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**

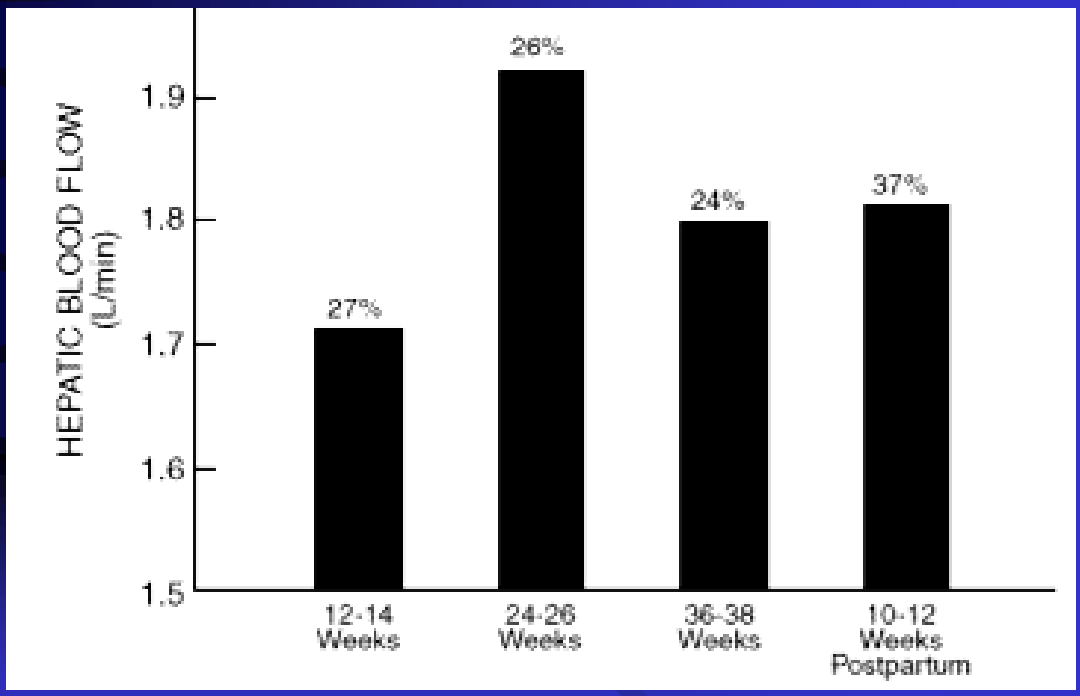
Cardiovascular System Changes

- 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

- Cardiovascular system
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  - Increase in cardiac output
  - Regional blood flow changes
- Respiratory Changes

Respiratory Changes

- Compensated respiratory alkalosis
- Lowered P_aCO_2
- pH 7.44

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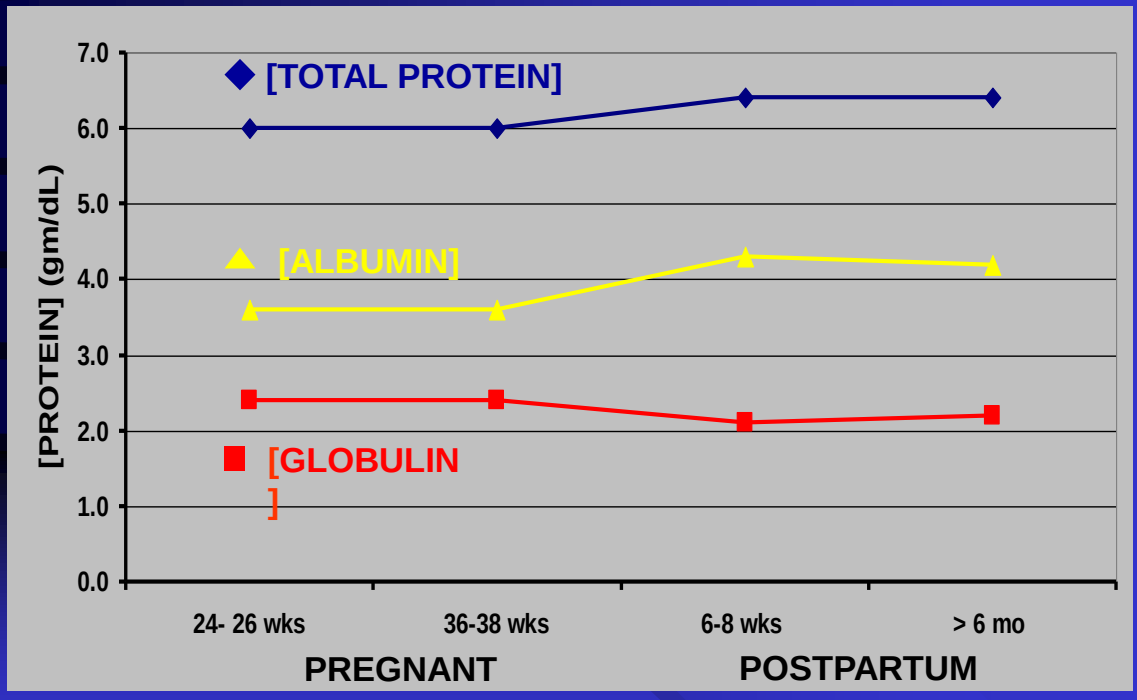
- Decrease in albumin concentration

PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM



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.

Pregnancy Physiology Potentially Affecting Pharmacokinetics

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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

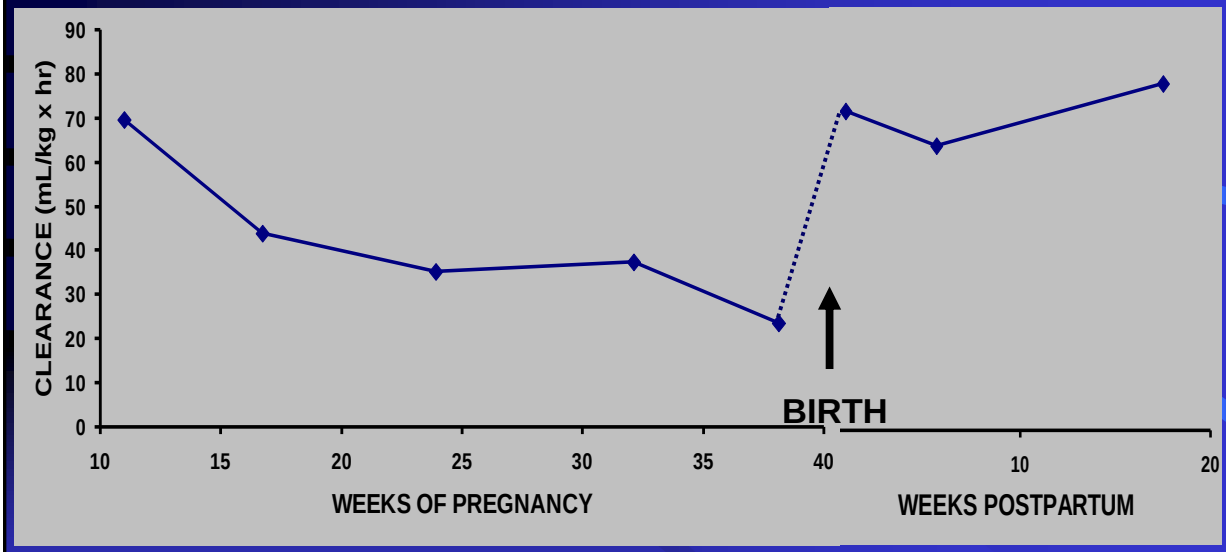
CYP3A4

- Hydroxylation
- Increased activity during pregnancy

CYP1A2

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

Caffeine Clearance – CYP 1A2

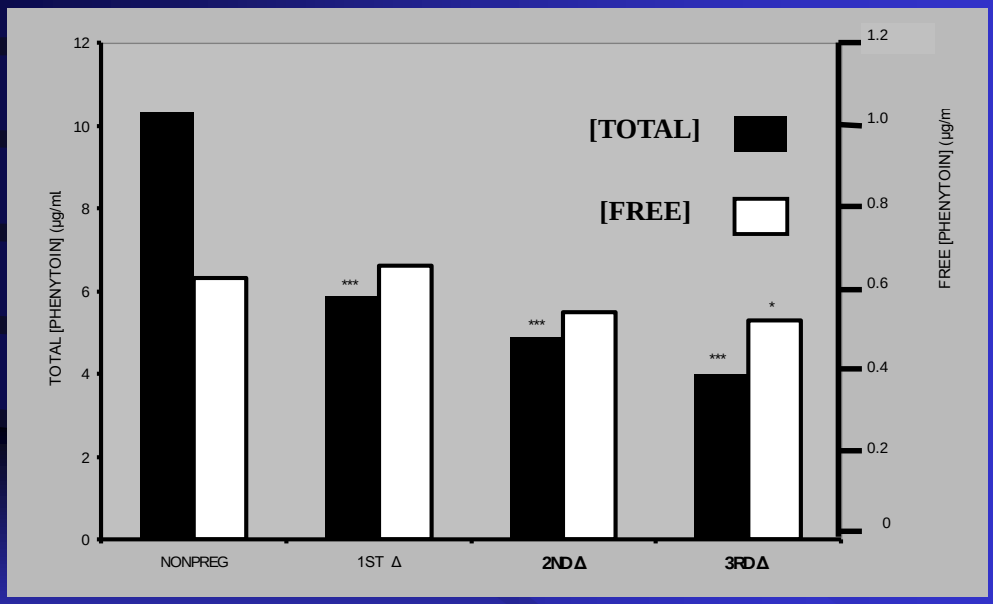


Aldridge A, et al. Semin Perinatol 1981;5:310-4.

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

- Cardiovascular System
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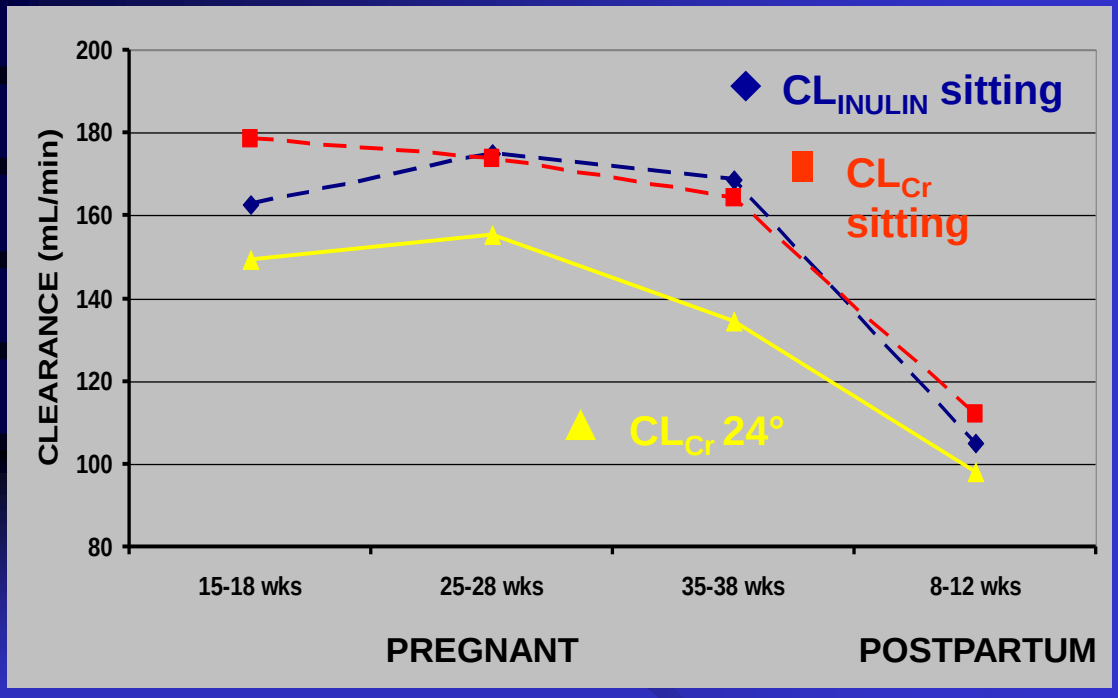
  - Increase in Cardiac Output
  - Regional Blood Flow Changes
- Respiratory Changes
- Decrease in Albumin Concentration
- Enzymatic Activity Changes
- Increase in GFR

GFR DURING PREGNANCY AND POSTPARTUM



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

Pregnancy Physiology Potentially Affecting Pharmacokinetics

- Cardiovascular System
  - Plasma Volume Expansion
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- Respiratory Changes
- Decrease in Albumin Concentration
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- Increase in GFR
- Gastrointestinal Changes

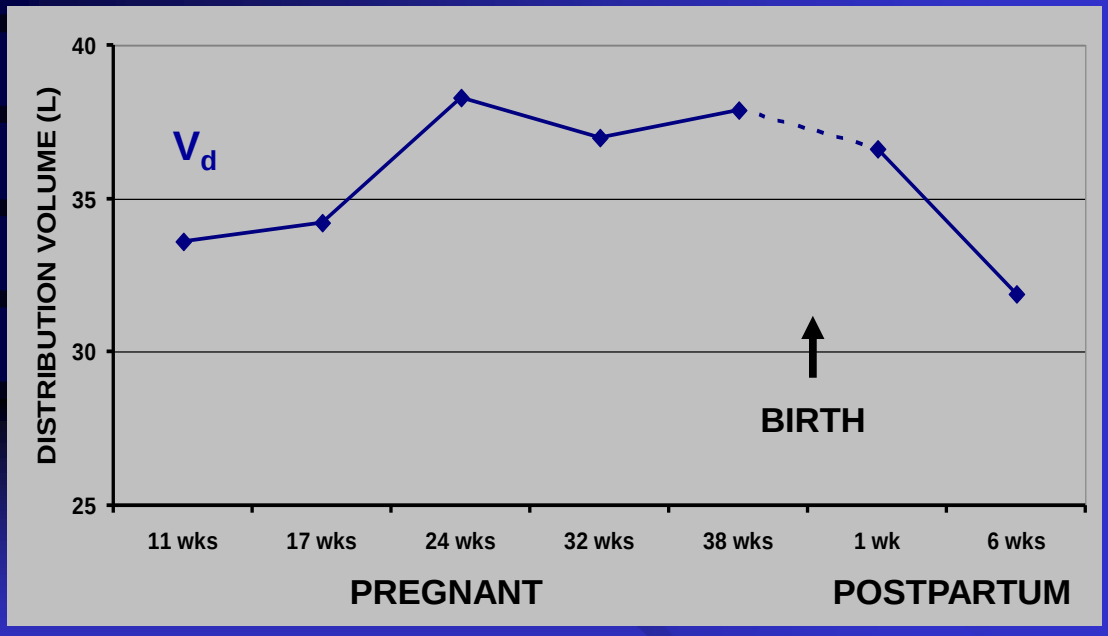
Gastrointestinal Changes

- Decreased gastric acidity
- Gastric emptying
  - Delayed in laboring women
  - No difference between 1st & 3rd Δ in non-laboring women
  - No difference from postpartum
- Increased orocecal transit time in 3rd Δ
  - Progesterone effect
  - Pancreatic polypeptide inverse correlation

Maternal Physiologic Changes Altering PK of Drugs

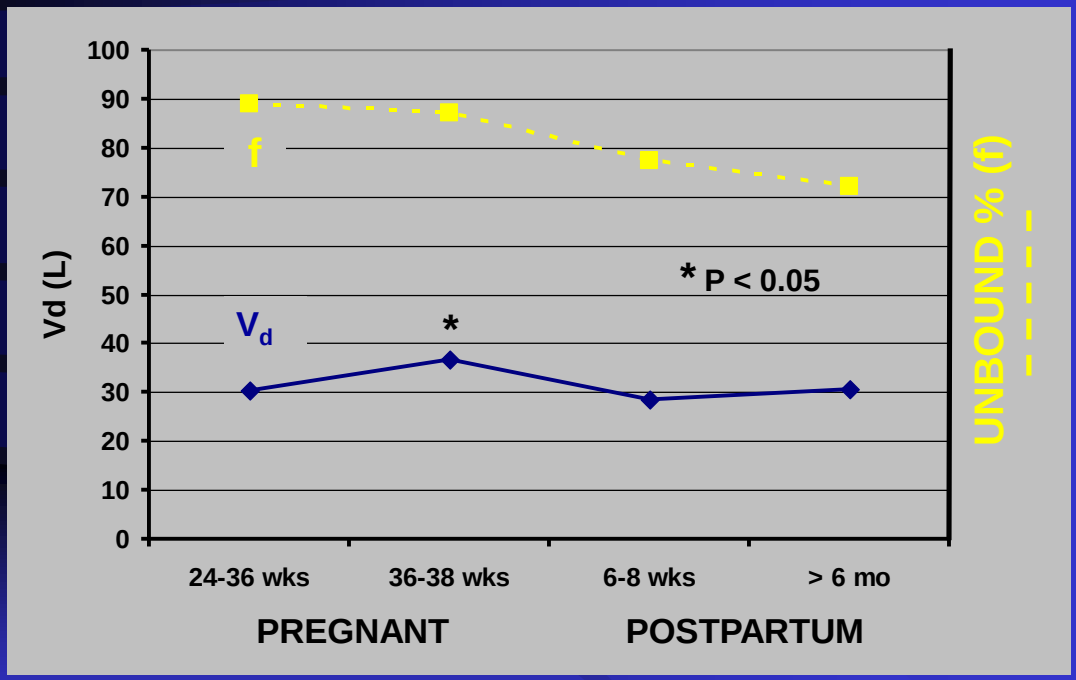
- Volume Expansion

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

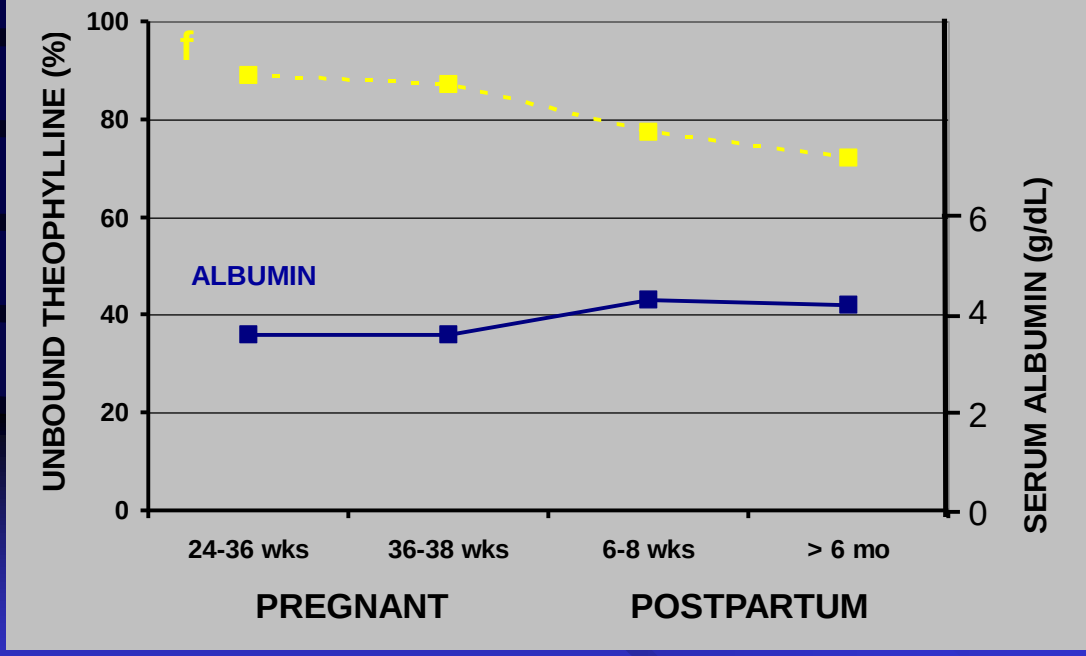


Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

Maternal Physiologic Changes Altering PK of Drugs

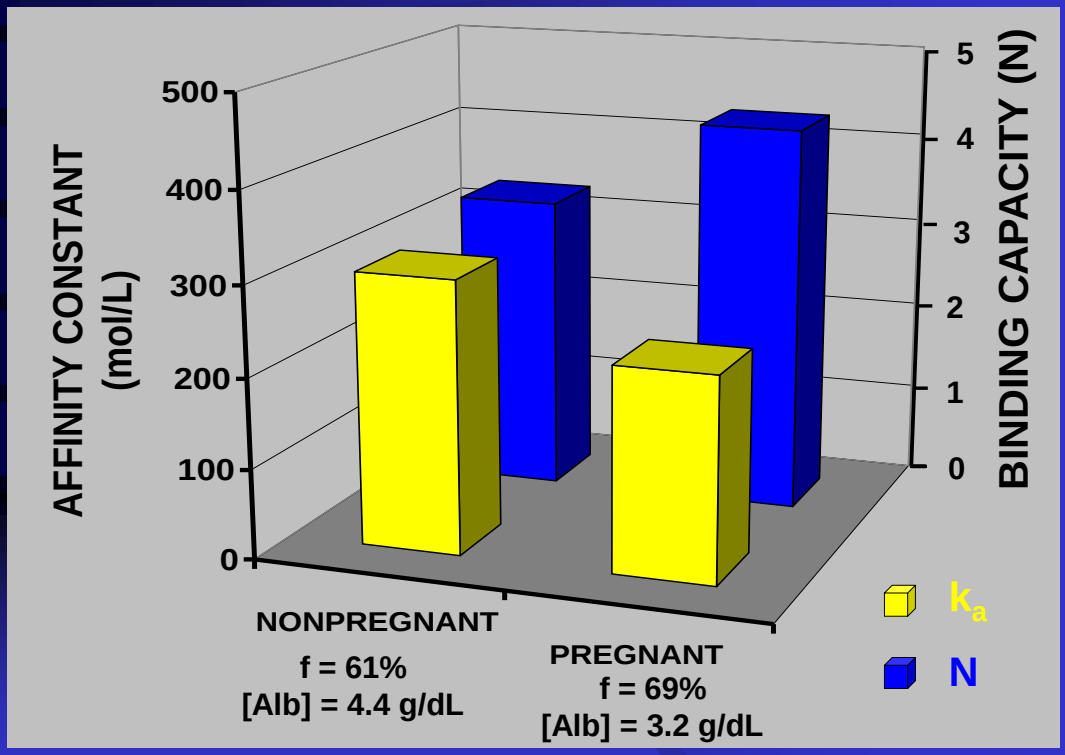
- Volume expansion
- Protein binding-increase in free fraction of drugs bound to albumin

THEOPHYLLINE PROTEIN BINDING DURING PREGNANCY AND POSTPARTUM



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

Theophylline Protein Binding

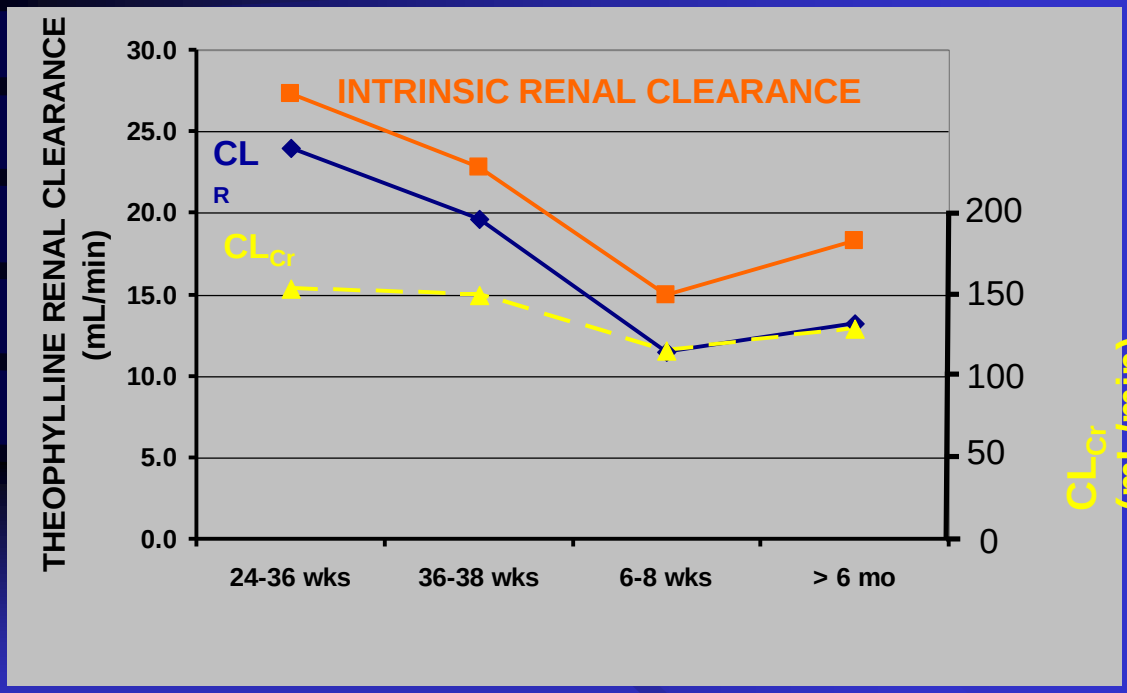


Connelly TJ, et al. Clin Pharmacol Ther 1990;47:68-72.

Maternal Physiologic Changes Altering PK of Drugs

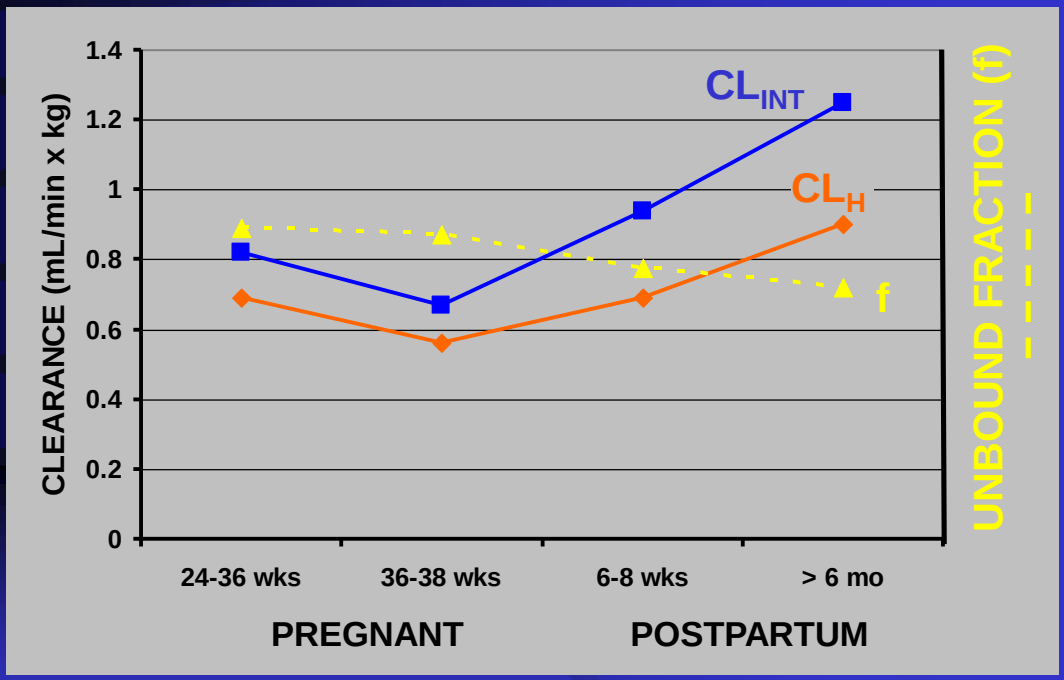
- Volume expansion
- Protein binding
- Clearance changes

THEOPHYLLINE RENAL CLEARANCE DURING PREGNANCY AND POSTPARTUM



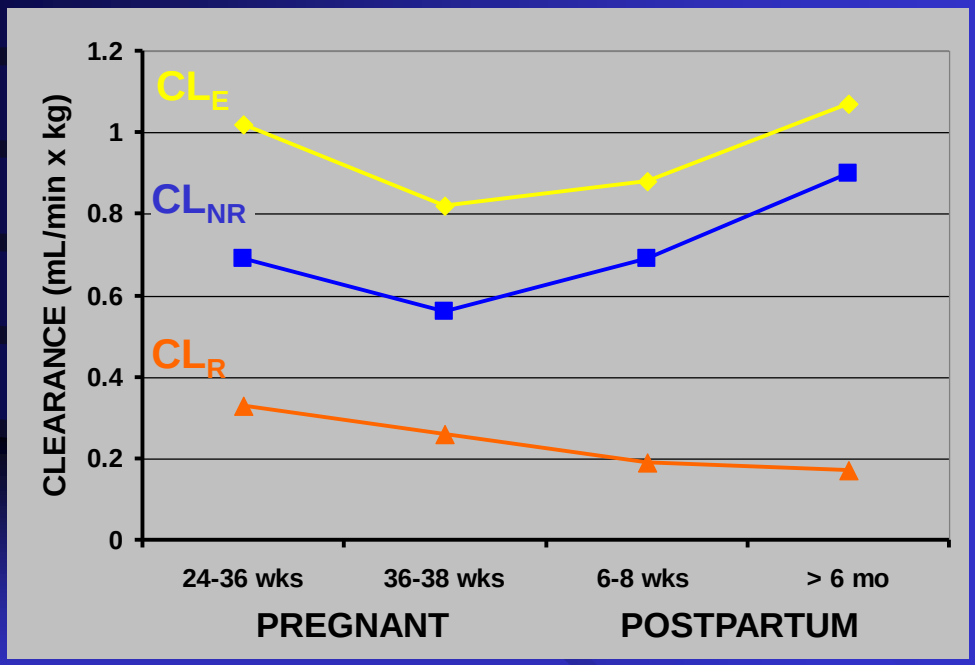
Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

THEOPHYLLINE CL_H AND CL_{INT} DURING PREGNANCY AND POSTPARTUM



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

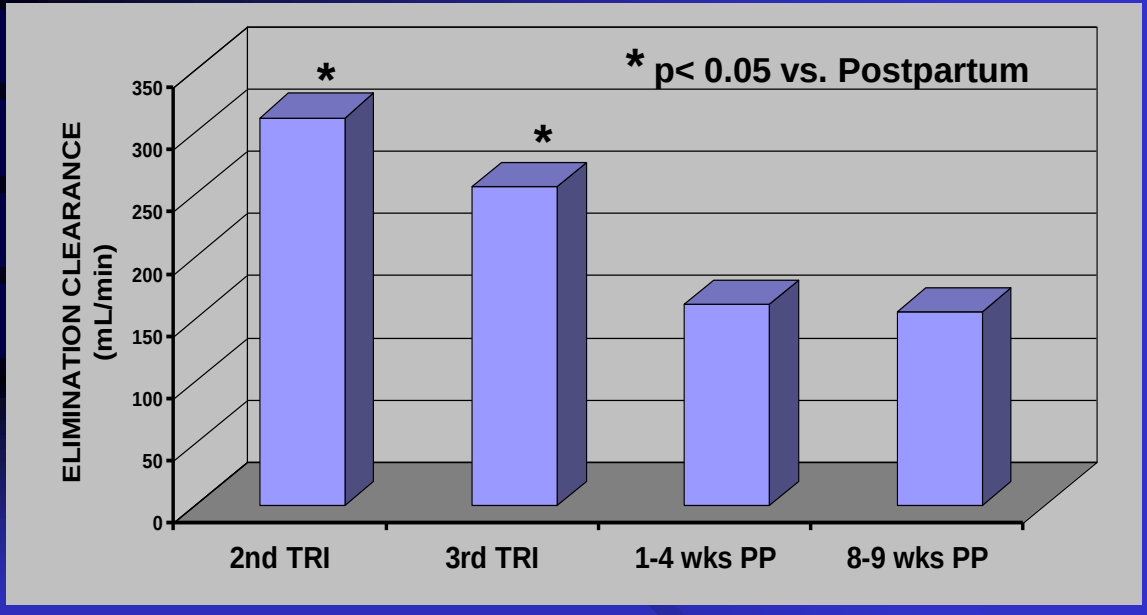
THEOPHYLLINE CLEARANCE DURING PREGNANCY AND POSTPARTUM



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

METHADONE CLEARANCE DURING AND AFTER PREGNANCY

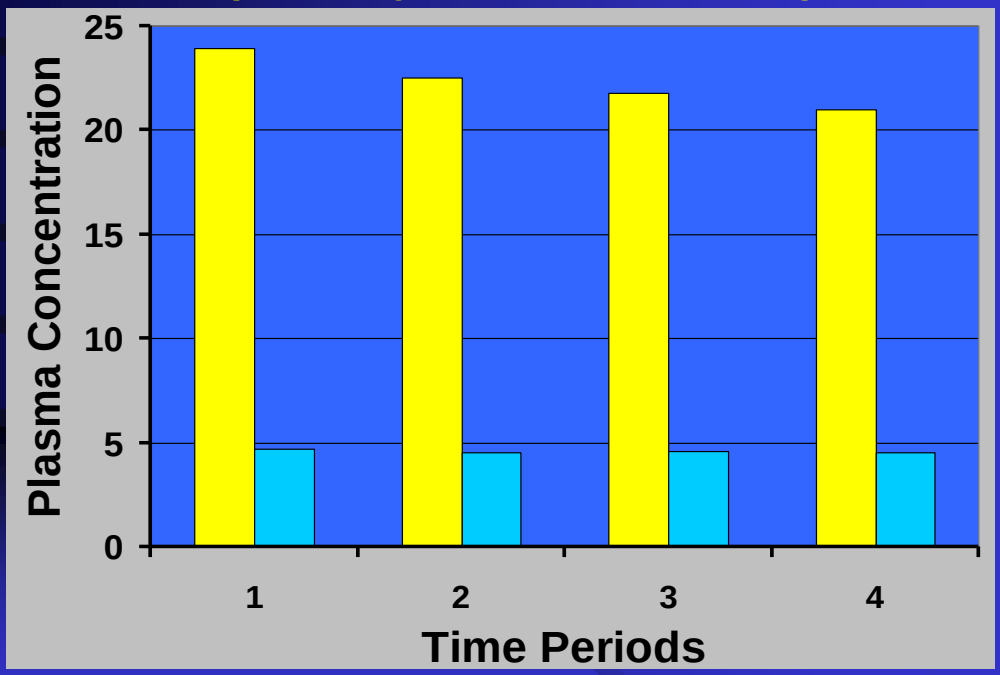
(Primarily a CYP3A4 Substrate)



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

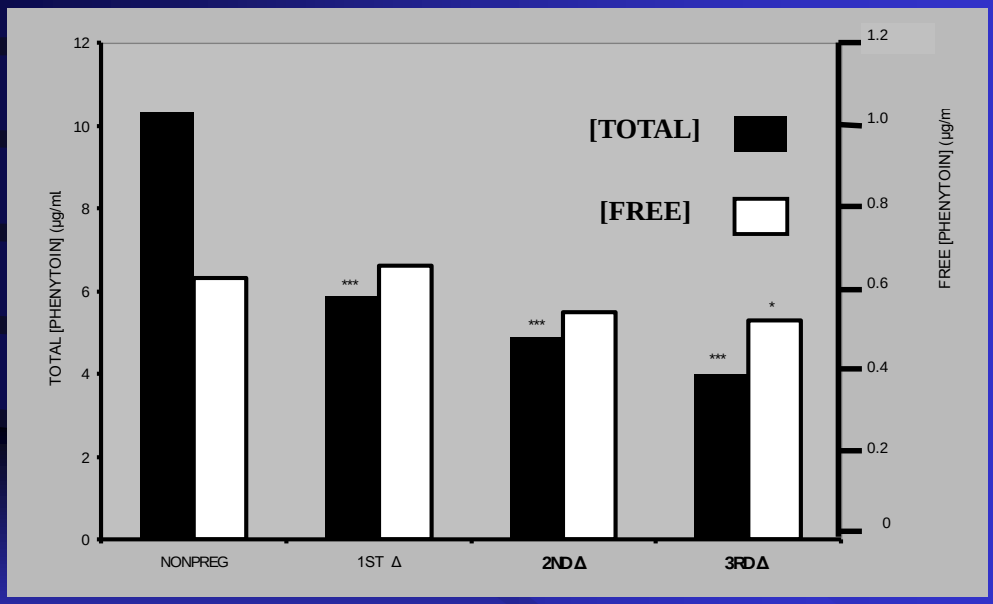
Carbamazepine Plasma Concentrations During Pregnancy

(Primarily CYP 3A4 Substrate)



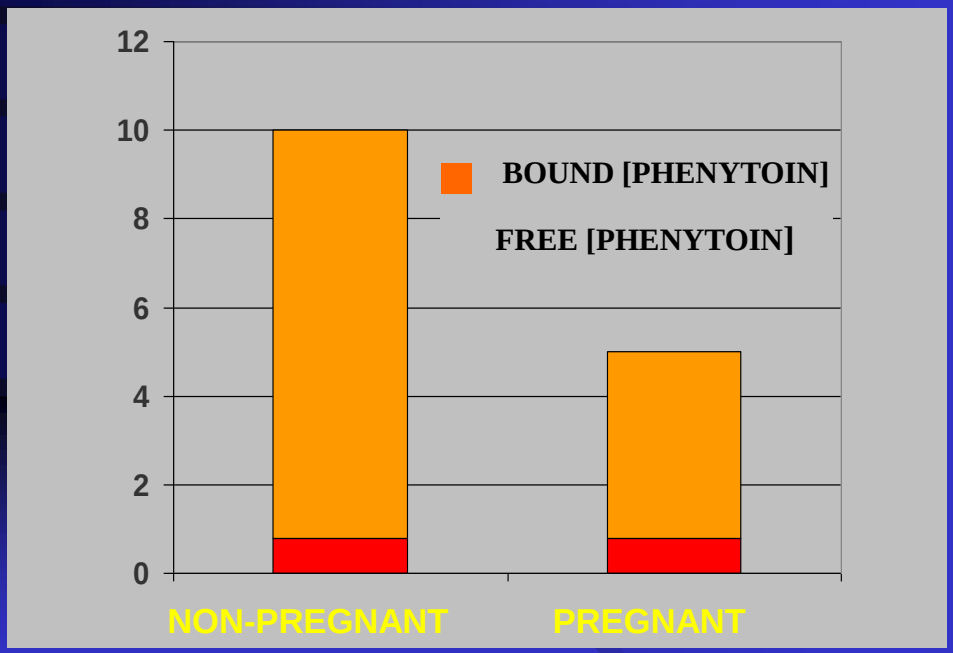
Tomsom T, et al. Epilepsia 1994; 35:122-30.

Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9

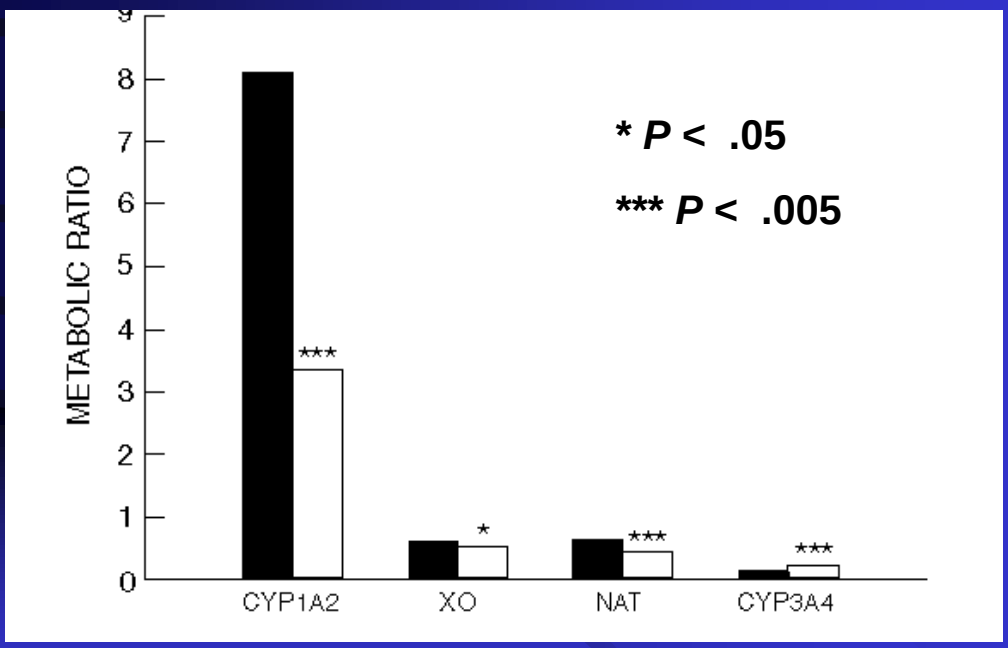


Tomson T, et al. Epilepsia 1994;35:122-30.

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

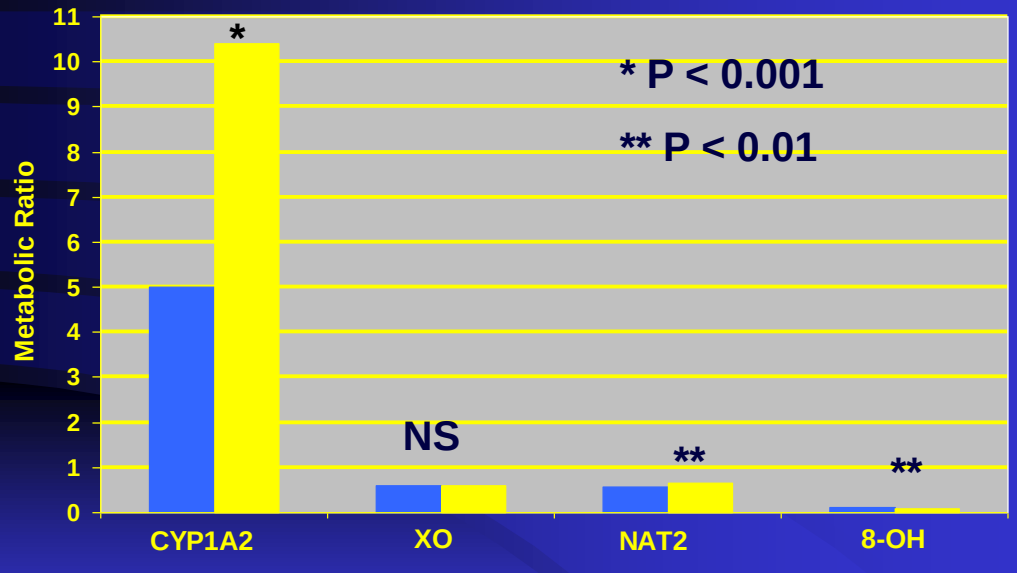


CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN



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 **
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

Philipson A et al. Am J Obstet Gynecol 1982; 142: 823.

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 Cl ml/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.

Enoxaprin 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

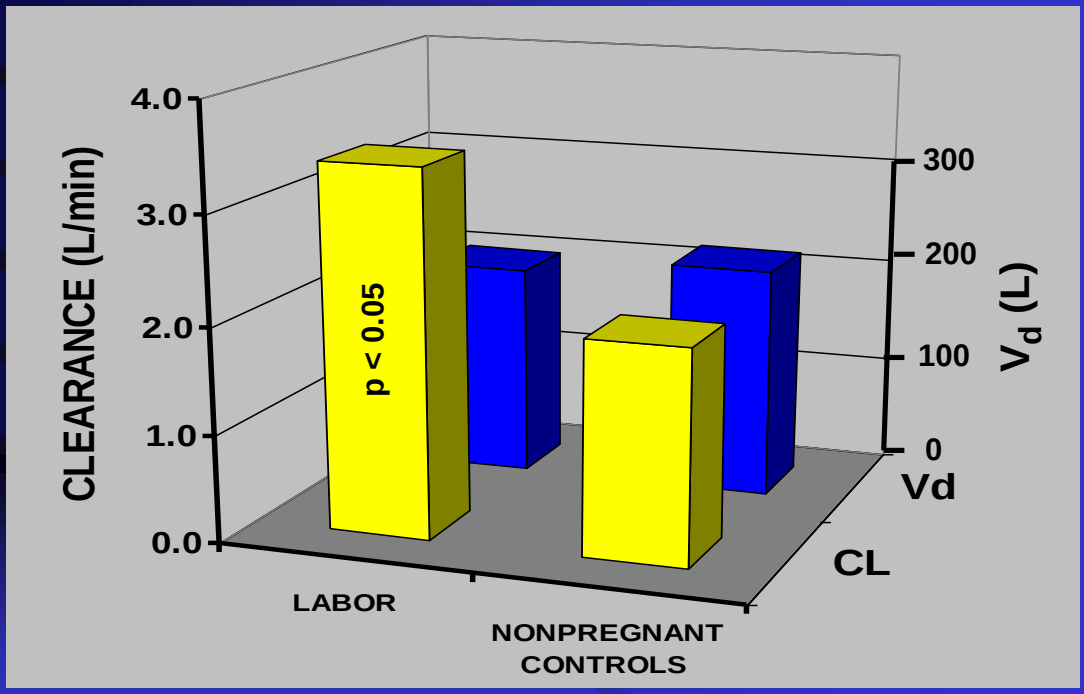
- The pro-drug Valacyclovir converted by first pass metabolism to Acyclovir
- Non-pregnant Valacyclovir gives 3 - 5 times higher plasma level as Acyclovir
- Valacyclovir PK study in pregnancy gave plasma levels 3 times higher than Acylovir

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



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

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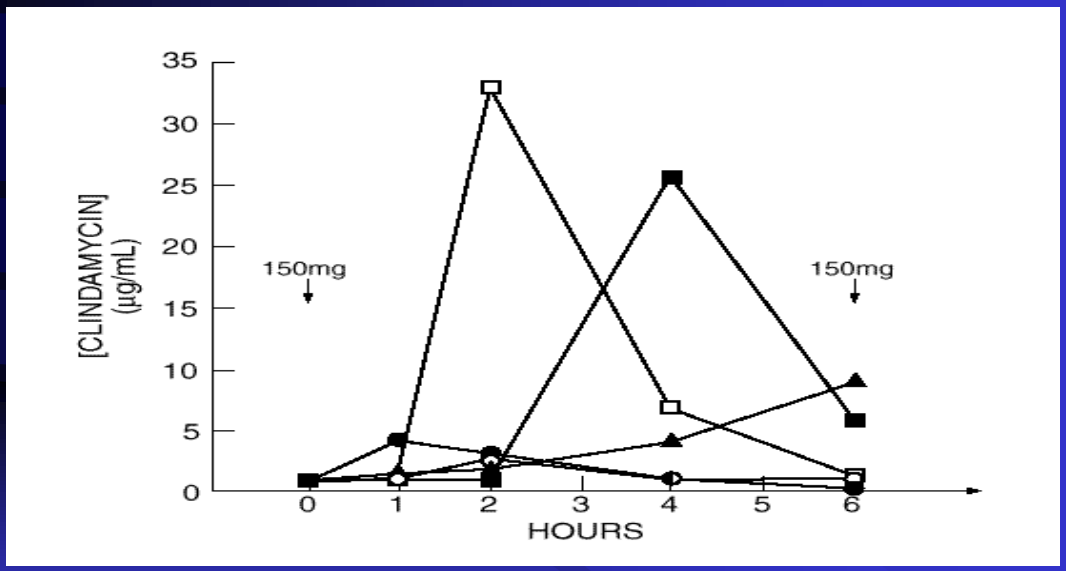
Philipson A et al. Am J Obstet Gynecol 1982; 142: 823.

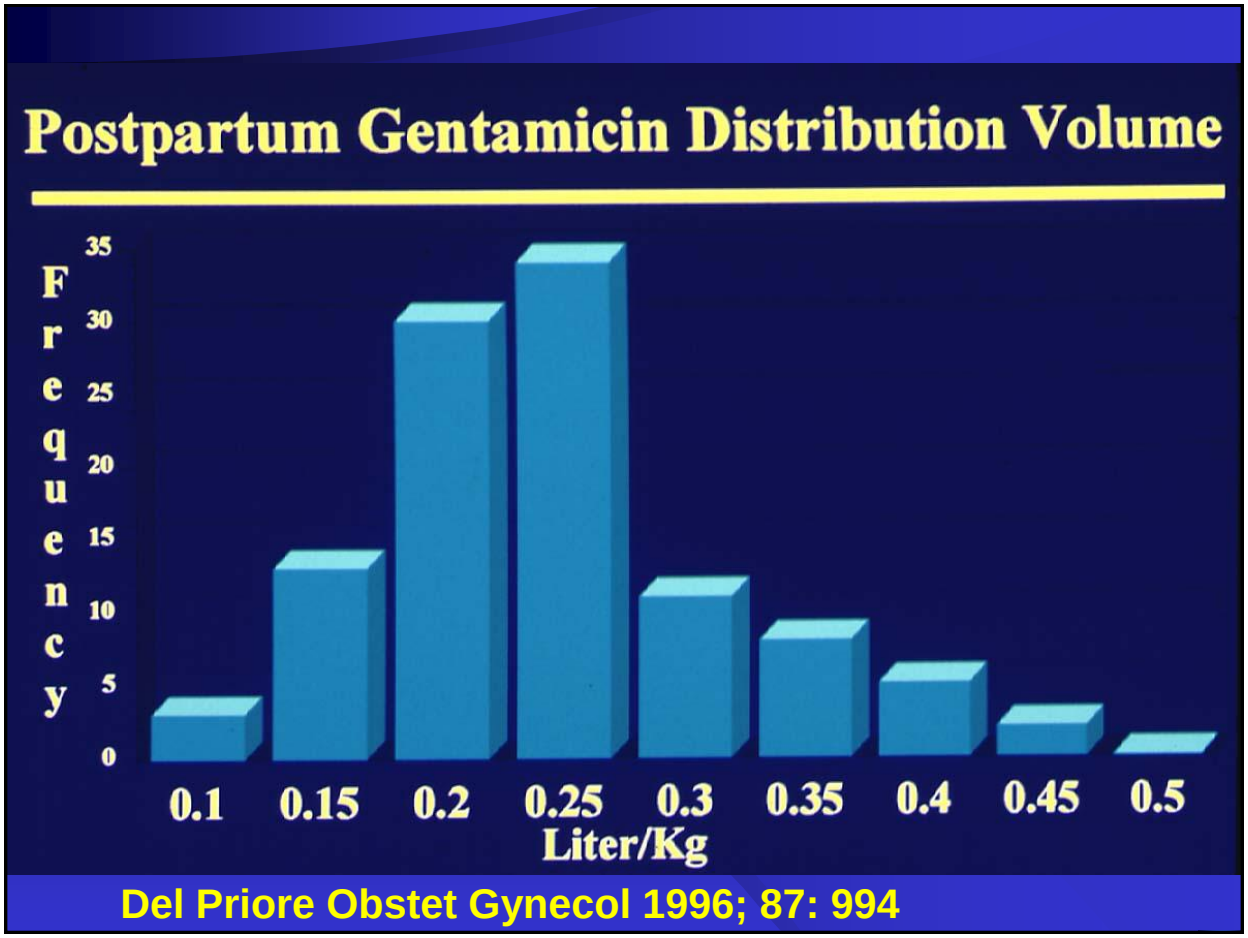
Postpartum PK Considerations

- 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
Frequency
35
30
25
20
15
10
5
0
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Liter/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

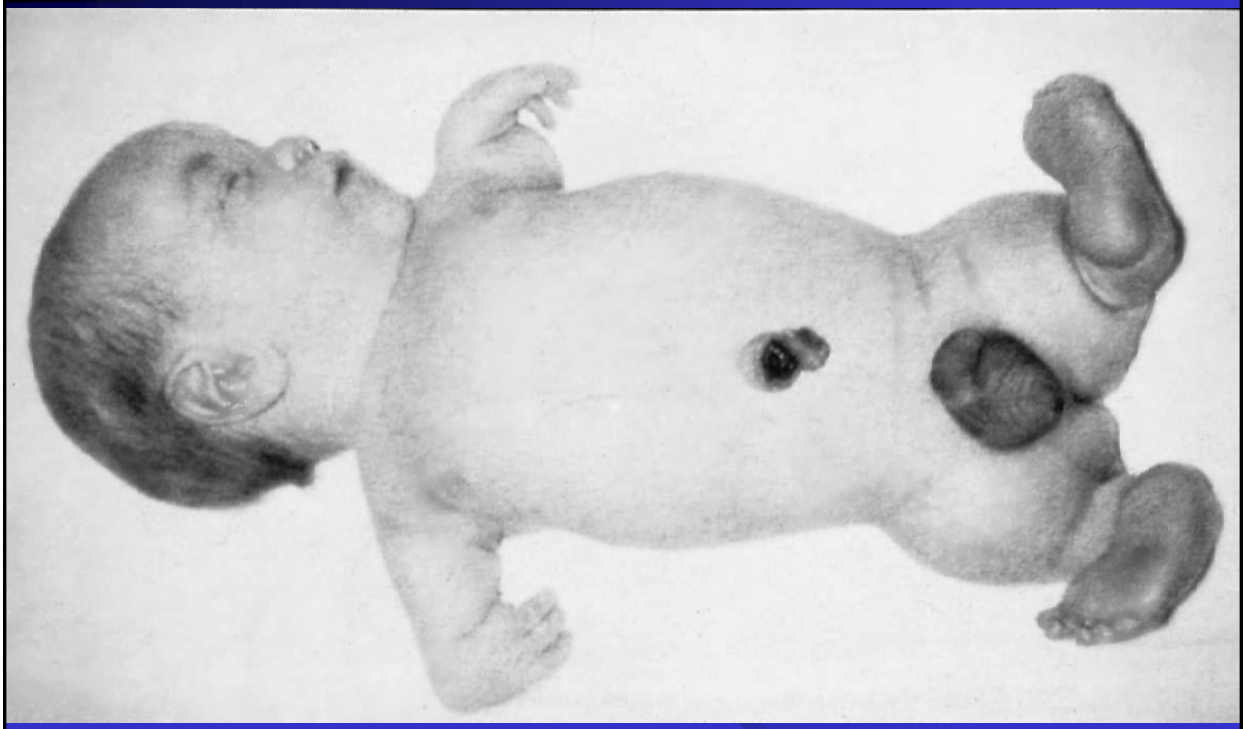
General Principles of Teratology

- 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



General Principles of Teratology

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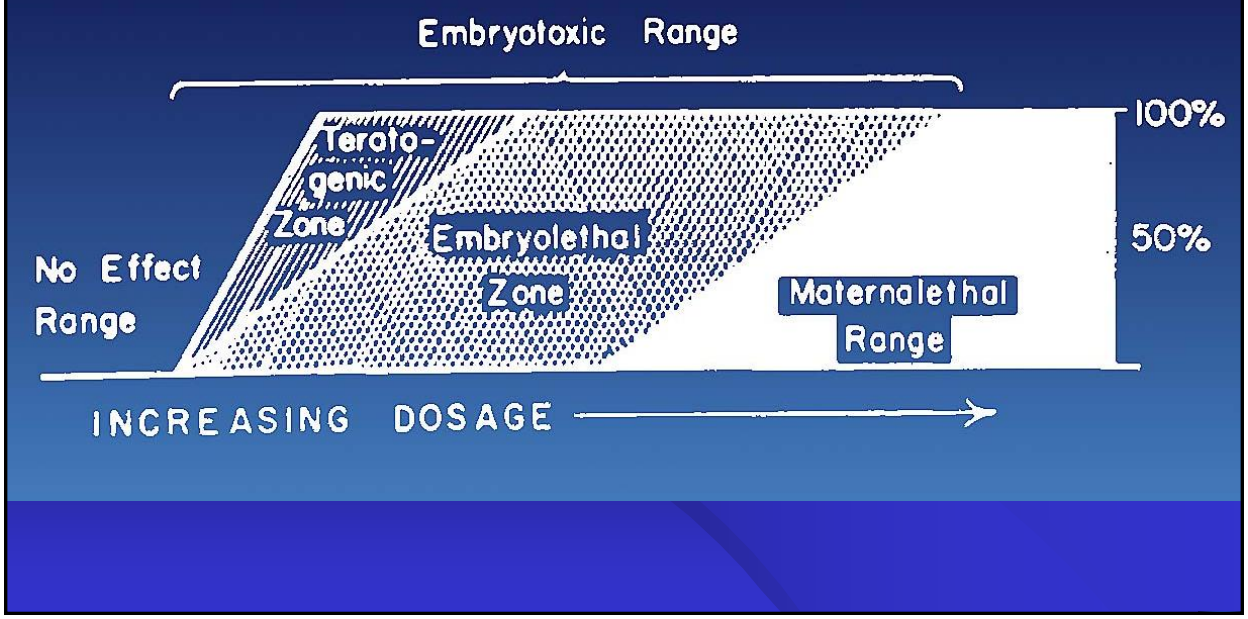
DOSE-RESPONSE RELATIONSHIP



General Principles of Teratology

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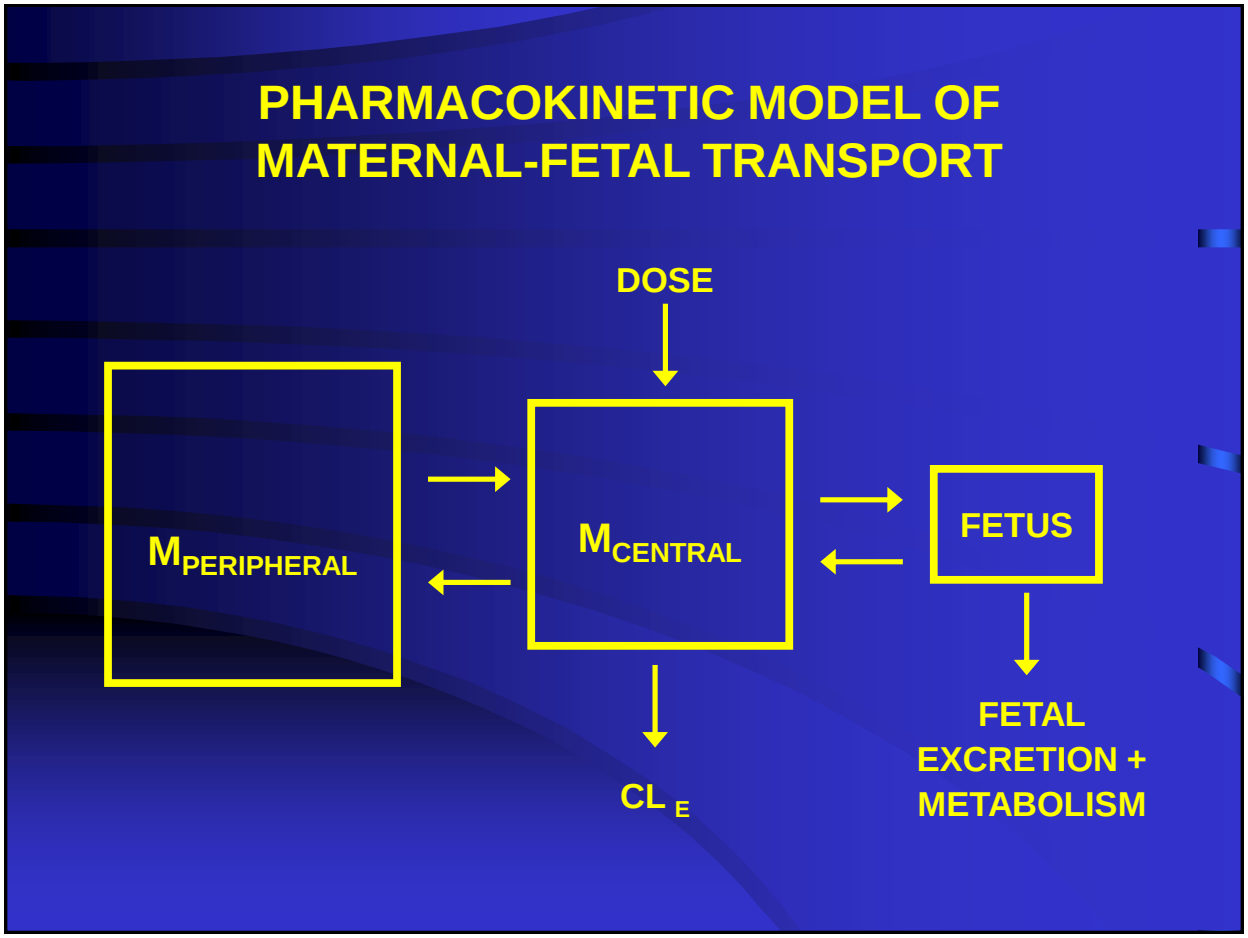
Placental Transport

- Passive diffusion
- P-glycoprotein expressed on trophoblastic cells of placenta
- Active transport of P-glycoprotein substrates back to the mother
- Pore system
- Endocytosis


PHARMACOKINETIC MODEL OF
MATERNAL-FETAL TRANSPORT
DOSE
M PERIPHERAL
M CENTRAL
FETUS
CL E
FETAL
EXCRETION +
METABOLISM

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

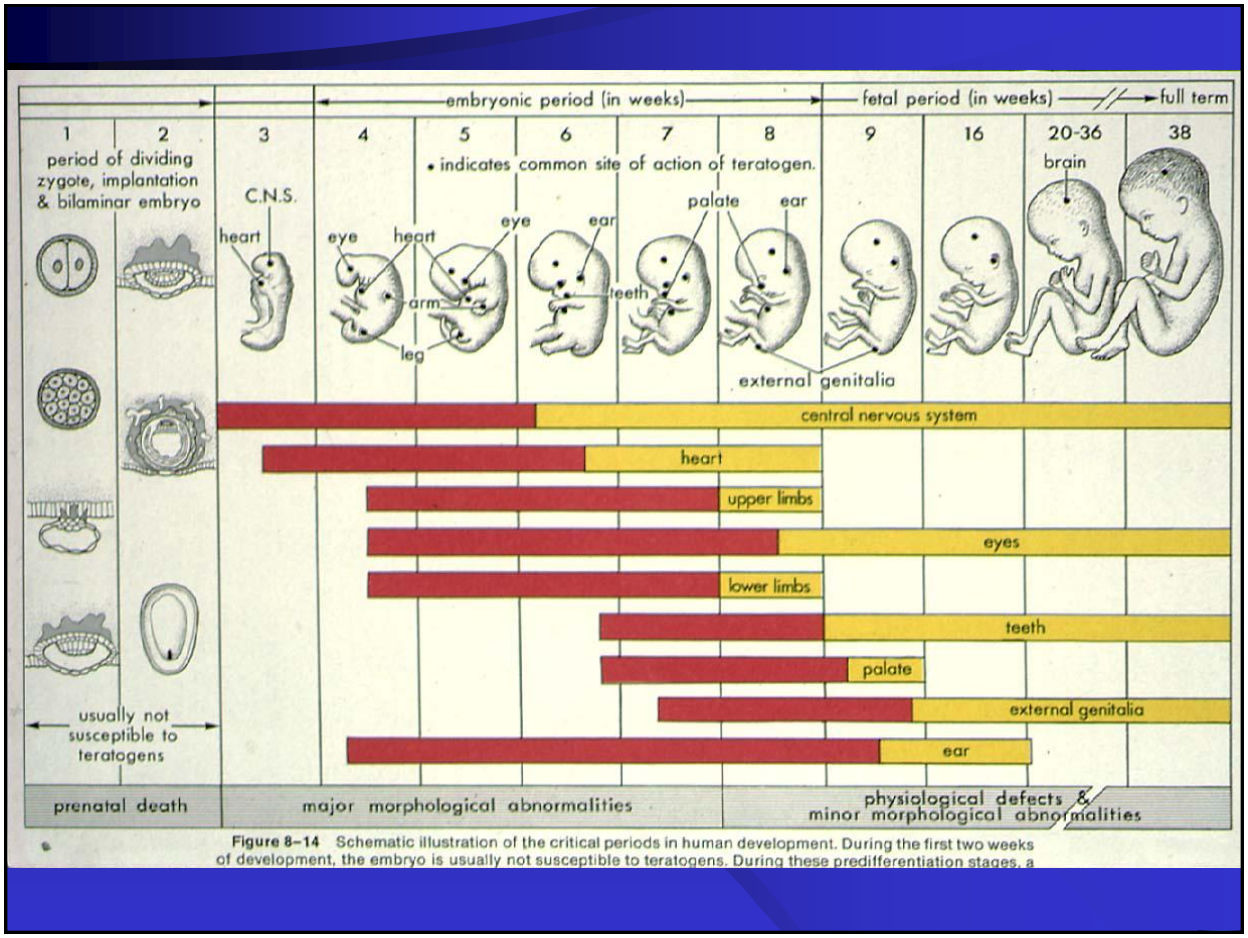


Figure 8–14 Schematic illustration of the critical periods in human development. During the first two weeks of development, the embryo is usually not susceptible to teratogens. During these predifferentiation stages, a

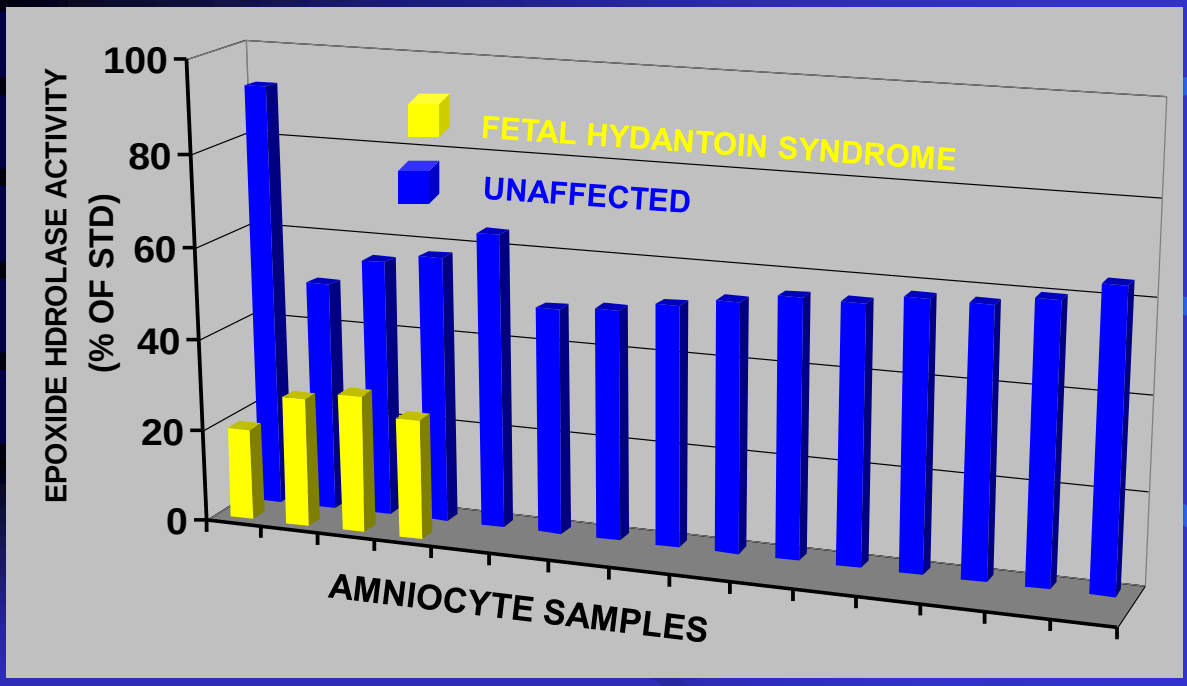
General Principles of Teratology

- 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



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 ✂ 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 mechansim 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?

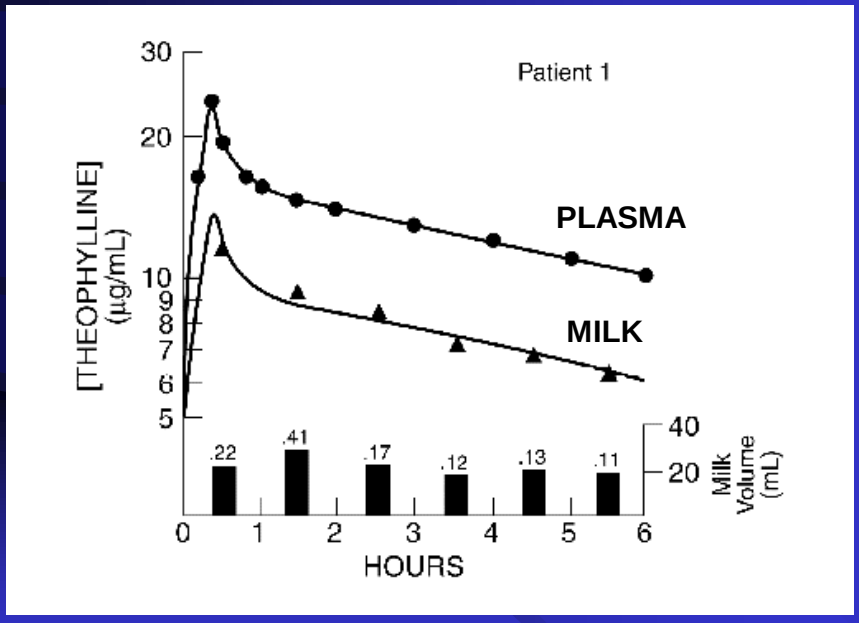
Evaluation of Drugs in Breast Milk

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

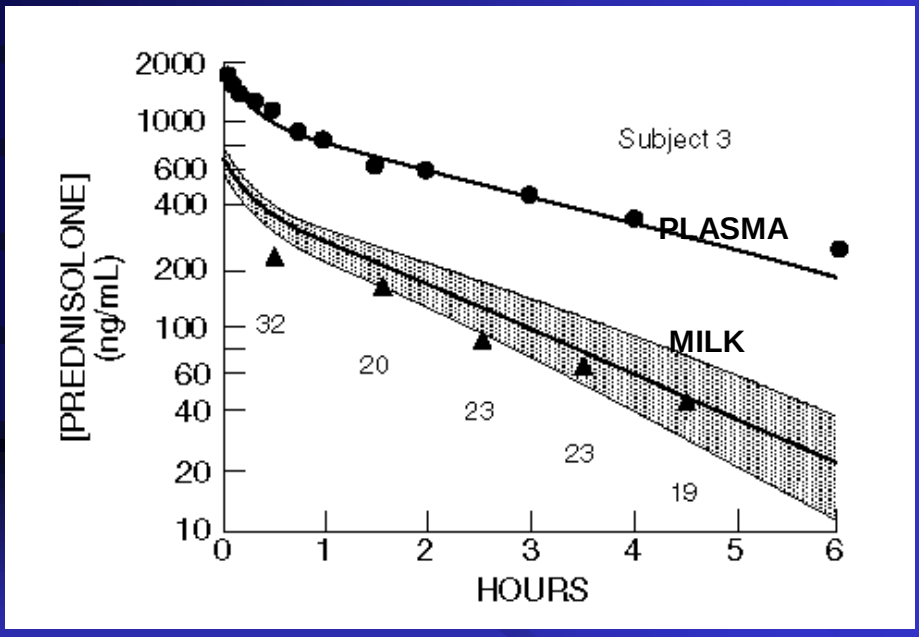
Drugs in Breast Milk

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

KINETIC ANALYSIS OF THEOPHYLLINE PLASMA AND MILK CONCENTRATIONS



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