Innovative Data Analytics To Inform Pharmacokinetics and Dosing in Pregnancy

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Medication use in Pregnancy – Current Status

Increasing medication use

- In the US, 9 out of 10 women take medication during pregnancy
- 80% of pregnant women take \( \geq 1 \) medication during first trimester

Off-label use

- 90% of medications approved do not have labeling for pregnant women
- After PLLR implementation in 2015, only 10% have data for pregnancy from human studies

Lack of pregnancy drug trials (PDT)

- Only 0.32% of the active registered trials are PDT, in a 2014 global survey
- Among active PDTs, only 4.4% had pharmacokinetic evaluations
- Only 7% of the active PDTs were funded by pharmaceutical industry

PLL: Pregnancy & Lactation Labeling Rule

https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html
Dedicated PK trials in pregnant women by NICHD – OPRCs and academic researchers has informed clinical practice

- 01 - Glyburide 3rd trimester
  - Higher dose may be needed in pregnant women
  - Umbilical cord levels ~ 70% of maternal plasma
  - 53% lower AUC in pregnant (N= 40) vs non-pregnant women (N = 40)

- 02 - Oseltamivir 1st, 2nd & 3rd trimester
  - No dosing adjustment needed in pregnant women
  - 30% lower AUC in pregnant (N= 40) vs non-pregnant women (N = 40)

- 03 - Labetalol 2nd, 3rd trimester & post-partum
  - No dose adjustments needed during pregnancy
  - 1.4 – 1.6-fold higher apparent clearance in pregnant (N= 57) vs post-partum women

- 04 - Isoniazid, Pyrazinamide & Ethambutol 3rd trimester & post-partum
  - No clinically meaningful change in AUC in pregnant vs post-partum (N = 29)
  - Higher dose may be needed during pregnancy
  - Umbilical cord levels ~ 70% of maternal plasma

Typical study duration: 2 to 5 years

OPRC – Obstetric-Fetal Pharmacology Research Center


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Type of study design dictates the type of pharmacokinetic analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Pharmacokinetic Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Glyburide</td>
<td>Non-compartmental analysis (NCA) &amp; Compartmental PK modeling</td>
</tr>
<tr>
<td>02</td>
<td>Oseltamivir</td>
<td>Non-compartmental analysis (NCA) + Population PK modeling</td>
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**Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling. U.S. Food and Drug Administration. Published April 27, 2020.**


Recommendations on dosing adjustments may be needed

<table>
<thead>
<tr>
<th>Fold change:</th>
<th>Recommendations on no dosing adjustments needed</th>
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<tbody>
<tr>
<td>( \frac{AUC_{\text{pregnant}}}{AUC_{\text{nonpregnant}}} \geq 2 \text{ times lower} )</td>
<td>( \frac{AUC_{\text{pregnant}}}{AUC_{\text{nonpregnant}}} &lt; 2 \text{ times lower} )</td>
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</table>
Alternate strategies to inform PK & dosing in pregnancy with potential to move from “Off-patent to Approval”

**Use of RWD + Bayesian methods**

**RWD**

- Use of electronic health records (EHR) for drugs undergoing TDM
  - Create matched datasets (pregnant/non-pregnant)
  - Empirical Bayesian/Population PK modeling
  - Case study: Vancomycin in pregnant women

**PBPK + Bayesian**

- Pregnancy PBPK model informed prior for Bayesian PK modeling & design of pragmatic PK trials
  - PBPK model to inform drugs to be studied using pragmatic PK trials using EHR
  - PBPK model informed prior for Bayesian PK modeling of drugs with sparse data from RWD

RWD: Real World Data
TDM: Therapeutic Drug Monitoring

PBPK: Physiologically Based Pharmacokinetics
Use of electronic medical records for drugs undergoing TDM – Vancomycin case study

**Decision**
- Is there a need to adjust vancomycin dosing in pregnant women?

**Information**
- Retrospective electronic medical records of pregnant women
- At least 2 concentrations, dose, gestational age, bodyweight, CrCl, fat free mass

**Analysis**
- Population PK model modeling – prior vancomycin models used as a starting point

Vancomycin case study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>34</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28 (17-38)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (147-173)</td>
</tr>
<tr>
<td>Total body weight (kg)</td>
<td>74 (43-157)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>27 (7-40)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.56 (0.27-1.97)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>176 (43-389)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>45 (30-60)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 (19-70)</td>
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</tbody>
</table>

Population PK model
- Two Compartmental PK model
- Peripheral volume and inter-compartmental clearance fixed based on prior literature

Covariate model
- Creatinine clearance and fat-free mass on clearance
- Fat-free mass on volume

Decision
- Is there a need to adjust vancomycin dosing in pregnant women?
  - No dosing adjustments needed. AUC was similar between pregnant and non-pregnant subjects
Pregnancy PBPK model informed Bayesian framework to prioritize study of drugs, design and analysis

List of drugs

Clinically meaningful lower exposure in pregnant subjects

High priority for drugs to be studied

Prioritize drugs based on evidence of need

Pragmatic PK/PD trial – informative sampling with Bayesian features to update as data is accrued

Bayesian PK/PD modeling using pregnancy PBPK model informed prior/literature
- Sparsely collected data from real-world studies
- Dose individualization

Apply Pregnancy PBPK model

No clinically meaningful change in exposure in pregnant subjects

Low priority for drugs to be studied
Bayesian PK/PD modeling framework

1. PRIOR
   Prior PK model parameters in non-pregnant subjects/
   Pregnancy PBPK model parameters

2. POSTERIOR
   Posterior PK model parameters in pregnant women (uncertainty)

Updated prior
Opportunities & Challenges

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<th>Use of RWD + Bayesian methods</th>
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### Opportunities

- Reflects real world clinical practice
- Heterogeneous, generalizable
- Incorporation of prior knowledge for design/analysis
- PBPK model informed prior or prior from drug literature for sparse data

### Challenges

- Lack of information on relevant variable, not part of routine care
- Data quality – careful curation needed
- Ensure validity of the pregnancy PBPK model
- Availability of trained personnel to implement Bayesian methods & PBPK models
Consortium of multiple stakeholders (academia, OPRCs, FDA, pregnancy community) needed to promote “Off-label to approval” pipeline

**Goal**

By 2030, aspire to renew labeling information of 10 priority off-patent medications used in pregnancy

1. **CALL TO ACTION**
   - Establish the collaboration between stakeholders & pregnancy community

2. **PILOT PROJECT**
   - Demonstrate the process from inception to approval for 2 drug products

3. **REVIEW**
   - Evaluate results of pilot product to ensure that a repeatable process is feasible

4. **FACILITATE SCALE UP**
   - Finalize the systematic, reproducible process to achieve pregnancy labeling

5. **PROMOTE**
   - Offer training to encourage other clinical pharmacology fellows to undertake such projects