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Predicting and Verifying Maternal- Fetal Exposure to Drugs during Pregnancy

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Background

- When a mother takes a drug, the fetus is de-facto exposed to the drug
- Neither feasible nor desirable to determine maternal-fetal exposure to all drugs or natural products/supplements taken by pregnant women
- Therefore, to inform fetal risks, we have developed a systems/mechanisitic pharmacology approach to predict maternal-fetal exposure to drugs throughout pregnancy
- Elucidate the extent of changes in physiology (e.g. blood flow) and pharmacology (e.g. drug metabolism and transport) for model drugs and then generalize to other drugs
- This approach is based on **P**hysiologically **B**ased **P**harmaco**k**inetic (PBPK) modeling and simulations

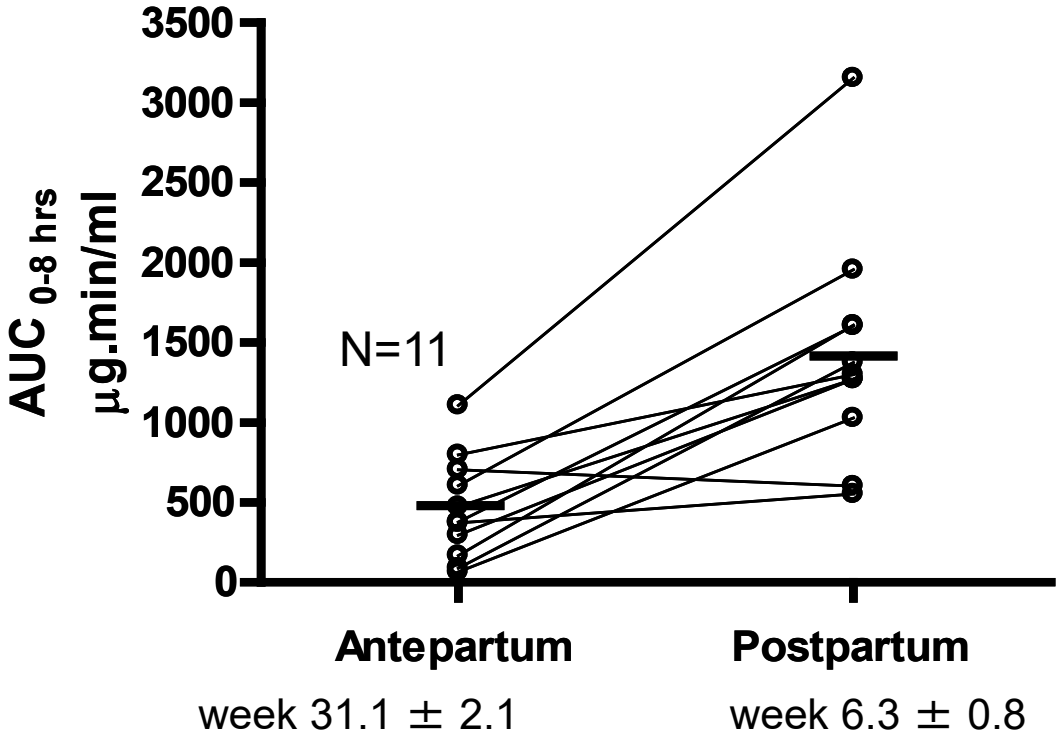
What Determines Fetal Drug Exposure?

1. Maternal drug conc.:
   - pregnancy produces many physiological changes (e.g. ↓ or ↑ in drug metabolism) that affect drug disposition

2. Transport (influx or effux) and/or diffusion across the placenta:
   - The placenta is richly endowed with influx and efflux transporters (e.g. P-glycoprotein, BCRP etc.)

3. Placental/fetal metabolism:
   - Important for some drugs

Pronounced Decrease in Maternal Expsoure to Indinavir, a HIV Drug, in Third Trimester (T3) Pregnant Women

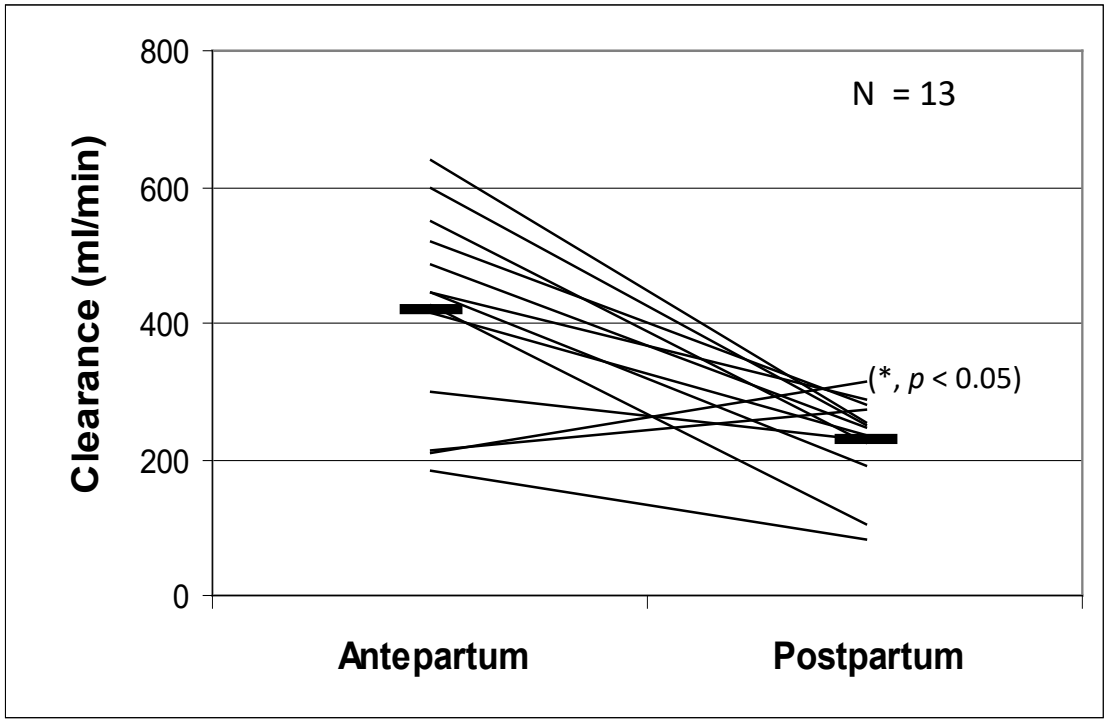


Unadkat et al., Antimicrob Agents Chemother2006

- Indinavir $AUC_{0\text{-}8h}$ is ~30% of antepartum AUC (3-fold higher oral CL) vs. postpartum
- Indinavir is a CYP3A and P-gp substrate.
- Based on these data, FDA recommended that administration of indinavir alone is NOT recommended during pregnancy

CYP3A Activity is Induced during Pregnancy

Unbound metabolic clearance of midazolam to 1'-OH midazolam



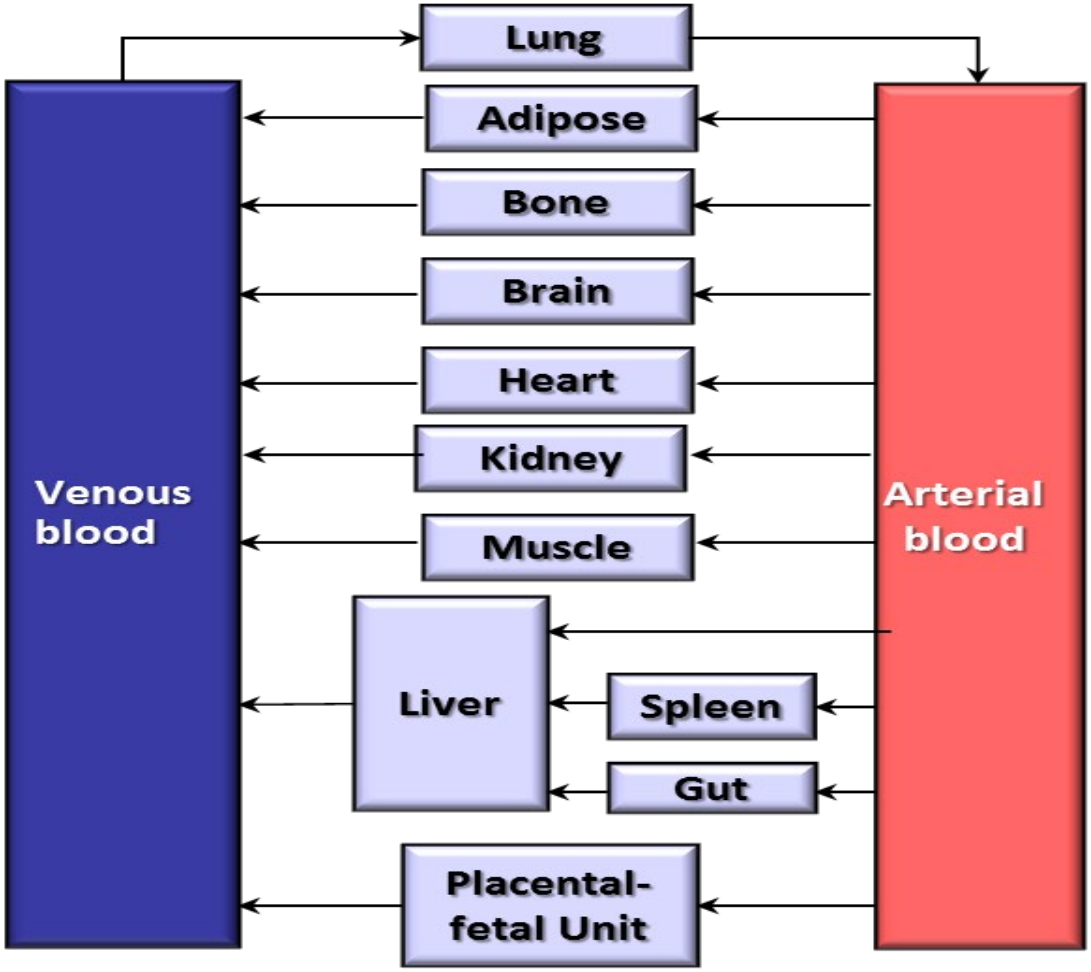
- Increase in hepatic and not intestinal CYP3A4/5 activity

Hebert MF.. Unadkat JD et al., Clin Pharmacol Ther. 2008

Changes in In Vivo Hepatic Enzyme Activity During Pregnancy Measured by Phenotyping Studies

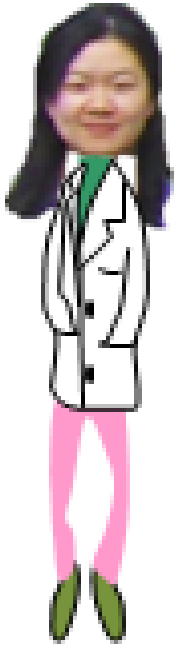
Metabolizing enzymes	Enzymatic activity changes during pregnancy	Substrates
CYP 450s	↓ CYP1A2	Caffeine
	↑ CYP2A6	Nicotine
	↑ CYP2C9	Phenytoin
	↓ CYP2C19	Proguanil
	↑ CYP2D6	Metoprolol , Dextromethorphan
	↑ CYP3A4	Midazolam
	↑ CYP2B6	Methadone
UGTs	↑UGT 1A1	Labetalol
	↑UGT 1A4	Lamotrigine

Can Maternal Disposition of CYP-Cleared Drugs be Accurately Predicted Using PBPK M&S?



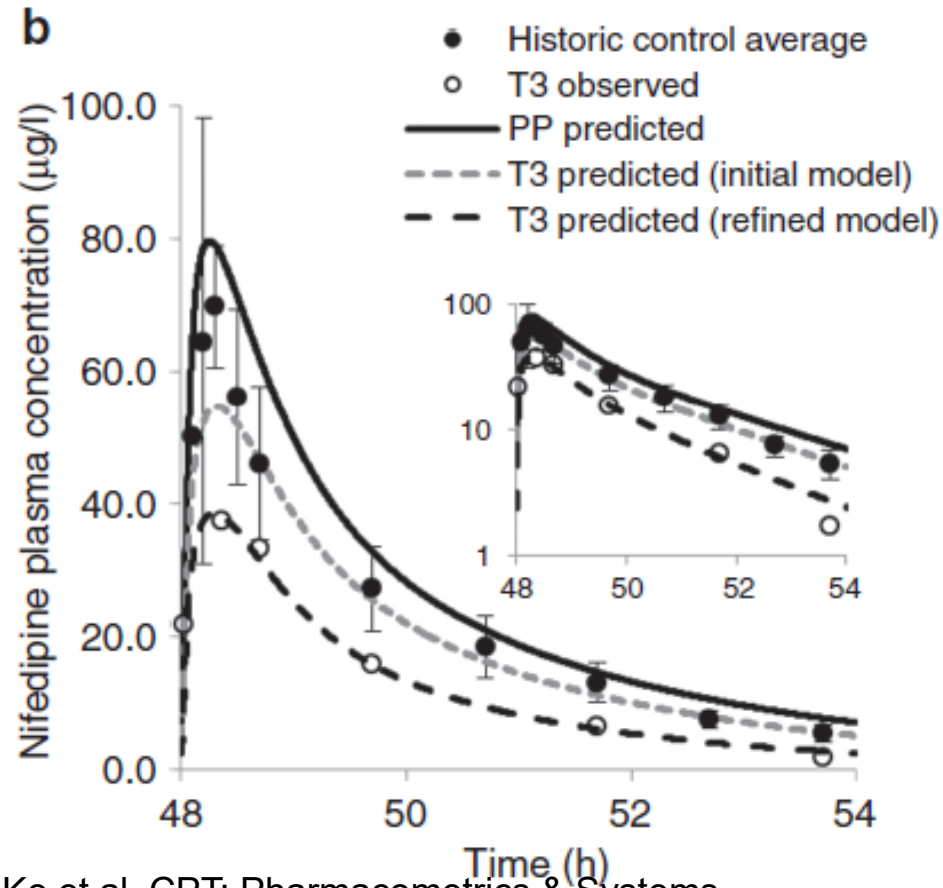
Verification of m-PBPK model

CYP3A **Midazolam (Dextromethorphan)** **Nifedipine, Indinavir**	**CYP1A2** **Caffeine** **Theophylline**
CYP2D6 **Metoprolol** **Dextromethorphan/Dextrorphan, Paroxetine, Clonidine**	**Multiple CYPs** **Methadone, Glyburide**



Alice Ke

Our m-PBPK Model Successfully Predicted the Disposition of Several CYP3A-cleared Drugs during T3 - Based on Midazolam Data



Ke et al. CPT: Pharmacometrics & Systems Pharmacology, 2012

- Based on midazolam data, our m-PBPK model successfully predicted the 3rd trimester (T3) disposition of two predominantly CYP3A-cleared drugs (i.e. nifedipine and indinavir)
- This induction is hepatic rather than intestinal
- Human hepatocyte studies suggest that CYP3A enzymes are equally induced throughout pregnancy

Summary

- Our m-PBPK model successfully predicted the third trimester maternal disposition of many CYP-metabolized drugs including theophylline and glyburide.
- The model needs to be verified at earlier gestational ages once such data become available.

Expansion of m-PBPK to predict fetal drug exposure through a m-f- PBPK model

- Verification of such a model can be done ONLY at term when umbilical plasma concentrations can be obtained

Maternal-Fetal-PBPK (m-f-PBPK) structure

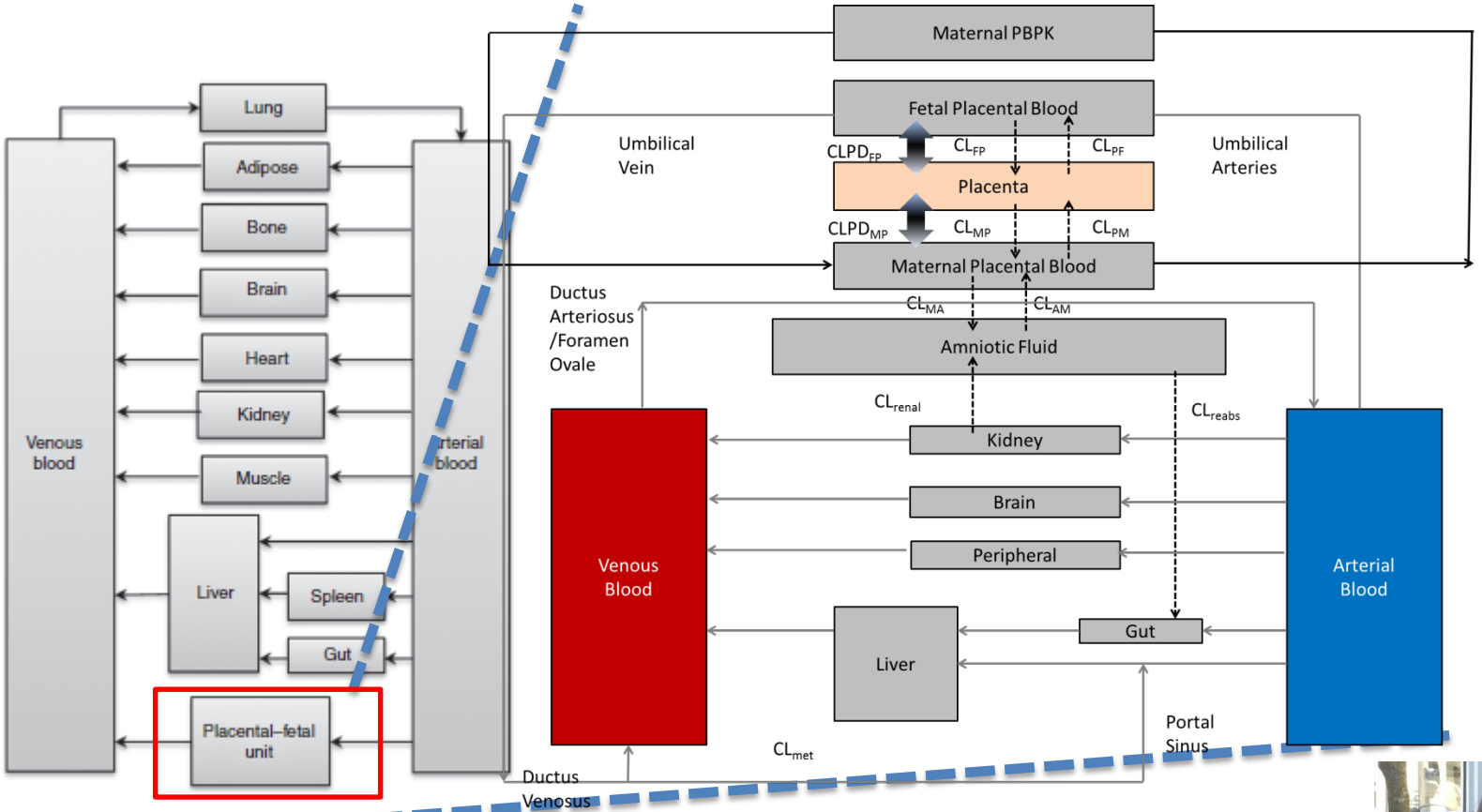
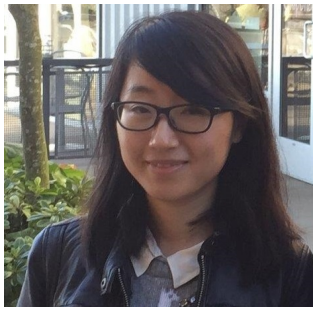


Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic model (PBPK) model. The PBPK model is an extension of the Simcyp 13-compartment full-PBPK model, and includes a lumped compartment to represent placental–fetal organs including the fetus, placenta, and the amniotic fluid. Reproduced from Lu *et al.* 2012.[13]

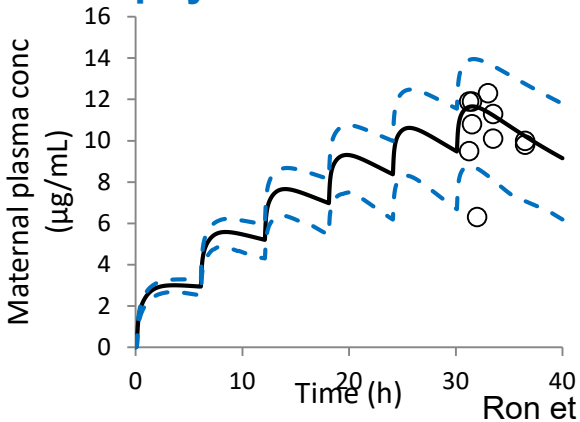
Ke et al 2012

Contains fetal organs that are important for fetal drug disposition
Zhang et al. DMD 2017



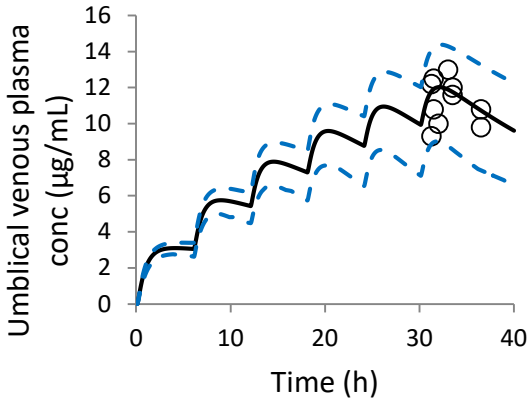
m-f PBPM Model Verification using passive diffusion drugs: Theophylline and Zidovudine (AZT)

Theophylline Maternal



Ron et al, 1994

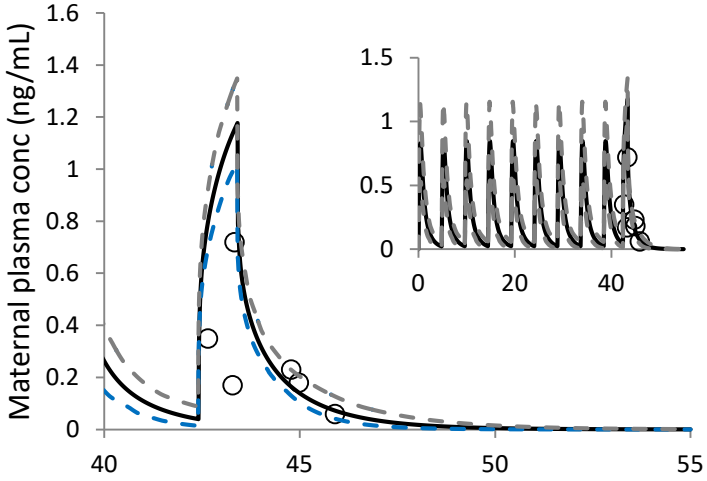
Fetal



200mg theophylline dosed orally prior to C-section

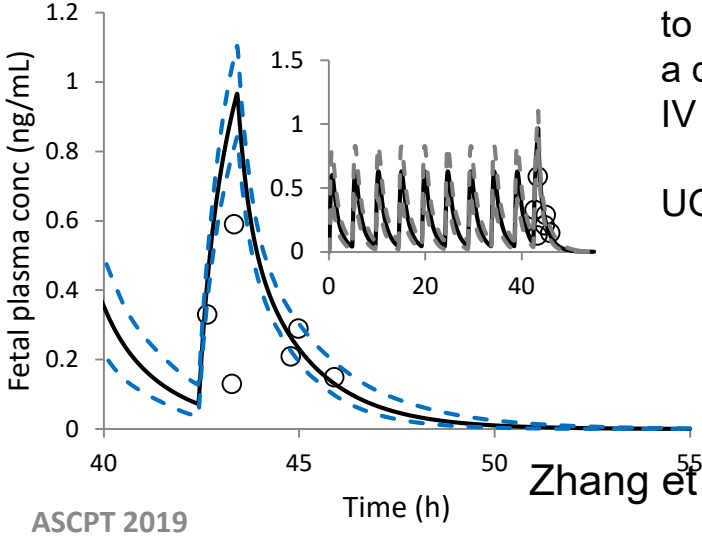
1A2 substrate

Zidovudine Maternal



D'Sullivan et al, 1993

Fetal

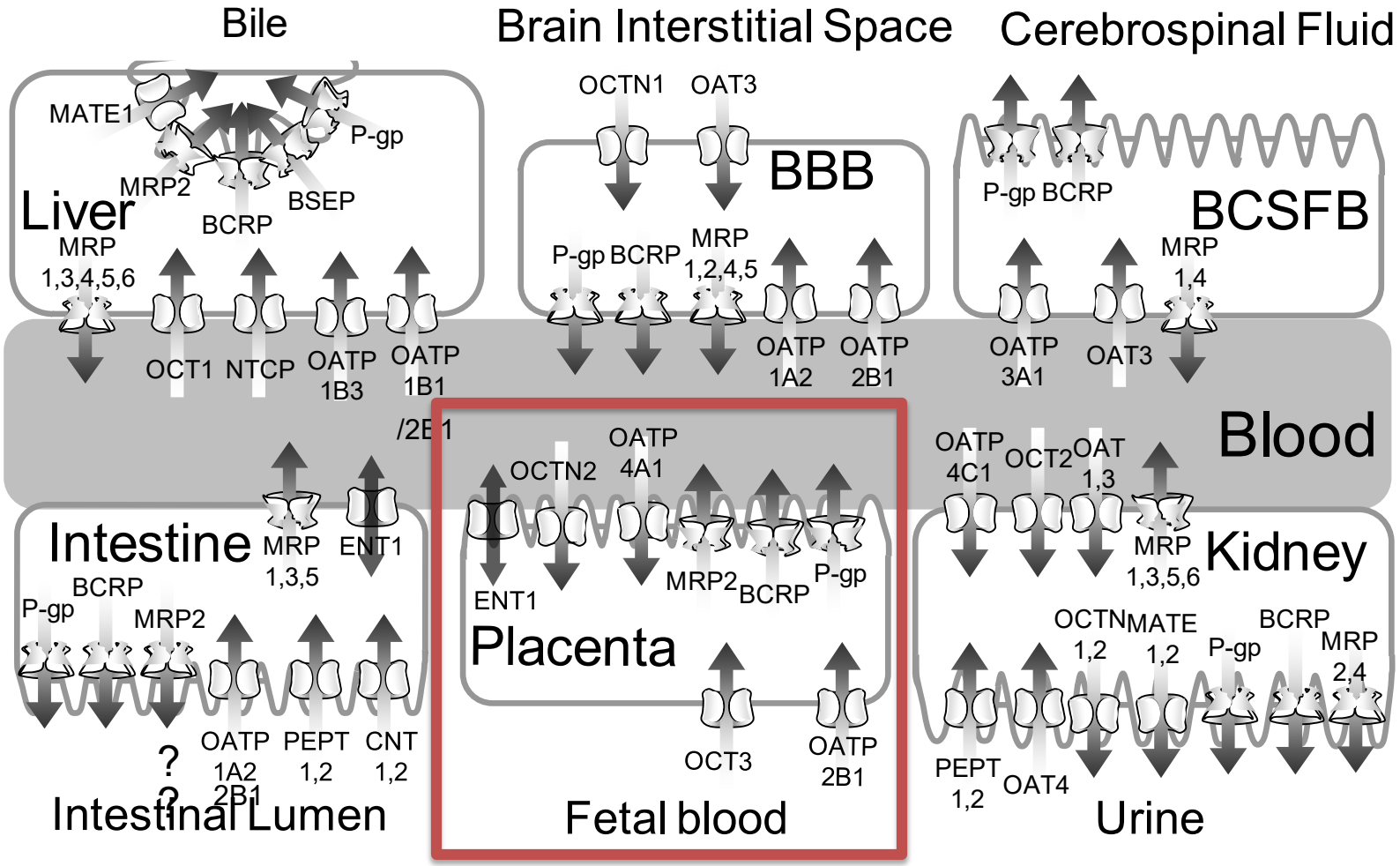


Zhang et al., DMD 2017

Zidovudine was dosed to term women 5 times a day followed by a 1-h IV infusion

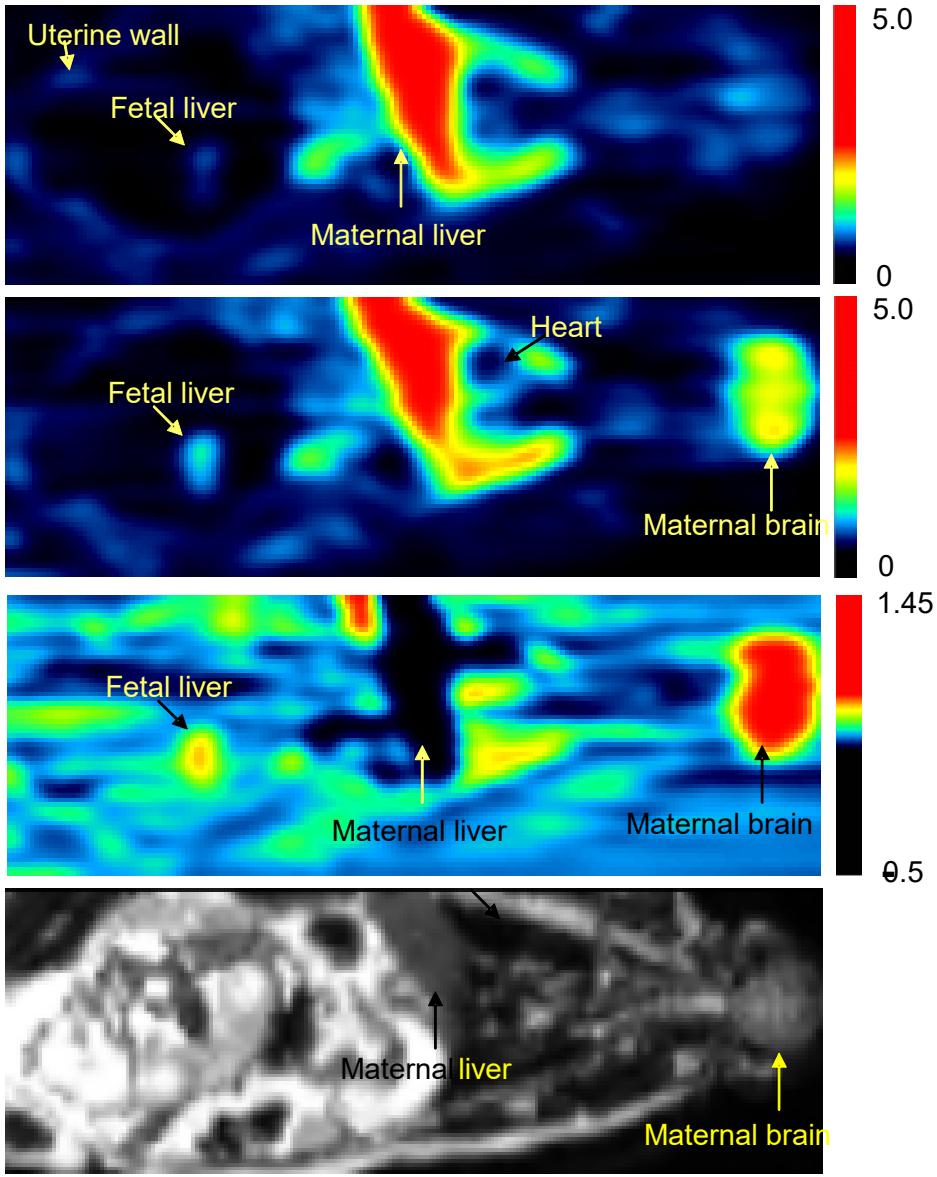
UGT2B7 substrate

Tissue/Membrane Localization of Drug Transporters



Unadkat JD, *Enzyme-and Transporter-Based Drug-Drug Interactions:* 2010.

Placental P-gp Excludes P-gp Substrates from the Fetus



PET – before CsA

PET – during CsA

PET – pixel-by-pixel subtraction of A from B

MRI

Eyal et al.,
J Nucl. Med, 2009
Chung et al., Br J Pharmacol, 2010

Maternal-Fetal-PBPK (m-f-PBPK) structure

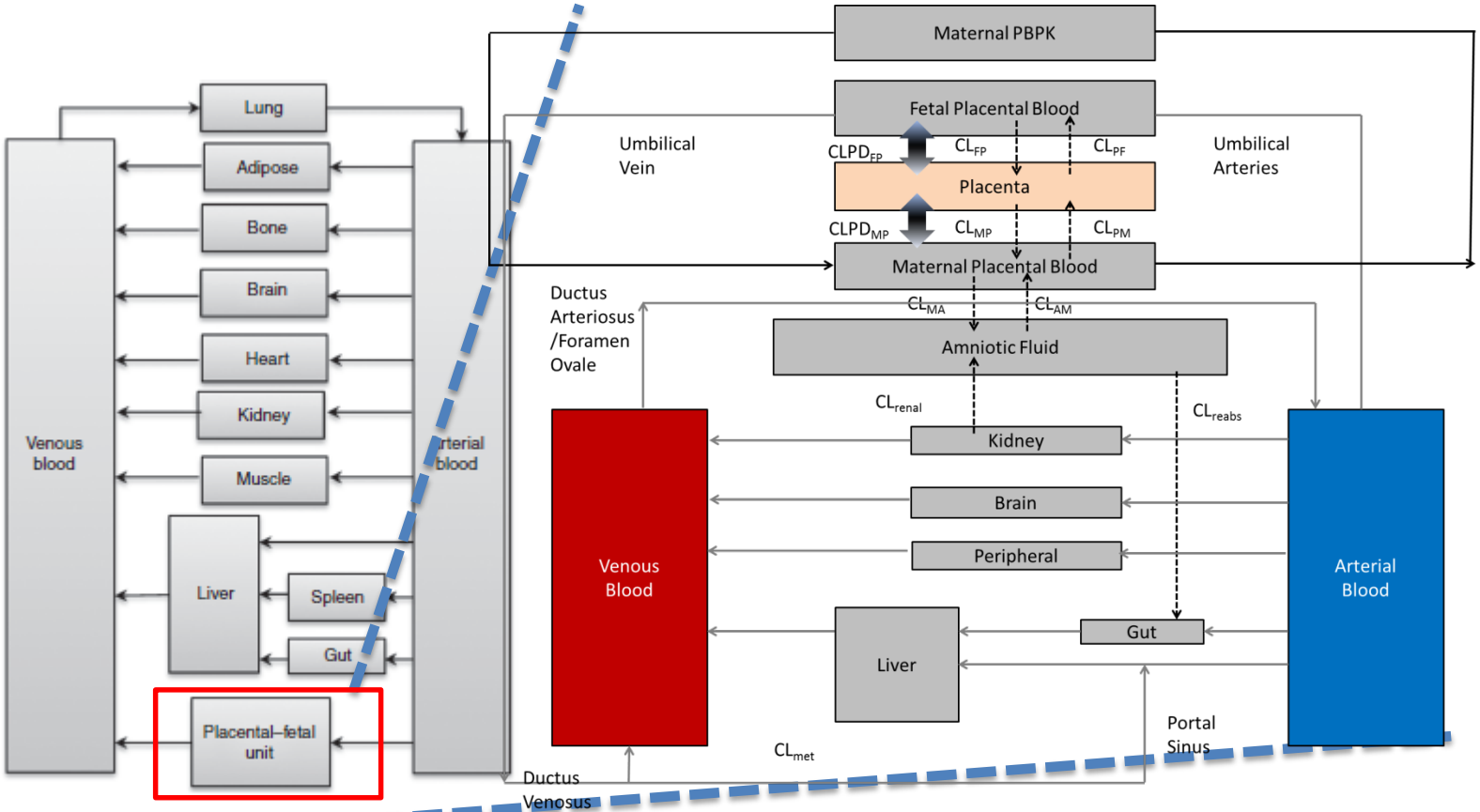
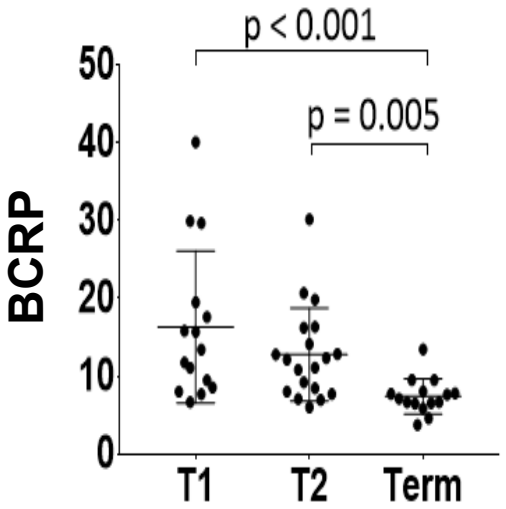


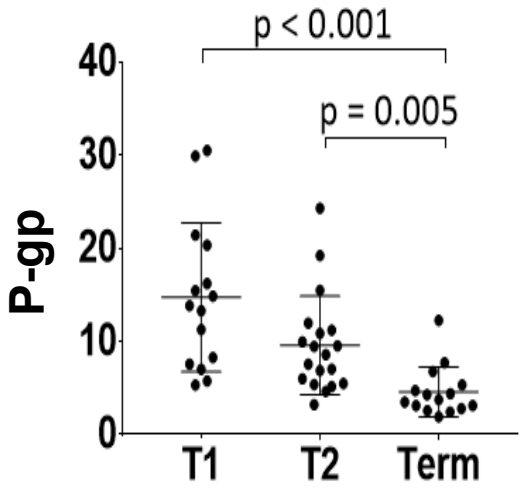
Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic model (PBPK) model. The PBPK model is an extension of the Simcyp 13-compartment full-PBPK model, and includes a lumped compartment to represent placental–fetal organs including the fetus, placenta, and the amniotic fluid. Reproduced from Lu *et al.* 2012.[13]

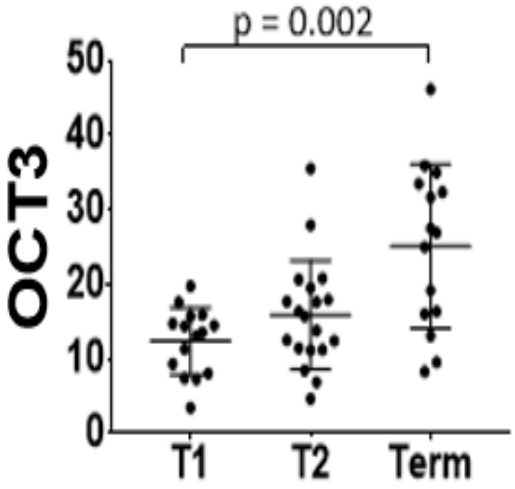
Zhang et al. DMD 2017

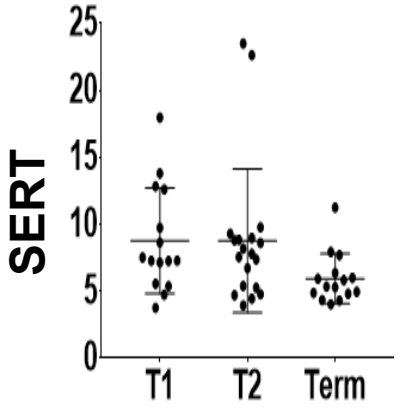
Ke et al 2012

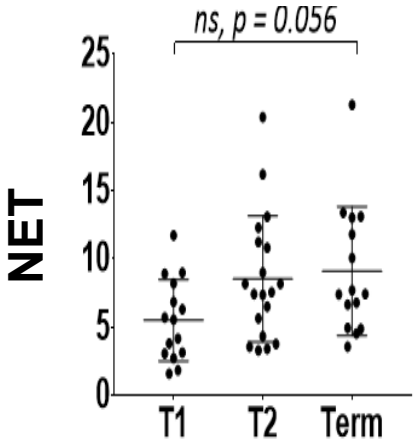
The Abundance of Placental Transporters (pmole/g placenta) Changes with Gestational Age

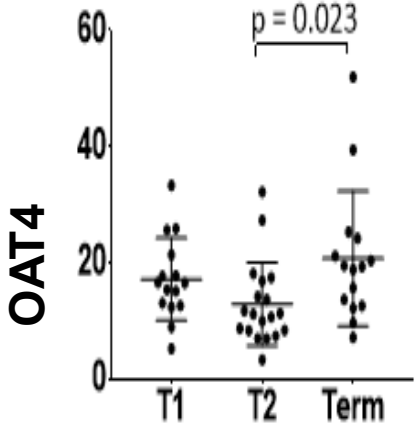


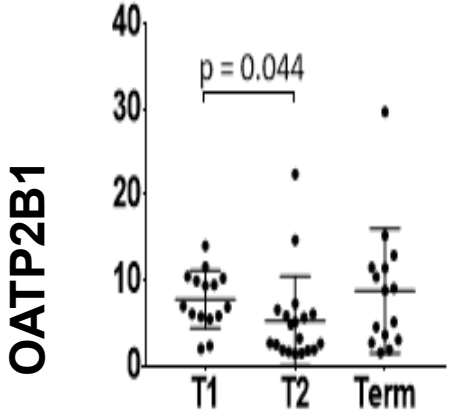












Summary

- Our novel maternal-fetal PBPK model well-predicted the maternal-fetal disposition (at term) of drugs that passively diffuse across the placenta
- Placenta drug transport and/or fetoplacental metabolism may modulate fetal drug exposure to a significant extent
- These processes can be incorporated into the model once proteins that metabolize or transport drugs are quantified by LC-MS/MS in the placenta and fetal liver of different gestational ages (in progress)
- Once available, our m-f-PBPK will be verified using data obtained at term of drugs that are transported or metabolized by the placenta

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Unadkat lab contributors

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Collaborators

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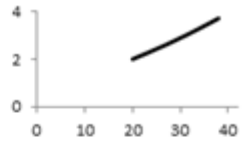
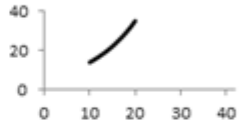
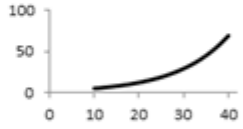
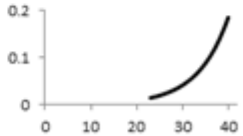
Univ. of WA Health Sciences

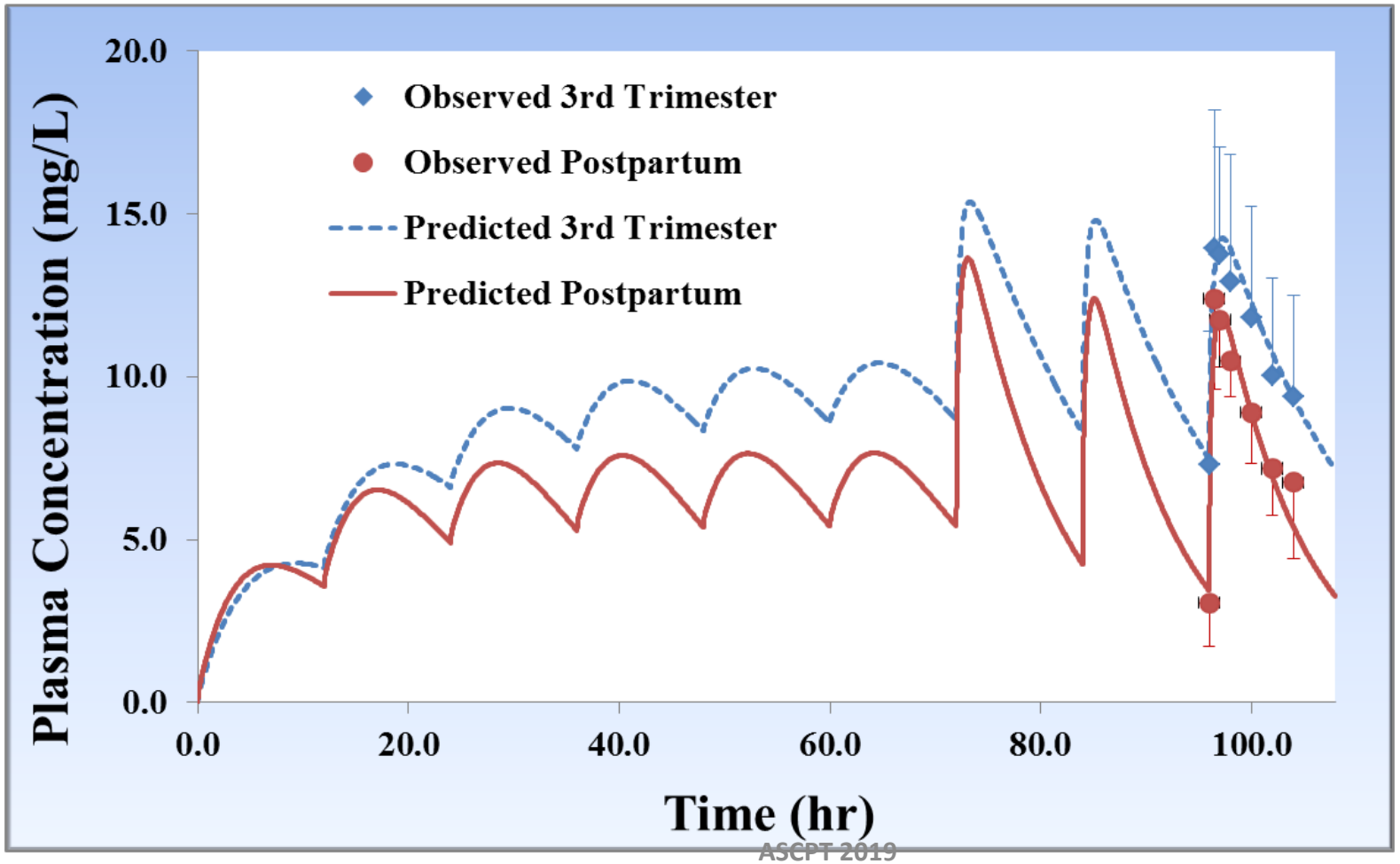
Populating m-f-PBPK model with Physiological Parameters

Table 1: Key fetal physiological parameters

Parameter (units)	Formula[a]	References	Graph[b]
Maternal pl… blood flow (…			
Fetal serum … (mg/dL)			
Fetal serum … glycoprotei… (mg/dL)			
Fetal brain … (mL)			
Fetal total gut volume (mL)	$-54.3+8.90GA-0.479GA^2+0.0088GA^3$	Nagata, Koyanagi et al. 1990; Parulekar 1991; Archie, Collins et al. 2006;	
Fetal kidney v… (mL)			
Fetal umbilical … flow (L/h)			
Ductus venosu… flow (L/h)			
Fetal portal vein blood flow (L/h)	$0.714+0.0489GA+0.0008GA^2$ (R^2= 1.00; GA: 20-38 weeks)**	Bellotti, Pennati et al. 2004; Haugen, Kiserud et al. 2004; Kessler, Rasmussen et al. 2008	
Fetal brain blood flow (mL/min)	$5.56e^{0.0921GA}$ (R^2 = 0.999; GA: 10-20 weeks)†	Rudolph AM 1971; Kenny, Plappert et al. 1986	
Fetal kidney blood flow (mL/min)	$2.18e^{0.0865GA}$ (R^2 = 0.707; GA: 10-41 weeks)†	Rudolph AM 1971; Kenny, Plappert et al. 1986; Veille, Hanson et al. 1993	
Fetal glomerular filtration clearance (L/h)	$0.00046e^{0.15GA}$ (R^2 = 0.69; GA: 23-40 weeks)††	Arant 1978; Hansen, Oh et al. 1983; Coulthard 1985; van den Anker,de Groot et al. 1995	

Many of fetal physiological parameters have not been measured at early gestational age (i.e. before week 20) Zhang et al., DMD 2017

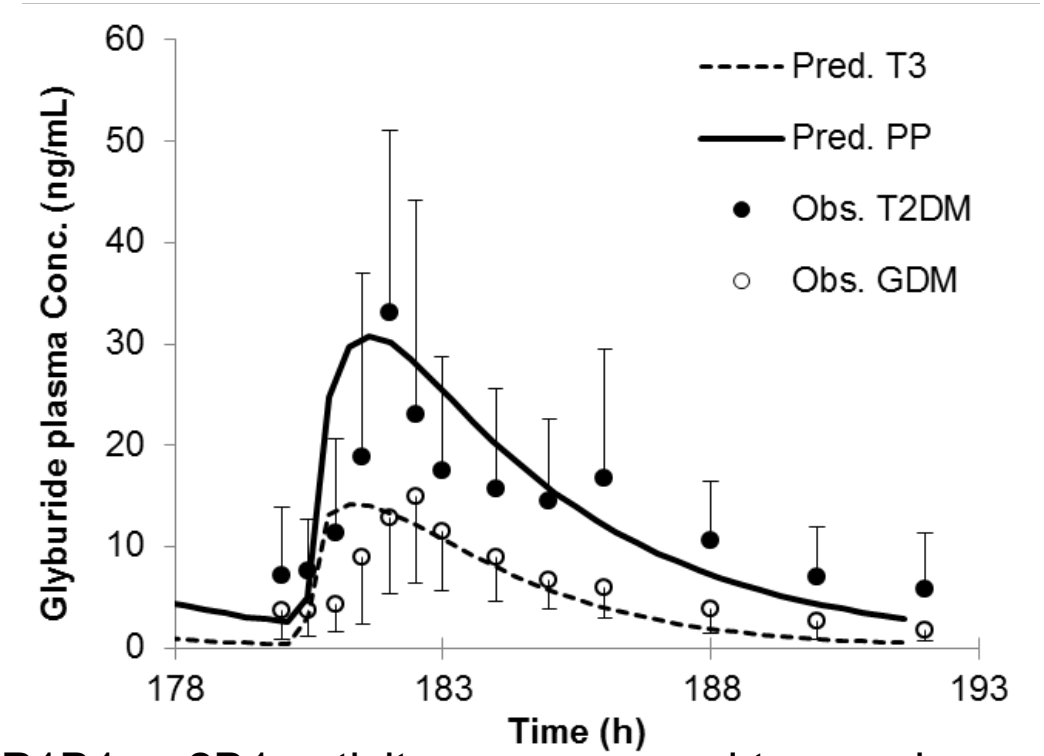
Our m-PBPK Model Successfully Predicted Steady-State PK of Theophylline During T3 - Based On Caffeine Data



Ke AB et al., Drug Metab Dispos: 2013.

Gardner et al., Eur J Clin Pharmacol 1987 (n=10)

Our m-PBPK model Successfully Predicted Disposition of Drugs Cleared by Multiple Enzymes e.g. Glyburide - CYP3A4 (~50%), CYP2C9 (~30%) and CYP2C19 (~20%)



- Hepatic OATP1B1 or 2B1 activity was assumed to remain constant throughout pregnancy.

Ke AB et al., Brit J Clin Pharmaco: 2013

NY TIMES

SCIENCE

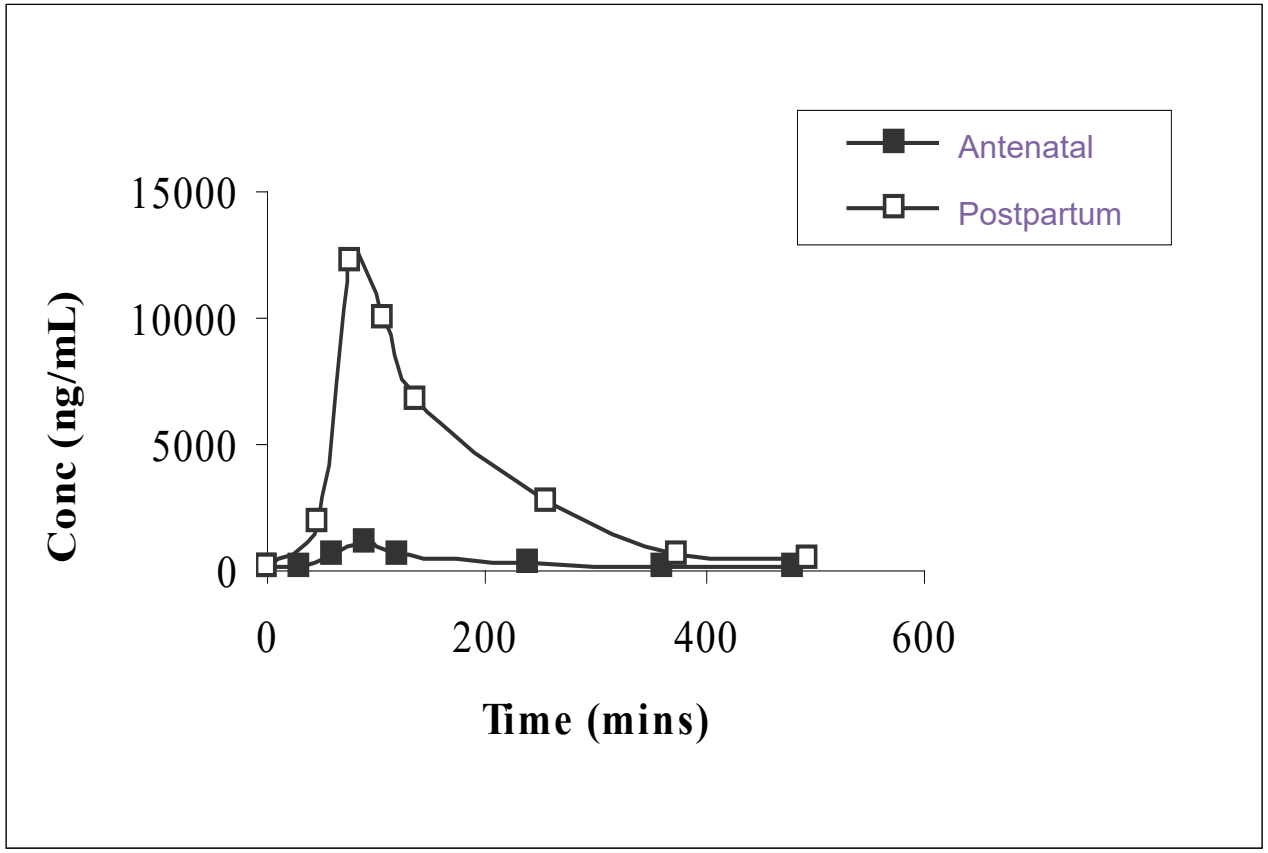
Surge in Narcotic Prescriptions for Pregnant Women

By CATHERINE SAINT LOUIS

APRIL 13, 2014

In the US, 1 in 5 pregnant women are prescribed and take narcotic analgesics

Maternal Exposure To Some Drugs is Profoundly Changed During Pregnancy: Indinavir, a HIV drug



Unadkat JD, et al., Antimicrob Agents Chemother. 2007 51:783-6.

Recommended Cmin is 150–800 ng ml−1

Can Maternal Disposition of CYP-Cleared Drugs be Accurately Predicted During Third Trimester (T3)?

- A maternal-fetal PBPK model developed in collaboration with Simcyp

- Populated with gestational-age dependent changes in physiological changes (e.g. tissue blood flow, plasma protein conc.)

- Populated with the third trimester (T3) changes in CYP activity using phenotyping data

- Predicted the T3 disposition of other drugs cleared by these CYP enzymes

Site of CYP3A Induction: hepatic or intestinal or both?

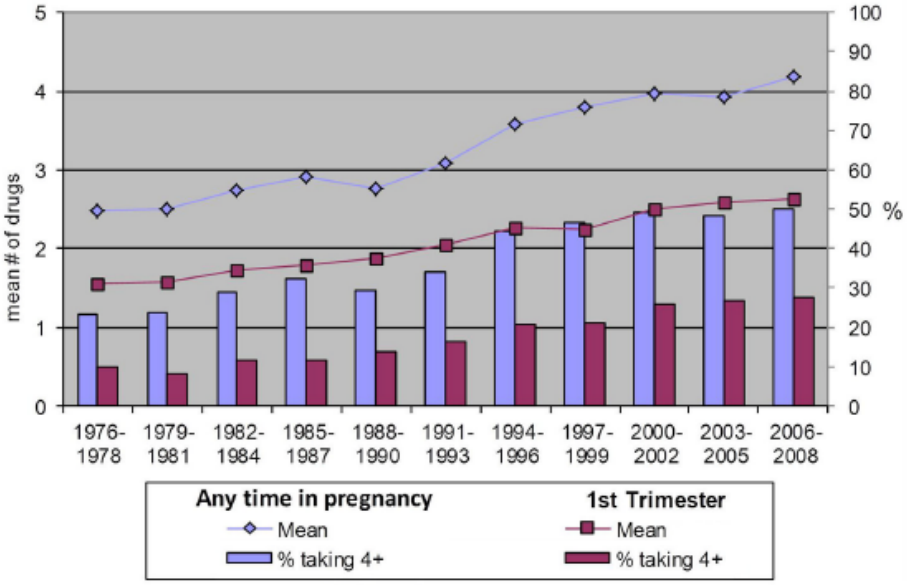
- PBPK M&S demonstrated that 90-100% increase in hepatic CYP3A activity ALONE could universally explain the AUC changes of all three CYP3A substrates, midazolam, nifedipine, indinavir
- Hepatic rather than intestinal CYP3A induced by pregnancy
- This conclusion was supported by transgenic mice expressing the CYP3A promoter-luciferase consruct

Ke et al. CPT: Pharmacometrics & Systems Pharmacology, 2012

Challenges

- Phenotyping extent of changes in metabolic enzymes and transporter activity earlier in pregnancy (1st and 2nd trimester)
- Verification of model predictions using independent data sets for both maternal and fetal drug exposure
- How does disease affect maternal-fetal drug exposure (e.g. gestational diabetes, preecmplasia etc.).

Pregnant Women and their Fetuses are Therapeutic Orphans



- About 82% of pregnant women ingest one or more drugs during pregnancy despite:
  - Lack of data on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs in pregnant women.
  - Changes in PK/PD of drugs during pregnancy
- Therefore, drugs are administered to pregnant women/fetuses off-label

Mitchell et al, Am J Obstet Gynecol. 2011