

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**

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Body Fluid Spaces in Pregnant and Nonpregnant Women

	WEIGHT (kg)	PLASMA VOLUME (mL/kg)	ECF SPACE (L/kg)	TBW (L/kg)
NONPREGNANT		49		
	< 70		0.189	0.516
	70 – 80		0.156	0.415
	> 80		0.151	0.389
PREGNANT		67		
	< 70		0.257	0.572
	70 – 80		0.255	0.514
	> 80		0.240	0.454

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**

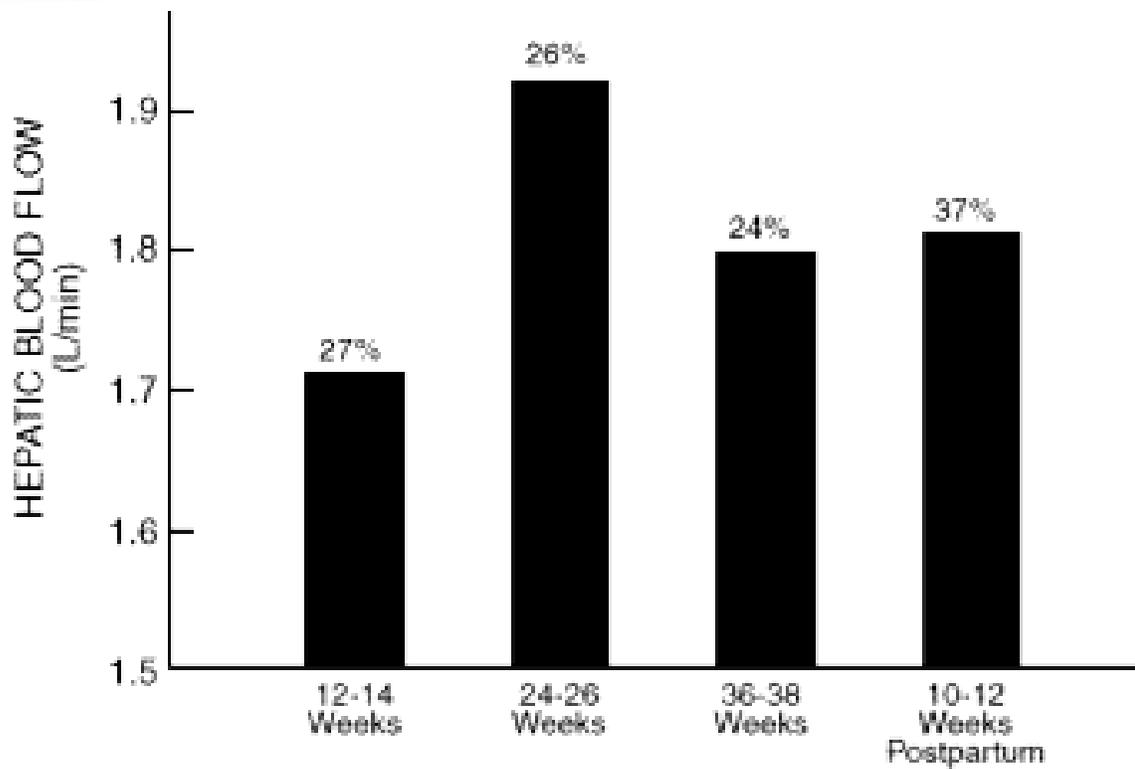
Cardiovascular System Changes

- **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)



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

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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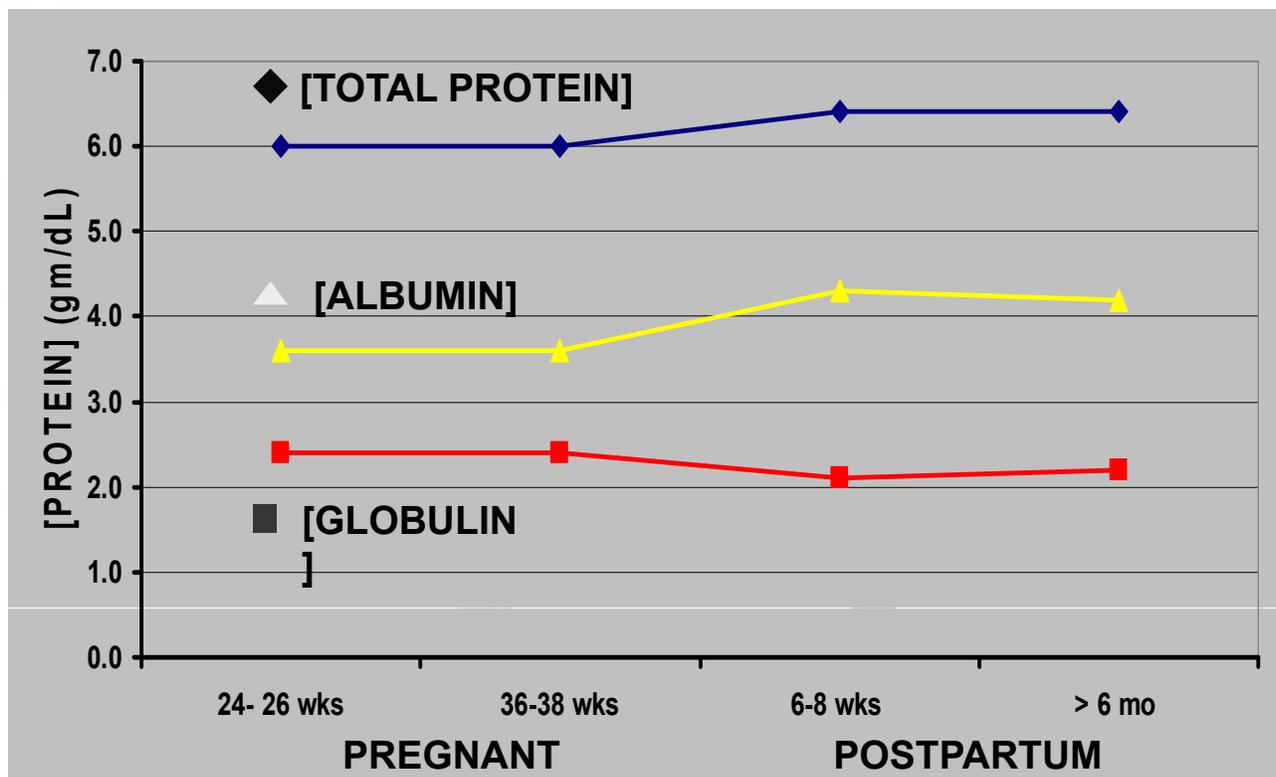
Respiratory Changes

- **Compensated respiratory alkalosis**
- **Lowered $P_a\text{CO}_2$**
- **pH 7.44**

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PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM



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, \downarrow [ALBUMIN] REFLECTS EITHER \downarrow SYNTHESIS RATE OR \uparrow 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**

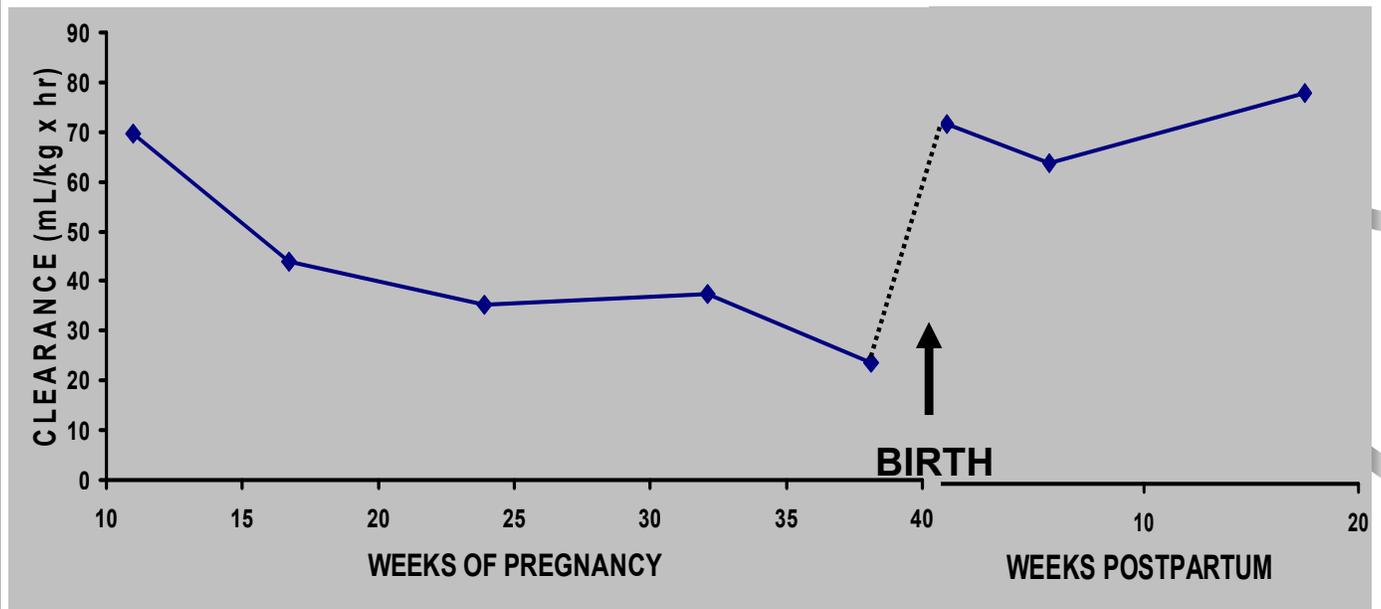
CYP3A4

- **Hydroxylation**
- **Increased activity during pregnancy**

CYP1A2

- **Activity decreased progressively during pregnancy**
- **Progressive lengthening of caffeine half-life**

Caffeine Clearance – CYP 1A2

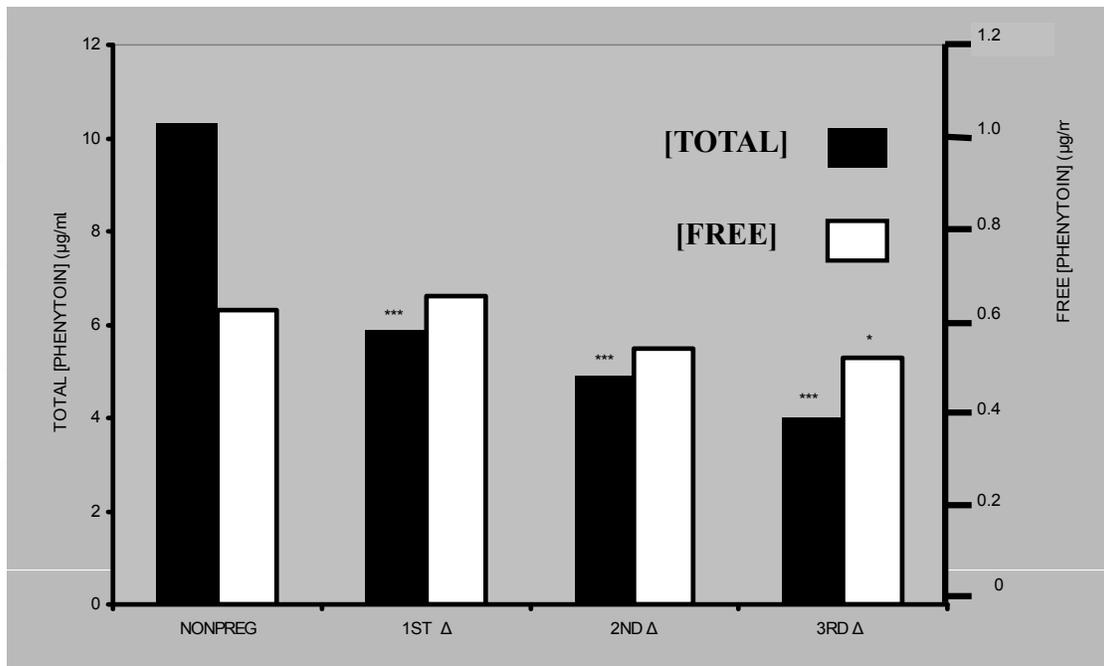


Aldridge A, et al. *Semin Perinatol* 1981;5:310-4.

CYP2C9

- **Activity shown to increase during pregnancy**
- **Lowered total concentration of phenytoin during pregnancy**

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9



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

CYP2D6 Activity

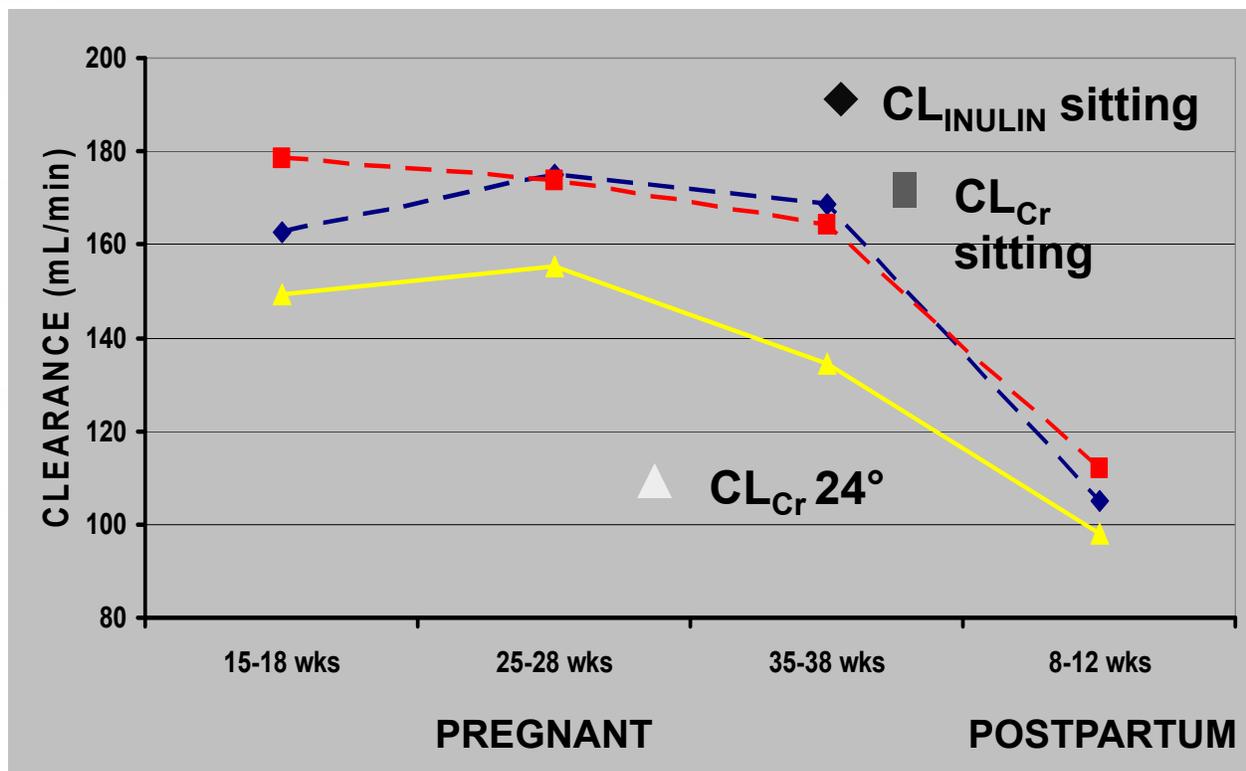
- **Genetic determined polymorphism**
- **Increased clearance of metoprolol observed during pregnancy**
- **Increased clearance in homozygous and heterozygous extensive metabolizers**
- **No change in homozygous poor metabolizers**

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

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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- **Decrease in Albumin Concentration**
- **Enzymatic Activity Changes**
- **Increase in GFR**

GFR DURING PREGNANCY AND POSTPARTUM



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

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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- **Gastrointestinal Changes**

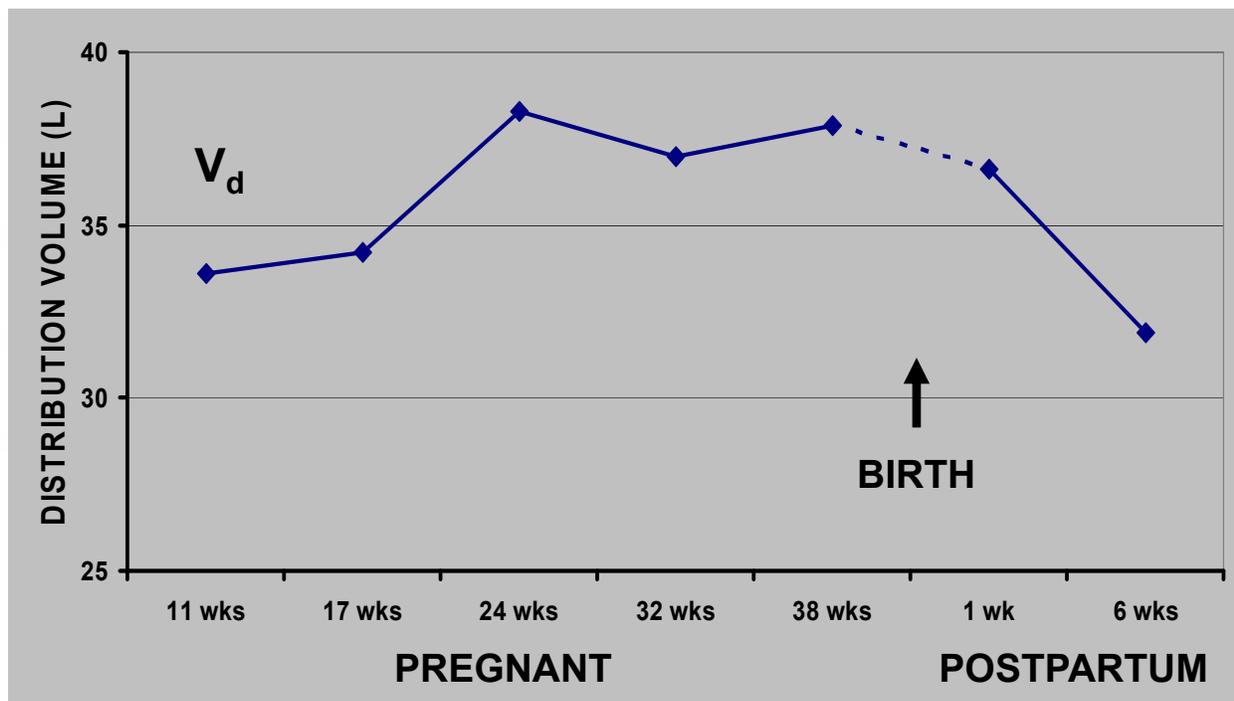
Gastrointestinal Changes

- **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

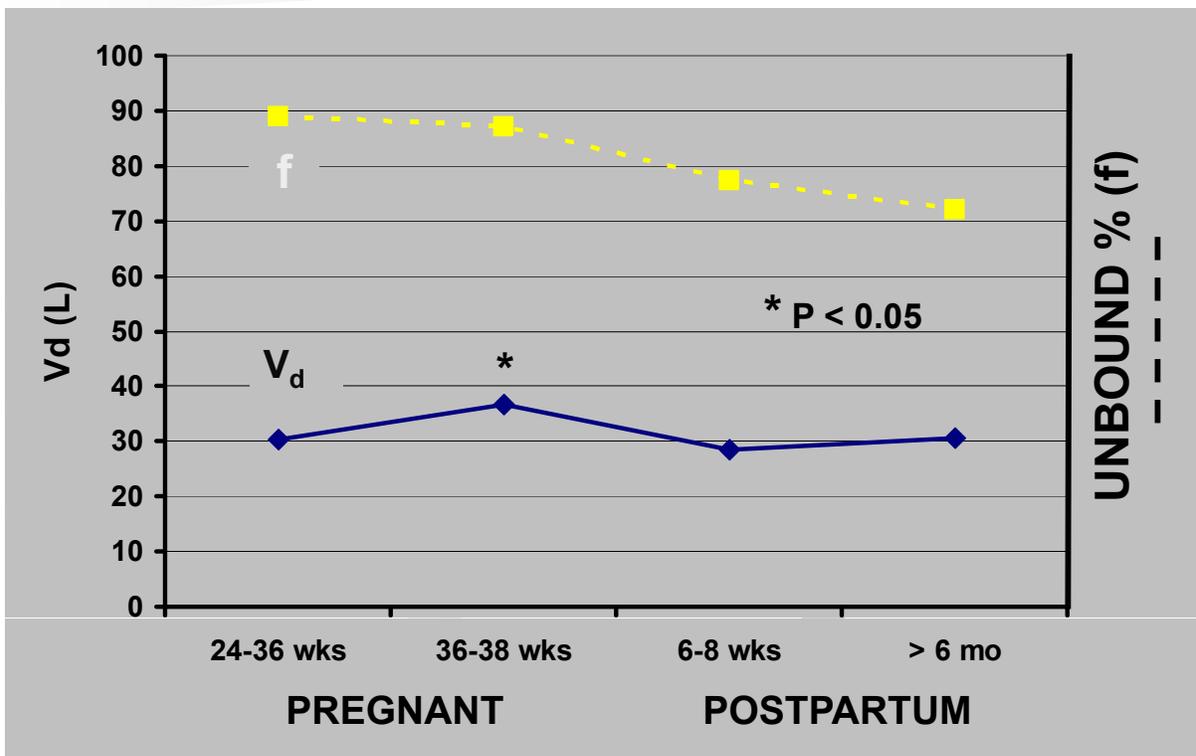
- **Volume Expansion**

CAFFEINE V_d (MARKER FOR TBW) DURING PREGNANCY AND POSTPARTUM



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

THEOPHYLLINE V_d DURING PREGNANCY AND POSTPARTUM

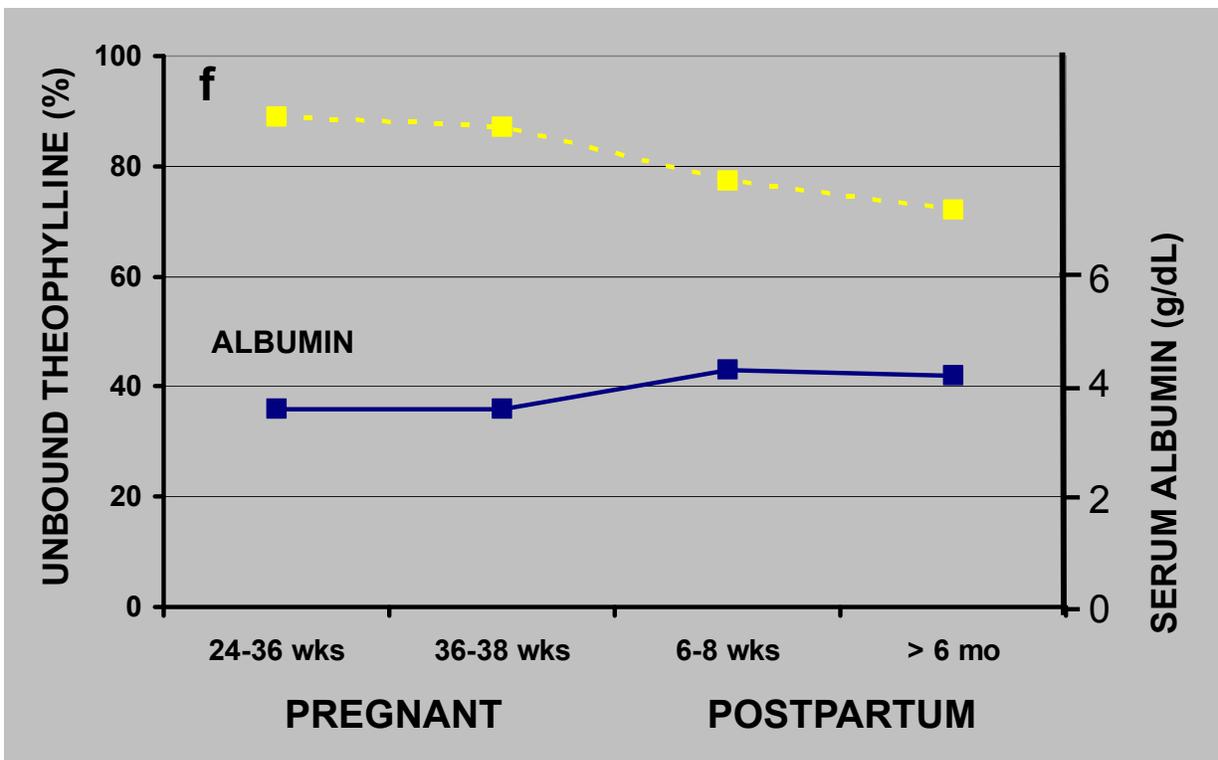


Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

Maternal Physiologic Changes Altering PK of Drugs

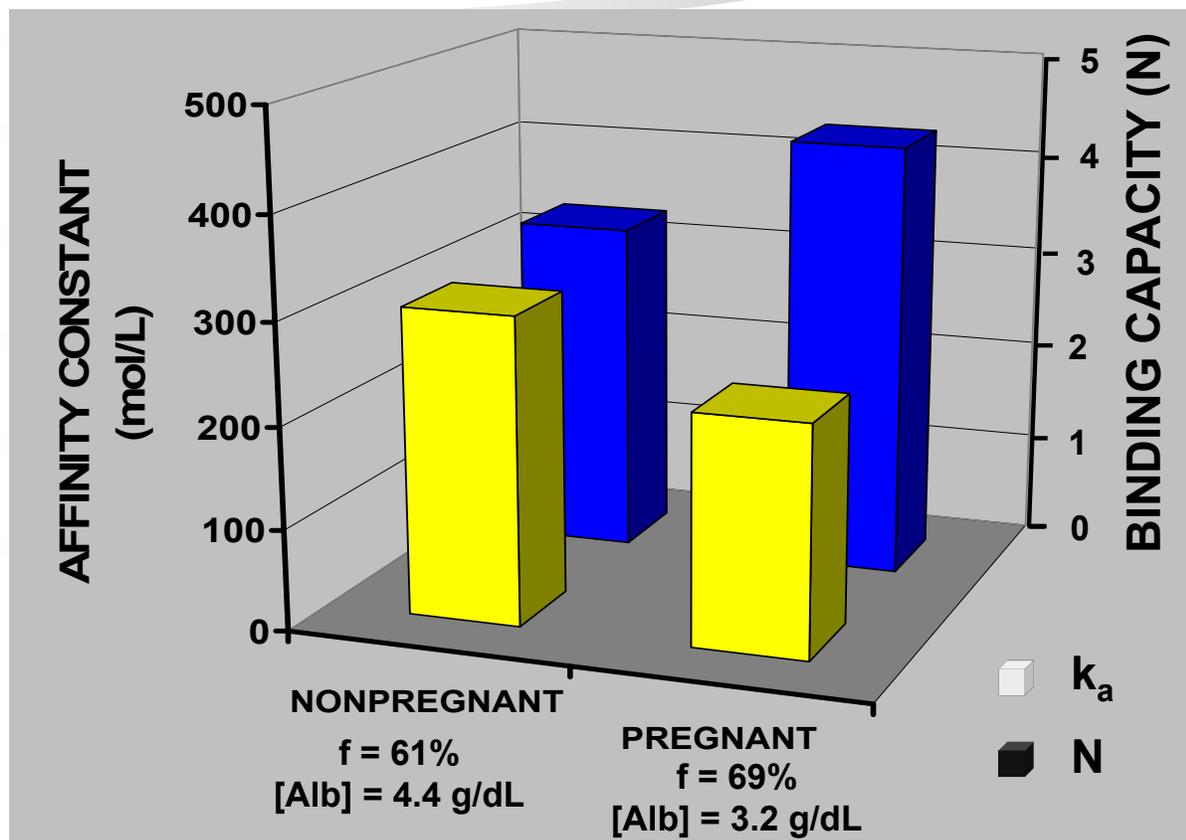
- **Volume expansion**
- **Protein binding-increase in free fraction of drugs bound to albumin**

THEOPHYLLINE PROTEIN BINDING DURING PREGNANCY AND POSTPARTUM



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

Theophylline Protein Binding

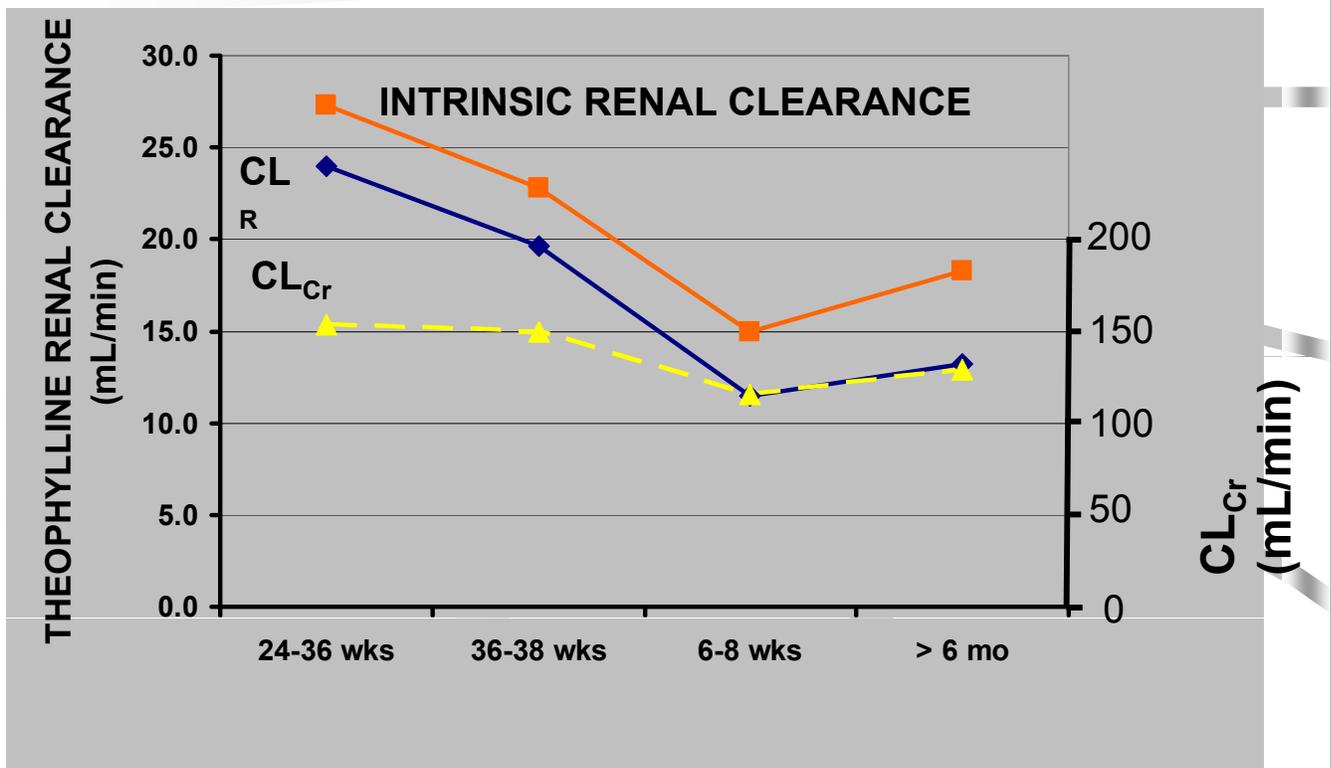


Connelly TJ, et al. Clin Pharmacol Ther 1990;47:68-72.

Maternal Physiologic Changes Altering PK of Drugs

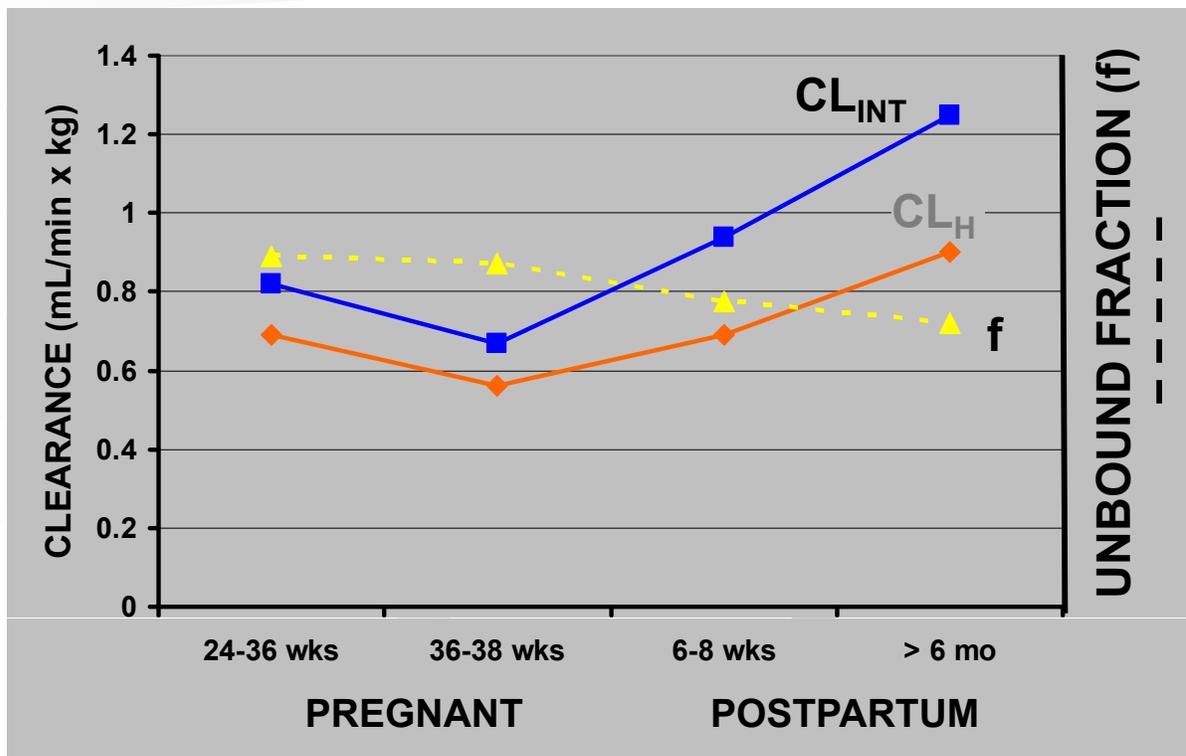
- **Volume expansion**
- **Protein binding**
- **Clearance changes**

THEOPHYLLINE RENAL CLEARANCE DURING PREGNANCY AND POSTPARTUM



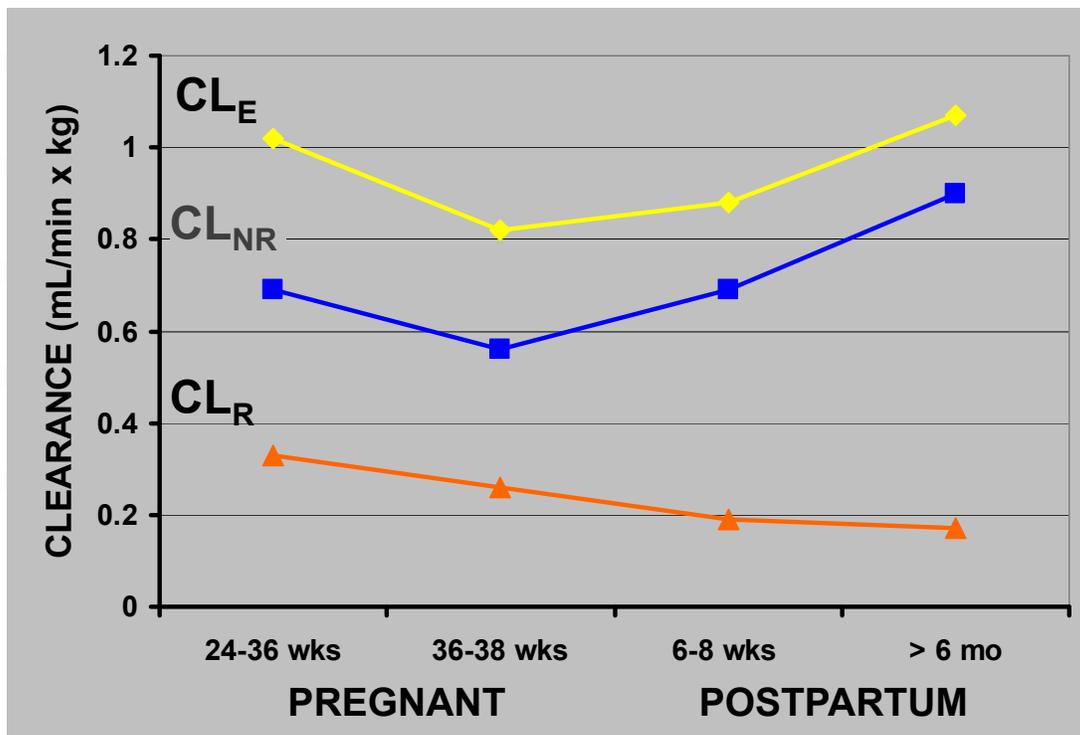
Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

THEOPHYLLINE CL_H AND CL_{INT} DURING PREGNANCY AND POSTPARTUM



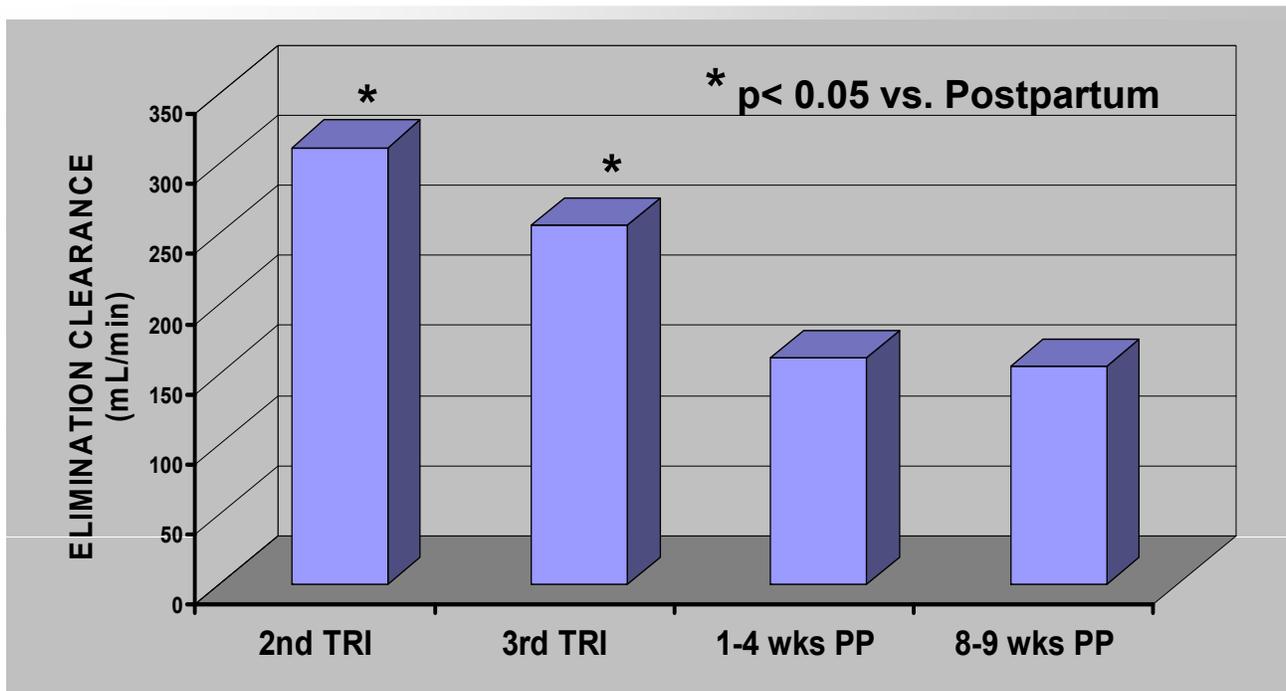
Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

THEOPHYLLINE CLEARANCE DURING PREGNANCY AND POSTPARTUM



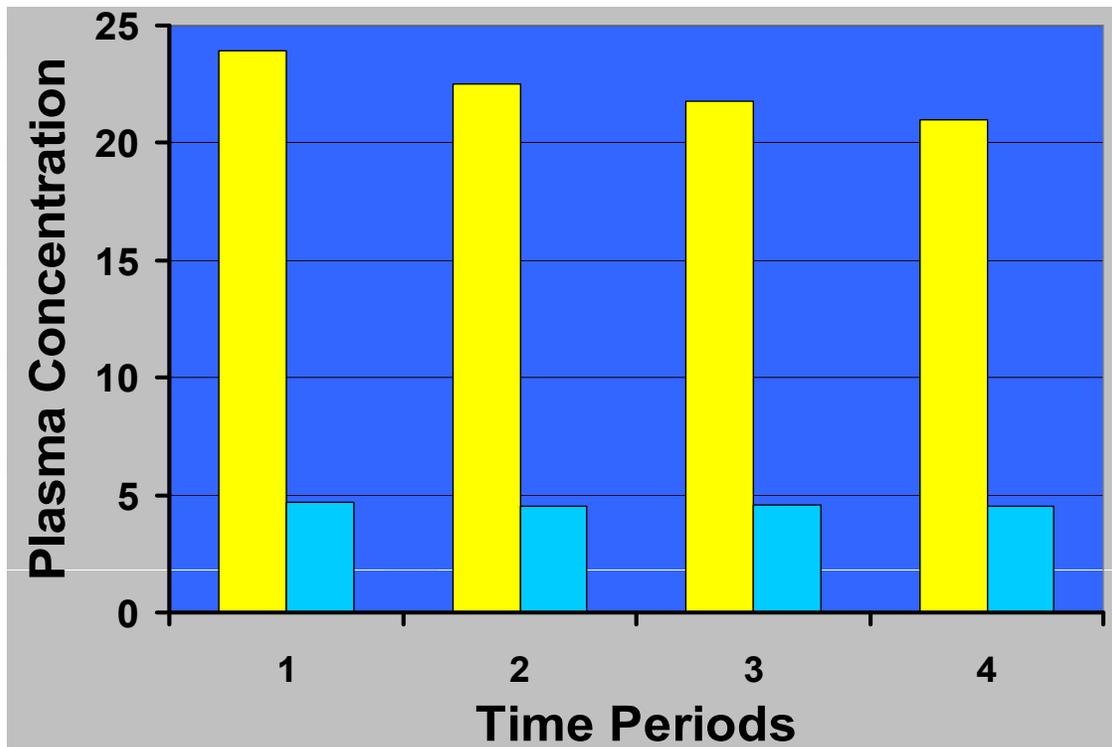
Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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



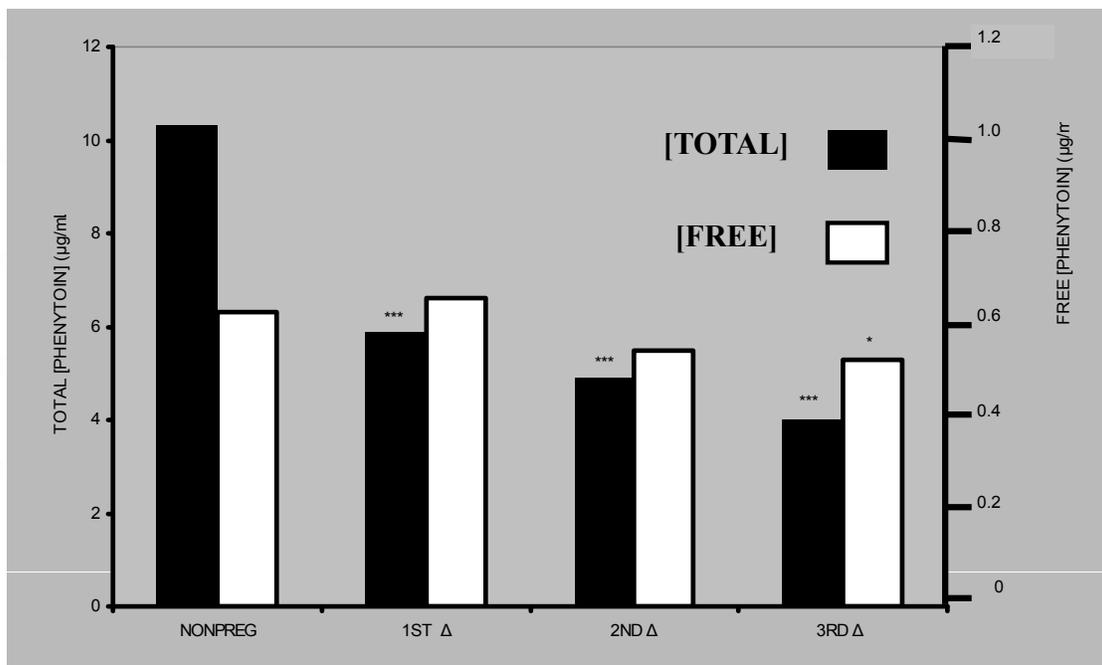
Pond SM, et al. J Pharmacol Exp Ther 1978;233:1-6.

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



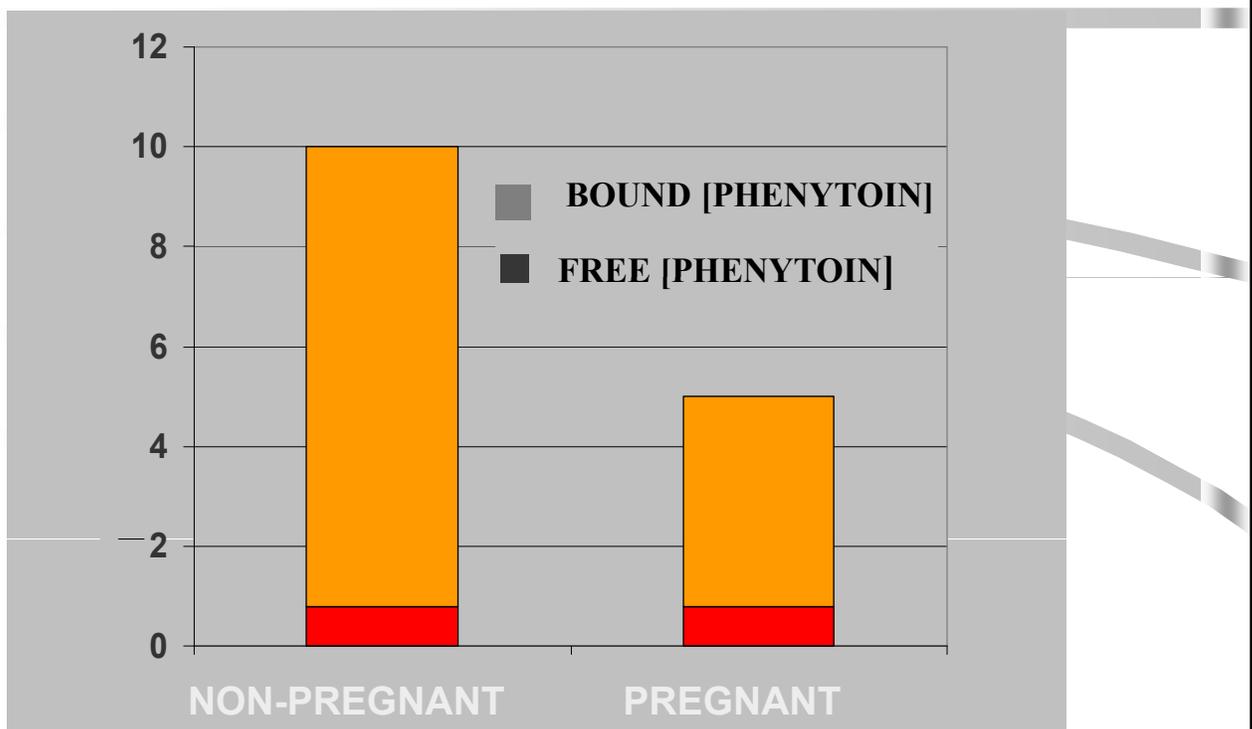
Tomsom T, et al. *Epilepsia* 1994; 35:122-30.

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

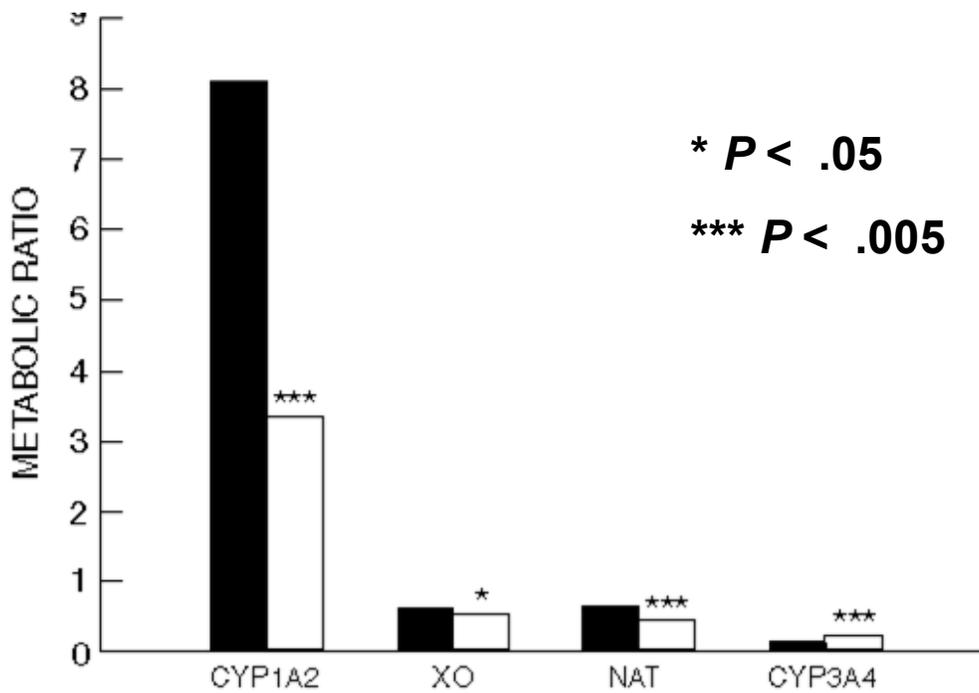


Tomson T, et al. *Epilepsia* 1994;35:122-30.

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

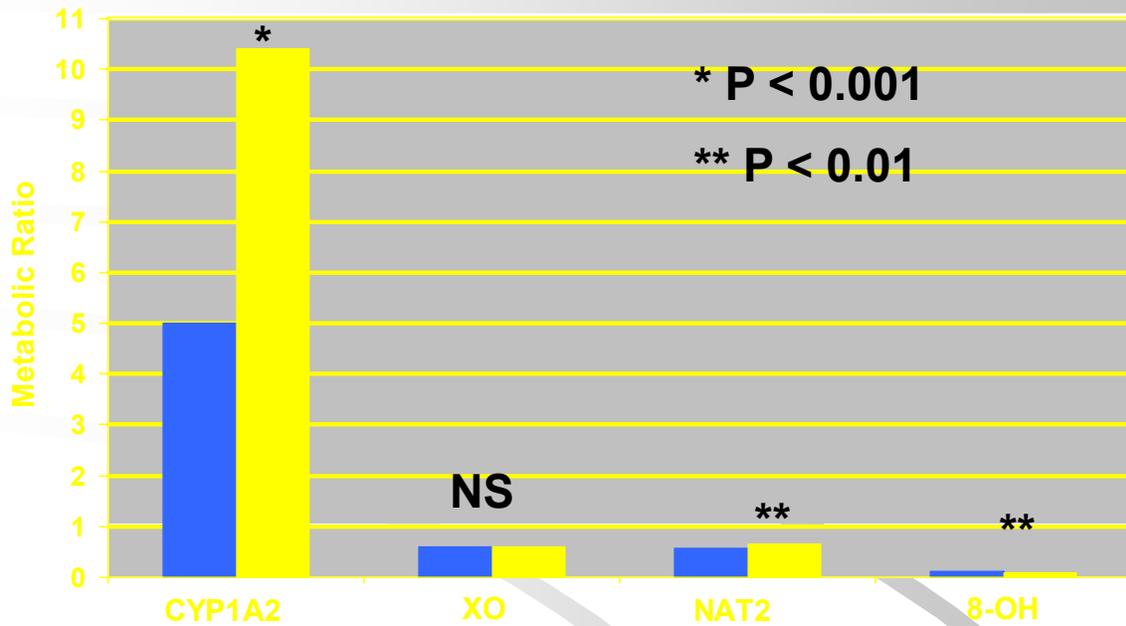


CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN



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

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



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

Betamethasone PK in Singleton and Twin Pregnancies

Parameter	Singleton	Twin
V_d (L)	67.5 ± 27.9	70.9 ± 28.4
Cl (L/h)	5.7 ± 3.1	8.4 ± 6.4 **
$T_{1/2}$ (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

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.

Enoxaprin PK during Pregnancy

- **T_{\max} shows no change**
- **C_{\max} lower during pregnancy**
- **CI 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**
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Oral Ampicillin 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

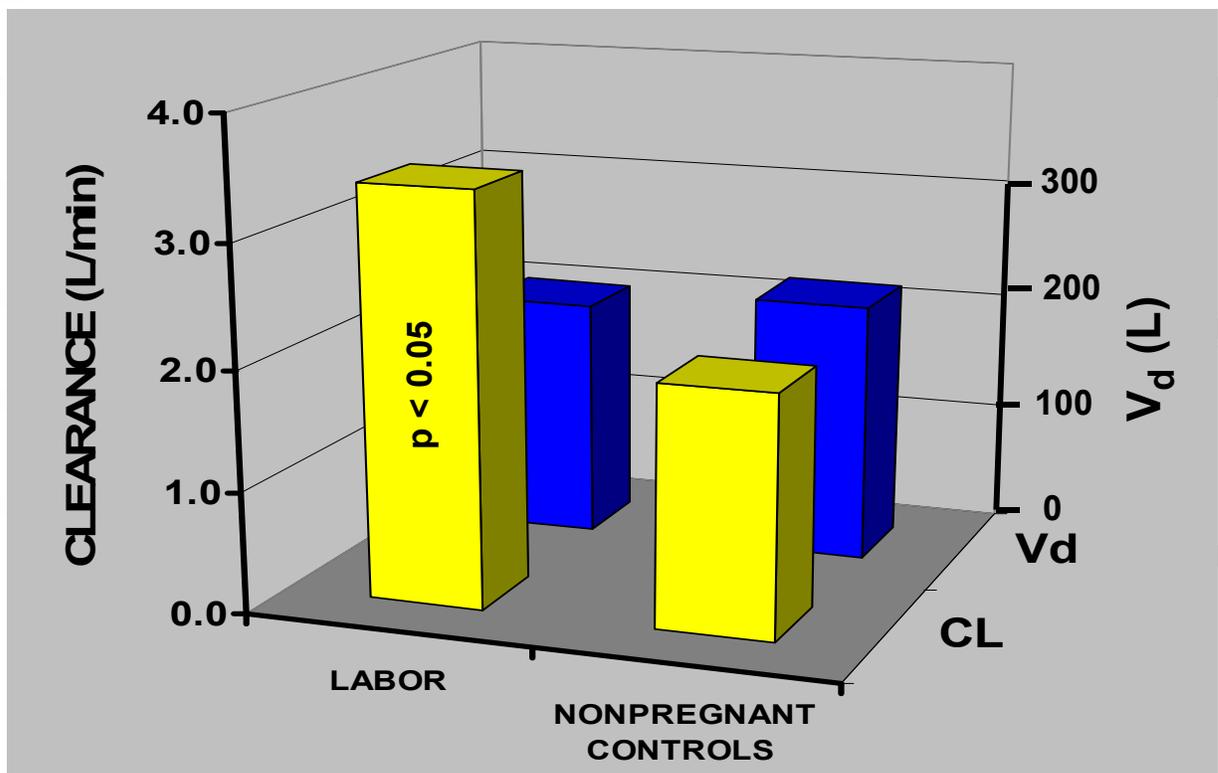
- **The pro-drug Valacyclovir converted by first pass metabolism to Acyclovir**
- **Non-pregnant Valacyclovir gives 3 - 5 times higher plasma level as Acyclovir**
- **Valacyclovir PK study in pregnancy gave plasma levels 3 times higher than Acylovir**

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



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

Pharmacokinetics of Cefuroxime in Pregnancy

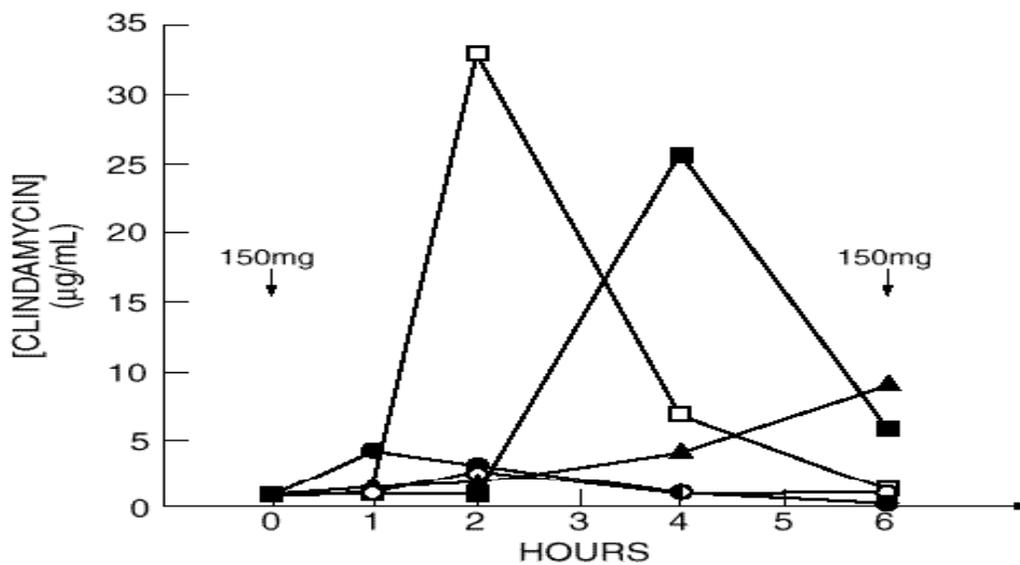
Category	V _D (L)	Cl (ml/min)	T(½)
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*p<0.05 on comparison to PP

Postpartum PK Considerations

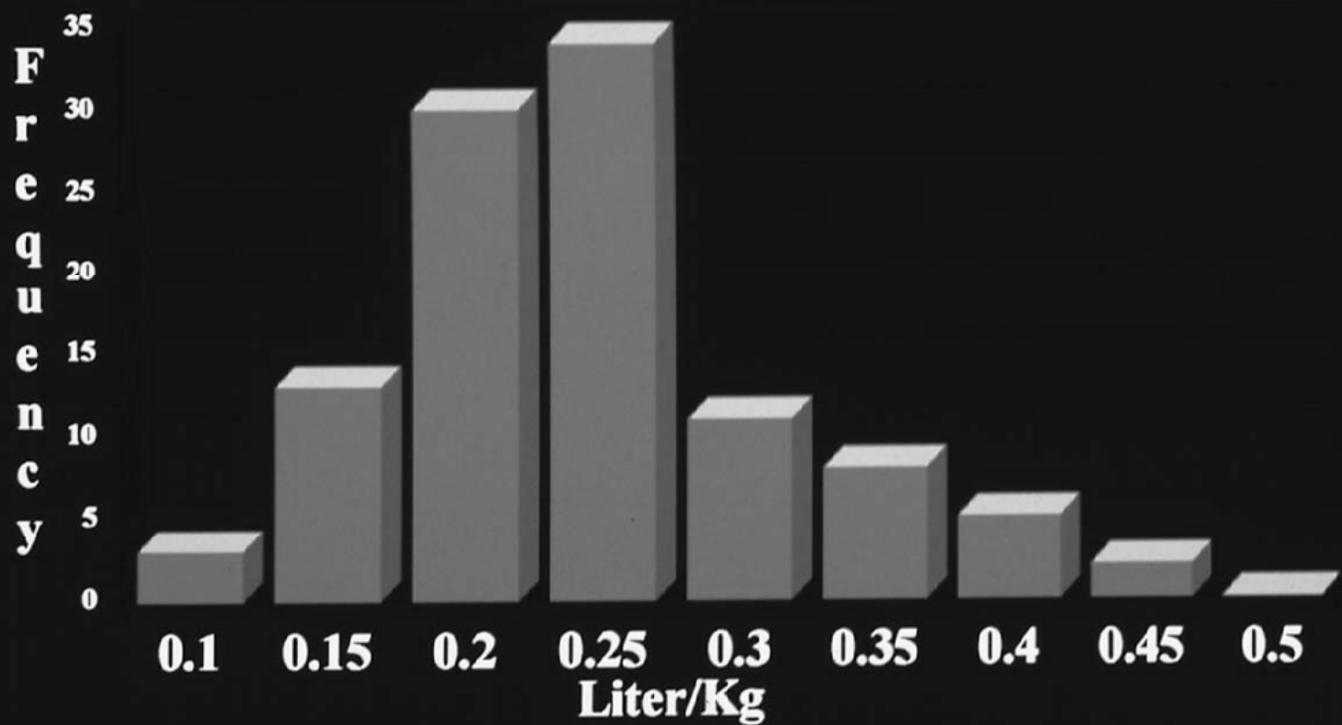
- **Increased cardiac output maintained**
- **GFR increased**
- **Diuresis**
- **Breastfeeding**
- **Great variability**

Postpartum Clindamycin Pharmacokinetics



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

Postpartum Gentamicin Distribution Volume



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**

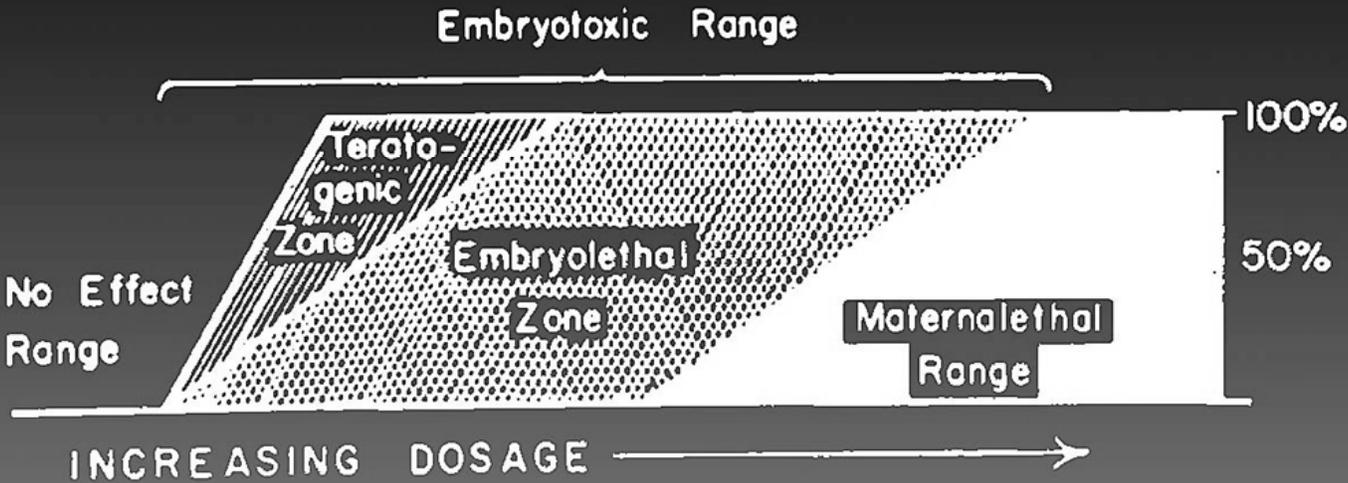
PHOCOMELIA DUE TO THALIDOMIDE



General Principles of Teratology

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DOSE-RESPONSE RELATIONSHIP



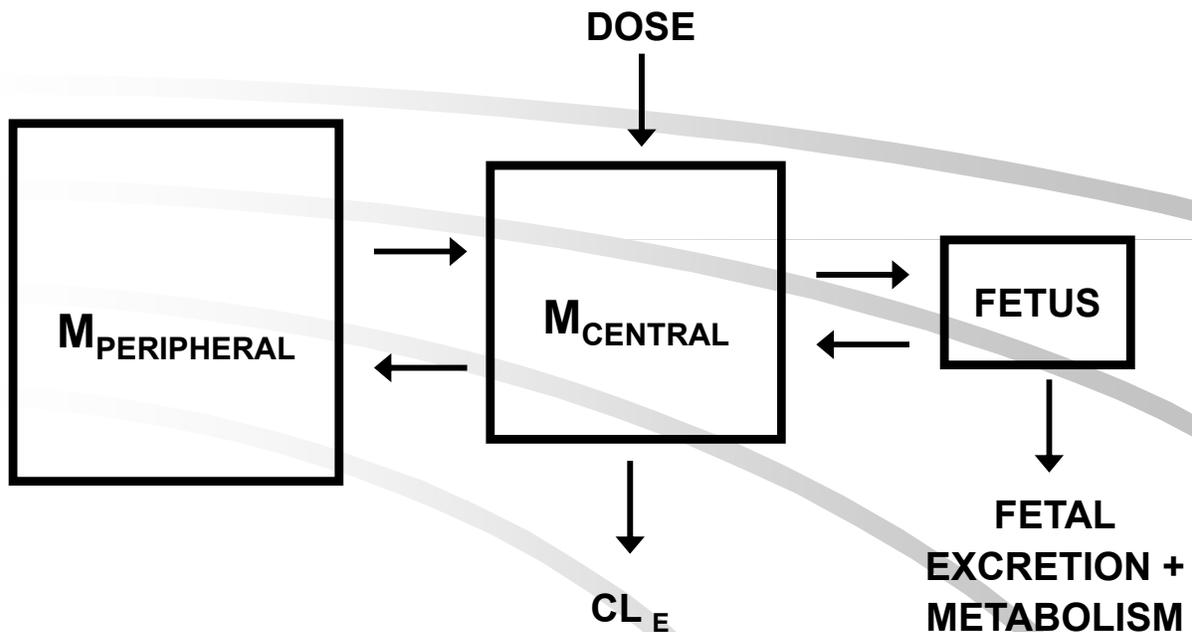
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Placental Transport

- **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

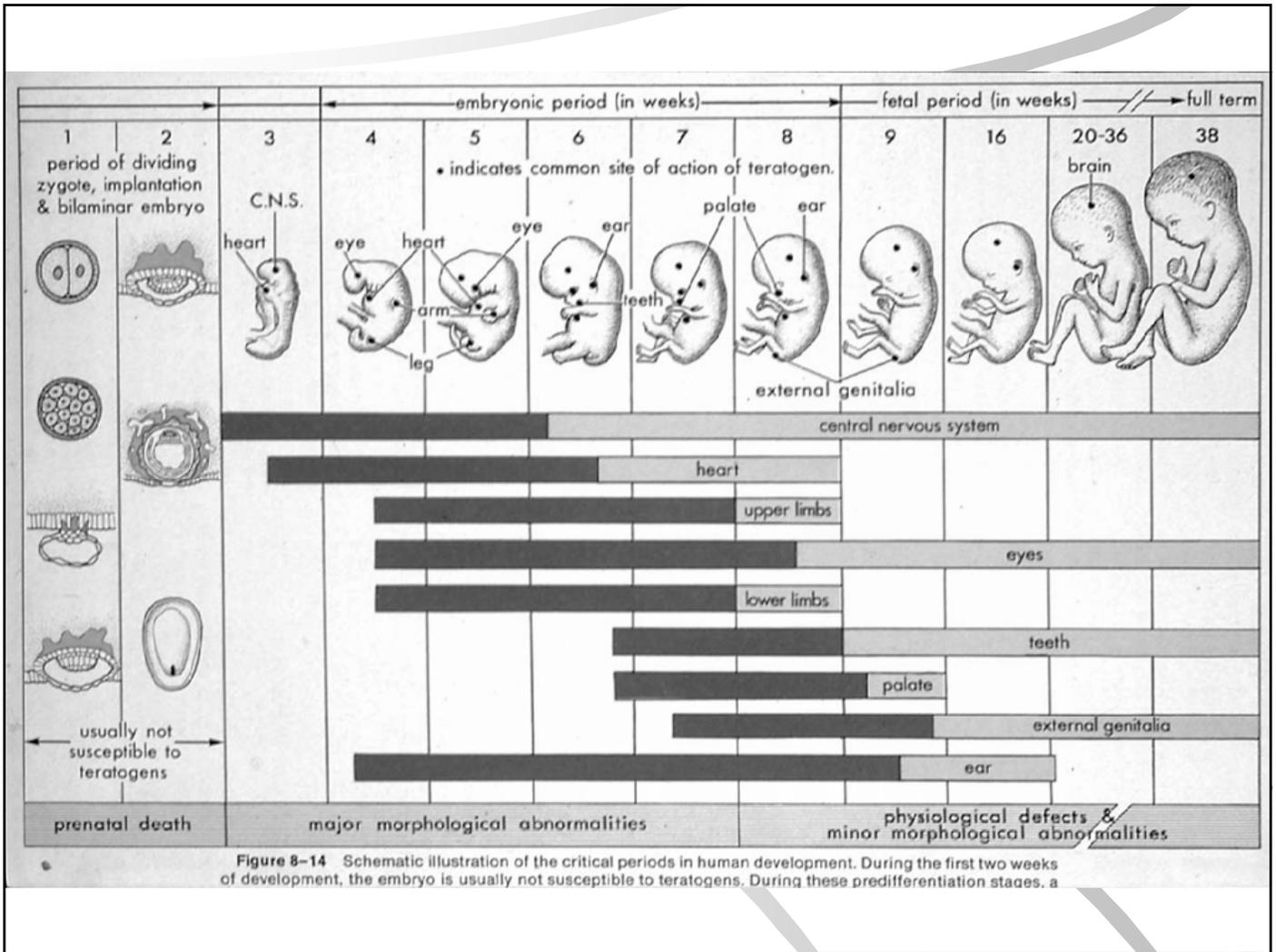


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All or Nothing Period



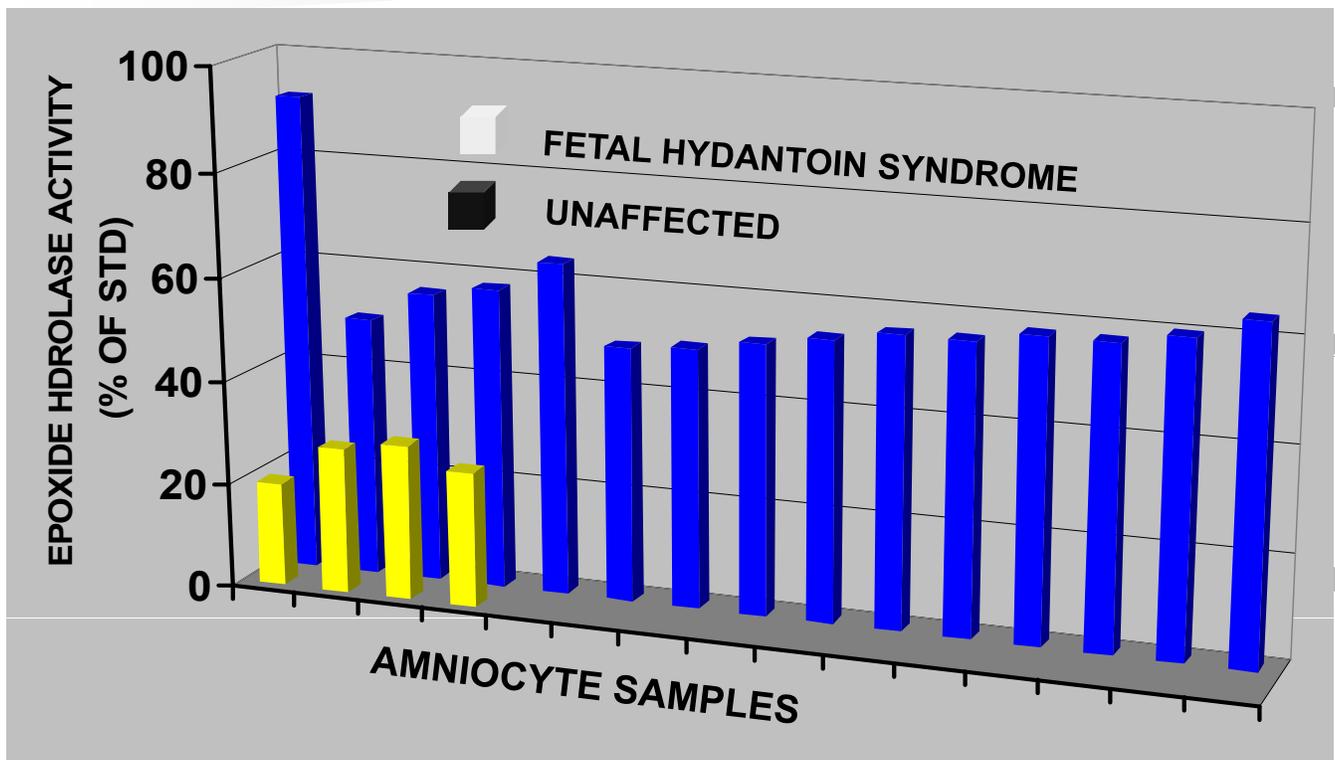
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Phenytoin

- **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



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 α 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?**

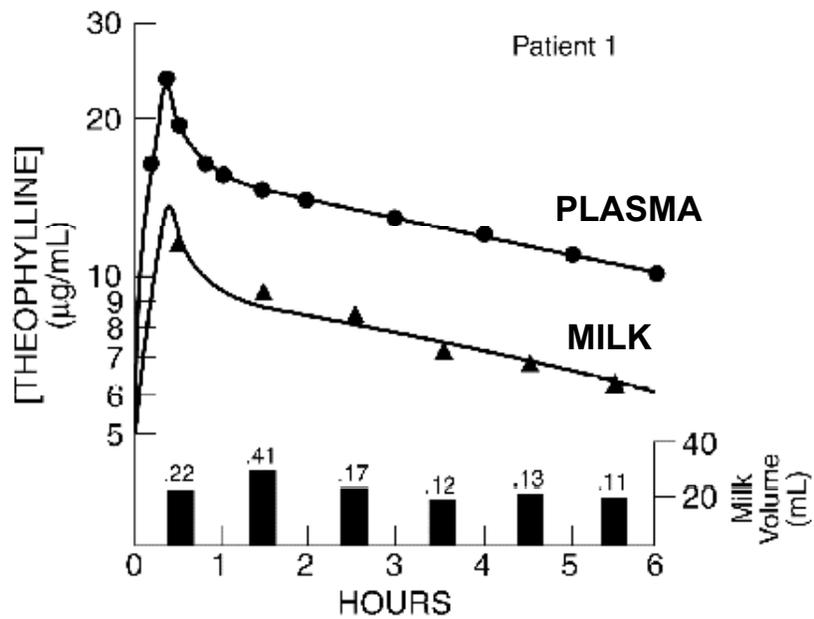
Evaluation of Drugs in Breast Milk

- **Measure the M / P ratio**
- **Estimate breast milk dose**
- **Estimate infant dose**
- **Measure blood level in the infant**

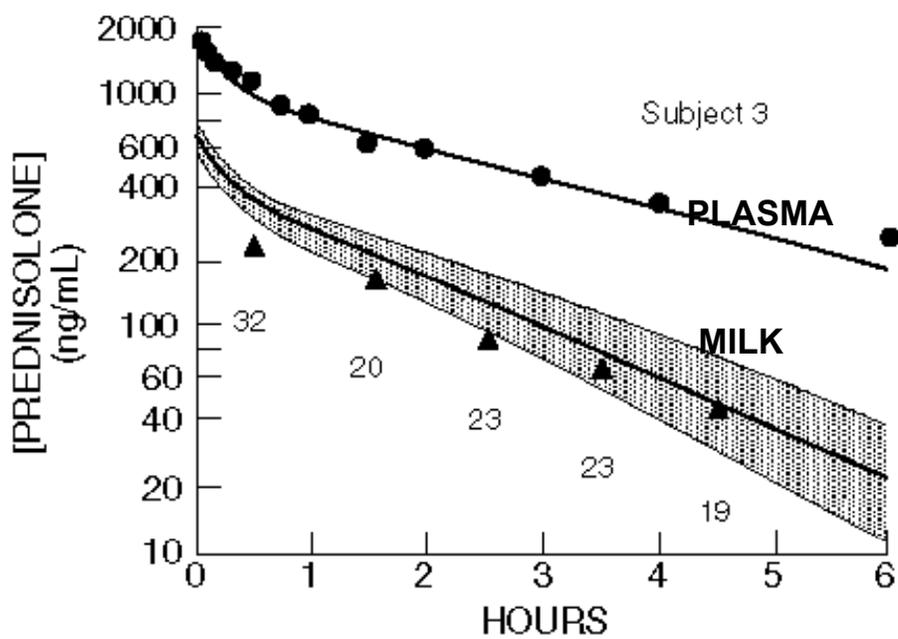
Drugs in Breast Milk

- **Free drug transferred into milk**
- **Milk concentrations usually less than serum concentrations**
- **Exchange is bi-directional**

KINETIC ANALYSIS OF THEOPHYLLINE PLASMA AND MILK CONCENTRATIONS



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**

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**