Drug Therapy During Pregnancy and the Perinatal Period

Marilynn C. Frederiksen, M.D.
Associate Professor Clinical Ob/Gyne
Feinberg Medical School,
Northwestern University

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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

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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

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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

Robson SC, et al. Br J Obstet Gynaecol 1990;97:720-4.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

Cardiovascular system

- Plasma volume expansion
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- Regional blood flow changes

Respiratory Changes

Respiratory Changes

Compensated respiratory alkalosis

Lowered P_aCO_2

pH 7.44

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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.

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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.

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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.

Aldridge A, et al. Semin Perinatol 1981;5:310-4.

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.

Tomson T, et al. Epilepsia 1994;35:122-30.

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

Wadelius M, et al. Clin Pharmacol Ther 1997; 62: 400.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

Cardiovascular System

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- 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.

Davison JM, Hytten FE. Br J Obstet Gynaecol Br Commonw 1974;81:588-95.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

Cardiovascular System

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- Increase in Cardiac Output
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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 Δ**
- **No difference from postpartum**

Increased orocecal transit time in 3rd Δ
- **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.

Aldridge A, et al. Semin Perinatol 1981;5:310-4.

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.

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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.

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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

Connelly TJ, et al. Clin Pharmacol Ther 1990;47:68-72.

Maternal Physiologic Changes Altering PK of Drugs

Volume expansion

Protein binding

Clearance changes

THEOPHYYLINE 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.

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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).

Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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.

Pond SM, et al. J Pharmacol Exp Ther 1978;233:1-6.

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

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

Tomsom T, et al. Epilepsia 1994; 35:122-30.

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

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

Tomson T, et al. Epilepsia 1994;35:122-30.

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.

Bologa M, et al. J Pharmacol Exp Ther 1991;257:735-40.

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

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

Tsutsumi K, et al. Clin Pharmacol Ther 2001; 70: 121.

Betamethasone PK in Singleton and Twin Pregnancies

Parameter	Singleton	Twin
Vd (L)	**67.5 ± 27.9**	**70.9 ± 28.4**
Cl (L/h)	**5.7 ± 3.1**	**8.4 ± 6.4 ****
T½ (h)	**9.0 ± 2.7**	**7.2 ± 2.4 ***

*** P < .017** **** P < .06**

Ballabh P, et al. Clin Pharmacol Ther 2002; 71, 39.

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

Tran TA, et al. Neurology 2002; 59: 251-55.

Pharmacokinetics of Cefuroxime in Pregnancy

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

*p<0.05 on comparison to PP

Pharmacokinetics of Amoxicillin in Pregnancy

Study Period	Cl_R (L/hr)	Cl_S (ml/min)
18 - 22 wks	24.8±6.7*	280 ± 105*
30 – 34 wks	24.0 ± 3.9*	259 ± 54*
Postpartum	15.3 ± 2.6	167 ± 47

P < 0.001 as compared to PP

Andrew MA et al. Clin Pharmacol Ther 2007; 81: 547.

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

Bourget P, et al. J Clin Pharm Ther 1991;16:167-76

Metformin PK in Pregnancy

C_{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

Hughes RCE et al. Diabetes Medicine 23:323-6, 2006.

Pharmacokinetics of Metformin during Pregnancy

	2nd Δ	3rd Δ	PP
Cl_R ml/min	723 ± 243*	625 ± 130*	447 ± 132
Cr Cl ml/min	240 ± 70*	207 ± 56**	165 ± 44
Secretion Clml/min	480 ± 190*	419 ± 78*	313 ± 98

* P < 0.01 **P < 0.05

Eyal S, et al. Drug Metab Dispos. 2010 38: 833-40

Heparin PK during Pregnancy

Shorter time to peak heparin concentration and effect

Lower peak effect

Brancazio et al. Am J Obstet Gynecol 1995; 173:1240.

Enoxaparin PK during Pregnancy

T_{max} shows no change

C_{max} lower during pregnancy

Cl decreases in late pregnancy

Lower anti-factor Xa activity

AUC lower during pregnancy

Casele, et al. Am J Obstet Gynecol 1999; 181: 1113

Maternal Physiologic Changes Altering PK of Drugs

Volume expansion

Protein binding

Clearance changes

Gastrointestinal changes

Oral Ampicllin Pharmacokinetics in Pregnancy

Parameter	Pregnant	Nonpregnant
AUC(cm^2)	8.2±4.1	12.6±4.3*
Peak Level (µg/ml)	2.2±1.0	3.7±1.5*
Bioavailability (%)	45.6±20.2	48.1±19.3**

*P < 0.001

** NS

Philipson A. J Inf Dis 1977;136:370-6.

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

Kimberlin DF, et al. Amer J Obstet Gynecol 1998; 179: 846

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

Gerdin E, et al. J Perinat Med 1990;18:479-87.

Pharmacokinetics of Cefuroxime in Pregnancy

Category	V_D (L)	Cl (ml/min)	T(½)
Pregnant	17.8± 1.9	282±34*	44±5*
At Delivery	19.3±3.1	259±35*	52±10
Postpartum	16.3±2.1	198±27	58±8

*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

Steen B, et al. Br J Clin Pharmacol 1982; 13: 661

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

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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.

Buehler BA, et al. N Engl J Med 1990;322:1567-72.

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

Parman T, et al. Nature Medicine 1999; 5:582

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