Pregnancy-induced anatomical and physiological changes relevant to PBPK modeling

Fetal Pharmacology and Therapeutics Workshop
FDA and University of Maryland Center of Excellence in Regulatory Science and Innovation
Oct 21-22, 2021

Anne Zajicek, MD, PharmD
Deputy Associate Director for Clinical Research
Immediate Office of the Director
National Institutes of Health
Disclosure

• I have nothing to disclose.

• My presentation reflects my views only, not those of the NIH or the federal government.
Topics

• Maternal Anatomic and Physiologic Changes
• Placental Functions and Maturation
• Fetal Maturation
Fig. 1. Therapeutic process. Steps in the processing and transport of drugs from the mother to the proposed site of action in the fetus are shown.

Maternal Physiologic Changes in Pregnancy

**GI**
- Gastric emptying time *
- GES tone
- GI motility

**Cardiac**
- Stroke Vol
- HR
- Cardiac Output
- SVR, MAP

**Pulmonary**
- RR
- Tidal Volume
- Minute Vent

**Hepatic**
- Blood Flow
- Protein Binding
- Clearance
- CYPs
- Transporters

**Volume**
- TBW
- Plasma vol
- Fat vol

**Renal**
- Blood Flow
- GFR
- Secretion
- Reabsorption
- Transporters

**Uterus**
- Size
- Blood flow
- Placental cl
- Fetal cl

*Increases
Decreases
May increase or decrease

<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>α1-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>↑ 2,771%</td>
</tr>
<tr>
<td>Hepatic blood flow (L/h)$^c$</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

$^a$Mean percentage change (%) relative to prepregnancy level.

$^b$Glomerular filtration rate measurement is based on insulin clearance.

$^c$Literature data on hepatic blood flow are contradictory; hence, no effect is assumed.
Other Changes during Pregnancy

- Elevated clotting factors and hypercoagulability
- Dilutional anemia
- Slight uncompensated respiratory alkalosis
TABLE 1

Summary of changes in P450 probe and sensitive marker drug disposition and in disposition of UGT markers at different stages of pregnancy

<table>
<thead>
<tr>
<th>Target P450</th>
<th>Marker Drug</th>
<th>Effect on Marker Clearance during Gestation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First Trimester</td>
<td>Second Trimester</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Caffeine, theophylline</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Efavirenz</td>
<td>~↑</td>
<td>~↑</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Metoprolol (dextromethorphan UR)</td>
<td>(↑)</td>
<td>(↑)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Phenytoin</td>
<td>~↓</td>
<td>↑</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Midazolam</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>UGT1A4</td>
<td>Lamotrigine</td>
<td>~↓</td>
<td>↑</td>
</tr>
<tr>
<td>UGT2B7</td>
<td>Zidovudine</td>
<td>~↑</td>
<td></td>
</tr>
</tbody>
</table>

UGT, UDP glucuronosyltransferase; UR, urinary ratio.

*a Efavirenz area under the curve was unaffected, but Cmin was significantly decreased during the third trimester. Efavirenz is an inducer and inactivator of CYP2B6, and this may confound the findings.

Isoherranen, N., & Thummel, K. E. (2013). Drug metabolism and transport during pregnancy: how does drug disposition change during pregnancy and what are the mechanisms that cause such changes?. Drug metabolism and disposition: the biological fate of chemicals, 41(2), 256–262. https://doi.org/10.1124/dmd.112.050245
### TABLE 2
Summary of changes in transporter probe and sensitive marker drug disposition at different stages of pregnancy

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Marker Drug</th>
<th>Effect on Clearance during Gestation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>Digoxin</td>
<td>↑</td>
<td>(Hebert et al., 2008)</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Glyburide</td>
<td>↑</td>
<td>(Hebert et al., 2009)</td>
</tr>
<tr>
<td>OCT2</td>
<td>Metformin</td>
<td>↔</td>
<td>(Hughes et al., 2006; Eval et al., 2010; de Oliveira Baraldi et al., 2011)</td>
</tr>
<tr>
<td>OAT1</td>
<td>Zidovudine, lamivudine</td>
<td>↔</td>
<td>(Moodley et al., 1998)</td>
</tr>
<tr>
<td>OAT3</td>
<td>Acyclovir, zidovudine</td>
<td>↔</td>
<td>(Frenkel et al., 1991; Haddad et al., 1993)</td>
</tr>
</tbody>
</table>

OCT, organic cation transporter; OAT, organic anion transporter; P-gp, P-glycoprotein.

aWhile glyburide is listed as an in vivo substrate of OATP1B1, it is cleared by CYP3A4 and CYP2C9 and is a substrate of BCRP (breast cancer resistance protein). Hence, it is not possible to determine which enzyme is responsible for the increased clearance of glyburide during pregnancy in vivo.

bThe secretion clearance of metformin was significantly increased during the third trimester, although oral clearance was not significantly increased.
FIG. 1. The cellular steps involved in angiogenesis. Hypoxia induces the production of nitric oxide (NO) and the expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 and -2 (Ang 1 and Ang 2), which interact with extracellular matrix (ECM) proteases to increase permeability of the capillary vessel wall. Destabilization then allows endothelial cells to migrate and proliferate to form tubules, aided by VEGF, angiopoietins, guidance molecules, growth factors, cytokines, and degradation of the ECM. Maturation of the newly formed vessel is accompanied by increased expression of antiangiogenic factors, many released as a result of proteolysis. PDGF, platelet-derived growth factor; S1P1, sphingosine-1-phosphate-1; TGFβ, transforming growth factor-β.

Serial Blood Pressures before, during and after pregnancy

- Prepregnancy: 104 * 71
- Early Pregnancy: 105 * 65
- Second Trimester: 103 * 63
- Third Trimester: 105 * 68
- Postpartum: 104 * 69

* P <0.05 versus previous value
The Placental Barrier: the Gate and the Fate in Drug Distribution
https://doi.org/10.1007/s11095-017-2286-0
Fig 1. Placental transporter proteins are expressed on either side of the placenta.

Maternal use of drug substrates of placental transporters and the effect of transporter-mediated drug interactions on the risk of congenital anomalies.
https://doi.org/10.1371/journal.pone.0173530
Fig 6. Placenta volume vs. gestational age.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215906
Fetal Drug Exposure

- Placental transporter/counter-transporter function
- Fetal
  - Renal function
  - Hepatic/metabolic function
  - Maturity of blood-brain barrier
Fig 17. Fetal kidney mass vs. gestational age.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215906
Renal Function at Birth

Fetal Hepatic Phase II Enzymes

Table 2.

In Vitro Ontogeny of Human Hepatic Phase II Enzymes (Adapted From Ref. 55, 56)

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>Fetus</th>
<th>Neonate (0-1 month)</th>
<th>1 month to 1 year</th>
<th>Adult</th>
<th>Ontogeny Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDP glucuronosyltransferase (UGT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT1A1</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Adult levels attained by 3-6 mo</td>
</tr>
<tr>
<td>UGT1A6</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Maturation complete until puberty</td>
</tr>
<tr>
<td>UGT2B7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Adult levels attained by 2-3 mo</td>
</tr>
</tbody>
</table>

Maternal-Fetal Drug transport

**Diffusion**

- Active transport
- Active Counter-transport

**Factors affecting transport**
- Blood flow
- Lipid Solubility
- Molecular weight
- Protein Binding
- Ionization
Summary

• The maternal, placental and fetal compartments are growing and maturing interdependently over the gestation.
• Changes in maternal physiology are dramatic, and intended to increase nutrient flow to the fetus and waste from the fetal to maternal compartments.
• There are many unknowns.
Questions?

• Anne Zajicek
• 301-742-4885
• zajiceka@mail.nih.gov