Drug Therapy During Pregnancy and the Perinatal Period

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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
  o Plasma volume expansion
  o Increase in cardiac output
  o Regional blood flow changes
Fluid Spaces in Pregnant and Non-Pregnant Women

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%
  - 50% by 8 weeks gestation
- Increase in stroke volume and heart rate
  - Stroke volume in early pregnancy
  - 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
  - Plasma volume expansion
  - Increase in cardiac output
  - Regional blood flow changes

- Respiratory Changes

- Decrease in albumin concentration
PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM

- **[TOTAL PROTEIN]**
- **[ALBUMIN]**
- **[GLOBULIN]**

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, $\downarrow$ [ALBUMIN] REFLECTS EITHER $\downarrow$ SYNTHESIS RATE OR $\uparrow CL_E$. 
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**
Enzymatic Activity Changes

• Thought to be related to pregnancy hormonal changes
• N-demethylation inhibited by progesterone, not by estrogen
Overview of Drug Metabolism

- Phase I and Phase II Hepatic Metabolism

Phase I: Conversion into potentially less toxic metabolites
Phase II: Addition of moieties that make the drug more water soluble
to facilitate renal clearance: sugars, sulfates, amino acids
Pregnancy Enzymatic Changes

cyp1a2
cyp2d6
cyp3a

14-18 wks   24-26 wks   36-40 wks
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

**CYP2D6 Genotype & Phenotype**

<table>
<thead>
<tr>
<th>Metabolic Phenotype</th>
<th>Genotype</th>
</tr>
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<tbody>
<tr>
<td>Poor metabolizer</td>
<td>No functional gene</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>One active gene</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Two active genes</td>
</tr>
<tr>
<td>Ultra Rapid metabolizer</td>
<td>Multiple copies of active genes</td>
</tr>
</tbody>
</table>

- Genetically determined
- Activity can vary 1000 fold
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
  o Delayed in laboring women
  o No difference between 1st & 3rd in non-laboring women
  o No difference from postpartum
• Increased orocecal transit time in 3rd
  o Progesterone effect
  o 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\textsubscript{d} DURING PREGNANCY AND POSTPARTUM


\begin{align*}
\text{UNBOUND } f_\% \ (f) \\
\text{Vd (L)}
\end{align*}

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


 BINDING CAPACITY

AFFINITY CONSTANT (mol/L)

NONPREGNANT

f = 61%

[Alb] = 4.4 g/dL

PREGNANT

f = 69%

[Alb] = 3.2 g/dL

Maternal Physiologic Changes Altering PK of Drugs

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


INTRINSIC RENAL CLEARANCE

CL\textsubscript{R}

CL\textsubscript{Cr} (mL/min)

Theophylline Renal Clearance during Pregnancy and Postpartum
THEOPHYLLINE $\text{CL}_H$ AND $\text{CL}_{INT}$ DURING PREGNANCY AND POSTPARTUM

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)
### Betamethasone PK in Singleton and Twin Pregnancies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Singleton</th>
<th>Twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (L)</td>
<td>$67.5 \pm 27.9$</td>
<td>$70.9 \pm 28.4$</td>
</tr>
<tr>
<td>CI (L/h)</td>
<td>$5.7 \pm 3.1$</td>
<td>$8.4 \pm 6.4$ **</td>
</tr>
<tr>
<td>$T\frac{1}{2}$ (h)</td>
<td>$9.0 \pm 2.7$</td>
<td>$7.2 \pm 2.4$ *</td>
</tr>
</tbody>
</table>

* P < .017   ** P < .06

Lamotrigine Clearance in Pregnancy

- Phase II biotransformation by glucuronidation
- Increased clearance in second and third trimesters (> 65%)
- May require dose adjustment
- Rapid decrease in clearance in the first two weeks postpartum

# Pharmacokinetics of Cefuroxime in Pregnancy

<table>
<thead>
<tr>
<th>Pt Cat.</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>$24.8 \pm 6.7^*$</td>
<td>$280 \pm 105^*$</td>
</tr>
<tr>
<td>30 – 34 wks</td>
<td>$24.0 \pm 3.9^*$</td>
<td>$259 \pm 54^*$</td>
</tr>
<tr>
<td>Postpartum</td>
<td>$15.3 \pm 2.6$</td>
<td>$167 \pm 47$</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

- $C_{\text{max}}$ 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><strong>Clₐ R ml/min</strong></td>
<td>723 ± 243*</td>
<td>625 ± 130’</td>
<td>447 ± 132</td>
</tr>
<tr>
<td><strong>Cr Cl ml/min</strong></td>
<td>240 ± 70’</td>
<td>207 ± 56**</td>
<td>165 ± 44</td>
</tr>
<tr>
<td><strong>Secretion Cl ml/min</strong></td>
<td>480 ± 190*</td>
<td>419 ± 78’</td>
<td>313 ± 98</td>
</tr>
</tbody>
</table>

* P < 0.01  
** P < 0.05  

Heparin PK during Pregnancy

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

Enoxaparin 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
## Oral Ampicillin Pharmacokinetics in Pregnancy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pregnant (Mean ± SD)</th>
<th>Nonpregnant (Mean ± SD)</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 Acylovir

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>CI (ml/min)</th>
<th>$T(\frac{1}{2})$</th>
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</thead>
<tbody>
<tr>
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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
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
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

100%

50%

Maternalethal Range

Embryolethal Zone

Teratogenic Zone

No Effect Range

Embryotoxic 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

$M_{PERIPHERAL}$

$M_{CENTRAL}$

DOSE

FETUS

CL_E

FETAL EXCRETION + METABOLISM
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
<table>
<thead>
<tr>
<th>Period</th>
<th>Embryonic Period</th>
<th>Fetal Period</th>
<th>Full Term</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>zygote, implantation &amp; bilaminar embryo</td>
<td>38 weeks</td>
<td>38 weeks</td>
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<tr>
<td>2</td>
<td>CNS.</td>
<td>20-36 weeks</td>
<td>38 weeks</td>
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<tr>
<td>3</td>
<td>heart</td>
<td>brain</td>
<td>20-36 weeks</td>
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<tr>
<td>4</td>
<td>eye</td>
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<td>5</td>
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<td>ear</td>
<td>20-36 weeks</td>
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<tr>
<td>6</td>
<td>heart</td>
<td>arm</td>
<td>20-36 weeks</td>
</tr>
<tr>
<td>7</td>
<td>arm</td>
<td>mouth</td>
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<td>8</td>
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<td>ear</td>
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<td>9</td>
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<td>20-36 weeks</td>
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</table>

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 phases, a
General Principles of Teratology

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- 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

EPOXIDE HDROLASE ACTIVITY (% OF STD)

FETAL HYDANTOIN SYNDROME
UNAFFECTED

AMNIOCYTE SAMPLES

Genetic Polymorphisms

• Increased risk of clefting in fetuses carrying atypical allele for transforming growth factor alpha 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

- 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

- 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

![Graph showing plasma and milk concentrations over time](image)

- **Patient 1**
- **Plasma**
- **Milk**

[Graph details including concentrations and time points]
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
Examples of Breast Feeding Drug Problems

• Cimetidine
  • Actively transported
  • M/P ratio 5.5

• Dapsone
  • Weak Base pKb of 13
  • High Protein Binding
  • Long half-life
  • Drug Entrapment in breast
  • Hemolytic anemia
Classic Breast Feeding Drug Problem

- **Codeine pro-drug for morphine**
- **Usually felt safe for short term usage**
- **Ultrarapid metabolizer**
  CYP2D6*2 A allele with CYP2D6*2×2 gene duplication
- **Glucoridation variant with increased production of active metabolite**
  UGT2B7*2 variant

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