

# **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**

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.**

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## **Respiratory Changes**

# **Respiratory Changes**

**Compensated respiratory alkalosis**

**Lowered  $P_a\text{CO}_2$**

**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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**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 (PHENYTOIN) ( $\mu\text{g/ml}$ ) and FREE (PHENYTOIN) ( $\mu\text{g/ml}$ ) in NONPREG, 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> 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**

**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.

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

# **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  $\Delta$**

**No difference from postpartum**

**Increased orocecal transit time in 3rd  $\Delta$**

**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  $V_d$  (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**

# **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.

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

## **THEOPHYLLINE CL<sub>h</sub> AND CL<sub>int</sub> DURING PREGNANCY AND POSTPARTUM**

**Clearance (mL/min × 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 2<sup>nd</sup> TRI, 3<sup>rd</sup> 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] ( $\mu\text{g/ml}$ ) for nonpreg, 1<sup>st</sup> TRI, 2<sup>nd</sup> TRI, and 3<sup>rd</sup> 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

<u>Parameter</u>	<u>Singleton</u>	<u>Twin</u>
Vd (L)	67.5 ± 27.9	70.9 ± 28.4
Cl (L/h)	5.7 ± 3.1	8.4 ± 6.4 **
T <sup>1/2</sup> (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 <sub>D</sub> (L)	Cl(ml/min)	T(1/2)
Pregnant	17.8 <sub>±</sub> 1.9	282 <sub>±</sub> 34*	44 <sub>±</sub> 5*
At Delivery	19.3 <sub>±</sub> 3.1	259 <sub>±</sub> 35*	52 <sub>±</sub> 10
Postpartum	16.3 <sub>±</sub> 2.1	198 <sub>±</sub> 27	58 <sub>±</sub> 8

\*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**

**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.**

## **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 Ampicillin Pharmacokinetics in Pregnancy

Parameter	Pregnant	Nonpregnant
AUC(cm <sup>2</sup> )	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 Acyclovir**

**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 <sub>D</sub> (L)	Cl (ml/min)	T(½)
Pregnant	17.8 <sub>±</sub> 1.9	282 <sub>±</sub> 34*	44 <sub>±</sub> 5*
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\*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] ( $\mu\text{g/mL}$ ) 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**

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**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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# 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 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 [Theophylline] ( $\mu\text{g/mL}$ ) 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**