

Predicting maternal-fetal exposure to drugs using a mechanistic PBPK model

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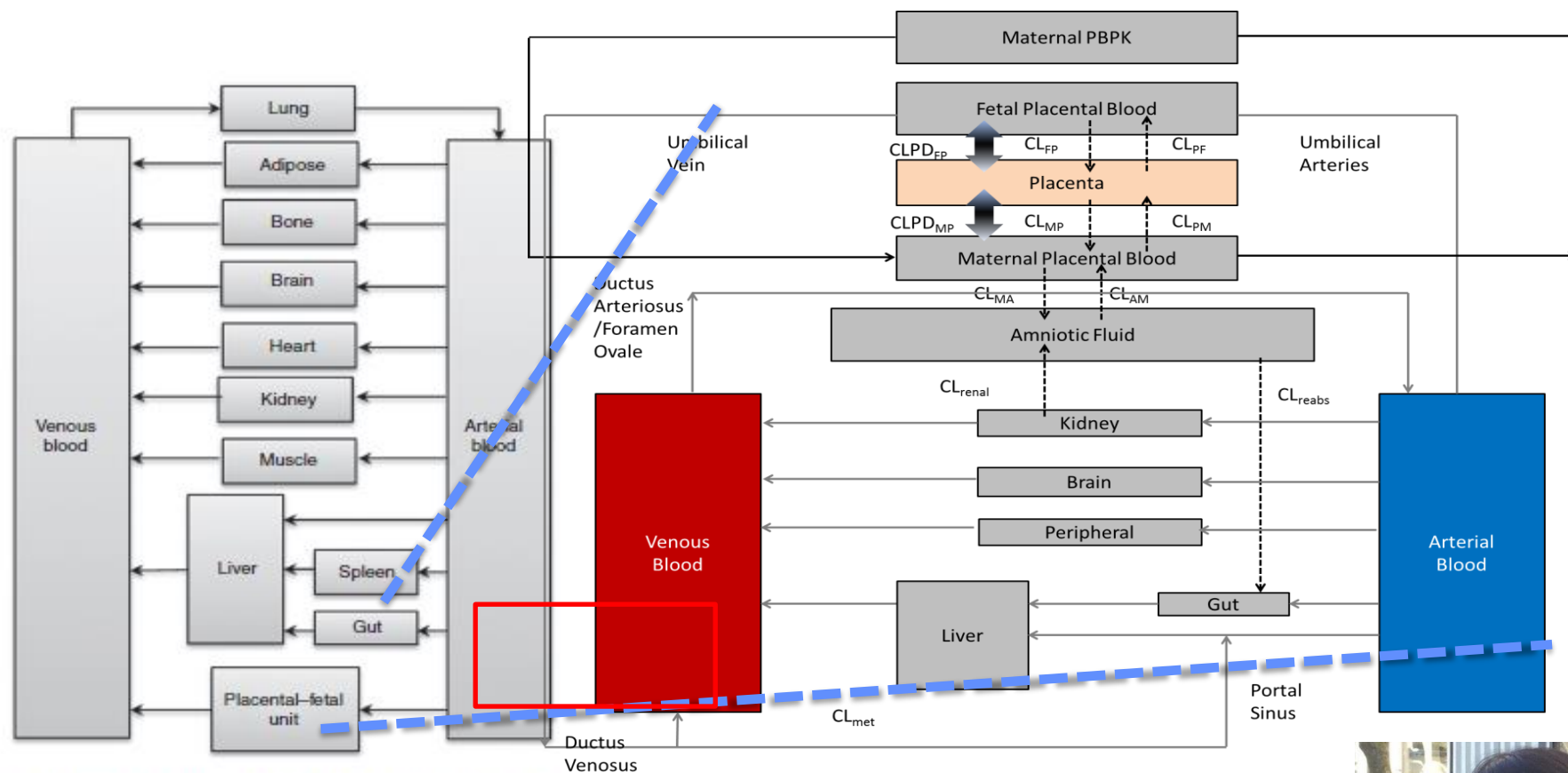


Predicting Maternal-Fetal Exposure to Drugs by Phenotyping Studies and a Maternal-Fetal (m-f) PBPK Model

- When pregnant women are given standard drug doses, maternal-fetal exposure to these drugs, and their efficacy and safety, will often differ from that in men or non-pregnant women because the PK of drugs are changed by pregnancy (e.g. CYPs are induced or repressed)
- It is neither feasible nor desirable to determine maternal-fetal exposure to all drugs or natural products/supplements taken by pregnant women
- Therefore, to inform correct maternal dosing regimen and minimize fetal risks, we have developed a systems/mechanistic pharmacology approach to predict maternal-fetal exposure to drugs throughout pregnancy:
  - First, elucidate the extent of changes in drug disposition (e.g. drug metabolism and transport) for model drugs (phenotyping studies)
  - Then use a maternal-fetal **Physiologically Based Pharmacokinetic** (m-f PBPK) model to predict the disposition of other drugs that are also metabolized/transported by the same mechanisms



Can Maternal Disposition of CYP-Cleared Drugs be Accurately Predicted by our m-f PBPK Model?

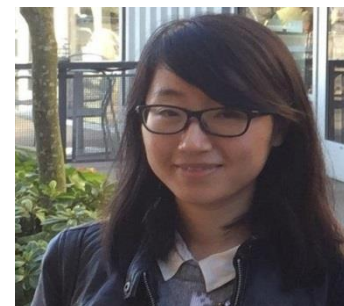


- Populate the model by pregnancy-specific physiological mechanistic data e.g. changes in CYP and transporter activity
- Then, predict the changes in m-f exposure to drugs not studied in pregnancy

Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic (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.* 2012.¹²

Zhang et al. DMD 2017

Ke et al 2012



Validation of our m-f PBPK model



CYP3A
Midazolam
(Dextromethorphan)
Nifedipine, Indinavir

CYP1A2
Caffeine
Theophylline

CYP2D6
Metoprolol
Dextromethorphan/Dextrorphan, Paroxetine, Clonidine

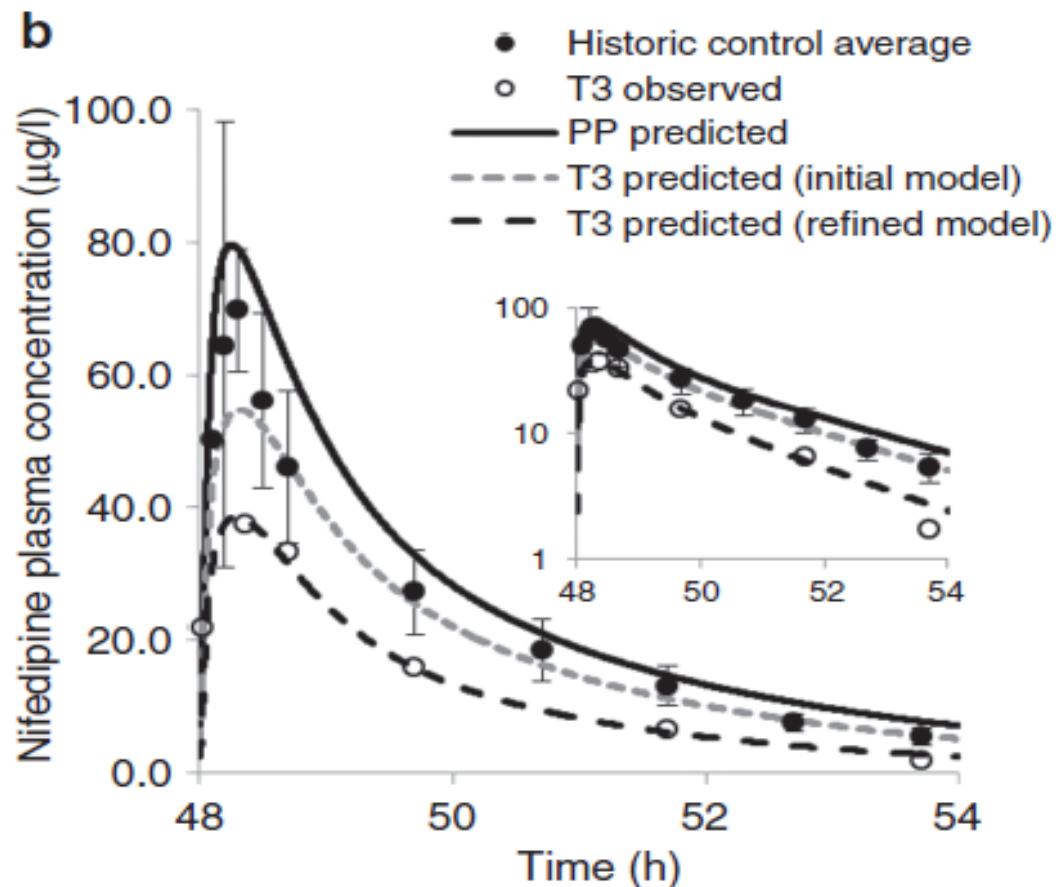
Multiple CYPs
Methadone, Glyburide



Alice Ke



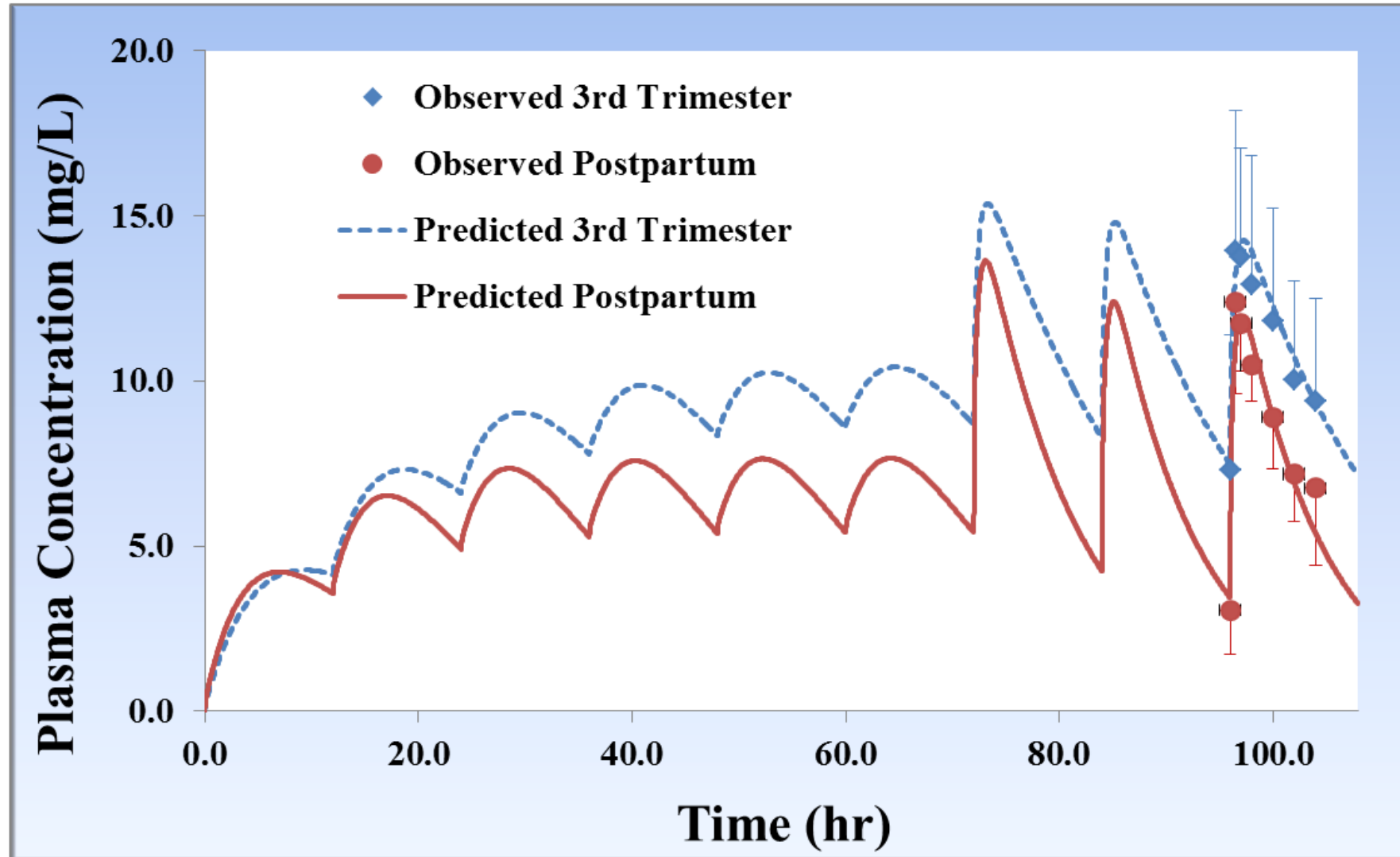
Successful Prediction of the Disposition of Several CYP3A-cleared Drugs during T3 Based on Midazolam Phenotyping Data



- 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



Successful Prediction of the Steady-State PK of a CYP1A2-metabolized drug, Theophylline, during T3, Based On Caffeine Phenotyping Data

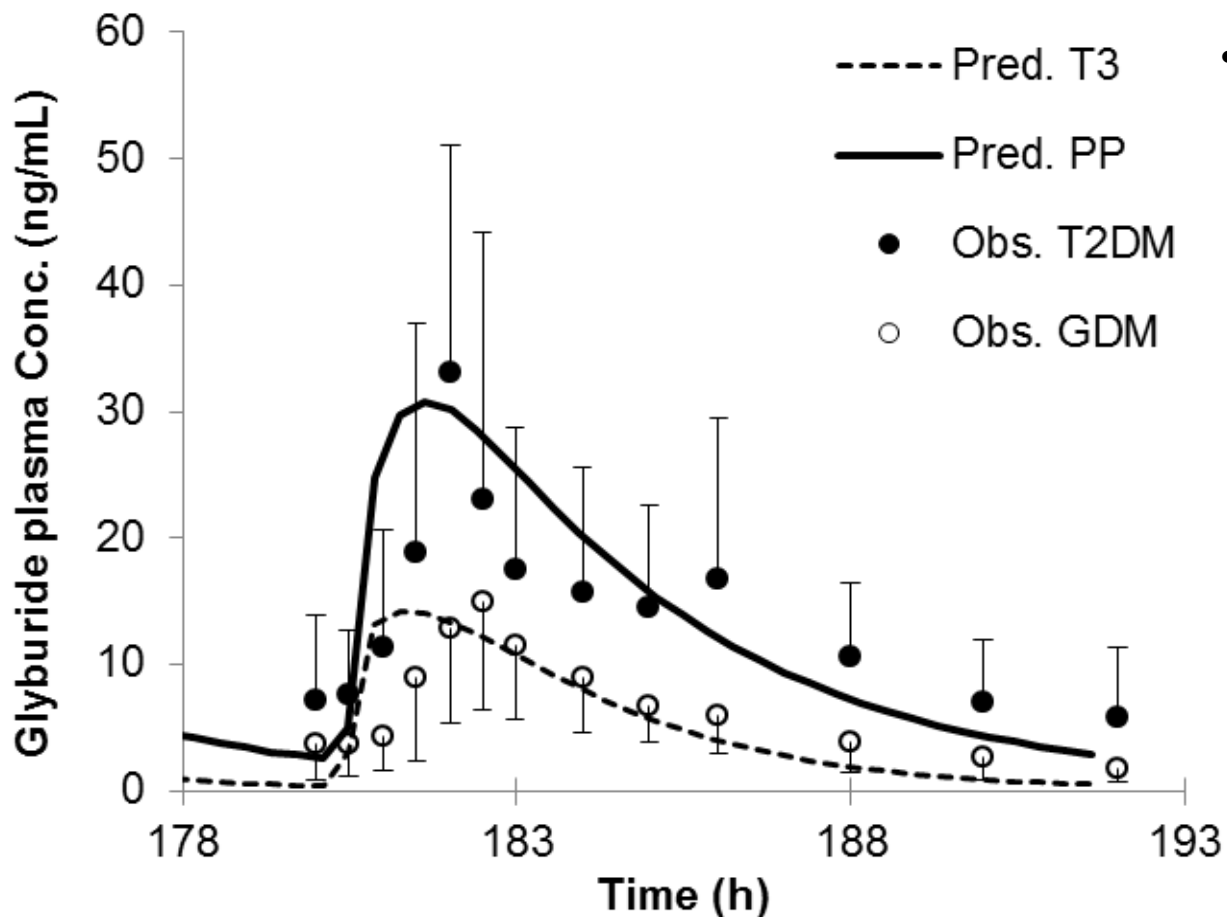


Ke AB et al.,
Drug Metab
Dispos:
2013.

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



Successful Prediction of the Disposition of Drugs Cleared by Multiple CYP Enzymes during T3 e.g. Glyburide - CYP3A4 (~50%), CYP2C9 (~30%) and CYP2C19 (~20%)



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



Can our m-f PBPK Successfully Predict Fetal Exposure to Drugs that Passively and Actively Cross the Placenta?

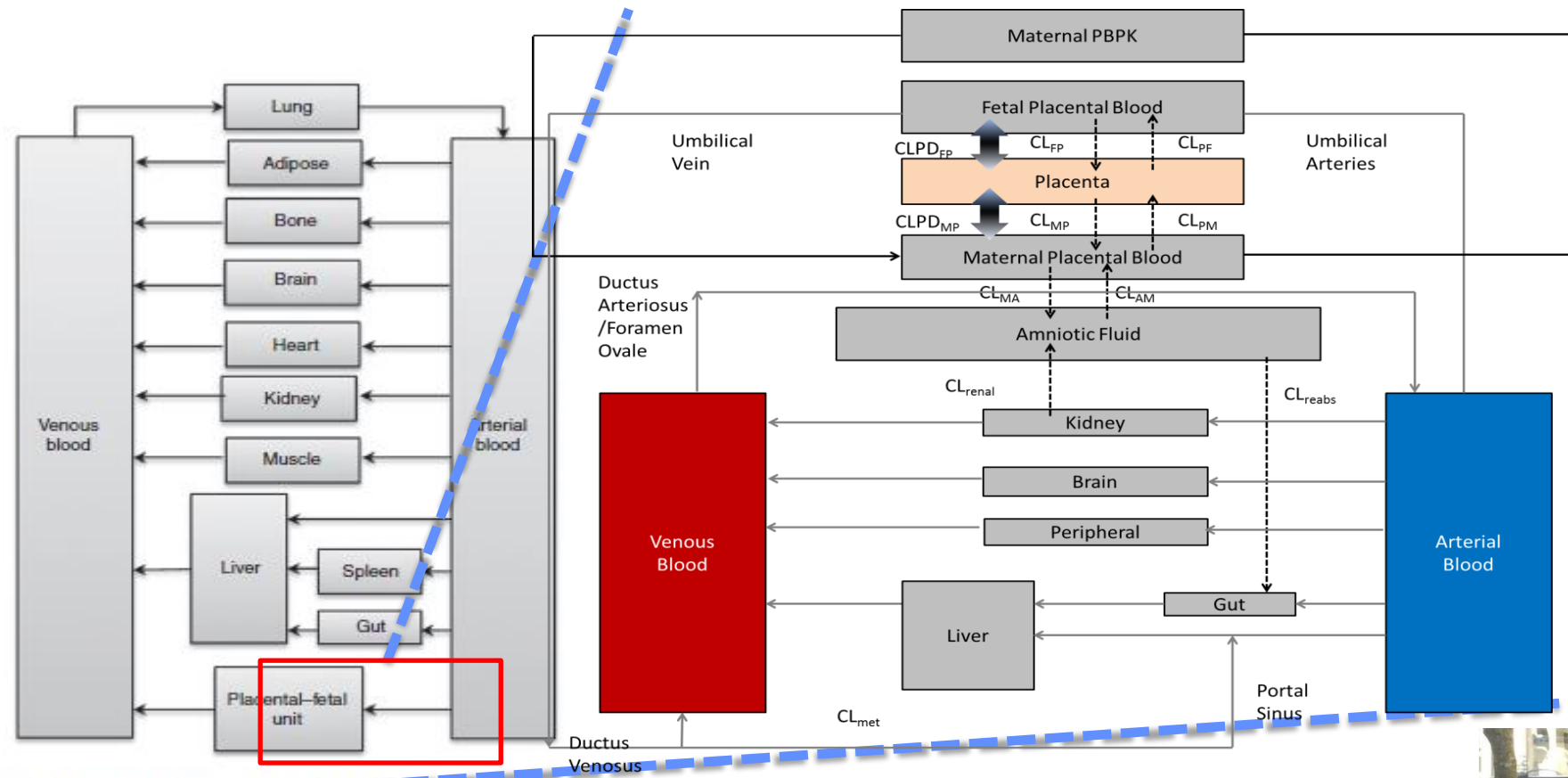
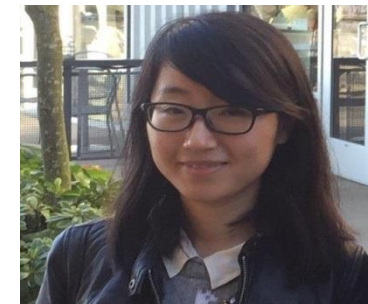


Figure 5 A schematic representation of the pregnancy physiologically based pharmacokinetic (PBPK) model. The PBPK model is an extension of the Simcyp 13-compartment full-PBPK model, and includes a lumped compartment to represent placental-fetal organs including the fetus, placenta, and the amniotic fluid. Reproduced from Lu *et al.* 2012.¹²

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

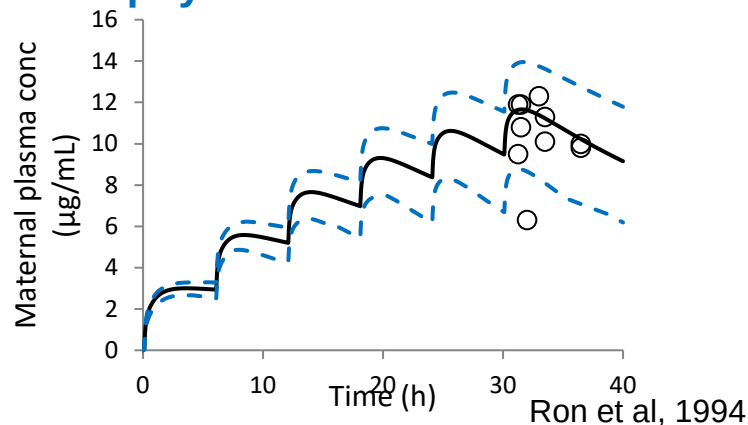
Ke et al 2012



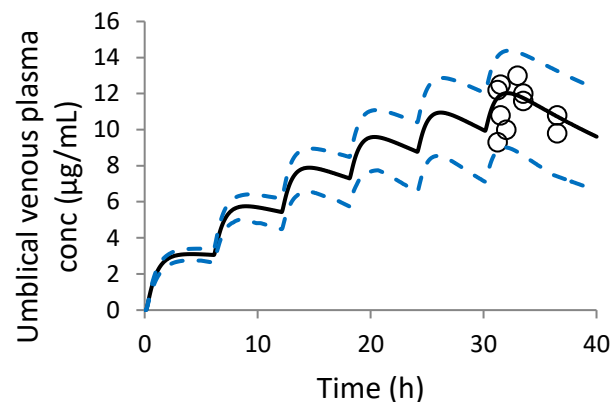


Successful Prediction of Fetal Exposure to Drugs that Passively Cross the Placenta: Theophylline and Zidovudine (AZT)

Theophylline Maternal



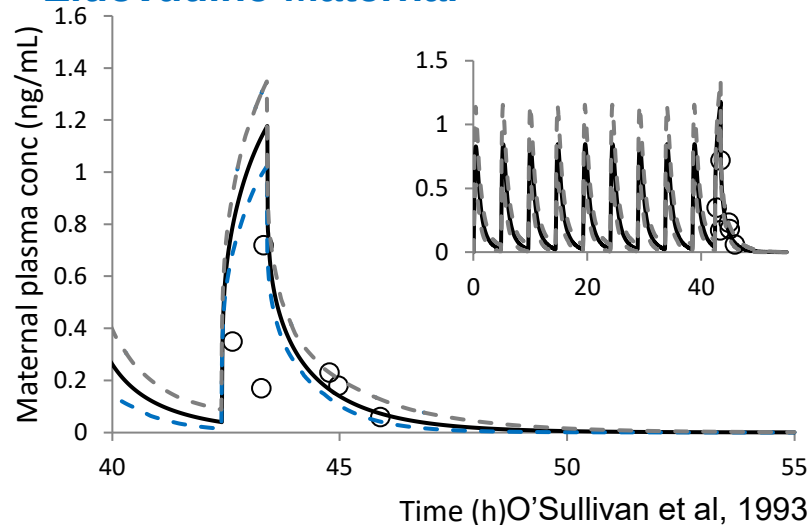
Fetal



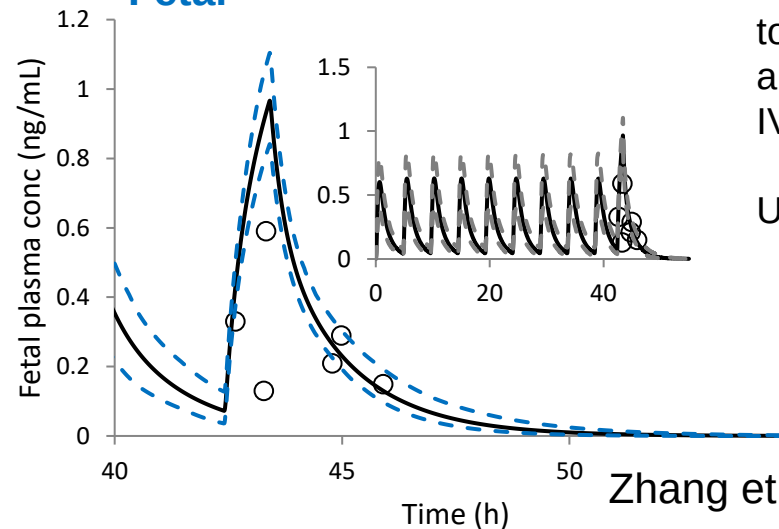
200mg theophylline
dosed orally prior to
C-section

CYP 1A2 substrate

Zidovudine Maternal



Fetal



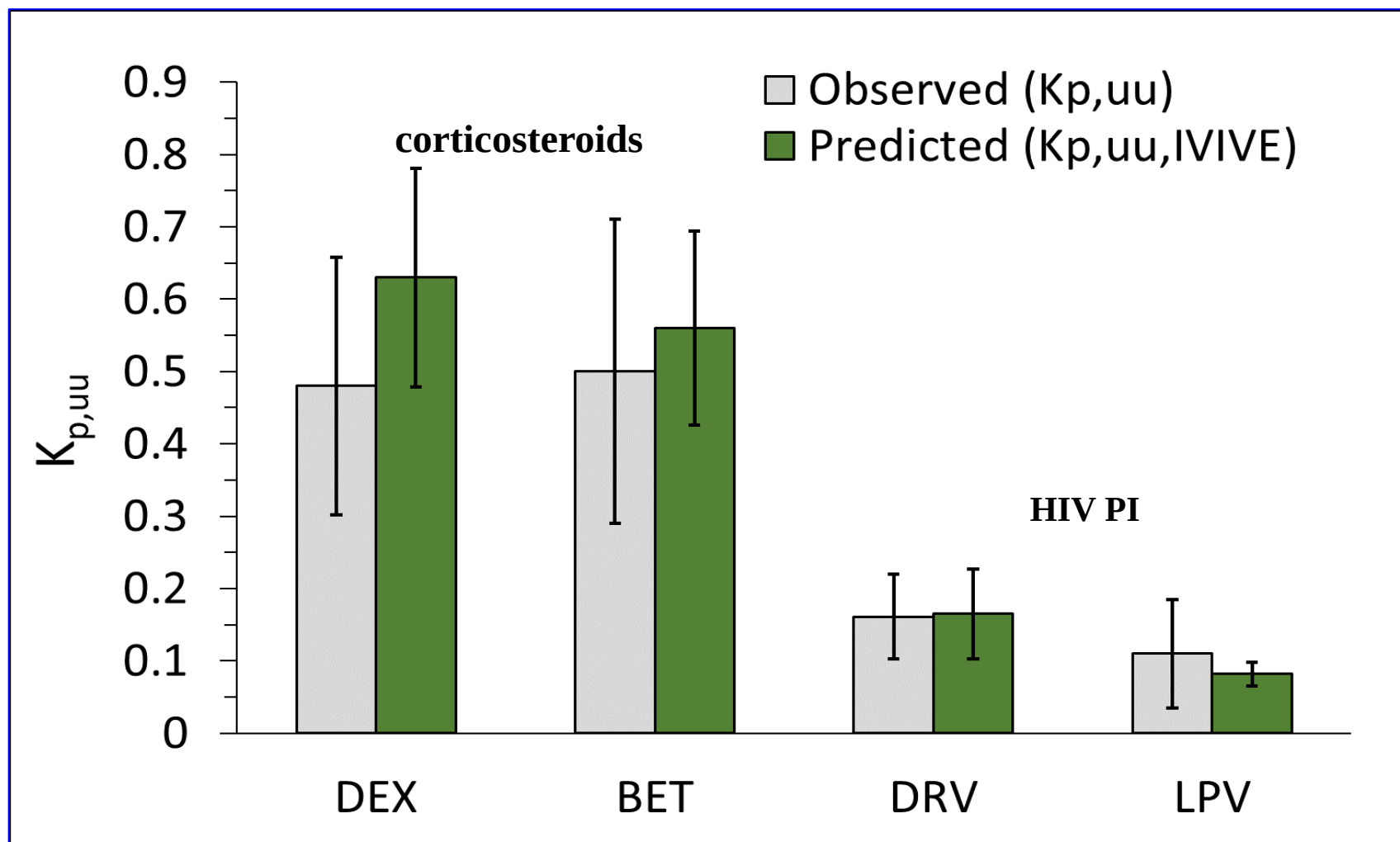
Zidovudine was dosed
to term women 5 times
a day followed by a 1-h
IV infusion

UGT2B7 substrate

Zhang et al., DMD 2017



Successful Prediction of Fetal Exposure to Drugs ($K_{p,uu}$, fetal –to-maternal unbound steady-state plasma conc. ratio) Effluxed by Placental P-gp



P-gp Substrates:

- Dexamethasone (DEX)
- Betamethasone (BET)
- Darunavir (DRV)
- Lopinavir (LPV)



Anoshchenko *et al.*, DMD 2021



Significance of Our Findings



- This success provides confidence in using our m-f PBPK model to predict maternal-fetal exposure throughout pregnancy:
  - To drugs predominately metabolized by the common CYP enzymes
AND
  - Drugs that passively cross the placenta or are transported by placental P-gp or other/multiple placental transporters (e.g., BCRP and P-gp)
- Such predictions can help guide design of drug dosing regimens for pregnant women that are safe and efficacious for the maternal-fetal dyad

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