand, J.H. Leu, A. Mirza, V. Smith, L.B. Schwartz, M.L. Tjoa, S. Saeed-Khawaja, Y. Komatsu, and J.B. Bussel, for the UNITY Study Group\*

Moise et al. N Engl J Med 2024;391:526-37

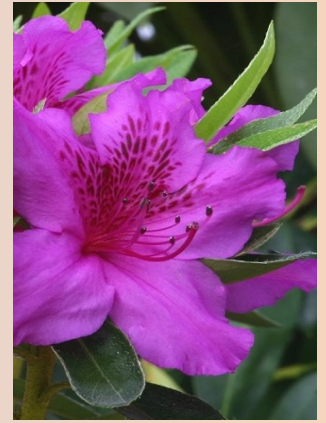
## Nipocalimab Phase II Trial Results

Parameter	Qualifying (previous) pregnancy	On-study pregnancy
Enrolled participants (11 RhD, 2 Kell)	13	13
Number with IUT	11 (84.6%)	6 (46.2%)
Live birth at $\geq 32$ weeks GA without an IUT	0	7 (53.8%)*
GA at first IUT (median, range; weeks)	20 <sup>4/7</sup> (17 <sup>1/7</sup> -23 <sup>5/7</sup> )	27 <sup>1/7</sup> (22 <sup>5/7</sup> -31 <sup>5/7</sup> )
Hydrops	7 (53.8%)	0
Live births	5 (38.5%)	12 (92.3%) <sup>†</sup>
GA at delivery (median, range; weeks)	23 <sup>6/7</sup> (18 <sup>3/7</sup> -36 <sup>6/7</sup> )	36 <sup>4/7</sup> (23 <sup>6/7</sup> -37 <sup>3/7</sup> )
Neonates with exchange transfusion	0	1 (8.3%)
Neonates with simple transfusion	4 (80%)	6 (50%)

*Moise et al. N Eng J Med 2024;391: 526-37*

## Nipocalimab Phase III trial

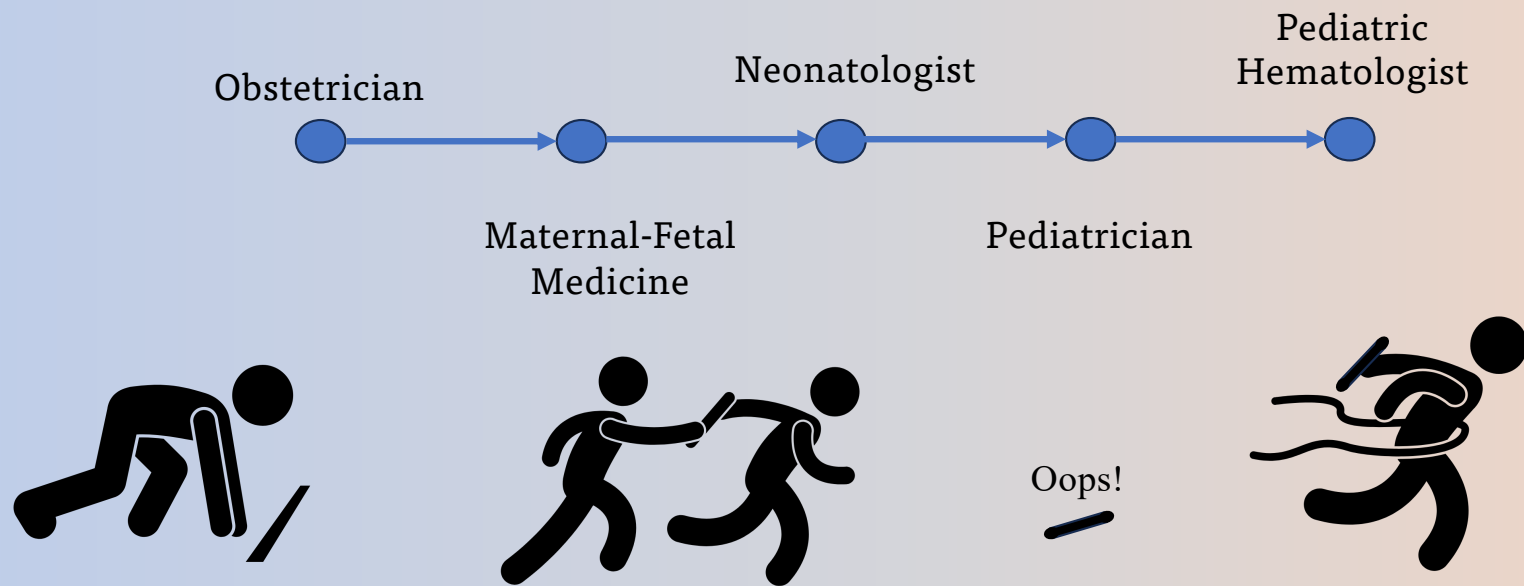
- Plan for a phase 3 randomized clinical trial (AZALEA) in pregnant individuals at risk for severe HDFN
- Key inclusion criteria
  - Alloimmunization of anti-D, C, E, c, or Kell
  - Antecedent pregnancy with documented HDFN-associated fetal anemia,  $\geq 1$  IUT, or fetal/neonatal death
  - Currently pregnant with an antigen-positive fetus by free fetal DNA
- Participants will be randomized 2:1 to nipocalimab vs placebo infusions



# Neonatal Care

# RED CELL ALLOIMMUNIZATION

## The Baton Pass



## Hemolytic Disease of the Fetus/Newborn Top-up Transfusions

Parameter	IUT (N = 193)	No IUT (N = 105)
Needing top-up transfusions	88%	60%
No. of transfusions	2 ( 2- 3)	2 (1 – 3)
Days to first top-up	16 (5 -27)	9 (5 – 25)
1 top-up	24%	43%
2 top-ups	37%	25%
3 top-ups	23%	19%
4 top-ups	11%	8%
5 top-ups	3%	5%
6 top-ups	2%	0%

*Ree et al. Brit J Haematol 2019;186: 565-73*

# Thank you