Pharmacokinetics of Drugs, Dose Optimization, & Fetal Exposure During Pregnancy: Still Learning

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What the Mother is Exposed to Effects the Unborn

- Cohort of 187 women pregnant within 5 zones of distance from WTC on 9/11/01 and 3 weeks after
- 39.6% S. of Murray St., 32.4% N. Murray – S. Chambers, 16.5% N. Chambers – S. Canal, 1.7% Brooklyn Heights, 0.6% NJ-Hudson
- Control: Pregnant pts delivering at Mt Sinai Med Center (n = 2367)
- No differences in mean gestational age, birthweight, preterm births
- Intrauterine growth restriction (IUGR; BW <10% for GA):
  - WTC = 15 (8.2%); Controls = 89 (3.8%); RR = 1.9 after adjustment for marital status, education, pre-preg wt, preg-induced HTN
- Speculate as due to polycyclic aromatic hydrocarbons, particulates

*Berkowitz GS, et al. JAMA 290(5):595; August 6, 2003*
PK & PD in Pregnancy: Principles

- Time-progressive physiological and body compositional changes, and augmentation or reduction of PK processes and rates, impose varying relationships of drug dosage to resultant concentrations.
- Potentiation or reduction in pharmacodynamic response.
- Drug monographs rarely contain pregnancy-specific dosage recommendations. FDA’s PLLR more defining & useful drug info.
- Differences in transplacental exposure → risk profile from teratogenicity to intrauterine physiological compromise to postnatal maladaptive conditions and drug withdrawal.
- Pharmacogenetic expression: organs of elimination & transporters, in mother, placenta, fetus produces more variability of dose-response.

Steinberg I. In: Cardiac Problems in Pregnancy (in press), 2018
Number of articles involving pharmacokinetics in pregnant patients

McCormack SA, Best B. Front Pediatr 2:9, 2014
2018: 160 PK studies involve pregnant patients (0.85% of all PK studies)
Physiologic & Pharmacokinetic Changes During Pregnancy

**Absorption:**
- Gastric Emptying Time $\uparrow$
- Intestinal Motility, Acid secr. $\downarrow$
- Pulmonary Function $\uparrow$ (TV, MV $\approx$ 40%)
- Cardiac Output $\uparrow$ (40-50%)
- Skin Blood Flow $\uparrow$

**Distribution:**
- Plasma Volume $\uparrow$ ($\approx$ 50%)
- ECF & Total Body Water $\uparrow$ (33-40%; TBW by 8 liters)
- Body Fat $\uparrow$
- Plasma Proteins $\downarrow$ (dilution; yielding further $\uparrow$ Vd)
Physiologic & Pharmacokinetic Changes During Pregnancy

**Metabolism:**
- Hepatic blood flow $\leftrightarrow, \uparrow$
- Hepatic enzyme efficiency $\uparrow$ (CYP2D6, 3A4, 2B6, 2A6) $\downarrow$ (2C19, 1A2)
- Hepatic conjugation $\uparrow$ (UGT1A4, 2B7, 2B6, 2A6) $\downarrow$ (NAT2)
- Extrahepatic metabolism $\uparrow$
- Plasma Proteins (Albumin, AAG) $\downarrow$ (dilution)

**Excretion:**
- Renal Plasma Flow $\uparrow$ (20-50% 2nd trim; 75% term)
- Glomerular Filtration $\uparrow$ (30-50%)
- Secretion $\uparrow$ P-gp expression
Physiologic/Pharmacokinetic Changes in Pregnancy

- ECF $\uparrow$
- ALBUMIN, AAG $\downarrow$
- FFA $\uparrow$
- PROTEIN BINDING $\downarrow$
- Fetal-placental Growth
- Vd $\uparrow$
- GFR $\uparrow$
- CYP, UGT

- $\uparrow$ C.O.

$\downarrow$ P.O. absorption

$\uparrow$ DOSE REQUIREMENTS

OR

$\nabla$ Presystemic CL
<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></td>
<td></td>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Caffeine*</td>
<td>CNS stimulant</td>
<td>↓ 33</td>
<td>↓ 48</td>
<td>↓ 65</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Asthma</td>
<td>↔</td>
<td>↔</td>
<td>↓ 34</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>NA</td>
<td>↑ 54</td>
<td>↑ 54</td>
</tr>
<tr>
<td>Phenytin&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Epilepsy</td>
<td>↑ 43</td>
<td>↑ 51</td>
<td>↑ 61</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Malaria</td>
<td>NA</td>
<td>↓ 60</td>
<td>↑ 60</td>
</tr>
<tr>
<td>Metoprolol*</td>
<td>Hypertension</td>
<td>NA</td>
<td>NA</td>
<td>↑ 459</td>
</tr>
<tr>
<td>Dextromethorphan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cough</td>
<td>↑ 26</td>
<td>↑ 35</td>
<td>↑ 48</td>
</tr>
<tr>
<td>Midazolam*</td>
<td>Sedation</td>
<td>NA</td>
<td>NA</td>
<td>↑ 99</td>
</tr>
<tr>
<td>Indinavir*</td>
<td>HIV infection</td>
<td>NA</td>
<td>NA</td>
<td>↑ 277</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabetes</td>
<td>NA</td>
<td>NA</td>
<td>↑ 106</td>
</tr>
<tr>
<td>Methadone</td>
<td>Addiction</td>
<td>NA</td>
<td>↑ 101</td>
<td>↑ 65</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Hypertension</td>
<td>NA</td>
<td>↑ 30</td>
<td>↑ 30</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Epilepsy</td>
<td>↑ 200</td>
<td>↑ 200</td>
<td>↑ 300</td>
</tr>
<tr>
<td>Zidovudine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HIV infection</td>
<td>NA</td>
<td>NA</td>
<td>↔</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Bacterial infection</td>
<td>NA</td>
<td>↑ 23</td>
<td>↑ 20</td>
</tr>
<tr>
<td>Metformin*</td>
<td>Diabetes</td>
<td>↑ 22</td>
<td>↑ 28</td>
<td>↑ 11</td>
</tr>
<tr>
<td>Digoxin*</td>
<td>Cardiac diseases</td>
<td>NA</td>
<td>NA</td>
<td>↑ 19</td>
</tr>
</tbody>
</table>

Levetiracetam Dose:Cp Ratio Through Pregnancy

Enoxaparin: Sub-therapeutic Trough antiXa Levels at a Given Therapeutic Peak

Lowest peak-to-trough fluctuation
Enoxaparin 40 mg daily dose

Enoxaparin 40 mg daily dose

\[ \uparrow t_{1/2} = 0.693 \quad \uparrow \uparrow Vd \]
\[ \uparrow CL \]

## Metoprolol Pharmacokinetics in Pregnancy & Postpartum: Induced CYP2D6 Metabolism


### Table 2. Paired Estimated Metoprolol Pharmacokinetic Parameters in Extensive (EM) and Intermediate Metabolizers (IM) During Mid-Pregnancy (22–26 Weeks) and Late (34–38 weeks) Pregnancy Compared to Postpartum (≥ 3 Months)

<table>
<thead>
<tr>
<th>Parameter EM and IM</th>
<th>Mid-Pregnancy (n = 5)</th>
<th>Postpartum (n = 5)</th>
<th>Late Pregnancy (n = 8)</th>
<th>Postpartum (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F (L/h)</td>
<td>361 ± 223(^a)</td>
<td>200 ± 131</td>
<td>568 ± 273(^a)</td>
<td>192 ± 98</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>4.02 ± 2.62(^a)</td>
<td>2.39 ± 1.68</td>
<td>6.37 ± 3.20(^a)</td>
<td>2.43 ± 1.29</td>
</tr>
<tr>
<td>CL(_{renal}) (ml/min)</td>
<td>112 ± 33</td>
<td>108 ± 25</td>
<td>139 ± 51(^a)</td>
<td>92 ± 31</td>
</tr>
<tr>
<td>MR in plasma</td>
<td>4.28 ± 8.53</td>
<td>2.39 ± 3.79</td>
<td>0.47 ± 0.46(^a)</td>
<td>1.07 ± 0.95</td>
</tr>
<tr>
<td>MR in urine</td>
<td>2.35 ± 4.88</td>
<td>1.31 ± 1.96</td>
<td>0.21 ± 0.17</td>
<td>0.53 ± 0.35</td>
</tr>
<tr>
<td>% dose recovered in urine as metoprolol</td>
<td>2.75 ± 2.38(^a)</td>
<td>4.86 ± 3.27</td>
<td>1.82 ± 1.21</td>
<td>3.45 ± 1.87</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>165 ± 40(^a)</td>
<td>100 ± 12</td>
<td>157 ± 29(^a)</td>
<td>119 ± 33</td>
</tr>
</tbody>
</table>
Metoprolol Pharmacokinetics in Pregnancy & Postpartum: Induced CYP2D6 Metabolism
Oddity of Oral Clonidine PK in Pregnancy:
CYP2D6 Overwhelms Renal Clearance

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Non Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CL (ml/min)</td>
<td>440 ± 168**</td>
<td>245 ± 72</td>
</tr>
<tr>
<td>Renal CL (ml/min)</td>
<td>153 ± 67</td>
<td>183 ± 55</td>
</tr>
<tr>
<td>Excreted Unchanged</td>
<td>36 ± 11%**</td>
<td>59 ± 18%</td>
</tr>
<tr>
<td>Non-Renal CL EM (ml/min) (n = 12)</td>
<td>311 (95% CI: 211 - 411)</td>
<td></td>
</tr>
<tr>
<td>Non-Renal CL PM (ml/min) (n = 2)</td>
<td>138, 182</td>
<td></td>
</tr>
<tr>
<td>Total CL (ml/min/70 kg)</td>
<td>1 y.o. child = 266</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacodynamics of Clonidine Therapy in Pregnancy: A Heterogeneous Maternal Response Impacts Fetal Growth

Sophia Rothberger¹, Darcy Carr¹, Debra Brateng¹, Mary Hebert¹,² and Thomas R. Easterling¹,²

Am J Hypertens 23(11):1234, 2010
IUGR

Warfarin Protein Binding and Clearance: Sequence and Reasoning

- Low extraction ratio drug (little metabolized with each liver pass)
- $\text{CL}_{\text{hepatic}} \approx \text{fraction unbound} \cdot \text{intrinsic CL}$
- Higher fraction unbound $\rightarrow$ higher clearance
- CYP 2C9 induction $\rightarrow$ higher clearance
- $C_{\text{pss}} = \text{fraction unbound} \cdot \text{CL}_{\text{hepatic}}$
- ↓ Albumin and warfarin’s fraction unbound increases; $C_{\text{pss}} \leftrightarrow$
- For any given total concentration of warfarin generated from a fixed dose, there will be a higher free concentration (active drug).
- Could this be why many valve patients may not need an increase in dose later in pregnancy, and why higher doses disproportionately produces fetopathy?
Labetalol hepatically cleared by UGT 1A1
↑ Pregnancy-induced CL 40 to 60%

Unique factor: RR-isomer (β-blocker) is cleared more rapidly in pregnancy when given PO. SR-isomer (alpha-blocker) is cleared less in gestational diabetes than in normal pregnancy ⇒ more exaggerated vasodilator response.

Nifedipine PK influenced by EM CYP3A5 genotype

Precision Dosing in the Pregnant Patient

• **Population Pharmacokinetic Modeling:**
  Structural models and statistical models, a composite of “fixed effects” - best quantitative covariates of the PK parameters (e.g. weight on Vd, CrCL on renal drug CL, genetic polymorphisms on hepatic CL); “random effects”: % CV, assay variability, dose imprecision, etc.
Precision Dosing in the Pregnant Patient

- **Bayesian Forecasting:**
  Iterative approach to predict future plasma levels, pharmacodynamic effect, and revise individual pharmacokinetic parameters using PopPK model-generated dose; predictions can be modified and doses altered by pathophysiological Δ and/or measured levels.
Precision Dosing in the Pregnant Patient

- Physiological-Based Pharmacokinetic Modeling (in-silico):

  Incorporates mathematical description of all anatomic & physiologic spaces (including fetal compartment), flow rates & extraction, drug partitioning, protein binding, transport & clearance to derive pharmacokinetic parameter estimates and more precise empiric dosing.
### TABLE 2
Final parameter estimates for the population PK model $^a$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>%IIV</th>
<th>%RSE</th>
<th>Bootstrap 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL, L/h, without preeclampsia</td>
<td>5.88</td>
<td>3.7</td>
<td>5.1</td>
<td>(5.35—6.55)</td>
</tr>
<tr>
<td>CL, L/h, with preeclampsia</td>
<td>3.98</td>
<td>41</td>
<td>4.5</td>
<td>(3.65—4.36)</td>
</tr>
<tr>
<td>V, L/70 kg</td>
<td>22.5</td>
<td>23.6</td>
<td>4.1</td>
<td>(20.7—24.4)</td>
</tr>
<tr>
<td>Residual error</td>
<td>0.73</td>
<td>18</td>
<td></td>
<td>(0.6—0.86)</td>
</tr>
</tbody>
</table>

CL, confidence interval; CL, clearance; IIV, the interindividual variability; PK, pharmacokinetic; RSE, relative standard error; V, volume of central compartment.

$^a$ Model parameterized by CL(L/hr) and V(L).

FIGURE 3
Simulation of 4-g loading dose of magnesium sulfate, followed by 2 g/h infusion among pregnant women with and without preeclampsia and women of lowest (55 kg), mean (88 kg), and greatest (157 kg) body weights in our study.

Putting a Model to Work: LMWH

• 35 y.o. female, 32 weeks GA, 90 kg with bioprosthetic valve receiving enoxaparin 1 mg/kg/dose q 12 hours. Her serum creatinine has risen elevated to 1.35 mg/dL. What anti-Xa level can be projected for her?

• POP PK Model:
  – \( V_d (L) = V_{d \text{ pop}} (\text{BW}/70) + 1.41 \) (if GA > 31 weeks)
  – \( CL (L/\text{hr}) = CL \text{ pop } [(\text{BW}/\text{Scr})/1.27]^{0.423} \)
  – \( V_d = 7.81 (90/70) + 1.41 = 11.45 \) Liters
  – \( CL = 0.81 [(90/1.35)/1.27]^{0.423} = 4.326 \) Liters/hour
  – \( Cpss = \text{Dose}/CL \times T = 90/(4.326 \times 12) = 1.73 \text{ IU/ml} \)
  – Cutting the dose to 50 q 12 ➞ anti Xa = 0.96 IU/ml
Systems Pharmacology & PBPM to Improve Drug Tx Precision in Pregnancy

**REVIEW**

Drug Dosing in Pregnant Women: Challenges and Opportunities in Using Physiologically Based Pharmacokinetic Modeling and Simulations

Alice Ban Ke¹*, Rick Greupink² and Khaled Abduljalil¹

*CPT Pharmacometrics Syst Pharmacol. 2018 Feb;7(2):103-110*
The degree of complexity of the PBPK model can vary according to the need.
Therapeutic Exposure of the Fetus

- **Fetus as “innocent bystander”** - Treatment of maternal disease with no fetal management intended, and potential risk to the fetus e.g. maternal epilepsy, anticoagulation, ψ
- **Fetus as functional beneficiary** - tocolysis, polyhydramnios
- **Fetus as co-beneficiary** - Treatment of maternal disease state that may also convene similar disease risk to the fetus and neonate e.g. antiretrovirals for HIV
- **Fetus as sole beneficiary** - Drug therapy for fetus; involves mother and placenta as vehicle for treatment or direct fetal administration (cordocentesis) e.g. RDS, IVH prophylaxis, Rx of fetal arrhythmias, hydrops fetalis

*Steinberg I. In: Cardiac Problems in Pregnancy (in press), 2018*
AED Malformations: Dose-Dependency

Valproate (mg/day)
- ≥1500 (n=99)
- 700-1499 (n=480)
- <700 (n=431)

Carbamazepine (mg/day)
- ≥1000 (n=207)
- 400-999 (n=1047)
- <400 (n=148)

Phenobarbital (mg/day)
- ≥150 (n=51)
- <150 (n=166)

Lamotrigine (mg/day)
- ≥300 (n=444)
- <300 (n=836)

Malformation rate (%)
Lithium and Cardiac Malformations

• Cohort study of 1,325,563 pregnancies in Medicaid women who delivered a live-born infant 2000 – 2010
• Infants exposed to lithium during the 1st trimester compared with unexposed infants
• Incidence and adjusted risk ratio for cardiac malformations with lithium exposure = 2.41% vs 1.15%; RR = 1.65 (95% CI: 1.02 - 2.68)
• Daily Dose-dependent risk:
  – ≤ 600 mg: 1.11 (95% CI: 0.46 - 2.64)
  – 601 – 900 mg: 1.60 (95% CI: 0.67 - 3.80)
  – > 900 mg: 3.22 (95% CI: 1.47 - 7.02)
