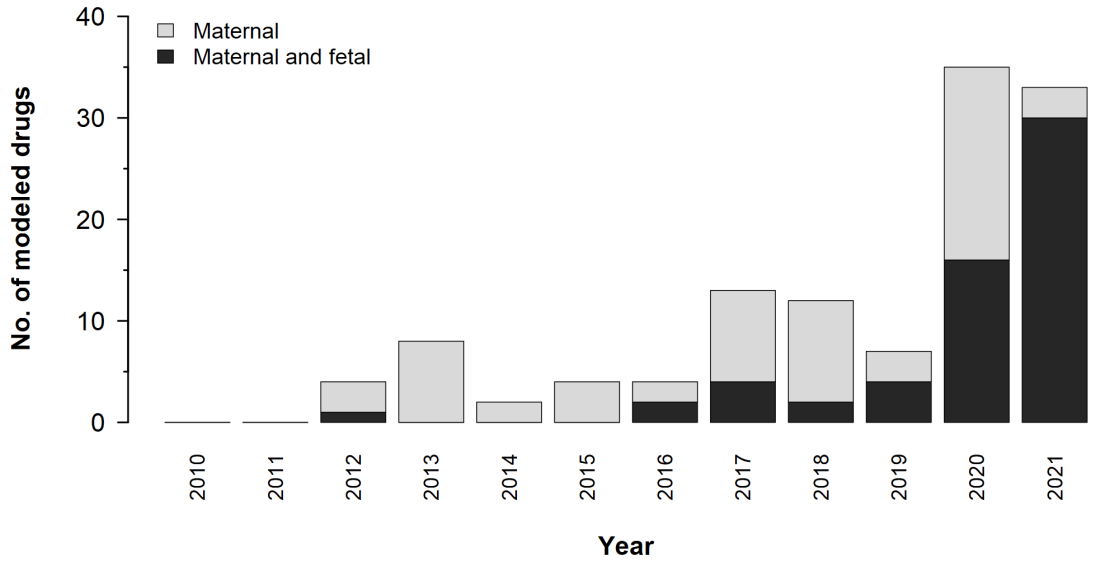
Mechanistic modeling of placental drug transfer and fetal-neonatal drug exposure

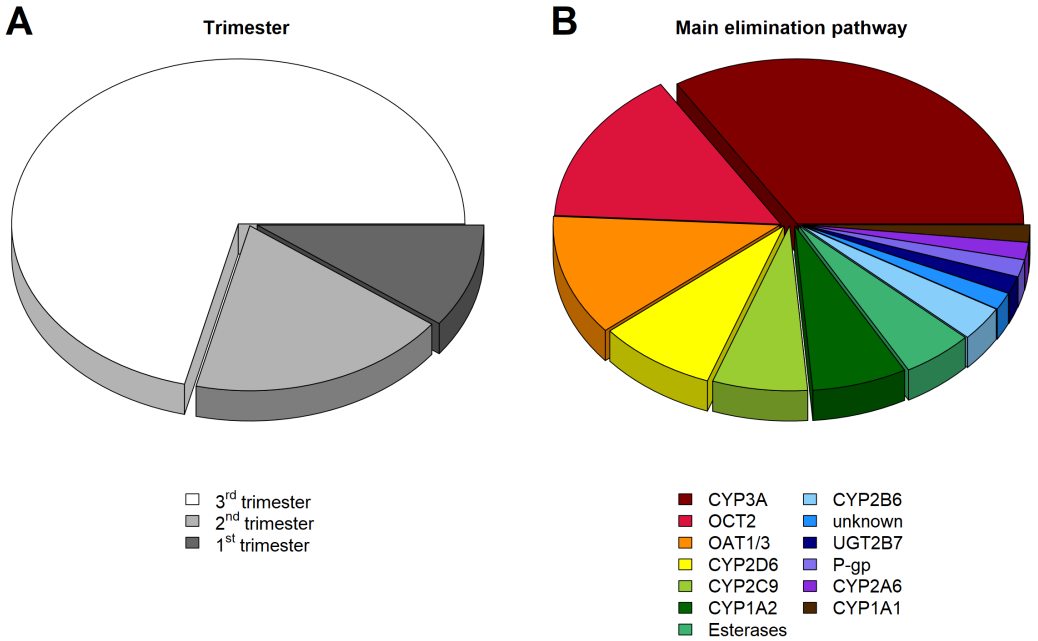
22/10/2021 / André Dallmann

Conflicts of interest / disclaimer

- I am an employee of Bayer AG
- I use Open Systems Pharmacology (OSP) software, tools, and models in my professional role

Maternal-fetal PBPK modeling: Where do we stand?





Dallmann et al. *Curr Pharm Des*. 2019;25(5):483-495.
doi: 10.2174/1381612825666190320135137.

Despite impressive progress much work is still left

- Model validation for the 1st trimester of pregnancy
- Drug absorption from the gastrointestinal tract
- Disease-effect on top of pregnancy-induced physiological changes
- Fully mechanistic model structure for the fetus
- Mechanistic description of placental drug transfer
- Coupling prenatal and postnatal PBPK models to enable simulating transition from maternal-fetal pharmacokinetics to postpartum and neonatal pharmacokinetics
- PBPK models for large molecules and new modalities (proteins, siRNA etc.)
- …

Characterization of Plasma Protein Alterations in Pregnant and Postpartum Individuals Living With HIV to Support Physiologically-Based Pharmacokinetic Model Development

Sherry Zhao[1], Mary Gockenbach[1], Manuela Grimstein[2], Hari Cheryl Sachs[1], Mark Mirochnick[3], Kimberly Struble[4], Yodit Belew[4], Jian Wang[5], Edmund V. Capparelli[6,7], Brookie M. Best[6,7], Tamara Johnson[1], Jeremiah D. Momper[6] and Anil R. Maharaj[8*]

Assessing the impacts on fetal dosimetry of the modelling of the placental transfers of xenobiotics in a pregnancy physiologically based pharmacokinetic model

Marc Codaccioni, Céline Brochot

Fetal Physiologically Based Pharmacokinetic Models: Systems Information on Fetal Cardiac Output and Its Distribution to Different Organs during Development

Khaled Abduljalil, Xian Pan, Ruth Clayton, Trevor N. Johnson & Masoud Jamei

Successful Prediction of Human Fetal Exposure to P-Glycoprotein Substrate Drugs Using the Proteomics-Informed Relative Expression Factor Approach and PBPK Modeling and Simulation

Olena Anoshchenko, Flavia Storelli, and Jashvant D. Unadkat

Integration of physiological changes during the postpartum period into a PBPK framework and prediction of amoxicillin disposition before and shortly after delivery

André Dallmann[1] · Anneke Himstedt[2,3] · Juri Solodenko[1] · Ibrahim Ince[1] · Georg Hempel[2] · Thomas Eissing[1]

Fetal protein binding is often omitted in PBPK models

Clinical Pharmacokinetics 14: 156-170 (1988)
0312-5963/88/0003-0156/$07.50/0

The Significance of Plasma Protein Binding on the Fetal/Maternal Distribution of Drugs at Steady-State

Martin D. Hill and *Fred P. Abramson*

George Washington University, School of Medicine and Health Sciences, Department of Pharmacology, Washington

Maternal and fetal plasma differ in their concentrations of the important drug binding plasma proteins, albumin and α_1-acid glycoprotein, with albumin being slightly more concentrated in fetal plasma, and α_1-acid glycoprotein being only 37% of the maternal concentration at term. In general, these differences relate linearly to the bound to free concentration ratio of drugs associated with these proteins. Although only the free concentration is generally considered to be the pharmacologically active form, these differences can dramatically affect the total concentration and relative distribution of drugs between maternal and fetal plasma.

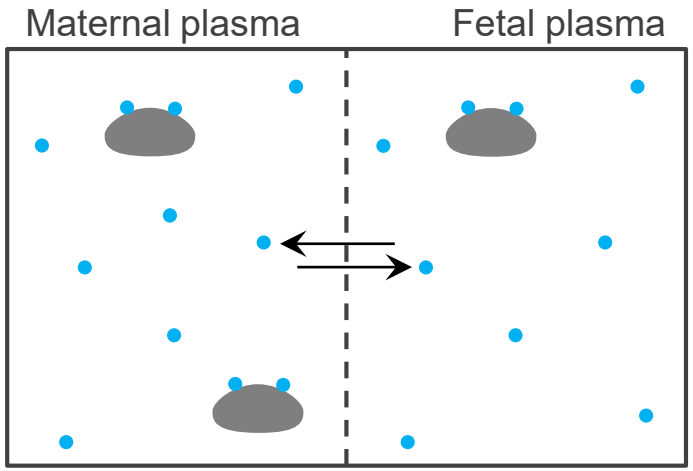
Different unbound drug fractions in mother and fetus affect the maternal-fetal concentration ratio

Only valid at pseudo-equilibrium!

[Albumin$_{fetus}$] < [Albumin$_{mother}$]

→ lower fetal protein binding

Fetal fu: 0.77

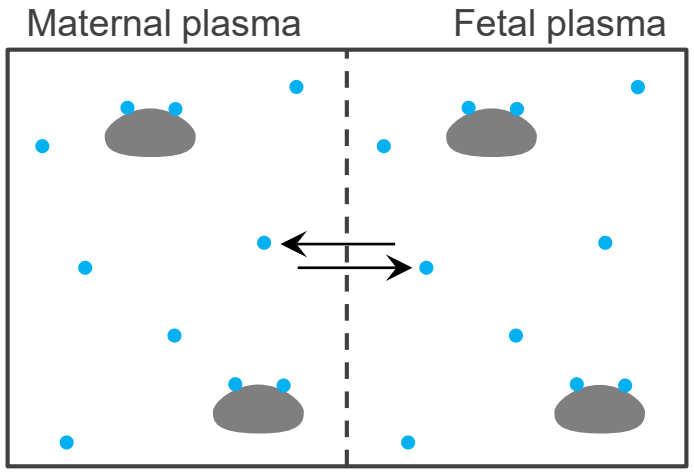


Fetal-maternal ratio: 0.82

[Albumin$_{fetus}$] = [Albumin$_{mother}$]

→ equal f_u in mother and fetus

Fetal fu: 0.4

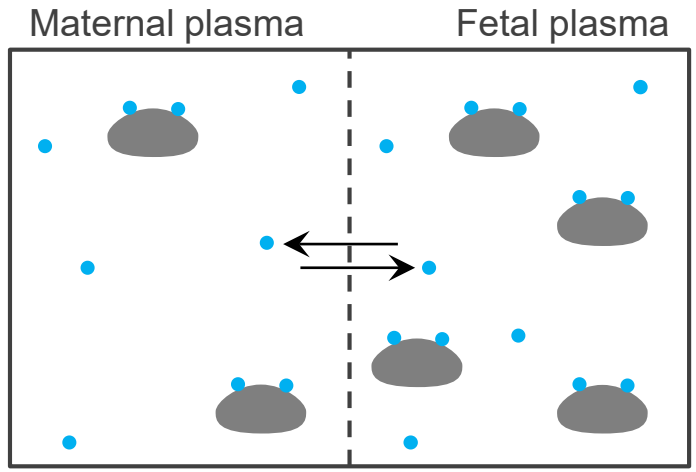


Fetal-maternal ratio: 1.0

[Albumin$_{fetus}$] > [Albumin$_{mother}$]

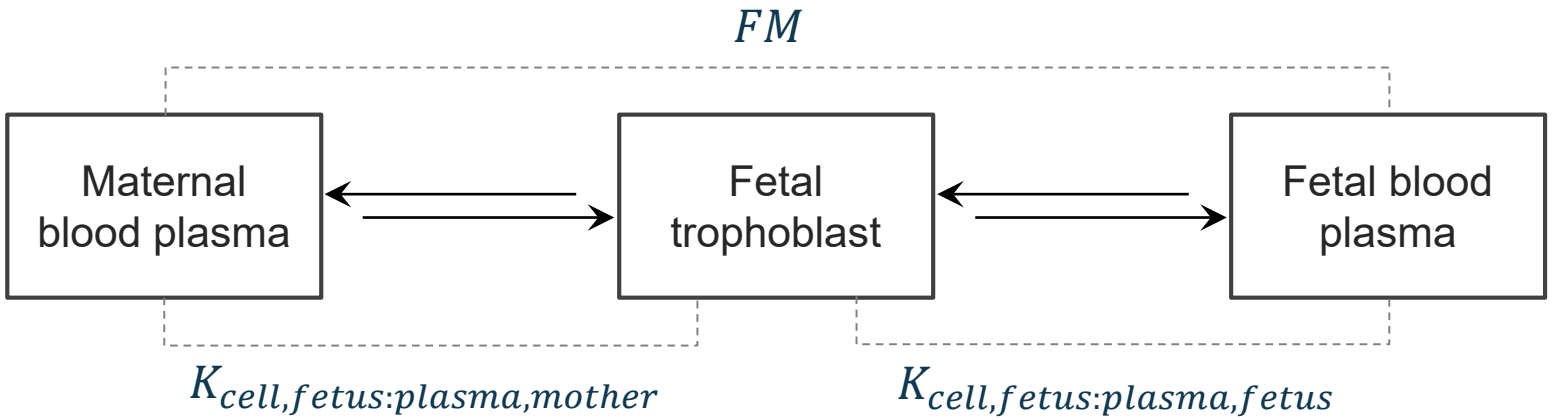
→ higher fetal protein binding

Fetal fu: 0.33



Fetal-maternal ratio: 1.5

Different unbound drug fractions in mother and fetus affect the maternal-fetal concentration ratio



$$Fetal{:}\,Maternal\ concentration\ ratio\ (FM) = K_{plasma,fetus:plasma,mother}$$

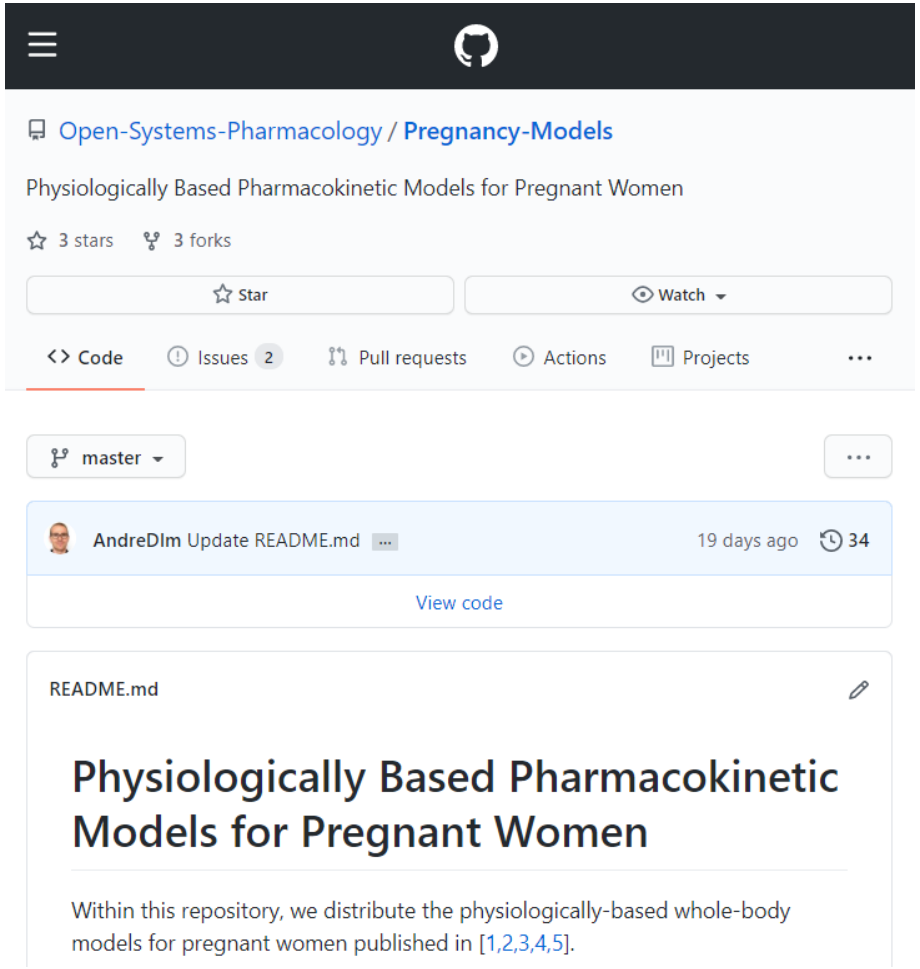
$$= \frac{K_{cell,fetus:plasma,mother}}{K_{cell,fetus:plasma,fetus}}$$

$$= \frac{f_{u,mother}}{K_{cell,fetus:water}} \times \frac{K_{cell,fetus:water}}{f_{u,fetus}}$$

$$= \frac{f_{u,mother}}{f_{u,fetus}}$$

Open Systems Pharmacology (OSP) software as open-source tool for PBPK modeling

- The Open Systems Pharmacology (OSP) software includes the PBPK tool **PK-Sim®** and the systems biology tool **MoBi®**
- **Open-source freeware** under GNU Public License v2.0 released on GitHub
- Fully transparent development of scientific content and qualification approaches on GitHub
- Inclusion of a pregnancy module for population PBPK modeling in PK-Sim®
- Repository for pregnancy PBPK models on GitHub (https://github.com/Open-Systems-Pharmacology/Pregnancy-Models)



Modeling differential protein binding in mother and fetus

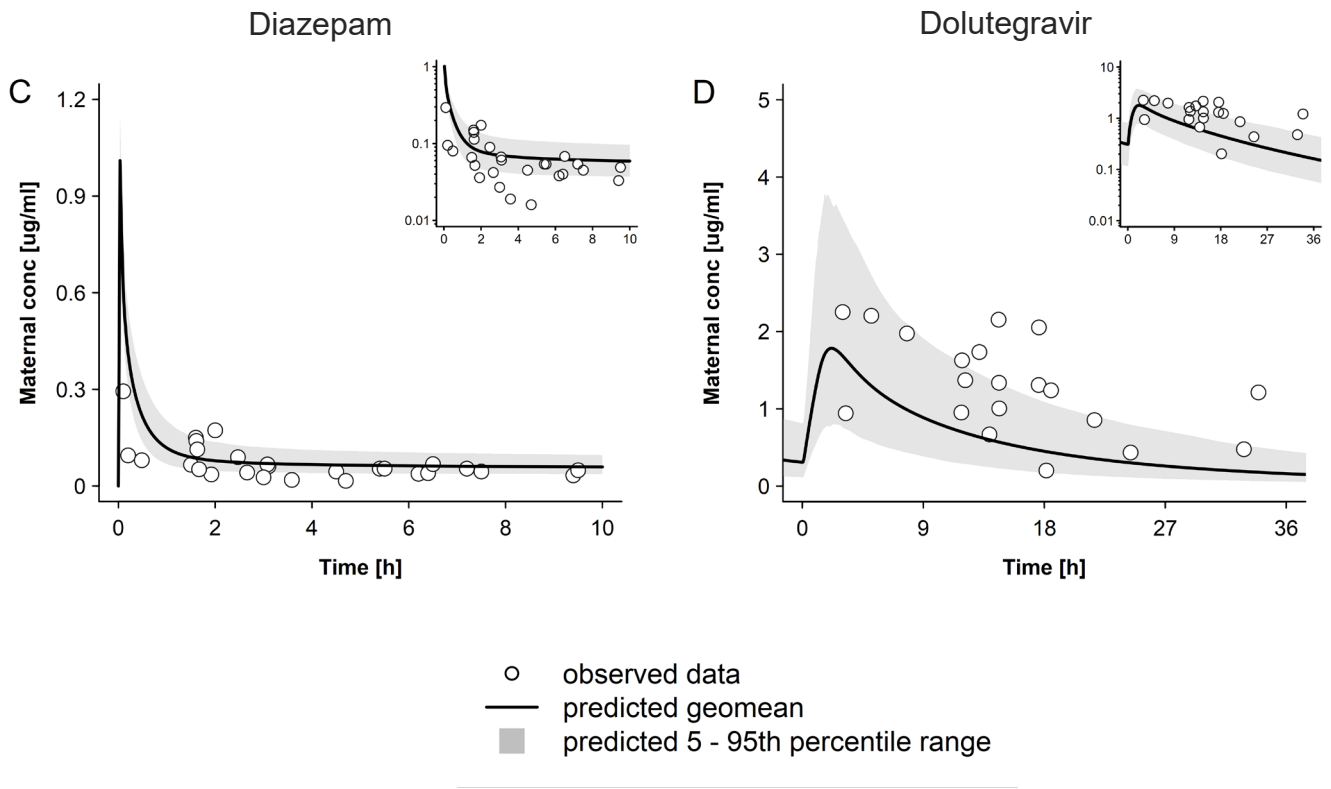
Maternal and fetal f_u

Drug	Fraction unbound in non-pregnant subjects	Maternal fraction unbound	Fetal fraction unbound
Acyclovir	0.85 (15)	0.88	0.86
Cefuroxime	0.67 (16)	0.73	0.68
Diazepam	0.020 (17)	0.027	0.021
Dolutegravir	0.0070 (18)	0.0088	0.0080
Emtricitabine	0.96 (15)	0.97	0.96
Metronidazole	0.89 (17)	0.92	0.89
Ondansetron	0.27 (17)	0.33	0.28
Raltegravir	0.17 (18)	0.24	0.23

→ **Diazepam:** $\frac{f_{u\_mother}}{f_{u\_fetus}} = 1.29$

→ **Dolutegravir:** $\frac{f_{u\_mother}}{f_{u\_fetus}} = 1.10$

Maternal plasma concentrations



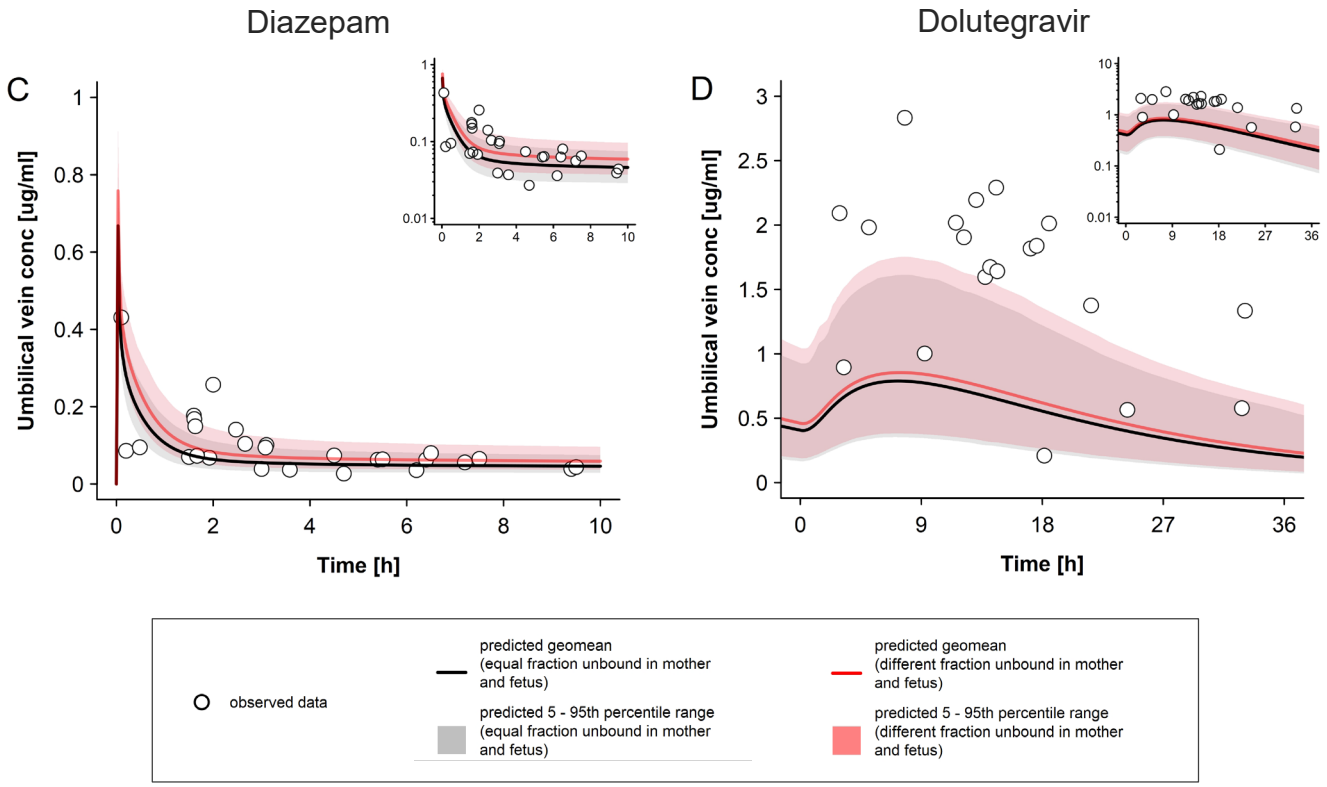
Liu et al. *Front Pediatr*. 2021;9:723006. doi: 10.3389/fped.2021.723006.

Protein binding differences between mother and fetus are small at term delivery

Maternal and fetal AUC_{tlast}

Drug	AUC_{tlast} predicted in umbilical cord plasma with equal maternal and fetal fraction unbound (μg h/mL)	AUC_{tlast} predicted in umbilical cord plasma with different maternal and fetal fraction unbound (μg h/mL)	Difference (%)
Acyclovir	1.9	2.0	5.3
Cefuroxime	36.5	38.2	4.7
Diazepam	0.67	0.85	26.9
Dolutegravir	15.0	16.5	10.0
Emtricitabine	10.2	10.1	–0.98
Metronidazole	12.3	12.7	3.3
Ondansetron	0.024	0.028	16.7
Raltegravir	3.0	3.2	6.7

Umbilical cord plasma concentrations

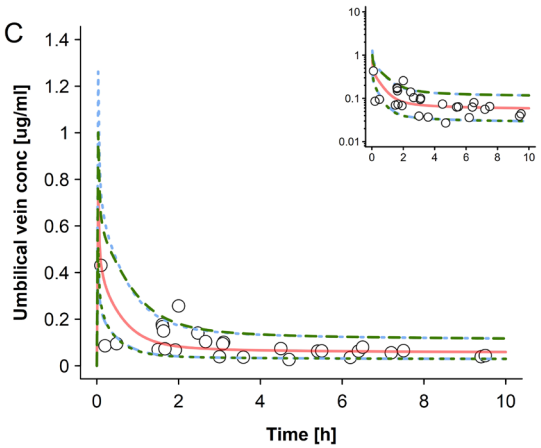


Liu et al. *Front Pediatr*. 2021;9:723006. doi: 10.3389/fped.2021.723006.

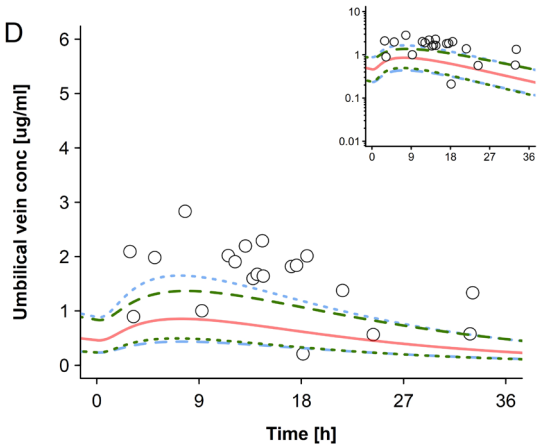
Different influx and efflux rates at both apical and basolateral membrane need to be considered

Variation in influx or efflux transport across the apical (maternal-facing) membrane of the trophoblasts

Diazepam



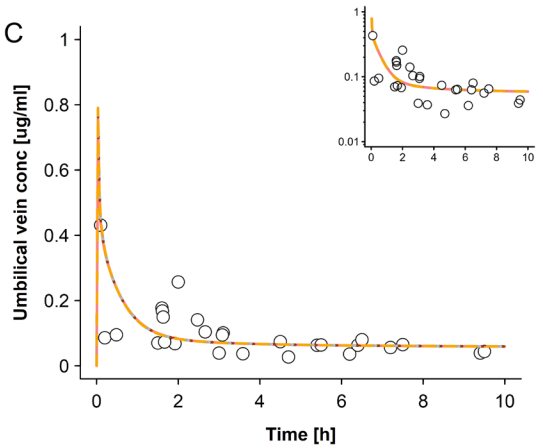
Dolutegravir



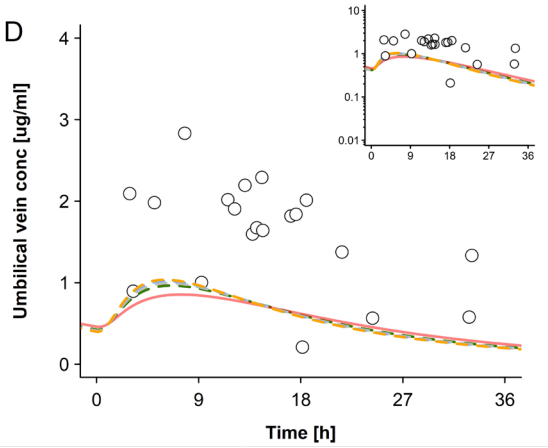
→ Drug transporters expressed in the apical membrane of the trophoblasts significantly modulate placental transfer

Variation in both influx and efflux transport across the basolateral (fetal-facing) membrane of the trophoblasts

Diazepam



Dolutegravir



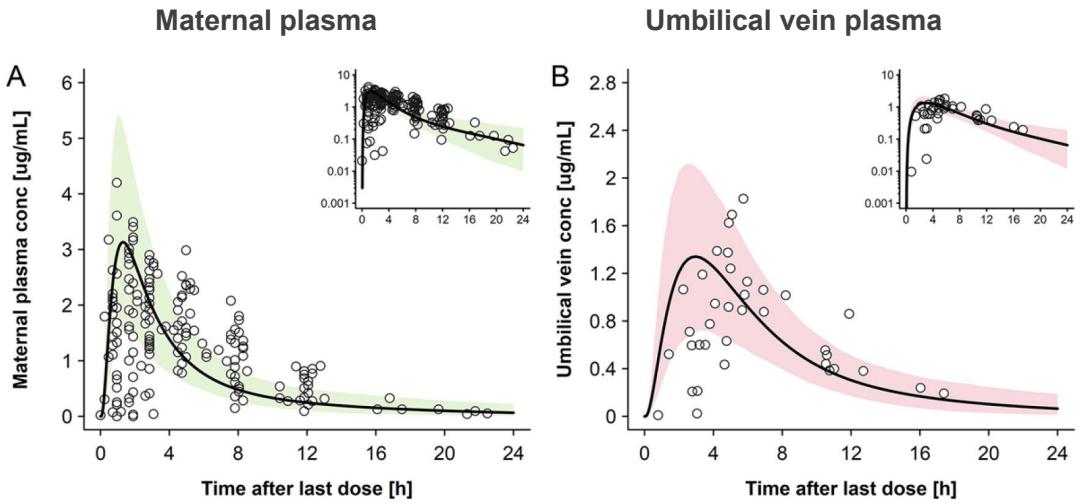
→ Transport rate across the basolateral membrane seems not to be rate-limiting step for diazepam and dolutegravir, but appears to be so for other compounds (e.g. cefuroxime)

Liu et al. *Front Pediatr*. 2021;9:723006. doi: 10.3389/fped.2021.723006.

Predicting fetal-neonatal drug exposure by coupling prenatal and postnatal PBPK models

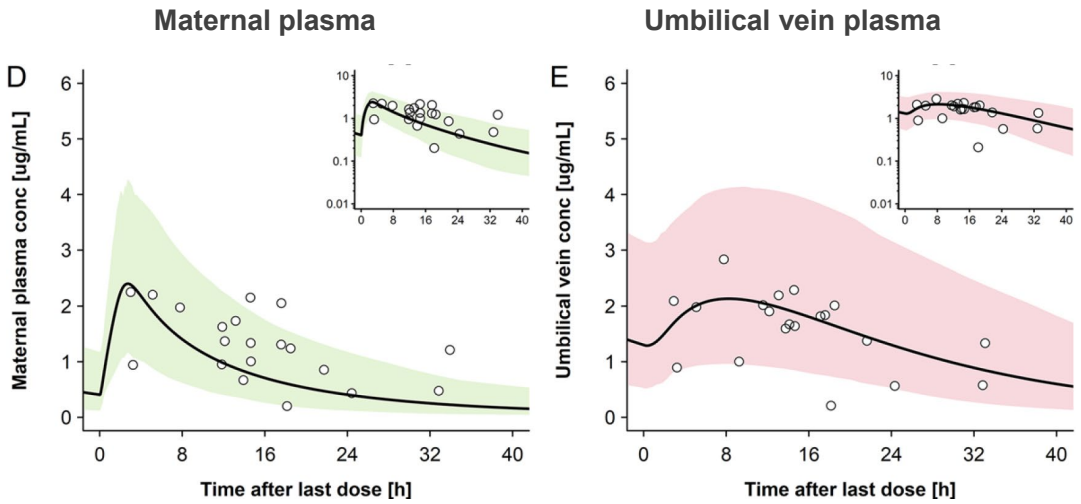
Emtricitabine

Delivery (at 33 – 42 weeks of gestation)



Dolutegravir

Delivery (at 36 – 40 weeks of gestation)



Drug	Mean delivery time (relative to last dose) [h]	Mean drug amount in fetal compartments [µmol]
Emtricitabine	4.9	9.58
Dolutegravir	11.8	4.89

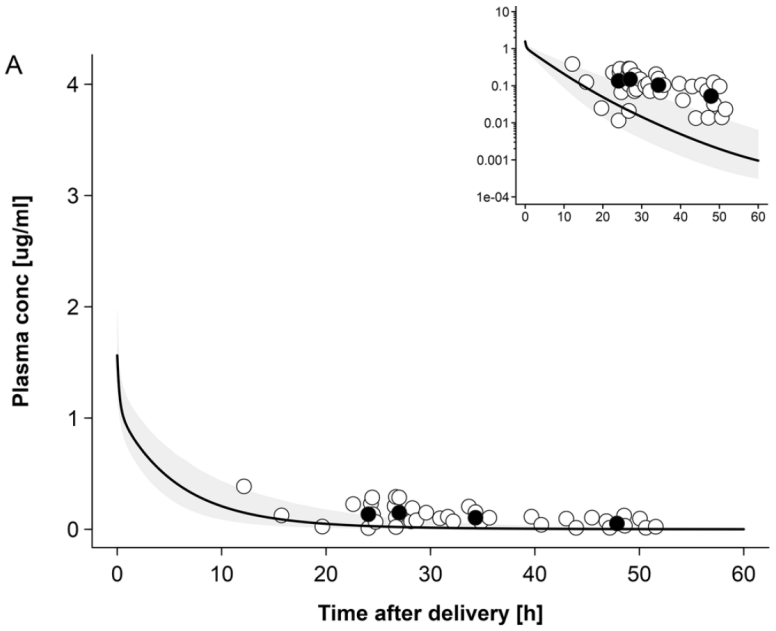
Liu et al. *Clin Pharmacokinet.* 2021;60(6):795-809. doi: 10.1007/s40262-020-00977-w

Maternal-fetal-*neonatal* PBPK modeling in action: Postnatal PK of transplacentally acquired drugs

Emtricitabine

Postnatal washout kinetics in neonates

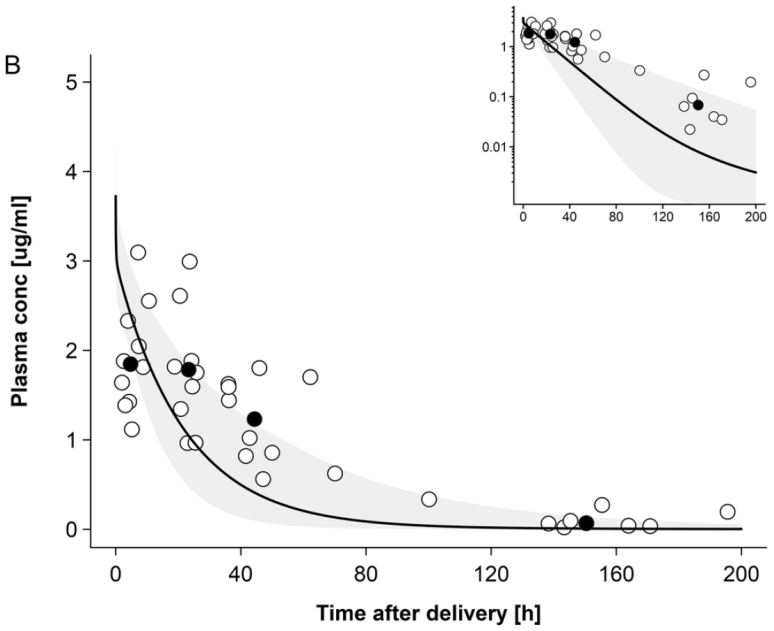
Assumed OCT2 activity: 30% of adult level



Dolutegravir

Postnatal washout kinetics in neonates

Assumed UGT1A1 activity: 60% of adult level



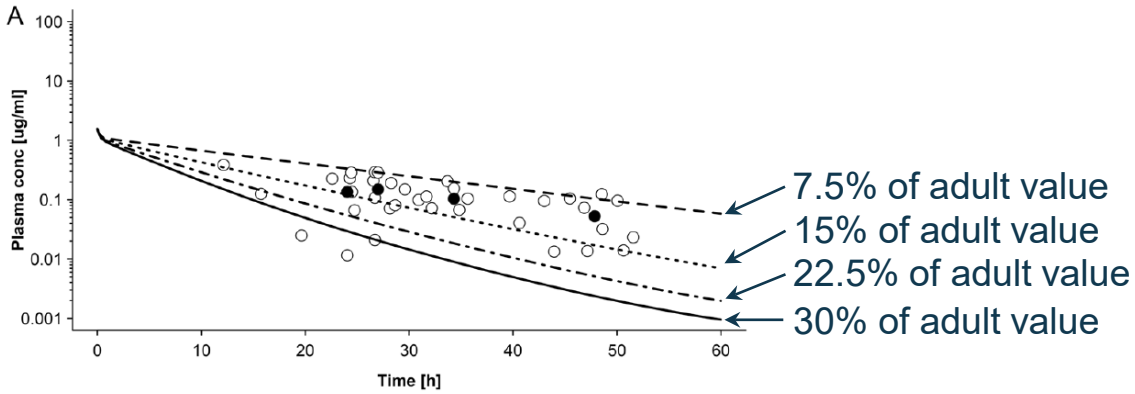
Liu et al. *Clin Pharmacokinet.* 2021;60(6):795-809. doi: 10.1007/s40262-020-00977-w

In postnatal week 1, the activity of OCT2 and UGT1A1 may be ~10% and ~30% of that in adults, respectively

Emtricitabine

Postnatal washout kinetics in neonates

Variations in tubular secretion via OCT2

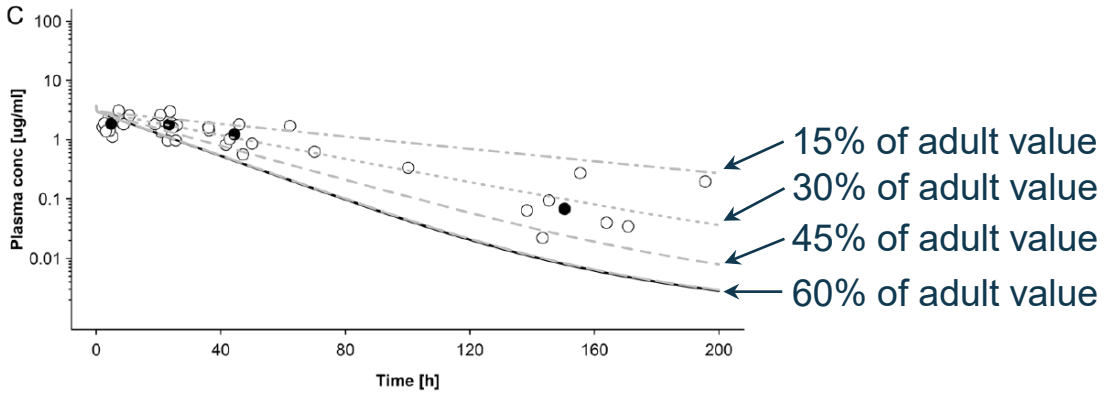


→ Sensitivity analyses results suggest that the specific activity of OCT2 in neonates with a postnatal age of <2.5 days is ~10% of that in adults

Dolutegravir

Postnatal washout kinetics in neonates

Variations in metabolism via UGT1A1



→ Sensitivity analyses results suggest that the specific activity of UGT1A1 in neonates with a postnatal age of <7 days is ~30% of that in adults

Liu et al. *Clin Pharmacokinet.* 2021;60(6):795-809. doi: 10.1007/s40262-020-00977-w

Conclusions

- In view of the limited participation of pregnant individuals in clinical trials, PBPK modeling can complement the PK understanding in cases where clinical data are sparse, missing or conflicting
- More drug examples are needed to build confidence in maternal-fetal PBPK models
- Model structures for the placenta and fetal compartments need to be mechanistically refined to enable predictions at earlier stages of gestation
- New PBPK modeling frameworks need to be developed for:
  - The use of new modalities (proteins, siRNA etc) in pregnant individuals
  - Simulating drug pharmacokinetics smoothly along the prenatal-peripartum-postpartum axis
- Collaboration between different stakeholders/research institutions is key to advance the field

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WASHINGTON, DC

Homa Ahmadzia

Thank you!

Bye-Bye