Placental Transfer of Immunosuppressive Biologics: Current Clinical Pharmacology Landscape

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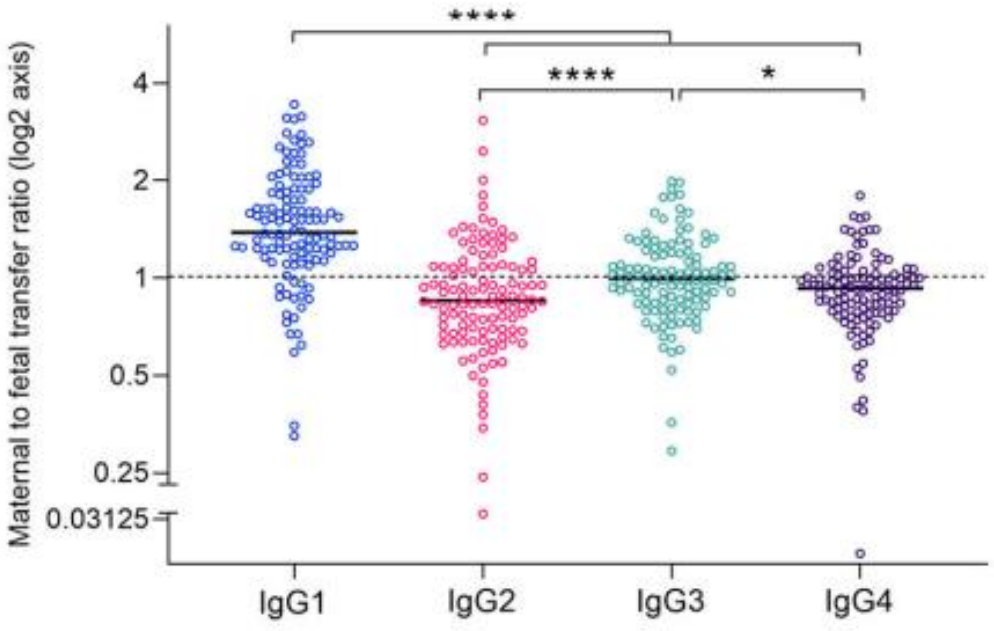
Transplacental passage of immunoglobulins is mediated by the neonatal Fc receptor (FcRn)

However, no association between placental FcRn expression and maternal-to-fetal transfer of IgG



FcRn, but not FcγRs, drives maternal-fetal transplacental transport of human IgG antibodies

Sara Borghi[a,1], Stylianos Bournazos[a,1], Natalie K. Thulin[b], Chao Li[c], Anna Gajewski[d], Robert W. Sherwood[e], Sheng Zhang[e], Eva Harris[f], Prasanna Jagannathan[b,g], Lai-Xi Wang[c], Jeffrey V. Ravetch[a,2,3], and Taia T. Wang[h,g,h,2,3]

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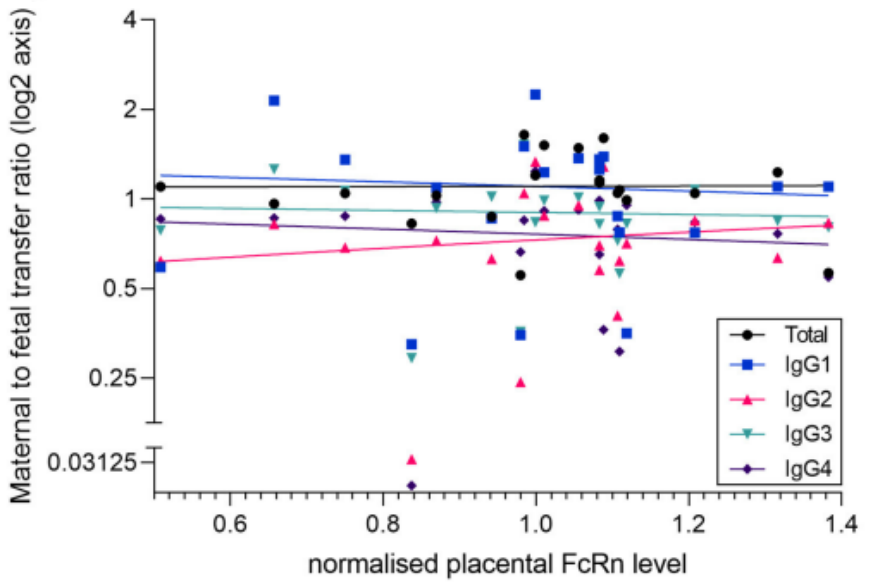


IgG1 preferentially transported; cord to maternal blood ratio expected to be ~1.5. In utero transfer of therapeutic mAbs postulated to be facilitated by placental FcRn while maternal FcRn is responsible for maintaining IgG half-life (including biologics)

Clements T et al. Front Immunol. 2020 Sep 11;11:1920.

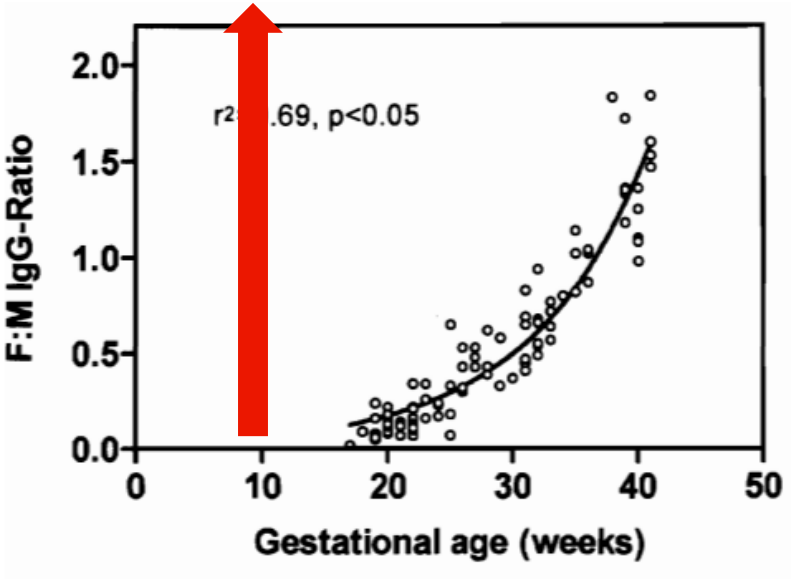
Maternal-fetal IgG transport increases with gestational age

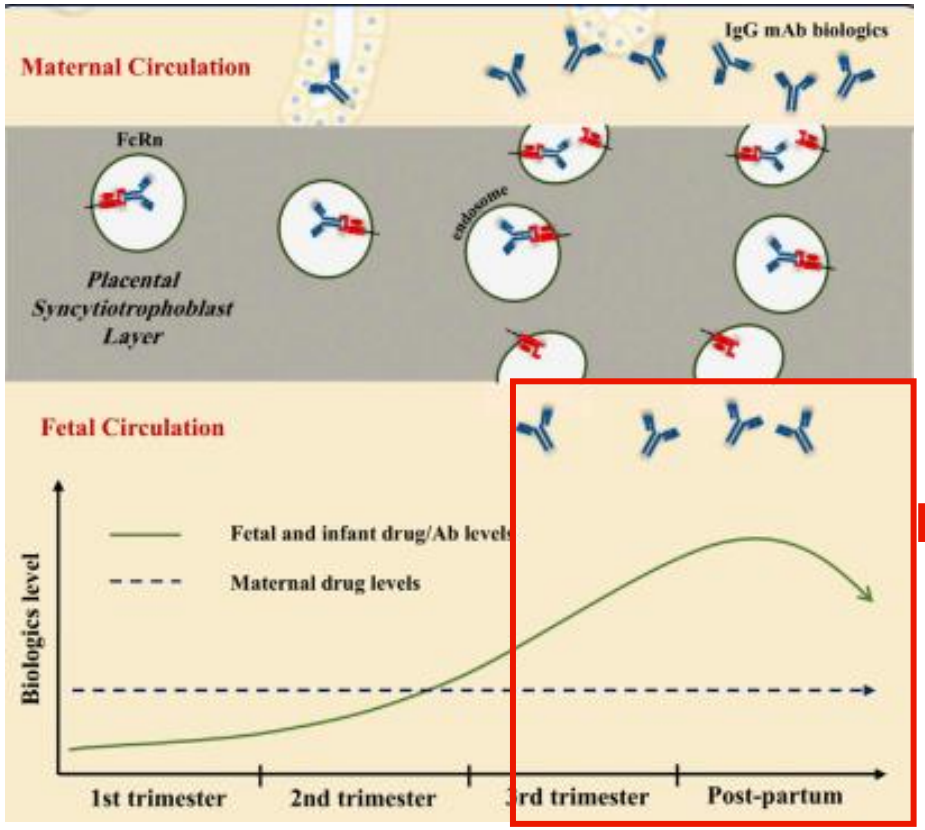
Transport increases throughout gestation exceeding maternal IgG towards term as evidenced by the fetal:maternal (F:M) IgG ratio

Table I. Concentrations of IgG and IgA in maternal coelomic fluid (CF) at 6–12 weeks of gestation

	MS IgG (mg/dl)	CF IgG (mg/dl)
Median	907	32
Range	600–1370	13–99
Interquartile range	760–1060	20–51

F:M ratio expected to be <0.1 during the first trimester



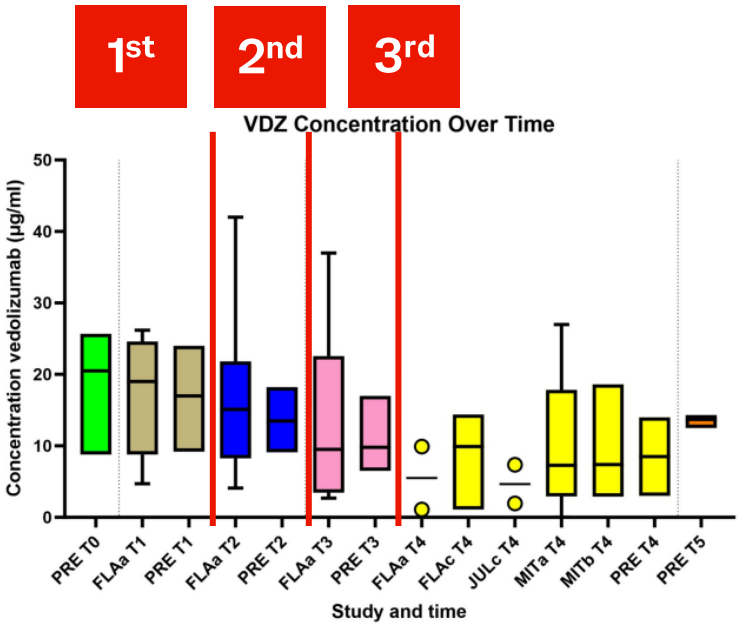


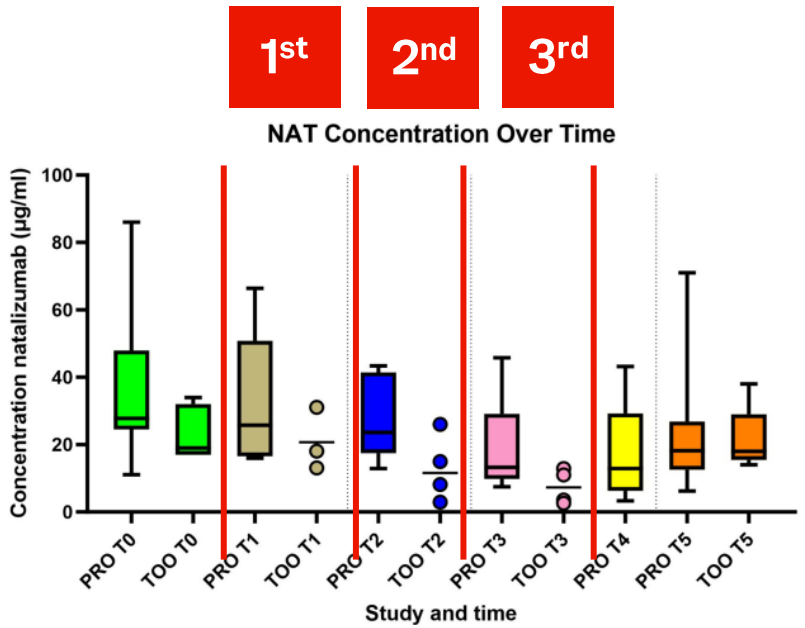
Given that most biologics are engineered with various IgG subtype constant regions, what is the current evidence surrounding in utero exposure for immunosuppressive monoclonals?

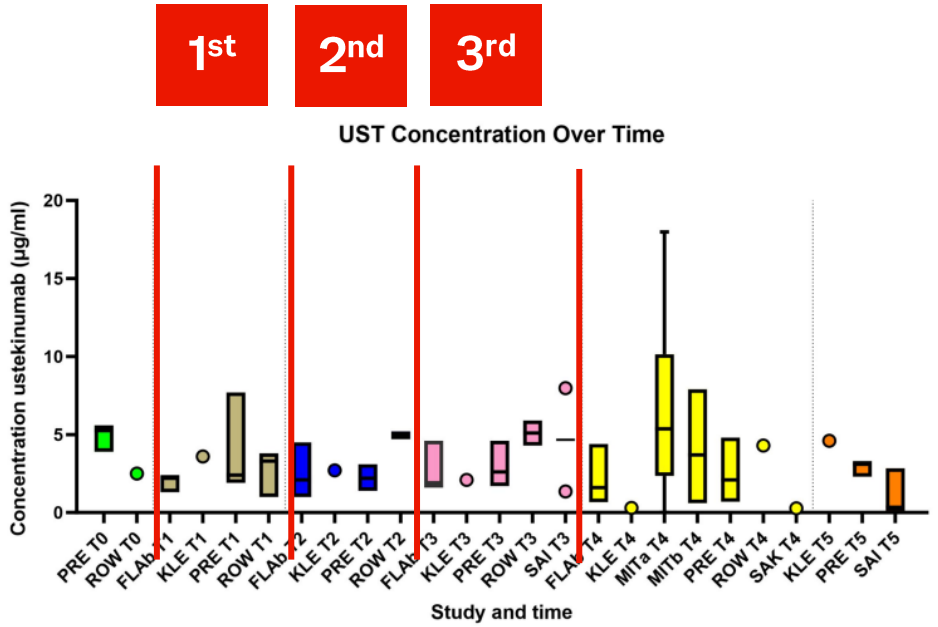
Jauniaux E et al. Hum Reprod. 1995 Dec;10(12):3297-300.
Malek A et al. Am J Reprod Immunol. 1996 Nov;36(5):248-55.
Beltagy A et al. Front Pharmacol. 2021 Feb 11;12:621247.

Evidence suggests modest to lower serum monoclonal antibody (mAb) exposure during pregnancy

Is transplacental crossing of immunosuppressive biologics similar to IgG?







NAT= Natalizumab; UST = Ustekinumab; VDZ = Vedolizumab
T0 = Pre-pregnancy; T1 = 1st Trimester; T2 = 2nd Trimester; T3 = 3rd Trimester; T4 = Delivery; T5 = Postpartum
Gendt JV et al. Clin Pharmacokinet. 2024 May;63(5):589-622.

Most biologics with immunosuppressive properties are IgG1

Class	Drug	mAb Structure	Evidence of transfer (F:M Ratio)	Study design
Anti-TNFa	Golimumab	IgG1	1.21 (n = 1)	**Case**
	Certolizumab-PEG	IgG1 (PEGlayted Fc)	<1.0	**Prospective, Observational**
	Infliximab	IgG1 (chimeric)	1.97 (1.50 – 2.43)	
	Adalimumab	IgG1	1.21 (0.94 – 1.49)	
Anti-Cytokine	Ustekinumab	IgG1	1.70 (1.2 – 2.5)	
Anti-Integrin	Vedolizumab	IgG1	0.70 (0.60 – 0.90)	
	Natalizumab	IgG4	1.63 (0.4 – 4.44)	**Case**
Anti-Complement	Eculizumab	IgG2/4	Detectable cord blood	
Anti-B Cell	Belimumab	IgG1	1.49 (n = 1)	

F:M ratio often used as surrogate of in utero exposure throughout gestation, however limitations exist given various sampling points along the concentration-time curve

Julsgaard M et al. Gastroenterology. 2016 Jul;151(1):110-9.
Prentice R et al. Clin Gastroenterol Hepatol. 2024 Mar 15:S1542-3565(24)00252-0.
Benoit L et al. Crohns Colitis. 2019 Apr 26;13(5):669-670.
Bitter H et al. Ann Rheum Dis. 2023 Apr;82(4):577-579.
Haghikia A. et al. JAMA Neurol. 2014 Jul 1;71(7):891-5.
Kelly RJ et al. N Engl J Med. 2015 Sep 10;373(11):1032-9.

Informative clinical PK data has mostly been observed with a limited number of immunosuppressive biologics

These include anti-TNFa, integrin, & cytokine monoclonals which have been used to contextualize most biologics with immunosuppressive activity

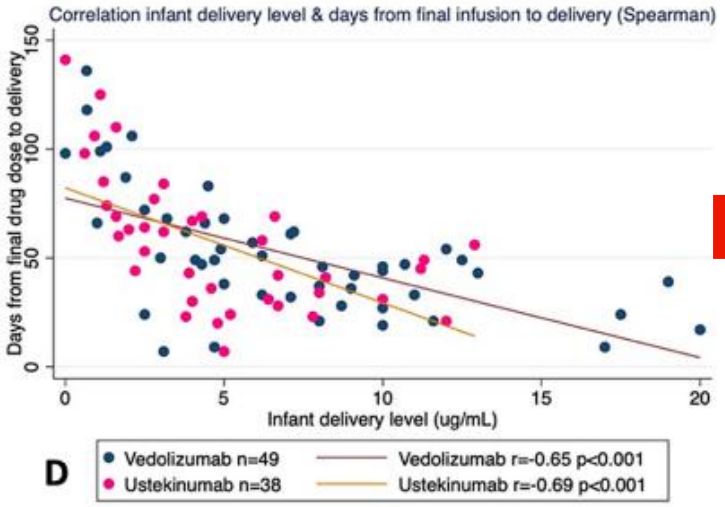
- **Mostly maternal-fetal (cord) paired blood samples to estimate in utero exposure**
  - Estimate the F:M ratio; gauge the magnitude of placental crossing near term
  - Estimate time to clearance using population PK/PD approaches

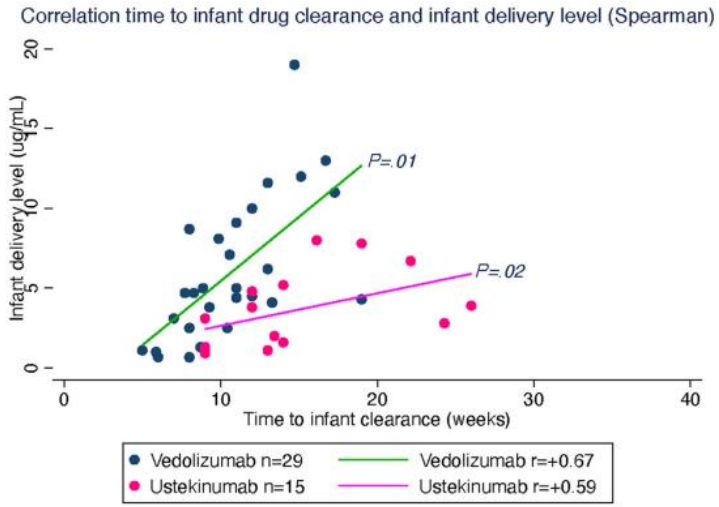
- **Post-natal infant collection allows estimation of the extent of persistence in the exposed infant**
  - Sampling beyond the birth collection in infants (e.g. 4, 8, 12 weeks, etc.) are informative
  - Address questions such as timing of live vaccine administration or exposure-response relationships for developmental or infection AEs

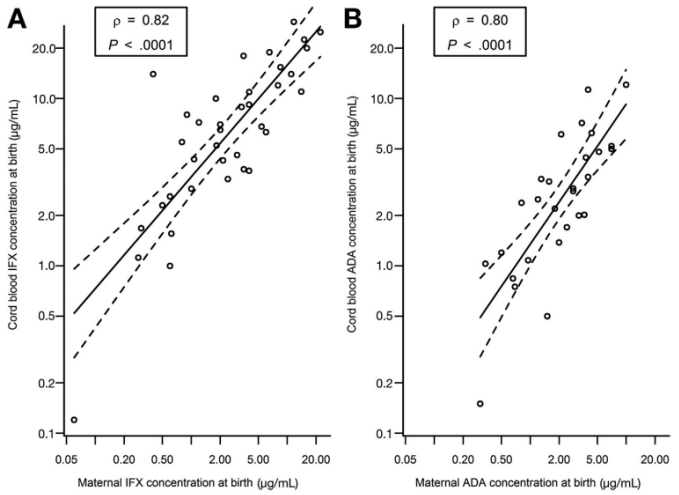
- **The relationship between exposure and target engagement/receptor occupancy in the infant is limited**
  - Mechanistic interpretation between exposure in the infant and downstream effector impact is limited
  - Limited to clinical observations for developmental and infection outcomes

Exposure and time to clearance of drug generally correlates with duration since last maternal dose

Time to undetectable levels generally depends on timing of previous dose at delivery







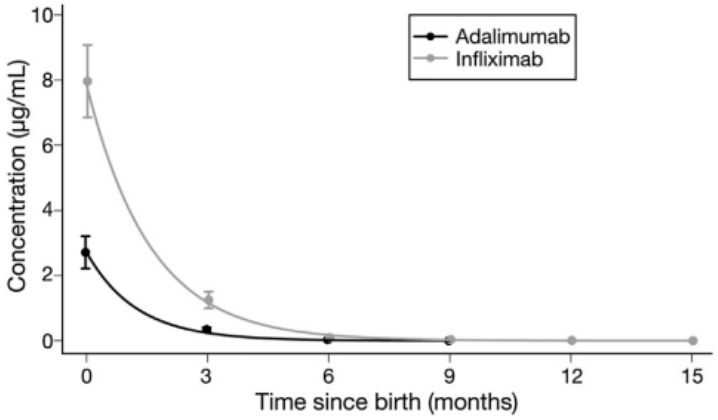


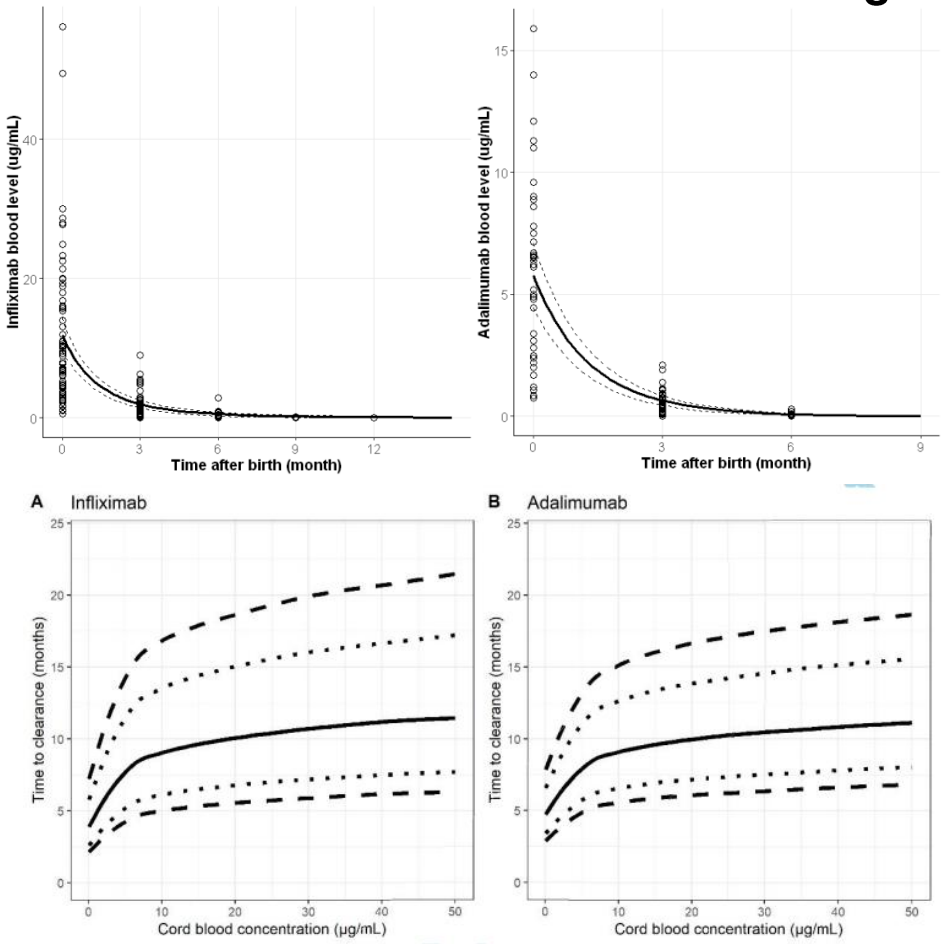
Figure 4. Mean (±SEM) and fitted neonatal clearance of adalimumab and infliximab.

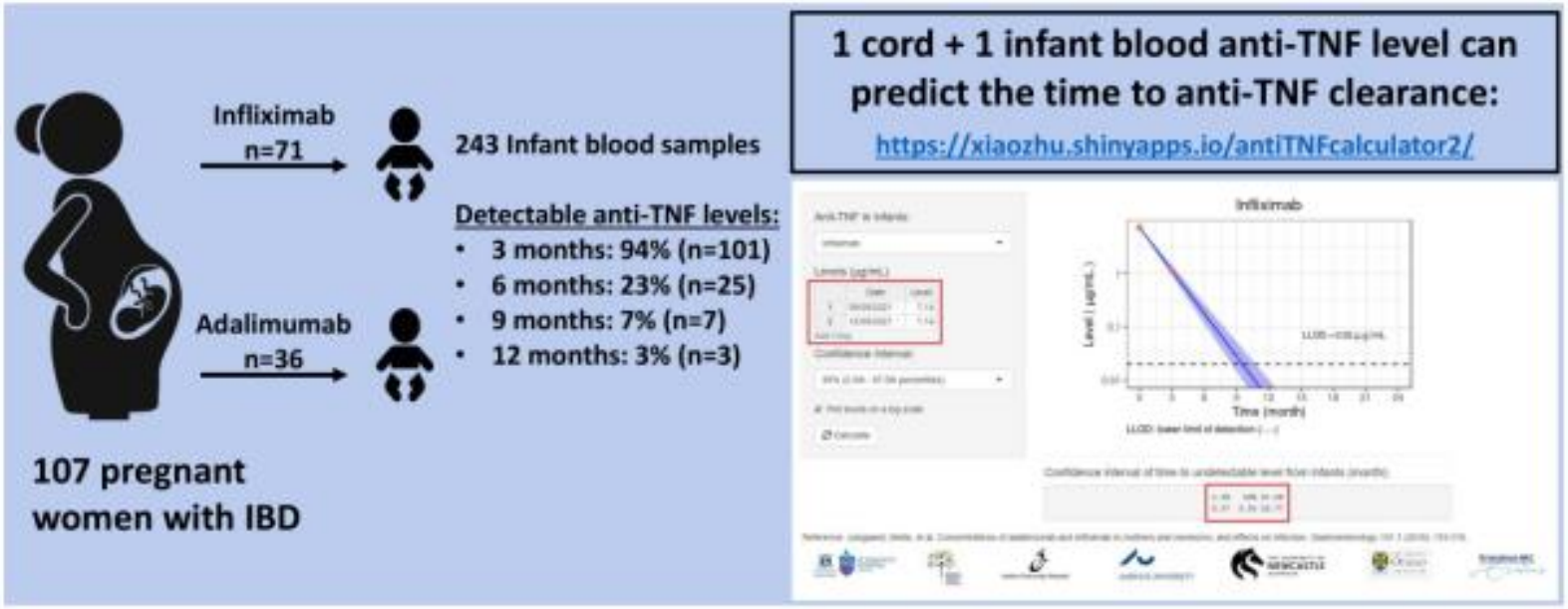
Drug	F:M Ratio
Vedolizumab	0.7
Ustekinumab	1.70
Infliximab	1.97
Adalimumab	1.21

Julsgaard M et al. Gastroenterology. 2016 Jul;151(1):110-9
Flanagan PR et al. Clin Gastroenterol Hepatol. 2024 Mar 15:S1542-3565(24)00252-0.

Study designs enabling birth and postnatal blood collection can inform clinical decisions and estimate infant clearance

The use of population PK modeling have been implemented to address questions such as time to undetectable concentrations enabling timing of live vaccination

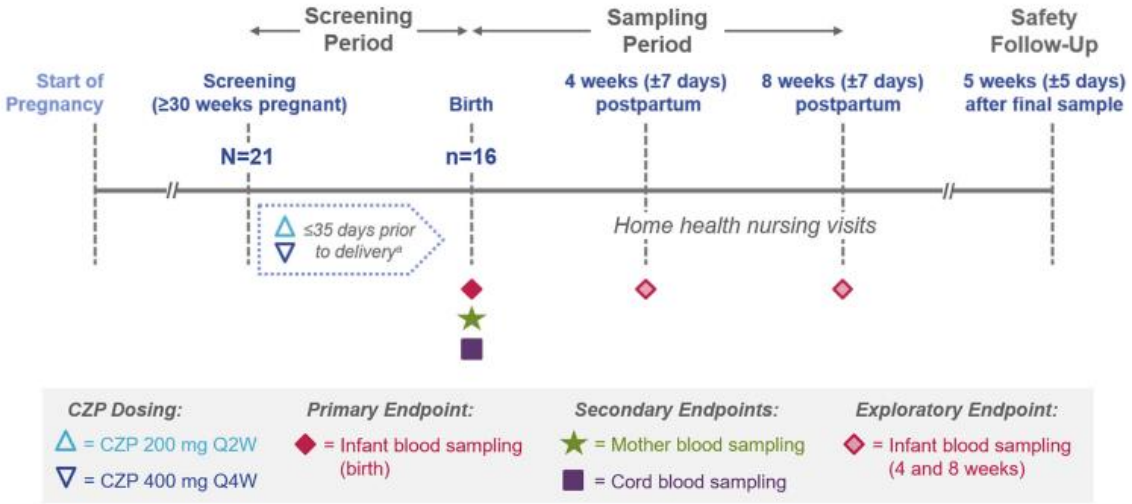


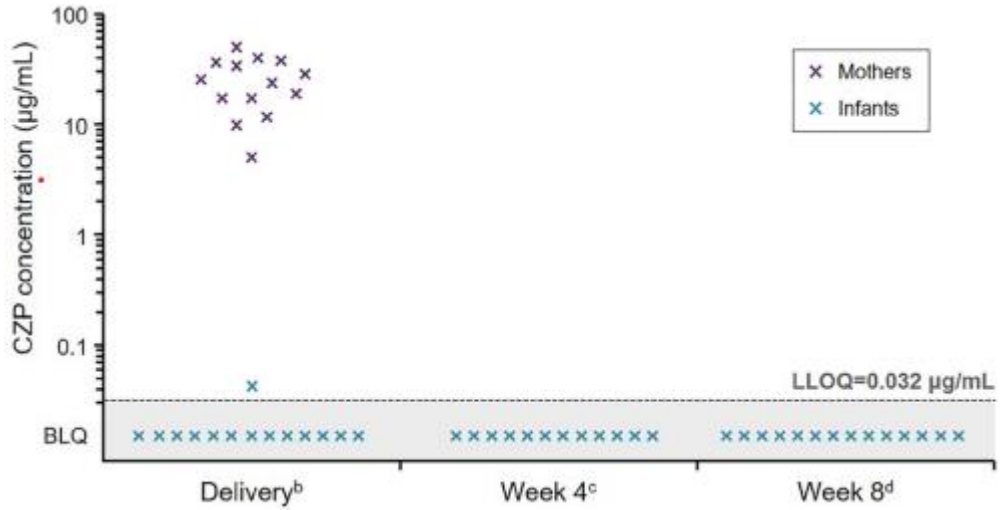


Liu Z et al. J Crohns Colitis. 2022 Dec 5;16(12):1835-1844.
Wieringa JW et al. J Crohns Colitis. 2024 Apr 23;18(4):506-515.

Mechanistic and compound considerations to guide study designs

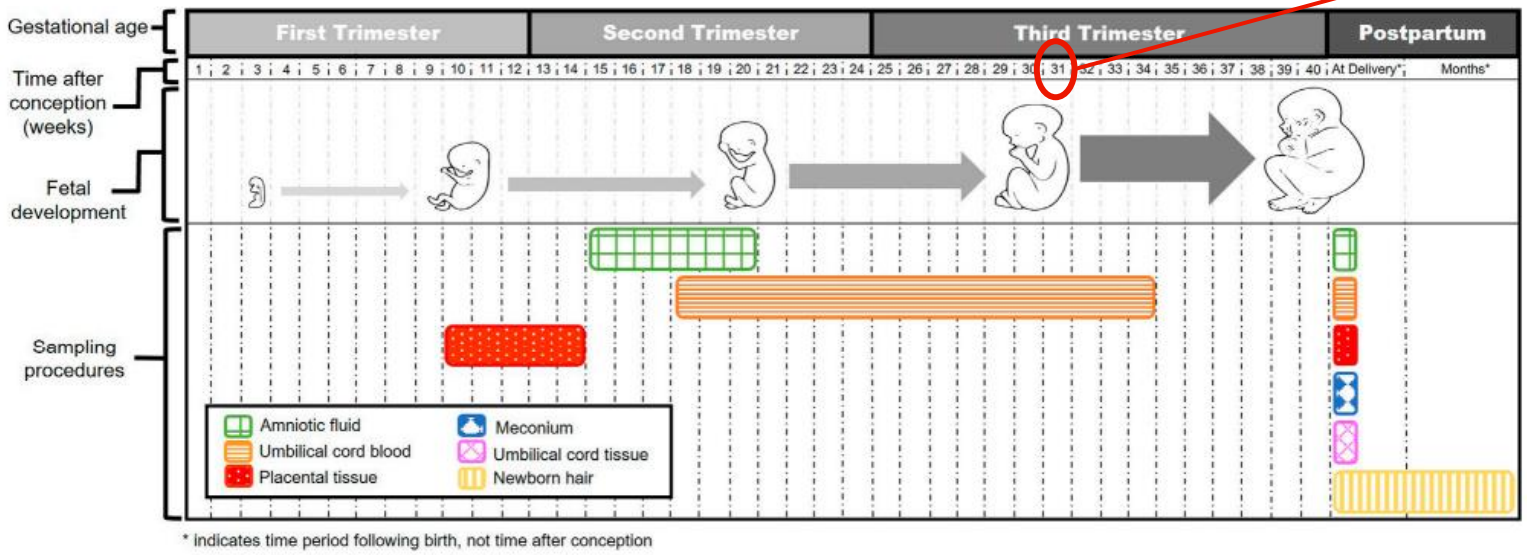
IgG Fc-free region are not expected to undergo FcRn mediated placental transfer which can minimize the number of infant sampling



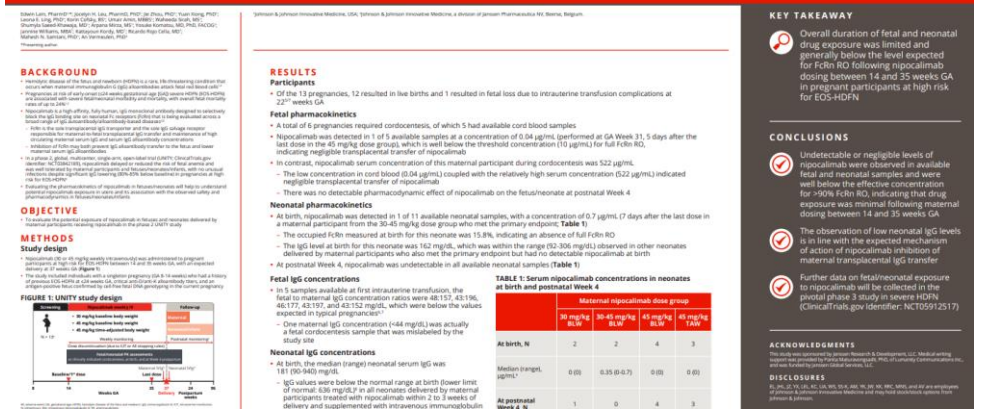


Studies evaluating in utero exposure of immunosuppressive biologics are limited to birth collection

Prospective cord blood collection most often collected at delivery to estimate maternal-fetal exposure in utero



Fetal and Neonatal Drug Exposure Following Nipocalimab Treatment in Pregnant Individuals at Risk of Early-onset Severe Hemolytic Disease of the Fetus and Newborn (EOS-HDFN)



GA Week 31 cordocentesis collection
F:M ratio < 0.1 (0.04 : 522 ug/mL)

Opportunistic cord blood collection for clinically indicated procedures (e.g. cordocentesis) throughout gestation is informative

Hudson RE et al. Front Pharmacol. 2023 Mar 23;14:1111601.
Lam E et al. Presented at the Society for Maternal Fetal Medicine (SMFM) Pregnancy Meeting; February 10-14, 2024; National Harbor, MD, USA.

Studies remain limited but the body of evidence is growing

Most of the clinical evidence generated are limited to post-marketing prospective PK studies; seldom observations from clinical development programs pre-approval

- **Placental transfer of monoclonal antibodies are mediated by FcRn**
  - IgG subtype; IgG1 > IgG3>IgG2=IgG4
  - Most biologics with IgG1 constant region have F:M ratios similar to native IgG1; considerations for fusion proteins with non-native IgG Fc portion (e.g. PEGylated)
- **Most clinical pharmacology data are collected from prospective post-marketing studies**
  - Time to clearance dependent on the time since last maternal dose and subsequent in utero and postnatal infant exposure
  - Limitations can arise with interpreting F:M ratios; most clinical experience coming from anti-TNFs
  - Study designs should consider maternal-neonate pair samples collected at birth but also longitudinal postnatal sampling; use of population PK/PD modeling to address time to clearance
  - Use of opportunistic samples as part of clinical care during gestation (i.e. at 2nd/3rd trimester) to evaluate drug levels in utero
- **Target engagement/exposure threshold**
  - Limited evaluations accounting the relationship between infant exposure of immunosuppressive biologics, target engagement and effect and/or outcome