Historical Efforts

What work best and not so much

Tools and approaches for now and the future
HISTORICAL EFFORTS TO SUPPORT PREGNANCY TRIALS

- Design
- Sampling
- Interpretation

• Pregnant women are often excluded from routine clinical trials.

• Consequently, appropriate dosing regimens for majority of drugs are unknown in this population, which may lead to unexpected safety issues or insufficient efficacy in this unstudied population.

• Establishing evidence through the conduct of clinical studies in pregnancy is still a challenge.
### THE PROBLEM LANDSCAPE

<table>
<thead>
<tr>
<th>Scope of the problem</th>
<th>Contributors to the problem</th>
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<tbody>
<tr>
<td>Inadequate pharmacological studies performed during pregnancy, lactation and postpartum</td>
<td>Pregnancy is an exclusion in most clinical trials</td>
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<tr>
<td>Limited data on pregnancy mediated changes in drug exposure and response</td>
<td>Inadequate funding for clinical pharmacology research in pregnant, lactating and postpartum women</td>
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<tr>
<td>Optimal dosing for pregnant, lactating, postpartum women unclear for most medications</td>
<td>Inadequate number of investigators qualified to perform or engaged in such studies</td>
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<tr>
<td>Impact of drug exposure on fetal growth and development is unclear for almost all medications used during pregnancy</td>
<td>Inconvenient study designs for participants</td>
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<tr>
<td>Limited data on drug transfer through breast feeding</td>
<td>Need for innovative sampling techniques and modeling approaches</td>
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<td>Limited incentive for industries (safety—liability issues)</td>
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# The “Proposed Solution” Landscape

<table>
<thead>
<tr>
<th>Ideal studies</th>
<th>Next best alternatives</th>
<th>Alternate approaches</th>
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<tbody>
<tr>
<td>• Drug exposure studies (Pharmacokinetics over a dosing interval) in first,</td>
<td>• Surrogate drug exposure studies (limited sampling strategy or trough level) in first,</td>
<td>• Predictions based on probe drug studies for DME and</td>
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<tr>
<td>second, third trimester and post-partum</td>
<td>second, third trimesters and post-partum</td>
<td>transporters</td>
</tr>
<tr>
<td>• Drug response studies over a dosing interval (first, second, third trimester</td>
<td>• Limited drug response studies (first, second, third trimester and post-partum)</td>
<td>• Population PK modeling</td>
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<td>and post-partum)</td>
<td>• Placental (in vitro) perfusion studies</td>
<td>• PBPK modeling and simulations</td>
</tr>
<tr>
<td>• Maternal drug safety assessments (first, second, third trimester and post-</td>
<td>• Cord blood sampling for fetal exposure assessments</td>
<td></td>
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<tr>
<td>partum)</td>
<td>• Milk to plasma ratio for drugs in lactating women</td>
<td></td>
</tr>
<tr>
<td>• Fetal / Neonatal drug safety assessments (monitoring of neonates and newborn)</td>
<td>• Placental perfusion studies</td>
<td></td>
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<tr>
<td>• Drug excretion in breast milk (total amount excreted in breast milk over a</td>
<td>• Placenta on a chip study</td>
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<tr>
<td>dosing interval)</td>
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DESIGN CONSIDERATIONS

- Who to study?
- When to study?
- How to study?
DESIGN CONSIDERATIONS

- Design Flexibility
- Focus on information gaps

Abbreviations: V = Visit, Wk gest = Weeks of gestation, OGTT = Oral glucose tolerance test, TEL = Telephone call, WBCB = Well baby check-up booklet, Q = Questionnaire
**General Considerations:**

- Samples should include plasma or whole blood and urine for assessing the concentration of the parent drug and active metabolites.

- Since plasma protein binding is often reduced during pregnancy, consider calculating unbound drug and metabolites, especially if the extent of plasma protein binding of the drug is high (>80%).

- PD endpoints, including relevant biomarkers and potentially even fetal PD endpoints, can be important.

- Informative study design considerations should be discussed with the FDA prior to study initiation.

- Simulations, regardless of model-type, can help.
## General Considerations:

**Table 2. Summary of recommendations on sampling strategies for pregnancy PK studies**

<table>
<thead>
<tr>
<th>Type of sampling</th>
<th>Method of analysis</th>
<th>Number of sampling points and participants</th>
<th>Trimester to sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive PK samples</td>
<td>Noncompartmental analysis (NCA)</td>
<td>Usually 7–12 samples over one dosing interval at steady state from 12–24 participants</td>
<td>Preferably first, second, and third; or second and third; or early third (28–32 weeks of gestation) plus sparse sampling at early visits.</td>
</tr>
<tr>
<td>Sparse samples</td>
<td>Nonlinear mixed effects (NLME) modeling</td>
<td>Randomly assign participants to sampling windows; or Patients randomly contribute two or more samples to cover dosing interval; or Most patients contribute one sample at a specified timepoint.</td>
<td></td>
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We can do better than this!
**INTERPRETATION**

- **Dose selection and optimization**: Leverage available PK data in nonpregnant patients/animal studies to optimize dosing in pregnancy using exposure matching.

- **Supportive evidence for efficacy**: Leverage prior knowledge of exposure-response in neonates for in-utero efficacy.

- **Clinical trial design**: Inform pregnancy clinical trial design using prior knowledge (PBPK, PK, disease modeling) and clinical trial simulation.

- **Safety**: Leverage prior knowledge of exposure-response in neonatal exposure for fetal safety.
Physiological changes and potential impact on PK of drugs.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Effect of pregnancy</th>
<th>Potential impact on pharmacokinetics</th>
<th>Clinical example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Decrease in gastrointestinal motility and gastric emptying time Increase in gastric pH Increase in gastrointestinal blood flow Alterations in enzymes and transporters involved in absorption of drugs</td>
<td>Increase or decrease in the rate of absorption Increase or decrease in bioavailability</td>
<td>Aspirin $C_{\text{max}}$ decreased by 29% during pregnancy (4) Lower $C_{\text{max}}$ of metoprolol during pregnancy (5)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increase in cardiac output Increase in total body water and fat Decrease in plasma protein binding</td>
<td>Increase in volume of distribution</td>
<td>Increase in volume of distribution of metoprolol during pregnancy (5)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Alterations of CYP and UGT enzyme activity Increase in hepatic blood flow</td>
<td>Increase or decrease in metabolism of substrates</td>
<td>Decrease in clearance of caffeine (CYP1A2 substrate) during pregnancy (6) Increase in Clearance of lamotrigine (UGT1A4 substrate) during pregnancy as compared to postpartum (7)</td>
</tr>
<tr>
<td>Excretion</td>
<td>Increase in renal blood flow Increase in glomerular filtration rate Alterations of enzymes and transporters involved in tubular reabsorption and secretion</td>
<td>Increase in renal excretion Increase or decrease in tubular reabsorption and secretion</td>
<td>Unbound renal secretion of digoxin increased during pregnancy due to increased P-gP activity (8) Increased renal secretion and renal clearance of amoxicillin during pregnancy as compared to postpartum (9)</td>
</tr>
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Over the past several years, there has been an increase in the application of modeling and simulation approaches such as population PK (PopPK) and physiologically based PK (PBPK) modeling to provide guidance on drug dosing in those special patient populations.

Population PK models rely on measured PK data, whereas physiologically based PK models incorporate physiological, preclinical, and clinical data into the model to predict drug exposure during pregnancy.

These modeling strategies offer a promising approach to identify the drugs with PK changes during pregnancy to guide dose optimization in pregnancy, when there is lack of clinical data.
“There are several available approaches to studying pharmacokinetic changes in pregnancy."

“Single trough screening studies can provide qualitative estimates of elimination clearance, which with the dosing rate determines the steady-state drug concentration, throughout pregnancy and into the postpartum period.”

“Population pharmacokinetic studies such as two stage pharmacokinetic studies and studies using a nonlinear mixed effects pharmacokinetic modeling approach can characterize pharmacokinetic changes more rigorously.”
TOOLS AND APPROACHES: POP-PK APPROACH

- Requires a simplified model structure of non-physiologic parameters which approximate the “pregnant state”
- Still often referred to as a minimal PBPK model
  - Fewer parameters
  - Difficult to capture time-based changes in underlying physiology
  - Fetus as a compartment?

TOOLS AND APPROACHES: PBPK APPROACH

- Physiologic representation of relevant actual parameters which can be verified against actual physiologic data
- Model reduction possible as appropriate / required
  - Physiologic parameters
  - Time-based changes in underlying physiology captured
  - Fetus as its own model structure

TOOLS AND APPROACHES: PBPK APPROACH

Physiological parameters that are modified for pregnancy prediction in Simcyp p-PBPK model.

List of parameters

- Cardiac output
- Total body weight
- Total fat
- Plasma volume
- Red blood cell volume
- Hematocrit
- Serum albumin
- Skin blood flow rate
- Adipose blood flow rate
- Renal blood flow rate
- Fetoplacental unit blood flow rate
- Enzyme and transporter activity

Basic structure of p-PBPK model in (A) Gatsroplus (B) SimCyp and (C) Open Systems Pharmacology
Recent PBPK examples demonstrate excellent performance with respect to historical PK trials.

Simulations across trimesters are compelling and consistent with expectations but need to be challenged with data in the future.
## TOOLS AND APPROACHES: FUTURE CONSIDERATIONS

<table>
<thead>
<tr>
<th>Maternal pharmacology</th>
<th>Fetal pharmacology</th>
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<tbody>
<tr>
<td>1. Lack of data on time course of changes in expression and activities of various</td>
<td>1. Actual fetal exposure / blood and tissue concentration prediction not available—</td>
</tr>
<tr>
<td>phase 1 and 2 enzymes during pregnancy and postpartum</td>
<td>need for validation with meaningful clinical data</td>
</tr>
<tr>
<td>2. Lack of data on Time course of changes in various transporters during pregnancy</td>
<td>2. Lack of data on exposure response relationship in fetus</td>
</tr>
<tr>
<td>and postpartum</td>
<td>3. Placental enzymes and transporter expression data to incorporate transplacental</td>
</tr>
<tr>
<td>3. Lack of data from same person during and post-delivery</td>
<td>transfer in PBPK model</td>
</tr>
<tr>
<td>4. Lack of PD measures—Relationship between exposure and response</td>
<td>4. Maternal-placental-fetal drug partitioning—factors impacting this such as plasma</td>
</tr>
<tr>
<td>5. Lack of information on potential impact of other comorbid conditions on PK/PD</td>
<td>protein binding in mother, fetus, and role of placental transporters</td>
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<tr>
<td>6. Lack of PBPK models of biologics</td>
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REPORT CARD:
HOW HAS THE MODELING PERFORMED THUS FAR?

- > 40 drugs analyzed via PBPK M&S to aid the design, analysis and dosing recommendations for pregnant women
- PK, PGx and some biomarker data available for analysis
- Various routes of administration accommodated
- Various model constructs and software solutions utilized
  - Various dosing scenarios across gestational age often evaluated
  - Comparison to non-pregnant state a common comparator
  - Strong emphasis on providing dosing guidance and recommendations
  - Some focus on study designs and sampling considerations.
- Performance against measure observations (when available) was excellent

REPORT CARD:

HOW HAS THE MODELING PERFORMED THUS FAR?


