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/mechanistic 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 Physiologically Based Pharmacokinetic (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 efflux) 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 Exposure to Indinavir, a HIV Drug, in Third Trimester (T3) Pregnant Women

- Indinavir AUC_{0-8h} is \approx 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

Unadkat et al., Antimicrob Agents Chemother 2006
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

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

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

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

<table>
<thead>
<tr>
<th>CYP3A</th>
<th>CYP1A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Caffeine</td>
</tr>
<tr>
<td>(Dextromethorphan)</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Nifedipine, Indinavir</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Multiple CYPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>Methadone, Glyburide</td>
</tr>
<tr>
<td>Dextromethorphan/Dextrorphan</td>
<td></td>
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<tr>
<td>Paroxetine, Clonidine</td>
<td></td>
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</tbody>
</table>

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

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

Contains fetal organs that are important for fetal drug disposition

Ke et al 2012

Zhang et al. DMD 2017

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

**Theophylline Maternal**
- Maternal plasma conc (μg/mL)
- Time (h)
- Ron et al., 1994

**Fetal**
- Umbilical venous plasma conc (μg/mL)
- Time (h)

**Zidovudine Maternal**
- Maternal plasma conc (ng/mL)
- Time (h)
- D’Sullivan et al., 1993

**Fetal**
- Fetal plasma conc (ng/mL)
- Time (h)

- 200mg theophylline dosed orally prior to C-section
  - 1A2 substrate

- Zidovudine was dosed to term women 5 times a day followed by a 1-h IV infusion
  - UGT2B7 substrate

Ron et al., 1994
O’Sullivan et al., 1993
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Zhang et al., DMD 2017
Tissue/Membrane Localization of Drug Transporters

Unadkat JD, *Enzyme-and Transporter-Based Drug-Drug Interactions: 2010.* ASCPT 2019
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

Zhang et al. DMD 2017

Ke et al 2012
The Abundance of Placental Transporters (pmole/g placenta) Changes with Gestational Age

- BCRP
  - T1: p < 0.001
  - T2: p = 0.005

- P-gp
  - T1: p < 0.001
  - T2: p = 0.005

- OCT3
  - Term: p = 0.002

- SERT
  - ns, p = 0.056

- NET

- OAT4
  - Term: p = 0.023

- OATP2B1
  - Term: p = 0.044

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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
Acknowledgement

Unadkat lab contributors

- Faye Zhang
- Marjorie Imperial
- Alice (Ban) Ke
- Gabriela Patilea-Vrana
- Olena Anoshchenko

Collaborators

- UWPKDAP faculty
- PACTG team
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- Srikanth Nallani (FDA)
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- Masoud Jamei, Gaohua Lu and
  Janak Wedagedera
  (SimCYP® Ltd, UK)

- Bhagwat Prasad, Qingcheng Mao, Joanne Wang

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- Timothy Tracy, University of Kentucky
- Uwe Fuhr, University of Cologne, Cologne, Germany
- Mia Wadelius, Uppsala University, Uppsala, Sweden

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Populating m-f-PBPK model with Physiological Parameters

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

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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

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 construct.

Challenges

• Phenotyping extent of changes in metabolic enzymes and transporter activity earlier in pregnancy (1\textsuperscript{st} and 2\textsuperscript{nd} 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, preeclampsia 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


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