Selecting the Right Dose for Pregnant Women Using PBPK

Ping Zhao, PhD, Integrated Development - Quantitative Sciences

FDA CERSI Fetal Pharmacology and Therapeutics Workshop, Oct, 2021
Physiologically-based Pharmacokinetic (PBPK) Modeling

A. Intrinsic/extrinsic Factors

Extrinsic
- Drug–drug interactions

Intrinsic
- Age
- Race
- Organ dysfunction
- Disease
- Pregnancy/lactation
- Gender
- Genetics
- Others

Environmental
- Medical practice
- Regulatory
- Others

Huang and Temple, 2008

B. PBPK Model components

System component
- Drug-independent

Drug-dependent component
- ADME, PK, PD and MOA
  - Metabolism
  - Active transport
  - Passive diffusion
  - Protein binding
  - Drug–drug interactions
  - Receptor binding

Blood
- Lung
- Rapidly perfused organs
- Slowly perfused organs
- Kidney
- Liver
- Intestines

PBPK Model

Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review


Clin Pharmacol Ther, 2011

Predict, Learn, Confirm

Individual or combined effects on human physiology

Dosing

Elimination

Degree of complexity of the PBPK model can vary according to the need.
Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?
Causes of Maternal Mortality Worldwide

- Other indirect causes: 7.2%
- Pre-existing disorder: 14.8%
- HIV: 5.5%
- Other direct causes: 9.6%
- Sepsis: 10.7%
- Hypertension: 14%
- Hemorrhage: 27.1%
- Embolism: 3.2%
- Abortion: 7.9%

% Total (60799 Deaths, 115 Countries, 2003-2009)

- **Indirect Causes**
  - Other indirect causes
  - Pre-existing disorder
  - HIV

- **Direct Causes**
  - Other direct causes
  - Sepsis
  - Hypertension
  - Hemorrhage
  - Embolism
  - Abortion

> Medicine intervention targeting some of these causes may reduce maternal mortality globally

Say et al, Lancet, 2014
The Problem

- in 2011 >80% of women in Europe, the Americas, and Australia “used at least one medicinal product during pregnancy”
- UK: Only five prescription medicines specifically licensed “for non-obstetric use in pregnancy”
- USA: Only 22% labels include “human data about pregnancy”

- Wide use of medicines during pregnancy yet clear dosing instructions are lacking

The Problem

• Exclusion of pregnant women from trials
• Difficulty of studying pharmacology in pregnant women
• Limited ability to generalize clinical data in pregnant women

➢ Off-label drug use during pregnancy is common
Dose Selection: An Exposure-based Exercise

Characterizing PK is critical for dose selection
Dose Selection: An Exposure-based Exercise

Amoxicillin in pregnant women

• ↓ Drug concentration

Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulations of Dosage Strategies

MA Andrew¹, TR Easterling², DB Carr², D Shen³,⁴, ML Buchanan³, T Rutherford³, R Bennett³, P Vicini¹ and MF Hebert²,³
Dose Selection in Pregnant Women

- Not suitable to address every question through the conduct of clinical PK studies

1st trimester?
Co-medication?
Infection?
Malnourishment?
Fetus exposure?

...
Physiologically-based Pharmacokinetic (PBPK) Modeling

A. Intrinsic/extrinsic Factors

Extrinsic
- Drug–drug interactions
Intrinsic
- Age
- Race
- Organ dysfunction
- Disease
- Pregnancy/lactation
- Gender
- Genetics
- Others

Medical practice
- Regulatory
- Others

Environment
- Smoking/diet
- Alcohol use

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)
- Lung
- Spontaneously perfused organs
- Kidney
- Liver
- Intestines

Drug-dependent component
- ADME, PK, PD and MOA
- Metabolism
- Active transport
- Passive diffusion
- Protein binding
- Drug–drug interactions
- Receptor binding

PBPK Model

Predict, Learn, Confirm

Individual or combined effects on human physiology

Dosing
Elimination

Degree of complexity of the PBPK model can vary according to the need

Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

P Zhao1, L Zhang1, J A Grillo1, Q Lin2, JM Bedlock1, YI Moore1, P Song3, SS Bres1, B Madabushi1, TC Wu1, BP Booth1, NA Rahman1, KS Reynolds1, E GI Berglund2, LJ Esho1 and S-M Huang1
Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?
Virtual Studies in Virtual Pregnant Women

A. Intrinsic/extrinsic Factors

B. PBPK Model components

- System component (drug-independent)
- Drug-dependent component

- Lung
- Rapidly perfused organs
- Slowly perfused organs
- Kidney
- Liver
- Intestines

Predict, Learn, Confirm

Individual or combined effects on human physiology

Degree of complexity of the PBPK model can vary according to the need

© Bill & Melinda Gates Foundation | 13

Virtual pregnant women/fetuses enable customized drug dosing in pregnant women
## Known Changes during Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T_1^a$</th>
<th>$T_2^a$</th>
<th>$T_3^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body weight (kg)</td>
<td>↑ 6%</td>
<td>↑ 16%</td>
<td>↑ 23%</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>↑ 11%</td>
<td>↑ 16%</td>
<td>↑ 32%</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>↑ 11%</td>
<td>↑ 27%</td>
<td>↑ 41%</td>
</tr>
<tr>
<td>Cardiac output (L)</td>
<td>↑ 18%</td>
<td>↑ 28%</td>
<td>↑ 33%</td>
</tr>
<tr>
<td>Plasma volume (L)</td>
<td>↑ 7%</td>
<td>↑ 42%</td>
<td>↑ 50%</td>
</tr>
<tr>
<td>Red blood cell volume (L)</td>
<td>↑ 4%</td>
<td>↑ 20%</td>
<td>↑ 28%</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>↓ 3%</td>
<td>↓ 8%</td>
<td>↓ 14%</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>↓ 5%</td>
<td>↓ 16%</td>
<td>↓ 31%</td>
</tr>
<tr>
<td>$\alpha_1$-AGP (g/L)</td>
<td>↓ 1%</td>
<td>↓ 22%</td>
<td>↓ 19%</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min)$^b$</td>
<td>↑ 19%</td>
<td>↑ 37%</td>
<td>↑ 40%</td>
</tr>
<tr>
<td>Effective renal plasma flow (L/h)</td>
<td>↑ 38%</td>
<td>↑ 48%</td>
<td>↑ 31%</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>↑ 28%</td>
<td>↑ 58%</td>
<td>↑ 26%</td>
</tr>
<tr>
<td>Uterine blood flow (L/h)</td>
<td>↑ 923%</td>
<td>↑ 1,567%</td>
<td>↑ 2,71%</td>
</tr>
<tr>
<td>Hepatic blood flow (L/h)$^c$</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

*T1, T2, T3: first, second and third trimesters*
**Known Changes during Pregnancy**

<table>
<thead>
<tr>
<th>Drug/probe</th>
<th>Indication</th>
<th>Effect on CL/F (%)</th>
<th>Metabolizing-enzyme activity changes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine*</td>
<td>CNS stimulant</td>
<td>↓ 33</td>
<td>↓ CYP1A2</td>
<td>48</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Asthma</td>
<td>↔</td>
<td>↔ CYP2A6</td>
<td>49</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>NA</td>
<td>↑ CYP2C9</td>
<td>50</td>
</tr>
<tr>
<td>Phenytoin*</td>
<td>Epilepsy</td>
<td>↑ 43</td>
<td>↑ CYP2C19</td>
<td>51</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Malaria</td>
<td>NA</td>
<td>↓ CYP2D6</td>
<td>52</td>
</tr>
<tr>
<td>Menprolol*</td>
<td>Hypertension</td>
<td>NA</td>
<td>↑ 459</td>
<td>53</td>
</tr>
<tr>
<td>Dextromethorphan*</td>
<td>Cough</td>
<td>↑ 26</td>
<td>↑ 48</td>
<td>48</td>
</tr>
<tr>
<td>Midazolam*</td>
<td>Sedation</td>
<td>NA</td>
<td>↑ 99</td>
<td>14</td>
</tr>
<tr>
<td>Indinavir</td>
<td>HIV infection</td>
<td>NA</td>
<td>↑ 277</td>
<td>8</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabetes</td>
<td>NA</td>
<td>↑ 106</td>
<td>9</td>
</tr>
<tr>
<td>Methadone</td>
<td>Addiction</td>
<td>NA</td>
<td>↑ 101</td>
<td>54</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Hypertension</td>
<td>NA</td>
<td>↑ 30</td>
<td>55</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Epilepsy</td>
<td>↑ 200</td>
<td>↑ 300</td>
<td>19</td>
</tr>
<tr>
<td>Zidovudine*</td>
<td>HIV infection</td>
<td>NA</td>
<td>↔</td>
<td>56</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Bacterial infection</td>
<td>NA</td>
<td>↔</td>
<td>22</td>
</tr>
<tr>
<td>Metformin*</td>
<td>Diabetes</td>
<td>↑ 22</td>
<td>↑ 28</td>
<td>20</td>
</tr>
<tr>
<td>Digoxin*</td>
<td>Cardiac diseases</td>
<td>NA</td>
<td>↑ 19</td>
<td>14</td>
</tr>
</tbody>
</table>

*T1, T2, T3: first, second and third trimesters*
Predict-Learn-Confirm: Enzymes

Liver CYP3A: 99% ↑ in T3
Learn: midazolam
Confirm: nifedipine and indinavir
Learn/confirm: induction only in liver, not gut

Model describing data in non-pregnant subjects

Model describing data in pregnant women

*PP: postpartum; T3: third trimesters
Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?
Value Proposition of PBPK Predictions

- Design of pregnancy studies (e.g., PK)?
- Off label use in pregnant women?
- Dose recommendation in the labels or description of untested PK scenarios in the label?

- Intended uses are dependent on level of confidence of the model
Verifying Enzyme Changes during Pregnancy

**CYP3A**: 99% ↑ in T3
- **Learn**: midazolam
- **Confirm**: nifedipine and indinavir
- **Learn/confirm**: induction only in liver, not gut

**CYP1A2**: 65% ↓ in T3; **CYP2D6**: 100-200% ↑ in T3
- **Learn**: caffeine, metoprolol
- **Confirm**: theophylline, paroxetine, dextromethorphan, clonidine

**CYP2C19, 62-68% ↓ in T2-T3; CYP2C9**: 50-60% ↑ in T2-T3
- **Learn**: in vitro by estradiol, proguanil, phenytoin
- **Predict**: Glyburide (CYP3A, 2C9, 2C19) and methadone (CYP3A, 2B6, 2C19) in T2 and T3

- **Fourteen (14) CYP substrates in virtual pregnant population**

*T2, T3: first, second and third trimesters*
Verifying Transporter Changes during Pregnancy

Oseltamivir carboxylate drug model
Hsu et al, Clin Pharmacokinet, 2014

Pregnancy model

OAT 1/3: 100%↑ in T3
Learn: oseltamivir carboxylate
Confirm: ciprofloxacin
Hsu et al, 2016
Grimstein et al, 2016

➢ Three (3) renally cleared, transporter substrates in virtual pregnant population

GFR: Glomerular filtration rate; OAT3: organic anion transporter 3.
Amoxicillin model: Acknowledging X Xiang (Fudan Univ) and K Abduljalil (Certara)
→ All independent predictions in pregnant and non-pregnant subjects

→ Future direction: renal transporter changes

➢ Six (6) renally cleared drugs in virtual Caucasians and Chinese Pregnant Populations
Verifying Fetal Model

Three (3) passive diffusion drugs in virtual Maternal-fetal (m-f) PBPK models
Expanding Maternal-Fetal Model (Univ Wash)

- Determine placenta transporter abundance
- Update m-f model
- Verify and apply m-f model

➢ Four (4) P-gp substrates in virtual m-f PBPK models
<table>
<thead>
<tr>
<th>Projects</th>
<th>Collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-f PBPK</td>
<td>University of Washington</td>
</tr>
<tr>
<td>Chinese Pregnancy Population</td>
<td>Peking University 3rd Hospital</td>
</tr>
<tr>
<td>Model Informed Drug Use during Pregnancy</td>
<td>Radboud University</td>
</tr>
<tr>
<td>Repository and Training</td>
<td>UK Medical and Health products Regulatory Agency (MHRA)</td>
</tr>
</tbody>
</table>
The vision

- Optimized clinical study design
- Informed off label use
- Quality digital evidence

Pre-clinical dev → Ph. I → Ph. II → Ph. III → Post-marketing

Conventional pregnancy assessment

Embryo-fetal development toxicity study

Clinical safety

Approval

In silico dose predictions
Thank you
Workshop objectives

1. Review general regulatory and ethical considerations for fetal pharmacology and therapeutics
2. Describe methods to assess clinical and nonclinical safety and efficacy assessments to support clinical trials of drugs in pregnancy and the fetus
3. Highlight advances and existing knowledge in fetal therapeutics
4. Discuss key aspects of maternal-fetal modeling and simulation