Clinical Pharmacology and Modelling of Drug Transfer Across the Placenta and Fetal Exposures: Biologics

FDA Public Workshop: Evaluating Immunosuppressive

Effects of In-Utero Exposure to Drug and Biologic Products

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Better Health, Brighter Future

Topics to be covered

- How do Biologics Cross the placenta
- How can we measure or predict fetal exposure ex-vivo ?
- Maternal IgG Transfer and Time-course –what does it tell us and insight into transfer of therapeutics
- Factors Affecting Maternal PK and Transfer to Uterus
- Newborn: Maternal Concentrations and Exposure in Mother
- Missing Data
- Potential for Adverse Events
- Future ?

Reminder: How do biologics transfer across the placenta ?

Early in pregnancy between 5-10 % of maternal levels can be detected, with comparable levels at full term

- **Limited transfer during first trimester-via diffusion and therefore extent is small due to size of molecule**
- **After the first trimester the neonatal Fc receptor matures (FcRn) actively transporting IgG's across the placenta .**
- **Maximal rate of transfer occurs after 36 weeks of gestation with preference for IgG1>IgG4> IgG3 then IgG2.**

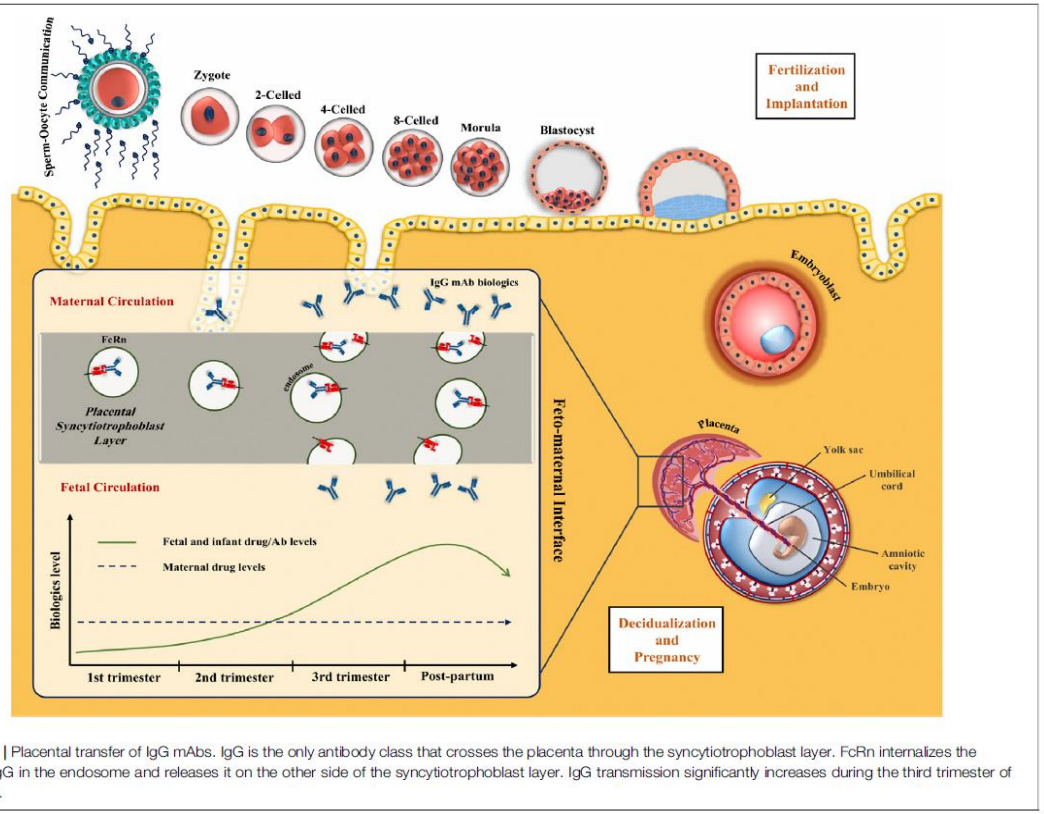


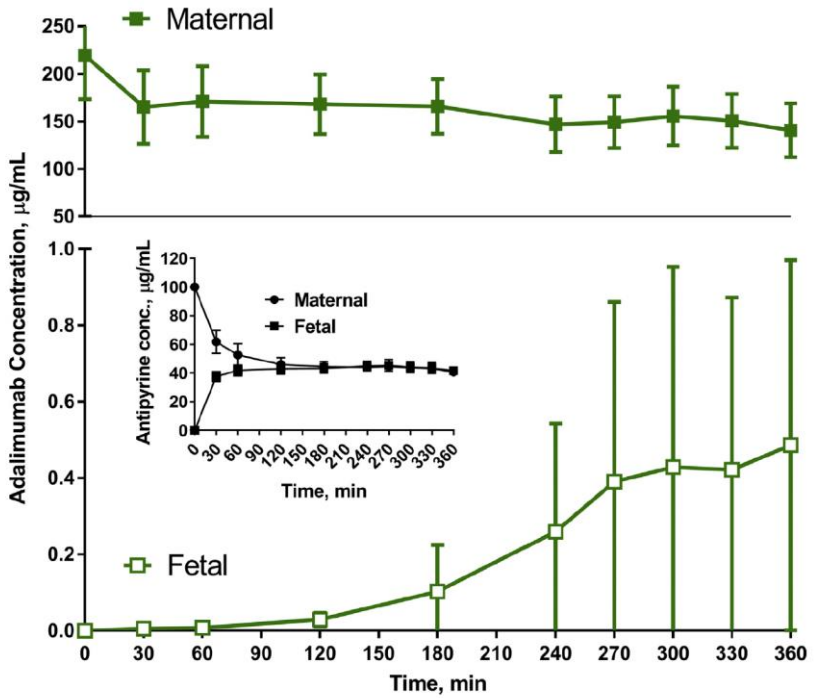
FIGURE 1 | Placental transfer of IgG mAbs. IgG is the only antibody class that crosses the placenta through the syncytiotrophoblast layer. FcRn internalizes the maternal IgG in the endosome and releases it on the other side of the syncytiotrophoblast layer. IgG transmission significantly increases during the third trimester of pregnancy.

Beltagy et al, Frontiers in Pharmacology, 12(Article 6212647), 2021

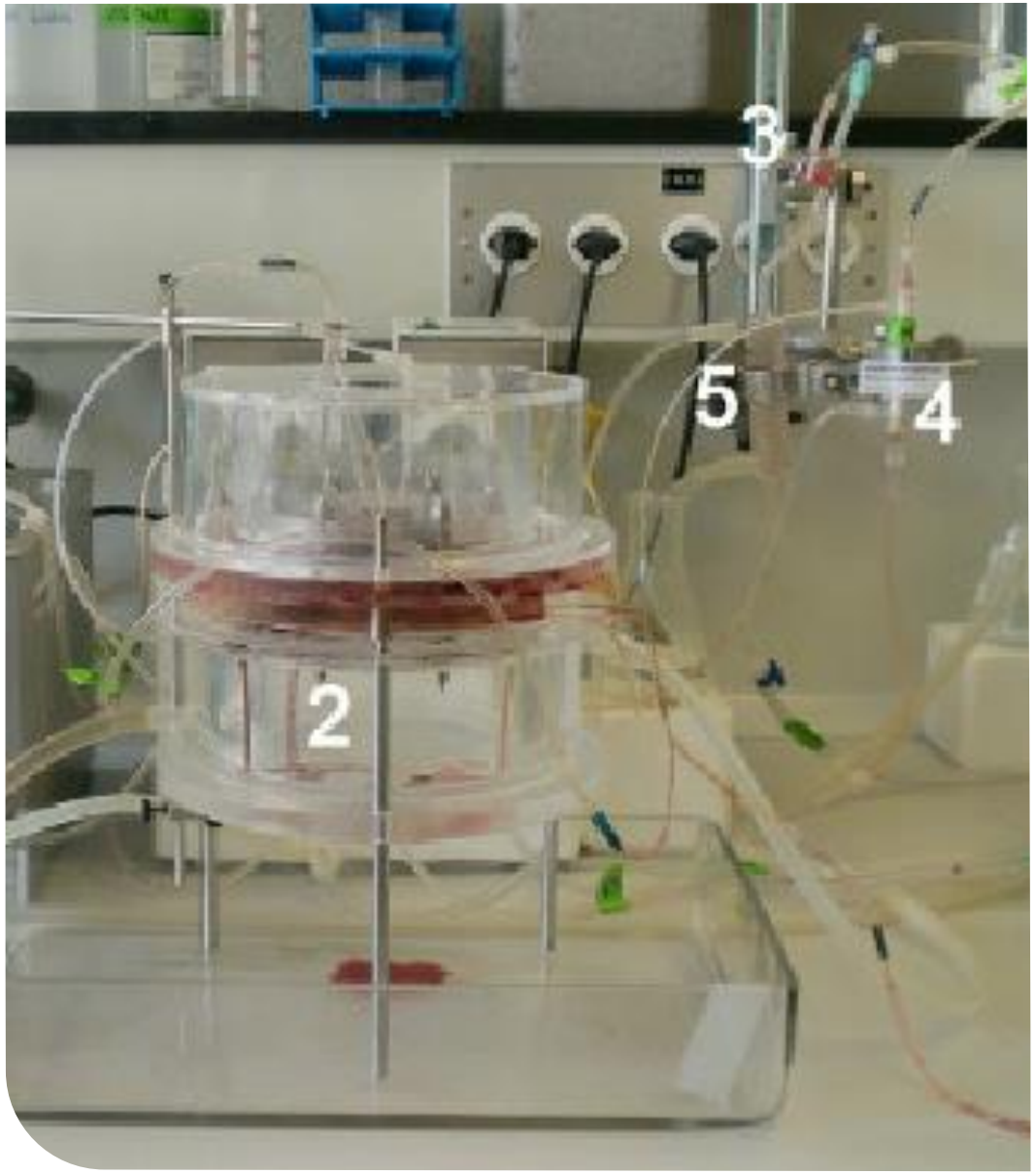
How can we measure fetal exposure *ex-vivo* (post-partum) ?

Human ex-vivo placental transfer model

- Donated placentas from healthy births (caesarean –sectioned deliveries)
- Normal morphology
- Experimental viability 4-6 h post birth



Adalimumab (270 µg/mL) and control antipyrine (100 µg/mL) were added to the maternal circuit at $t = 0$ and measured in both maternal and fetal circuits during the experimental period. Fetal transfer of adalimumab increased significantly after 60 minutes. Successful, consistent perfusion overlap was achieved in these studies because antipyrine (*inset*) transfer rapidly reached equilibrium between maternal and fetal circuits. Data are shown as mean ± standard deviation (n = 8).



Roy et al, American Journal of Obstetrics and Gynaecology, 2019

How can we predict? PBPK still a tool for the future for biologics.

Many mAb PBPK models exist for adults.. But currently nothing is published or available for pregnancy

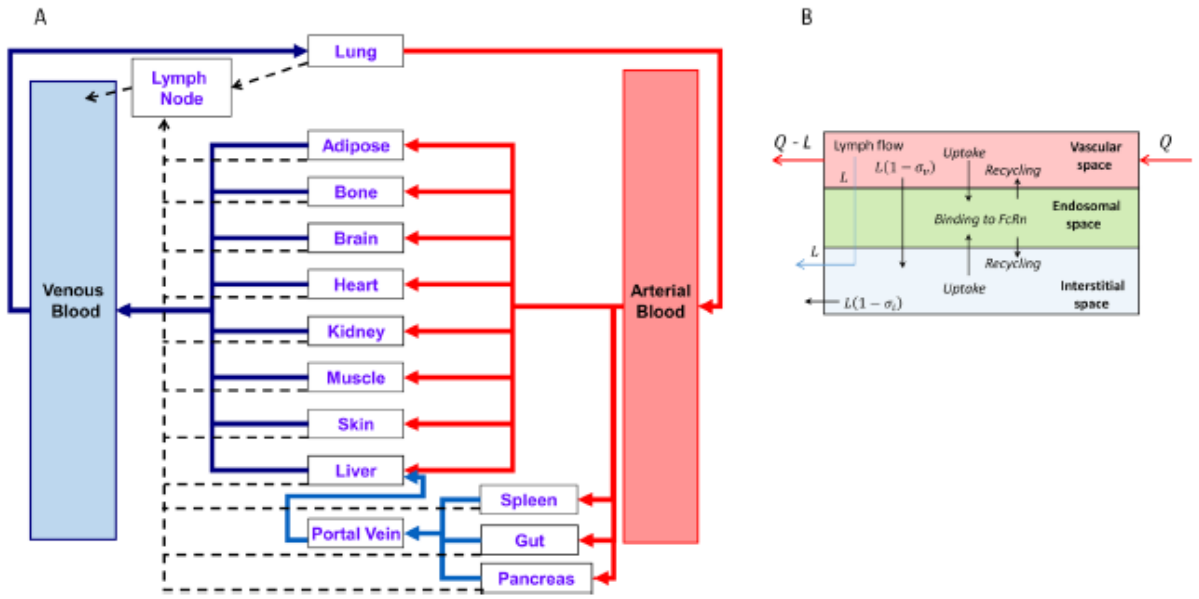


Fig. 1 Typical full PBPK model structure for mAbs (**A**); each tissue compartment is split into sub-compartments representing the interstitial, endosomal and vascular spaces (**B**). L, lymph flow; Q, blood flow; σ_v, vascular reflection coefficient; σ_l, lymphatic reflection coefficient

Many key physiological parameters still not quantified

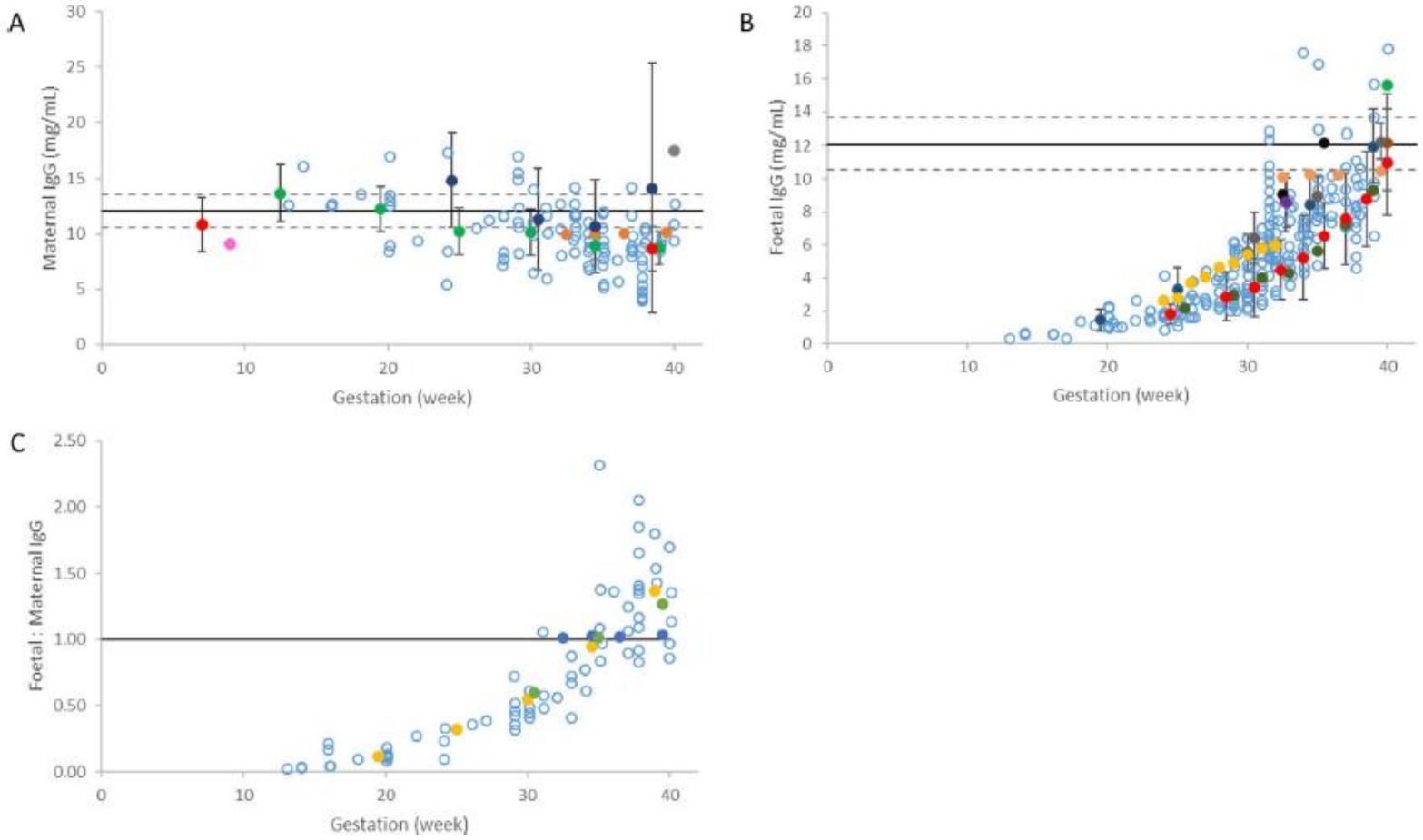
- IgG levels decrease during pregnancy – change in plasma volume and transport of IgG across the placenta.
- IgG in the fetus comes mainly from placental transfer, with fetal IgG ~0.2 % of umbilical cord concentration.
- Transfer is dependent on endocytosis and transcytosis, dependent on FcRn binding.
- Rate of endocytosis has been measured *in-vitro* in adults but not reported for fetal endothelial cells.
- The abundance of FcRn in fetus and placenta is unknown.
- Lymph flow changes during pregnancy are unknown.
- Target expression changes in mother, placenta and fetus e.g. reduction in inflammation and therefore cytokines or receptors.

Gill and Jones, AAPS Journal (2022),24:72

Other parameters impacting transfer and quantification and predictability

- Biological Format: IgG, Fab, Fab-PEG, Fusion Proteins, Fab-albumin binders
- Antigen Properties – are we binding to a receptor (e.g. Toculizumab) – TMDD versus a soluble cytokine, how does this change with pregnancy
- Agonist or Antagonist ?
- Is the target expressed in placenta or fetus and at what stage during gestation (e.g. TNFα is expressed in the placenta) ?
- Dose and frequency of administration
- Immunogenicity Risk
- Timing of last dose versus gestational age
- Time since last dose of biologic is inversely correlated with cord blood concentration
- Antibody concentration in mother is typically reduced during pregnancy – data reported always compares newborn: mother ratio at birth. Ratio higher than if compared with optimized therapeutic concentration

Extent of maternal IgG transfer: Provides insight into extent of transfer of therapeutic Biologics – In first trimester, limited transfer occurs

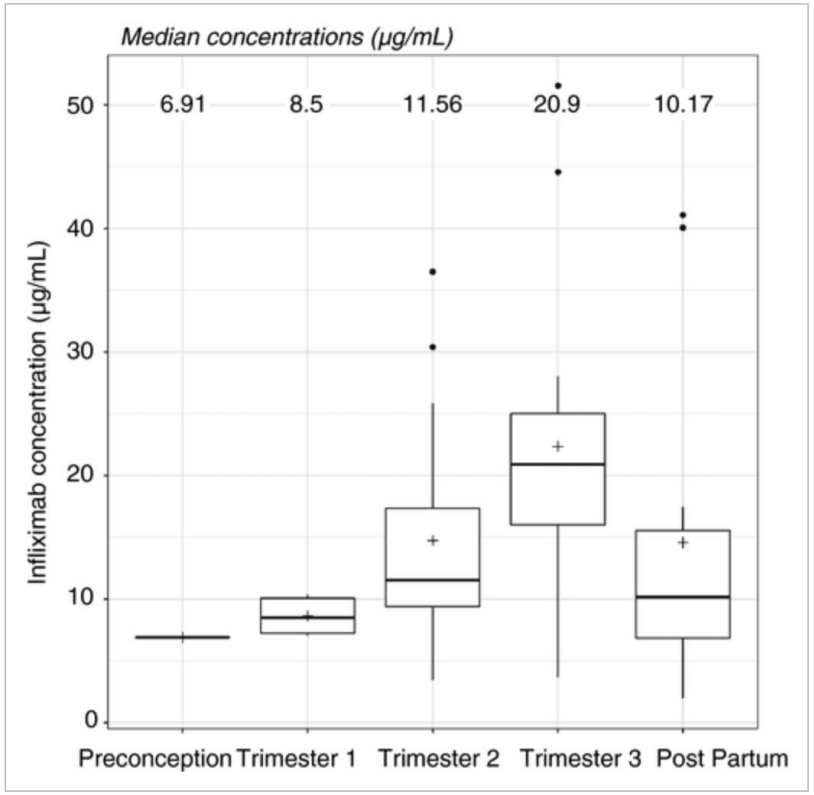


Gill and Jones, AAPS Journal (2022),24:72

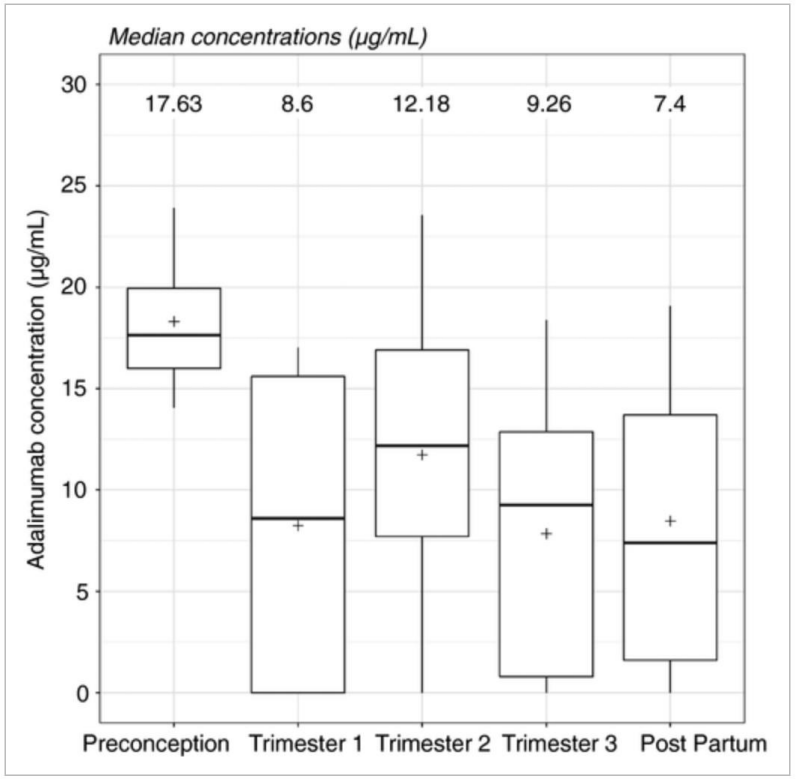
Does exposure change in mother during pregnancy?

General decrease in exposure with exception of Infliximab

Median infliximab concentrations by trimester



Median adalimumab concentrations by trimester

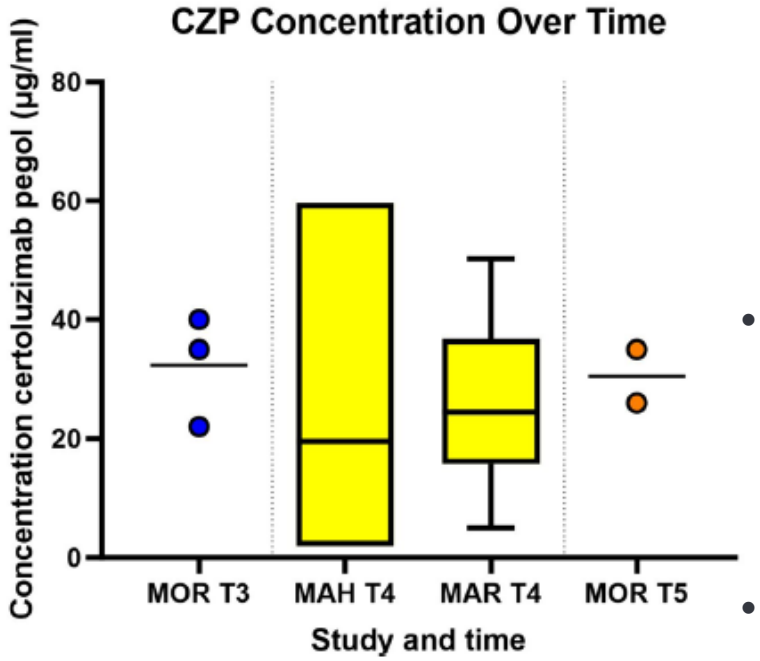


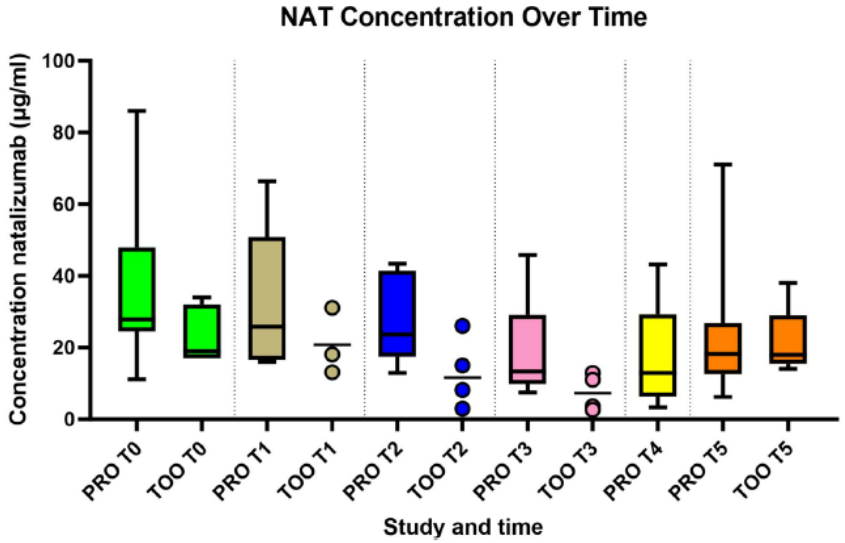
Seow CH, Leung Y, CasteeleNV et al. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. Aliment PharmacolTher2017;45:1329–1338

Decreases generally consistent with anatomical changes that occur during pregnancy: Blood volume increases of 40 % and volume of distribution

No evidence that maternal systemic FcRn increases during pregnancy

Insufficient evidence to suggest changes in exposure during pregnancy for certolizumab pegol



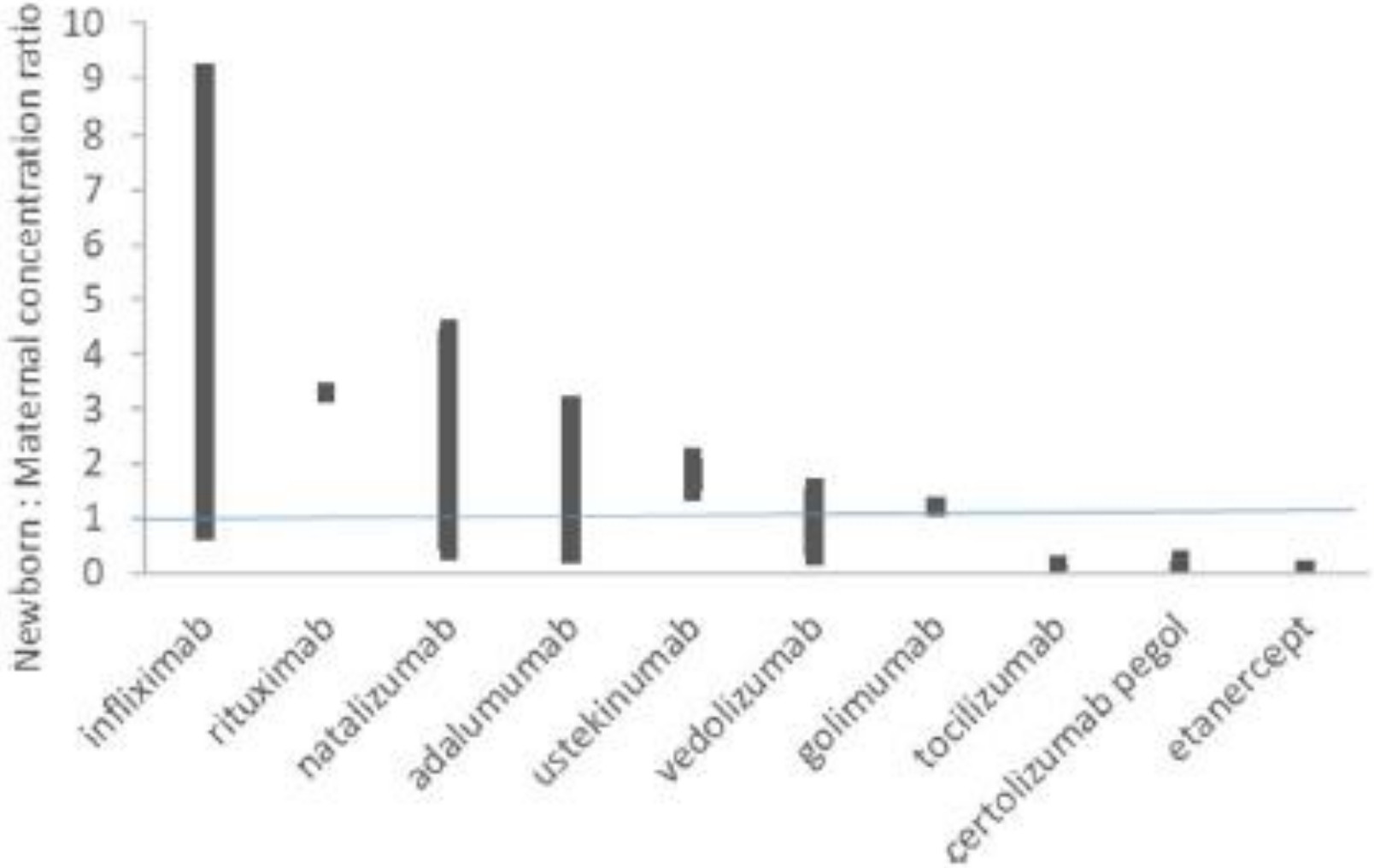


- Eculizumab –In pregnant women with COVID-19, plasma concentrations in pregnant women ranging from 25 weeks gestation to 1 day post-partum had peak (1h post-dose) and day 3 concentrations within the therapeutic range for the general population
- Natalizumab – decreases of 14.6 %, 30.9 % , 50 % and 55% (T1-T3 and post-partum) in study 1 and Study 2: 4.7 %, 39 % and 61 %

T1:First Trimester, T2: Second Trimester, T3: Third Trimester, T4: During Delivery, T5: Post-Partum

Gent et al, Pharmacokinetics of Mabs during pregnancy: A systematic Literature Review:2024

Range of newborn: maternal concentration ratio's reported (Marketed Drugs).



Typical Exposure Measures:

- Blood/plasma/serum trough concentrations during pregnancy –each trimester
- Blood/plasma or serum concentration in mother just after birth
- Blood/plasma/serum concentration in cord and infant at birth
- Ratio of New-born: Maternal Concentration
- Follow-up samples- frequency depending on drug

Gill and Jones: AAPS Journal (2022) 24:72

How long does the biologic remain in the infant after birth ?

Biologic	Drug Transfer to Fetus	Estimated Drug Clearance in infant	Level of Clinical Experience
Infliximab	High	3-7 months	++++
Adalimumab	Moderate	3-5 months	++++
Golimumab	Moderate	Unknown	+
Certolizumab Pegol	Minimal (Passive Diffusion)	NA	+++
Etanercept	Low	0-3 months	+++
Ustekinumab	Moderate	Unknown	+
Vedolizumab	Low-moderate	Likely < 3 months	+
Natalizumab	Low-moderate	Unknown	+
Rituximab	Moderate-high	Unknown	+
Belimumab	Unknown	Unknown	+

Pham-Huy et al, CMAJ 2021 :193:E1129-36

Missing data… what about the pharmacodynamics (PD)?

- How does the concentration or ratio give us insight in terms of safety ?
  - PD is rarely measured in infant e.g. in mothers taking corticosteroids during pregnancy, do we ever measure cortisol levels in the infant at birth?
  - Rarely is there a comparison with in-vitro data e.g. Inhibitory concentrations (Ic50 or Ic90) generated in cell assays or ratio to Binding Affinity (Kd)?
  - Understanding of whether the target is expressed in the placenta or developing fetus and where is site of action?
  - Does the effect of immunosuppression last beyond the measurable drug concentration – potentially ?

Potential for adverse events: Factors to consider

- Is the target expressed in fetus and when during gestation ?
- Transfer of pathogenic antibodies in patients with auto-immune disease (e.g. Myesthenia Gravis (MG), Lupus (SLE), Immune Thrombocytopenic purpura(iTP), Multiple Sclerosis (MS))

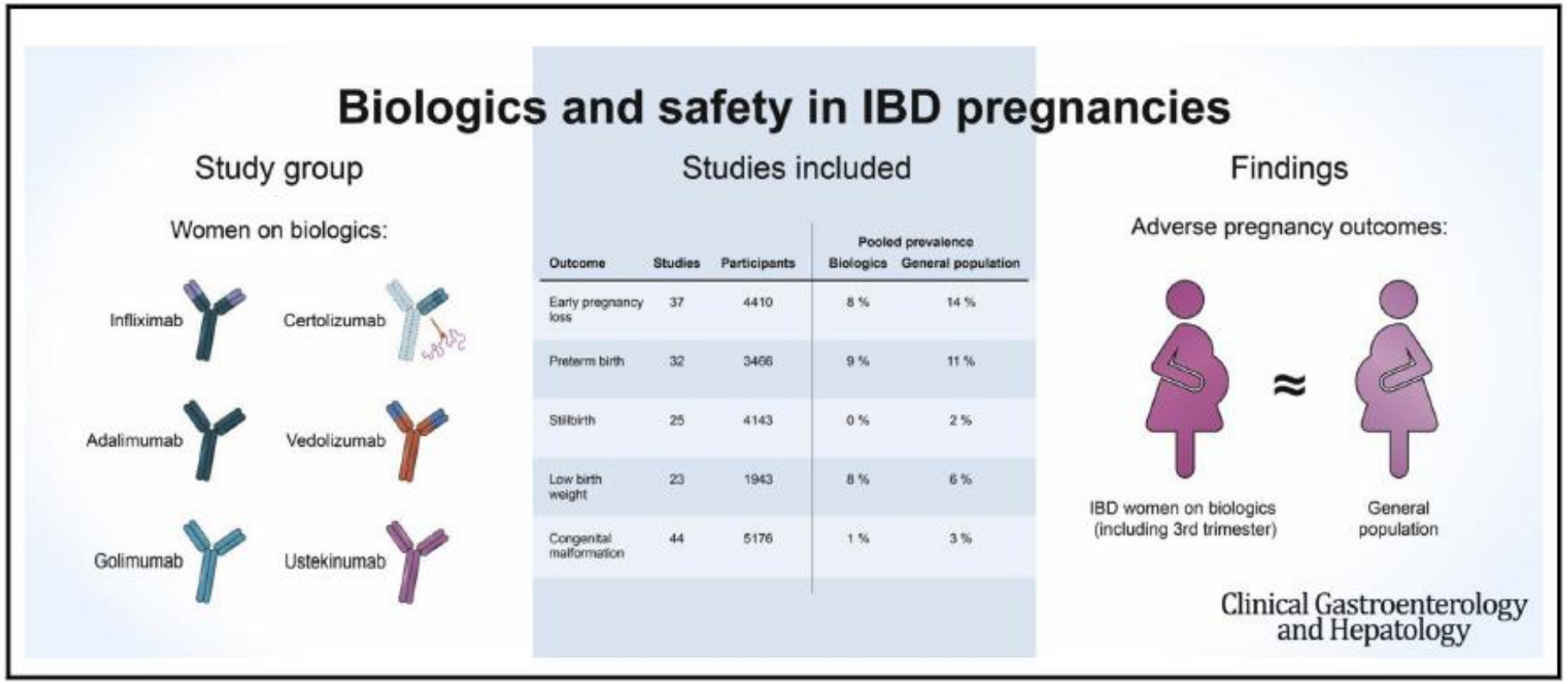
- A minority of biologics may lead to immunological and haematological abnormalities in the exposed infant

- Retrospective cohort studies and some prospective studies report a lack of associated risks of miscarriage, preterm delivery and congenital malformations

- Large prospective cohort PIANO study followed 1490 pregnancies that led to 1431 live births recently reported 1 year outcome data for 1010 infants exposed to monoclonal antibody biologics. Participants were women with IBD who received thiopurines (azathioprine,6 – mercaptopurine), biologics (infliximab, adalimumab, certolizumab, Ustekinumab) or both during pregnancy and participants who were un-exposed to both. Rates of congenital malformation, spontaneous abortion, preterm birth, low birth weight and infant infection were not increased compared to nonexposed group. However, pre-term birth was associated with a higher rate of infection in infants.

- Studies looking at the impact of exposure to anti-TNFs during pregnancy on infections have shown an increased risk in mother and not infant. Risk of infection was associated with pre-term delivery rather than the medication. Combined used of anti-TNF and thiopurines may increase risk of infection infants first year of life.

Potential for adverse events: Systemic review and meta-analysis Nielsen et al, Clinical Gastroenterology and Hepatolotgy, 2020:20:74-87



- A systematic review and meta-analysis, including 6963 patients showed that adverse pregnancy outcomes among patients with Irritable bowel syndrome (IBD) using biologics were similar to those of the general population.

Impact of Breast Feeding on Design of Uterine Exposure Study

- Risk of transfer of biologics in breast milk is generally lower than placental transfer
- The preferential secretion of IgG subclasses is different from the placental one, with IgG3 and IgG4 secreted more than IgG1, with Fab fragments even much lower.
- Potential for transfer of IgGs into milk and be ingested by the feeding child.
- However, given the large molecular weight and proteolytic environment in the digestive tract the risk of exposure from ingestion would be considered low.
- However, the expression of FcRn on the epithelial intestinal cells may promote uptake.
- Impact on study design: Likely to be limited, but may want to consider sampling 1-2 h post-dose to assess maximal exposure in newborn (in-uterine remaining exposure and added exposure through breast-feeding) and a sample pre-breast feeding to understand relative difference.

Future Direction?

- Currently no PBPK models for mAbs in pregnant woman to predict in-utero exposure
- Clinical data required to verify PBPK models in pregnancy are scarce and limited to individual study cases, and mainly for anti-TNFs
- Good in-vitro to in-vivo extrapolation (IVIVE) is required to allow prediction of exposure rather than relying on the generation of human PK data in pregnancy, currently no valid methods exist
- Significant work going on in industry and academia to generate further data, including *ex -vivo* placental perfusion assays to measure the transfer of mAbs and IgG across the placenta
- Data for key physiological processes affecting mAb PK in pregnant woman are still emerging. As more clinical data become available in pregnant (PK/ADA and PD) they can be used to validate PBPK models and build confidence in prediction
- Data from the anti-FcRn (Nipocalimab, Efgartigamod and Rozanolixizumab) class - both from non-human-primates (NHP ePPND studies) as well as clinical data in pregnant and non-pregnant women will also help close the gap.

ePPND: Enhanced pre- and postnatal development