Successful Prediction of Fetal Exposure to Transported and Non-transported Drugs Using In Vitro Studies and PBPK M&S

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The Pregnant Woman and Her Fetus are Drug Orphans

Medication use in pregnancy is prevalent

– Up to **80%** of pregnant women take drugs during pregnancy
– **90%** of drugs lack **approval** for use in pregnancy
– Some drugs are administered to pregnant women to treat the fetus (e.g. corticosteroids, HIV drugs)

Fetal/neonatal safety and efficacy of drugs is difficult (or often impossible) to determine, but:

• Fetal/neonatal safety/efficacy is driven by **fetal drug exposure**, which in turn is driven by:
  – Maternal drug exposure
  – Placental transport (often significant) or metabolism (usually negligible)
  – Fetal metabolism (usually negligible)
Assess Fetal Drug Exposure?
Difficult Though Possible

Fetal blood/plasma can be sampled only once and only at term (from umbilical vein, UV or artery - UA)

- Umbilical vein plasma/maternal plasma (UV/MP) drug concentration ratio at term is often incorrectly interpreted as a measure of fetal drug exposure

Correct “relative” Fetal Drug Exposure is: \( K_{p,uu} = \frac{f_{uf} \times AUC_f}{f_{um} \times AUC_m} \)

- \( K_{p,uu} = 1 \) for passively diffusing drugs, but <1 for those that are effluxed; need to also predict fetal Cmax
- can be obtained by pooling term data from multiple maternal-fetal dyads; but impossible < term
- therefore, alternative methods are needed to predict, rather than measure, \( K_{p,uu} \)
Maternal-Fetal PBPK (m-f PBPK) Model to Estimate $K_{p,uu}$

Incorporates changes in all gestational –age dependent physiological parameters including changes in:

- Cardiac output and organ blood flows
- Plasma proteins and plasma protein binding of drugs
- Activity/abundance of drug metabolizing enzymes or transporters including in the placenta

Zhang and Unadkat, 2017 DMD
Successful Prediction of Fetal Exposure to Drugs that Passively Cross the Placenta using our M-F PBPK Model

Model Verification using passive diffusion drugs

- **Theophylline Maternal**
  - Maternal plasma concentration vs. time
  - Ron et al., 1994

- **Fetal**
  - Fetal plasma concentration vs. time
  - 200mg theophylline dosed orally prior to C-section
  - 1A2 substrate

- **Zidovudine Maternal**
  - Maternal plasma concentration vs. time
  - O'Sullivan et al., 1993

- **Zidovudine Fetal**
  - Fetal plasma concentration vs. time
  - Zidovudine was dosed to term women 5 times a day followed by a 1-h IV infusion
  - UGT2B7 substrate

Zhang and Unadkat, 2017 DMD
Expansion of our M-F PBPK to Predict Fetal Exposure to Drugs that are Transported Across the Placenta

The Human Placenta is Richly Endowed with both Efflux and Influx Drug Transporters, the most important being P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP)

Maternal Blood

Syncytiotrophoblast

Fetal Compartment
Placental P-glycoprotein (P-gp) Excludes P-gp Substrates from the Fetus (e.g. $^{11}$C-verapamil)

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
Workflow to Predict Fetal $K_{p,uu}$ of Transported Drugs

Model Transporter: $P$-gp

P-gp Substrates:
1) Darunavir (DRV)
2) Lopinavir (LPV)
3) Dexamethasone (DEX)
4) Betamethasone (BET)

Prediction of $K_{p,uu}$ from In Vitro Studies

$$K_{p,uu} = \frac{REF \cdot (ER_{-TRQ} - ER_{+TRQ}) + 1}{REF + P-gp \text{ abundance in vitro}}$$

(1) In vitro Transwell
Apical Chamber ($A$)  Basal Chamber ($B$)

(2) In vivo placenta
Maternal Blood  Fetal Blood

Estimation of $K_{p,uu}$ from Observed In Vivo Data

m-1 PBPK Model

Anoshchenko et al., DMD 2021

Observed In Vivo Data

Dots: Paired observed umbilical vein (UV) and maternal plasma (MP) drug concentrations at term. Each pair obtained from a single maternal-fetal dyad
The Abundance of Placental Transporters (pmole/g placenta) Changes with Gestational Age

Anoshchenko L et al., DMD 2020
Successful Prediction of Fetal $K_{p,uu}$ Using the ER-REF Approach and our M-F PBPK Model

P-gp Substrates:
- Dexamethasone (DEX)
- Betamethasone (BET)
- Darunavir (DRV)
- Lopinavir (LPV)

Anoshchenko et al., DMD 2021
Significance of Findings

• This success provides confidence in using the ER-REF approach and PBPK M&S to estimate fetal drug exposure ($K_{p,uu}$, fetal AUC or $C_{\text{max}}$):
  
  ➢ to other placental P-gp substrate drugs or drugs of other/multiple placental transporters (e.g., BCRP and P-gp)
  ➢ at earlier gestational ages

• Our ER-REF approach and PBPK M&S can now be used to predict fetal exposure to any drug irrespective of whether it passively diffuses across the placenta or is also transported

• Prediction of fetal $K_{p,uu}$ is necessary to inform fetal efficacy and toxicity and optimize drug dosing regimen for pregnant women
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