Drug Therapy During Pregnancy and the Perinatal Period

Marilynn C. Frederiksen, M.D.  
Associate Professor Clinical Ob/Gyne  
Feinberg Medical School,  
Northwestern University
Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular system
  o Plasma volume expansion
  o Increase in cardiac output
  o Regional blood flow changes
• Respiratory Changes
• Decrease in albumin concentration
• Enzymatic activity changes
• Increase in GFR
• Gastrointestinal changes
Pregnancy Physiology Potentially Affecting Pharmacokinetics

- Cardiovascular system
  - Plasma volume expansion
  - Increase in cardiac output
  - Regional blood flow changes
## Body Fluid Spaces in Pregnant and Nonpregnant Women

<table>
<thead>
<tr>
<th></th>
<th>WEIGHT (kg)</th>
<th>PLASMA VOLUME (mL/kg)</th>
<th>ECF SPACE (L/kg)</th>
<th>TBW (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NONPREGNANT</strong></td>
<td>&lt; 70</td>
<td>0.189</td>
<td>0.516</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 – 80</td>
<td>0.156</td>
<td>0.415</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 80</td>
<td>0.151</td>
<td>0.389</td>
<td></td>
</tr>
<tr>
<td><strong>PREGNANT</strong></td>
<td>&lt; 70</td>
<td>0.257</td>
<td>0.572</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 – 80</td>
<td>0.255</td>
<td>0.514</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 80</td>
<td>0.240</td>
<td>0.454</td>
<td></td>
</tr>
</tbody>
</table>

Cardiovascular System Changes

- Plasma volume expansion
  - Begins at 6 - 8 weeks gestation
  - Volume of 4700 - 5200 ml peaks at 32 weeks gestation
  - Increase of 1200 - 1600 ml above non-pregnant women
Cardiovascular System Changes

• Cardiac output increases 30 - 50%
  o 50% by 8 weeks gestation
• Increase in stroke volume and heart rate
  o Stroke volume in early pregnancy
  o Heart rate in later pregnancy
Regional Blood Flow Changes

• Increased blood flow to uterus - 20% of cardiac output at term
• Increased renal blood flow
• Increased skin blood flow
• Increased mammary blood flow
• Decreased skeletal muscle blood flow
HEPATIC BLOOD FLOW IN PREGNANCY
(% CARDIAC OUTPUT)

U/S Measured Hepatic Blood Flow

Hepatic blood flow (L/min)

1st Trimester | 2nd Trimester | 3rd Trimester | NP

- Hep Art
- Hep Vein
- Liver Blood Flow

*P < .05
Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular system
  o Plasma volume expansion
  o Increase in cardiac output
  o Regional blood flow changes

• Respiratory Changes
Respiratory Changes

• Compensated respiratory alkalosis
• Lowered $P_a CO_2$
• pH 7.44
Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular system
  o Plasma volume expansion
  o Increase in cardiac output
  o Regional blood flow changes

• Respiratory Changes

• Decrease in albumin concentration
PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM

Is The Hypoalbuminemia of Pregnancy Dilutional?

- [GLOBULIN] IS NOT REDUCED
- DISTRIBUTION VOLUME DOES NOT AFFECT $C_{ss}$

$$C_{ss} = \frac{\text{SYNTHESIS RATE}}{CL_E}$$

- THEREFORE, ↓ [ALBUMIN] REFLECTS EITHER ↓ SYNTHESIS RATE OR ↑ $CL_E$. 


Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular system
  o Plasma volume expansion
  o Increase in cardiac output
  o Regional blood flow changes
• Respiratory Changes
• Decrease in albumin concentration
• Enzymatic activity changes
Enzymatic Activity Changes

- Thought to be related to pregnancy hormonal changes
- N-demethylation inhibited by progesterone, not by estrogen
- Probably acts via pregnane X receptor as a transcriptional regulator
CYP3A4

- Hydroxylation
- Increased activity during pregnancy
CYP1A2

- Activity decreased progressively during pregnancy
- Progressive lengthening of caffeine half-life
Caffeine Clearance – CYP 1A2

CYP2C9

- Activity shown to increase during pregnancy
- Lowered total concentration of phenytoin during pregnancy
Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

CYP2D6 Activity

- Genetic determined polymorphism
- Increased clearance of metoprolol observed during pregnancy
- Increased clearance in homozygous and heterozygous extensive metabolizers
- No change in homozygous poor metabolizers

Summary of Enzymatic Changes

Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular System
  o Plasma Volume Expansion
  o Increase in Cardiac Output
  o Regional Blood Flow Changes

• Respiratory Changes

• Decrease in Albumin Concentration

• Enzymatic Activity Changes

• Increase in GFR
GFR DURING PREGNANCY AND POSTPARTUM

Pregnancy Physiology Potentially Affecting Pharmacokinetics

- Cardiovascular System
  - Plasma Volume Expansion
  - Increase in Cardiac Output
  - Regional Blood Flow Changes
- Respiratory Changes
- Decrease in Albumin Concentration
- Enzymatic Activity Changes
- Increase in GFR
- Gastrointestinal Changes
Gastrointestinal Changes

- Decreased gastric acidity
- Gastric emptying
  - Delayed in laboring women
  - No difference between 1st & 3rd in non-laboring women
  - No difference from postpartum
- Increased orocecal transit time in 3rd
  - Progesterone effect
  - Pancreatic polypeptide inverse correlation
Maternal Physiologic Changes
Altering PK of Drugs

• Volume Expansion
CAFFEINE $V_d$ (MARKER FOR TBW) DURING PREGNANCY AND POSTPARTUM

THEOPHYLLINE $V_d$
DURING PREGNANCY AND POSTPARTUM

Maternal Physiologic Changes Altering PK of Drugs

- Volume expansion
- Protein binding-increase in free fraction of drugs bound to albumin
THEOPHYLLINE PROTEIN BINDING DURING PREGNANCY AND POSTPARTUM

Theophylline Protein Binding


- Nonpregnant: $f = 61\%$, $[\text{Alb}] = 4.4 \text{ g/dL}$
- Pregnant: $f = 69\%$, $[\text{Alb}] = 3.2 \text{ g/dL}$
Maternal Physiologic Changes Altering PK of Drugs

- Volume expansion
- Protein binding
- Clearance changes
THEOPHYLLINE RENAL CLEARANCE DURING PREGNANCY AND POSTPARTUM

THEOPHYLLINE CL\(_H\) AND CL\(_{INT}\) DURING PREGNANCY AND POSTPARTUM


**Diagram:**
- **CL\(_{INT}\) and CL\(_H\)**
- **Clearance (mL/min x kg)**
- **Pregnant and Postpartum**
- **Unbound Fraction (f)**
THEOPHYLLINE CLEARANCE DURING PREGNANCY AND POSTPARTUM

METHADONE CLEARANCE DURING AND AFTER PREGNANCY
(Primarily a CYP3A4 Substrate)

Carbamazepine Plasma Concentrations During Pregnancy
(Primarily CYP 3A4 Substrate)

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

FREE AND TOTAL PHENYTOIN LEVELS (DOSE = 300 MG/DAY)
CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN


* P < .05
*** P < .005
CAFFEINE METABOLITE / PARENT DRUG RATIOS IN HEALTHY PREGNANT AND NON-PREGNANT WOMEN


** P < 0.01

* P < 0.001

NS

Metabolic Ratio

CYP1A2
XO
NAT2
8-OH
Betamethasone PK in Singleton and Twin Pregnancies CYP3A4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Singleton</th>
<th>Twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₃ (L)</td>
<td>67.5 ± 27.9</td>
<td>70.9 ± 28.4</td>
</tr>
<tr>
<td>Cl (L/h)</td>
<td>5.7 ± 3.1</td>
<td>8.4 ± 6.4 **</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>9.0 ± 2.7</td>
<td>7.2 ± 2.4 *</td>
</tr>
</tbody>
</table>

* P < .017 ** P < .06

Lamotrigine Clearance in Pregnancy

- Phase II biotransformation by glucuronidation
- Estrogen upregulates UGT1A4
- Clearance increases by 27% as early as 8 weeks
- Clearance rises during second and third trimesters
- Clearance peaks in third trimester at 248 - 330% over baseline
- Requires dose adjustment and monitoring
- Rapid decrease in clearance in the first two weeks postpartum

### Pharmacokinetics of Cefuroxime in Pregnancy

<table>
<thead>
<tr>
<th>Pt Category</th>
<th>$V_D$(L)</th>
<th>$Cl$(ml/min)</th>
<th>$T(1/2)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>17.8±1.9</td>
<td>282±34*</td>
<td>44±5*</td>
</tr>
<tr>
<td>At Delivery</td>
<td>19.3±3.1</td>
<td>259±35*</td>
<td>52±10</td>
</tr>
<tr>
<td>Postpartum</td>
<td>16.3±2.1</td>
<td>198±27</td>
<td>58±8</td>
</tr>
</tbody>
</table>

*p<0.05 on comparison to PP

Pharmacokinetics of Amoxicillin in Pregnancy

<table>
<thead>
<tr>
<th>Study Period</th>
<th>$\text{Cl}_R$ (L/hr)</th>
<th>$\text{Cl}_S$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 22 wks</td>
<td>24.8 ± 6.7*</td>
<td>280 ± 105*</td>
</tr>
<tr>
<td>30 – 34 wks</td>
<td>24.0 ± 3.9*</td>
<td>259 ± 54*</td>
</tr>
<tr>
<td>Postpartum</td>
<td>15.3 ± 2.6</td>
<td>167 ± 47</td>
</tr>
</tbody>
</table>

* P < 0.001 as compared to PP

Tobramycin Pharmacokinetics

- CI higher in mid-trimester with a corresponding shorter half-life
- CI lower in the third trimester with a corresponding longer half-life

Metformin PK in Pregnancy

- Small molecule primarily eliminated by renal clearance but a OCT substrate
- $C_{\text{max}}$ in pregnancy 81% lower than postpartum values
- Mean metformin concentrations 69% of the postpartum values
- Mean AUC for metformin during pregnancy is 80% of the postpartum AUC

# Pharmacokinetics of Metformin during Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>2nd Δ</th>
<th>3rd Δ</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clₚ ml/min</td>
<td>723 ± 243*</td>
<td>625 ± 130’</td>
<td>447 ± 132</td>
</tr>
<tr>
<td>Cr Cl ml/min</td>
<td>240 ± 70*</td>
<td>207 ± 56**</td>
<td>165 ± 44</td>
</tr>
<tr>
<td>Secretion Cl ml/min</td>
<td>480 ± 190*</td>
<td>419 ± 78*</td>
<td>313 ± 98</td>
</tr>
</tbody>
</table>

* P < 0.01 **P < 0.05

Glyburide PK/PD in Pregnancy (CYP2D9)

- 2-fold increase in clearance
- Simulations projecting dosing 1.25 – 23.75 mg twice daily for optimal glucose control
- Non-pregnant dose range 1.25 – 10.0 mg twice daily
- ? Fetal effects – fetal conc 70% of maternal

Heparin PK during Pregnancy

- Shorter time to peak heparin concentration and effect
- Lower peak effect

Enoxaprin PK during Pregnancy

- $T_{\text{max}}$ shows no change
- $C_{\text{max}}$ lower during pregnancy
- CI decreases in late pregnancy
- Lower anti-factor Xa activity
- AUC lower during pregnancy

Maternal Physiologic Changes Altering PK of Drugs

- Volume expansion
- Protein binding
- Clearance changes
- Gastrointestinal changes
### Oralampicillin Pharmacokinetics in Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(cm²)</td>
<td>8.2±4.1</td>
<td>12.6±4.3*</td>
</tr>
<tr>
<td>Peak Level (µg/ml)</td>
<td>2.2±1.0</td>
<td>3.7±1.5*</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>45.6±20.2</td>
<td>48.1±19.3**</td>
</tr>
</tbody>
</table>

* P < 0.001 ** NS

PK of Oral Valacyclovir & Acyclovir

- The pro-drug Valacyclovir converted by first pass metabolism to Acyclovir
- Non-pregnant Valacyclovir gives 3 - 5 times higher plasma level as Acyclovir
- Valacyclovir PK study in pregnancy gave plasma levels 3 times higher than Acyclovir

Peripartum Pharmacologic Considerations

- Increased cardiac output
- Blood flow changes
- Uterine contractions
- ? Pharmacodynamic changes
MORPHINE PHARMACOKINETICS DURING LABOR

### Pharmacokinetics of Cefuroxime in Pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>$V_D$ (L)</th>
<th>$Cl$ (ml/min)</th>
<th>$T(\frac{1}{2})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>17.8 + 1.9</td>
<td>282 + 34*</td>
<td>44 + 5*</td>
</tr>
<tr>
<td>At Delivery</td>
<td>19.3 + 3.1</td>
<td>259 + 35*</td>
<td>52 + 10</td>
</tr>
<tr>
<td>Postpartum</td>
<td>16.3 + 2.1</td>
<td>198 + 27</td>
<td>58 + 8</td>
</tr>
</tbody>
</table>

* $p<0.05$ on comparison to PP

Postpartum PK Considerations

- Increased cardiac output maintained
- GFR increased
- Diuresis
- Breastfeeding
- Great variability
Postpartum Clindamycin Pharmacokinetics

Postpartum Gentamicin Distribution Volume

Frequency

0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5

Liter/Kg

Del Priore Obstet Gynecol 1996; 87: 994
Drug Studies for Pregnancy

• Pregnancy Specific Drugs
  o Tocolytic agents
  o Oxytocic agents
  o Eclampsia agents

• Drugs commonly used by women of childbearing potential
  o Antidepressants
  o Asthma drugs
Technical Considerations

• Ethical and IRB concerns
• Serial studies
  o Spanning pregnancy
  o Specific to peripartum period
  o Controls
• FDA Guidance: Pharmacokinetics in pregnancy-study design, data analysis, and impact on dosing and labeling 69 FR 63402, November 1, 2004.
Study Design

- Use population PK analysis
- Incorporate in vitro protein binding studies
- Use stable isotopes for bioavailability studies
- Use established tracer substances as reference markers
Teratogenesis
<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal</td>
<td>5%</td>
</tr>
<tr>
<td>Single Gene</td>
<td>15%</td>
</tr>
<tr>
<td>Multiple gene/Multifactorial</td>
<td>65%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
</tr>
<tr>
<td>Maternal Disease</td>
<td>1-2%</td>
</tr>
<tr>
<td>Irradiation</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Infection</td>
<td>2-3%</td>
</tr>
<tr>
<td>Drugs and Chemicals</td>
<td>4-5%</td>
</tr>
</tbody>
</table>
General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
- Teratogens must reach the conceptus
- Effects depend upon the development stage when exposed
- Genotype of mother and fetus effect susceptibility
General Principles of Teratology

• Teratogens act with specificity
PHOCOMELIA DUE TO THALIDOMIDE
General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
DOSE-RESPONSE RELATIONSHIP

INCREASING DOSAGE

Embryotoxic Range

Teratogenic Zone

Embryolethal Zone

Maternolethal Range

No Effect Range
General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
- Teratogens must reach the conceptus
Placental Transport

- Passive diffusion
- P-glycoprotein expressed on trophoblastic cells of placenta
- Active transport of P-glycoprotein substrates back to the mother
- Pore system
- Endocytosis
PHARMACOKINETIC MODEL OF MATERNAL-FETAL TRANSPORT

DOSE

\[ M_{\text{PERIPHERAL}} \leftrightarrow M_{\text{CENTRAL}} \]

\[ \text{FETAL EXCRETION + METABOLISM} \]

\[ \text{CL}_E \]
General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
- Teratogens must reach the conceptus
- Effects depend upon the development stage when exposed
All or Nothing Period
Figure 8-14. Schematic illustration of the critical periods in human development. During the first two weeks of development, the embryo is usually not susceptible to teratogens. During these undifferentiation stages, the major morphological abnormalities are...
General Principles of Teratology

- Teratogens act with specificity
- Teratogens demonstrate a dose-response relationship
- Teratogens must reach the conceptus
- Effects depend upon the development stage when exposed
- Genotype of mother and fetus effect susceptibility
Phenytoin

• Animal evidence for an arene oxide (epoxide) reactive metabolite
• Genetic susceptibility to the Dilantin Syndrome related to variation in Epoxide hydrolase activity
Prenatal Diagnosis of the Fetus at Risk

Genetic Polymorphisms

• Increased risk of clefting in fetuses carrying atypical allele for transforming growth factor α whose mothers smoke
• Decreased risk for fetal alcohol syndrome in African American women carrying alcohol dehydrogenase isoform 2
Mechanisms of Teratogenesis

• All theoretical
• Most not understood well
• Implications of a genetic component
Thalidomide

• Active metabolite CPS49 blocks angiogenesis in the limbs

• Replicates exact malformation seen in humans

Thalidomide

- Thalidomide causes DNA oxidation in animals susceptible to teratogenesis
- Pre-treatment with PBN (free radical trapping agent) reduced thalidomide embryopathy
- Suggesting that the mechanism is free radical-mediated oxidative DNA damage

Teratogen?

• Is there a specific pattern of abnormalities?
• Was the agent present during development of that organ system?
• Is there a dose-response curve?
• Could there be a genetic component?
Evaluation of Drugs in Breast Milk

Evaluation of Drugs in Breast Milk

- Measure the M / P ratio
- Estimate breast milk dose
- Estimate infant dose
- Measure blood level in the infant
Drugs in Breast Milk

• Free drug transferred into milk
• Milk concentrations usually less than serum concentrations
• Exchange is bi-directional
KINETIC ANALYSIS OF THEOPHYLLINE PLASMA AND MILK CONCENTRATIONS
KINETIC ANALYSIS OF PREDNISOLONE PLASMA AND MILK CONCENTRATIONS

SHADED AREA IS EXPECTED RANGE OF UNBOUND PLASMA CONC.
Factors Effecting the Milk / Plasma Concentration Ratio

- Maternal protein binding
- Protein binding in milk
- Lipid solubility of drug
- Physiochemical factors of drug effecting diffusion
Drugs Generally Contraindicated during Lactation

- Antineoplastics
- Immune suppressants
- Ergot Alkaloids
- Gold
- Iodine
- Lithium carbonate
- Radiopharmaceuticals
- Social drugs & drugs of abuse
- Certain antibiotics
General Recommendations

• Drugs considered safe for pregnancy are usually safe during lactation

• Decrease the drug dose to the infant by feeding just prior to a dose

• Infant blood levels can be monitored and should be less than therapeutic
Exceptions to These Rules

• Cimetidine
• Dapsone
• Codeine
Cimetidine

- Actively transported into breast milk giving a M/P ratio of 5.5
- Dose estimate to the infant is still low
- No infant toxicity reported

Dapsone

- Weak base with a Pkb of 13
- Highly protein bound
- Half-life of 20 hrs
- Physiochemical properties favoring entrapment of drug in breast
- Higher than expected dose to the infant
- Hemolytic anemia in infant

Codeine

- Codeine is metabolized to morphine
- Mothers may be ultrarapid metabolizers with the CYP2D6*2X2 gene duplication
  - Scandinavians 1%
  - Portugese and Greek 10%
  - Ethiopians 27%
Codeine (cont.)

- Morphine is inactivated by glucuronidation mainly to an inactive metabolite
- 2B7(UGT2B7) produces an active metabolite morphine-6-glucuronide
- The UGT2B7*2 variant increases production of mophine-6-glucuronide
- The combination of a mother who is an ultrarapid metabolizer and a baby carrying the glucuronide variant increases risk of life-threatening CNS depression in the neonate