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

Cardiovascular system
- Plasma volume expansion
- Increase in cardiac output
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Body Fluid Spaces in Pregnant and Nonpregnant Women

Chart that indicates the weight, plasma volume (mL/kg), ECF Space (L/kg) and TBW (L/kg) in nonpregnant and 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)

Bar chart showing the hepatic blood flow (L/min) at 12-14 weeks, 24-26 weeks, 36-38 weeks, and 10-12 weeks postpartum

Pregnancy Physiology Potentially Affecting Pharmacokinetics

Cardiovascular system
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Respiratory Changes
Respiratory Changes

Compensated respiratory alkalosis

Lowered $P_aCO_2$

pH 7.44
Pregnancy Physiology Potentially Affecting Pharmacokinetics

Cardiovascular system
Plasma volume expansion
Increase in cardiac output
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Respiratory Changes

Decrease in albumin concentration
PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM

Line graph showing [protein] (gm/dL) for pregnant women at 24-26 wks and 36-38 wks and at 6-8 weeks and >6 mo for postpartum. The graph shows globulin, albumin and total protein levels for each group.

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 ↓ SYNTHESES RATE OR ↑

$CL_E$. 

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Pregnancy Physiology Potentially Affecting Pharmacokinetics

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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
CYP3A4

Hydroxylation

Increased activity during pregnancy
CYP1A2

Activity decreased progressively during pregnancy

Progressive lengthening of caffeine half-life
Caffeine Clearance – CYP 1A2

Line chart showing clearance (mL/kg x hr) over specified weeks of pregnancy, at birth, and at specified weeks postpartum.

CYP2C9

Activity shown to increase during pregnancy

Lowered total concentration of phenytoin during pregnancy
Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

Bar chart showing TOTAL (PHENYOIN) (μg/ml and FREE (PHENYTOIN) (μg/ml in NONPREG, 1st, 2nd and 3rd trimesters of pregnancy.

Total phenytoin levels decline but free phenytoin levels are unchanged.

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

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
GFR DURING PREGNANCY AND POSTPARTUM

Line chart showing CLEARANCE (mL/min) for pregnant women at 15-18 wks, 25-28 wks and 35-38 wks and 8-12 wks 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
  - 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

Line chart showing distribution volume (L) in pregnant women at 11 wks, 17 wks, 24 wks, 32 wks, 38 wks and postpartum at 1 wk and 6 wks.

THEOPHYLLINE V_d
DURING PREGNANCY AND POSTPARTUM

Line chart showing Vd (L) and unbound fraction in pregnant women at 24-36 wks, 36-38 wks and postpartum at 6-8 wks and > 6 mo.

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

Unbound Theophylline (%) and serum albumin (g/dL) in pregnant women at 24-36 wks, 36-38 wks, and postpartum at 6-8 wks and > 6 mo.

THEOPHYLLINE PROTEIN BINDING

Bar chart showing affinity constant (mol/L) in non-pregnant f = 61% [Alb] = 4.4 g/dL and 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

Line chart indicating Theophylline renal clearance (mL/min) in pregnant women at 24-36 wks, 36-38 wks, and postpartum women at 6-8 wks and > 6 mo.

THEOPHYLLINE CLh AND CLint DURING PREGNANCY AND POSTPARTUM

Clearance (mL/min x kg) and unbound fraction (f) in pregnant women at 24-36 wks, 36-38 wks, and postpartum at 6-8 wks and > 6 mo

THEOPHYLLINE CLEARANCE DURING PREGNANCY AND POSTPARTUM

Clearance (mL/min x kg) in pregnant women at 24-36 wks, 36-38 wks, and postpartum at 6-8 wks and > 6 mo (CL_E, CL_NR, CL_R).

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

* p< 0.05 vs. Postpartum

Bar chart indicating elimination clearance (mL/min) during the 2nd TRI, 3rd TRI, 1-4 wks PP and 8-9 wks PP.

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

Bar chart indicating Plasma concentration over time periods 1, 2, 3, and 4.

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

Bar chart showing total and free [Phenytoin] (µg/ml) for nonpreg, 1\textsuperscript{st} TRI, 2\textsuperscript{nd} TRI, and 3\textsuperscript{rd} TRI.

FREE AND TOTAL PHENYTOIN LEVELS
(DOSE = 300 MG/DAY)

Bar chart showing bound [Phenytoin] and free [Phenytoin] in non-pregnant and pregnant women.
CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN

Bar chart showing metabolic ratio for CYP1A2, XO, NAT, and CYP3A4.

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

Bar chart showing metabolic ratio for CYP1A2, XO, NAT2, and 8-OH.

## Betamethasone PK in Singleton and Twin Pregnancies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Singleton</th>
<th>Twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd (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

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 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
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

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

$\text{Cl}$ 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</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

Clearance (L/min) in women during labor and in nonpregnant controls

**Pharmacokinetics of Cefuroxime in Pregnancy**

<table>
<thead>
<tr>
<th>Category</th>
<th>V₀ (L)</th>
<th>CI (ml/min)</th>
<th>T(½)</th>
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<tbody>
<tr>
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<td>17.8± 1.9</td>
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</table>

*p<0.05 on comparison to PP*
Postpartum PK Considerations

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

Graph showing [Clindamycin] (μg/mL) over hours

Postpartum Gentamicin Distribution

Volume

Frequency histogram of $V_D$ (liters/Kg)

Del Priore Obstet Gynecol 1996; 87: 994
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

Photograph of a human male infant with phocomelia.
General Principles of Teratology

Teratogens act with specificity

Teratogens demonstrate a dose-response relationship
DOSE-RESPONSE RELATIONSHIP

Graphic illustration of embryotoxic dose 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-gp substrates back to the mother

Pore system

Endocytosis
PHARMACOKINETIC MODEL OF MATERNAL-FETAL TRANSPORT

Diagram of maternal and fetal compartments.
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
Chart/graphic illustration of embryonic period and fetal period (in weeks)
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

Bar chart showing epoxide hydrolase activity (% of STD) over amniocyte samples in women with fetal hydantoin syndrome and in unaffected women.

Genetic Polymorphisms

Increased risk of clefting in fetuses carrying atypical allele for transforming growth factor (drawing of a pair of scissors) 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 radio
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 [Theophylline] (μg/mL) over hours for plasma and breast milk.
KINETIC ANALYSIS OF PREDNISOLONE PLASMA AND MILK CONCENTRATIONS

Graph showing [Prednisolone] (ng/mL) over hours for plasma and milk

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