Drug Therapy During Pregnancy and the Perinatal Period

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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

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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Body Fluid Spaces in Pregnant and Nonpregnant Women

<table>
<thead>
<tr>
<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>NONPREGNANT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>0.189</td>
<td>0.516</td>
<td>0.514</td>
</tr>
<tr>
<td>70 – 80</td>
<td>0.156</td>
<td>0.415</td>
<td>0.454</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>0.151</td>
<td>0.389</td>
<td>0.255</td>
</tr>
<tr>
<td>PREGNANT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>0.257</td>
<td>0.572</td>
<td>0.255</td>
</tr>
<tr>
<td>70 – 80</td>
<td>0.255</td>
<td>0.514</td>
<td>0.240</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>0.240</td>
<td>0.464</td>
<td>0.240</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

- **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

*P < .05
Pregnancy Physiology Potentially Affecting Pharmacokinetics

• Cardiovascular system
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  - 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
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  - Regional blood flow changes
• Respiratory Changes
  • Decrease in albumin concentration
PREGNANCY AND POSTPARTUM PROTEIN CONCENTRATIONS


Is The Hypoalbuminemia of Pregnancy Dilutional?

- [GLOBULIN] IS NOT REDUCED
- DISTRIBUTION VOLUME DOES NOT AFFECT $C_{ss}$
- $C_{ss} \leq$ SYNTHESIS RATE $\leq C_{L_E}$
- THEREFORE, ↓[ALBUMIN] REFLECTS EITHER ↓SYNTHESIS RATE OR ↑$C_{L_E}$.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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  - 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

Pregnancy Enzymatic Changes

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


Pregnancy Physiology Potentially Affecting Pharmacokinetics

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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**

![Graph showing changes in V_d during pregnancy and postpartum.](image)


**THEOPHYLLINE V_d DURING PREGNANCY AND POSTPARTUM**

![Graph showing changes in V_d during pregnancy and postpartum.](image)

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

Maternal Physiologic Changes Altering PK of Drugs

- Volume expansion
- Protein binding
- Clearance changes

THEOPHYLLINE RENAL CLEARANCE DURING PREGNANCY AND POSTPARTUM


THEOPHYLLINE CL\textsubscript{R} AND CL\textsubscript{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)

BOUND [PHENYTOIN]
FREE [PHENYTOIN]

CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN


* P < .05
** P < .005

* P < .05
** P < .005
**Caffeine Metabolite / Parent Drug Ratios in Healthy Pregnant and Non-Pregnant Women**


**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>Cl (L/h)</td>
<td>$5.7 \pm 3.1$</td>
<td>$8.4 \pm 6.4$ **</td>
</tr>
<tr>
<td>$T_{1/2}$ (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>V₀(L)</th>
<th>CI(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>Clᵣ (L/hr)</th>
<th>Clₛ (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

- Cl higher in mid-trimester with a corresponding shorter half-life
- Cl 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 $\Delta$</th>
<th>3rd $\Delta$</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ 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>

* $P < 0.01$
** $P < 0.05$


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

### Oral Ampicillin Pharmacokinetics in Pregnancy

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<tr>
<th>Parameter</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (cm$^2$)</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>V₀ (L)</th>
<th>Cl (ml/min)</th>
<th>T(½)</th>
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<tr>
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Postpartum PK Considerations
- Increased cardiac output maintained
- GFR increased
- Diuresis
- Breastfeeding
- Great variability

Postpartum Clindamycin Pharmacokinetics

Drug Studies for Pregnancy

- Pregnancy Specific Drugs
  - Tocolytic agents
  - Oxytocic agents
  - Eclampsia agents
- Drugs commonly used by women of childbearing potential
  - Antidepressants
  - Asthma drugs

Technical Considerations

- Ethical and IRB concerns
- Serial studies
  - Spanning pregnancy
  - Specific to peripartum period
  - 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
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
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
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
FETAL HYDANTOIN SYNDROME

UNAFFECTED

Prenatal Diagnosis of the Fetus at Risk


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

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