

## Drug Therapy During Pregnancy and the Perinatal Period

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February 12, 2009

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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)
<b>NONPREGNANT</b>		49		
	< 70		0.189	0.516
	70 – 80		0.156	0.415
	> 80		0.151	0.389
<b>PREGNANT</b>		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.

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### 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

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### 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

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## 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

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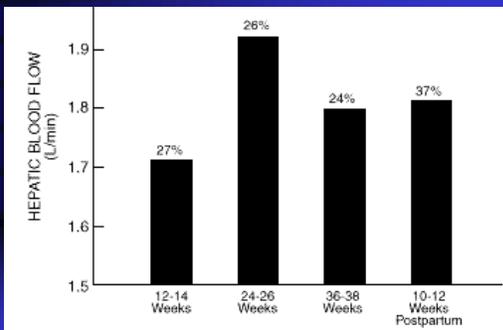
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## HEPATIC BLOOD FLOW IN PREGNANCY (% CARDIAC OUTPUT)



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

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## Respiratory Changes

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

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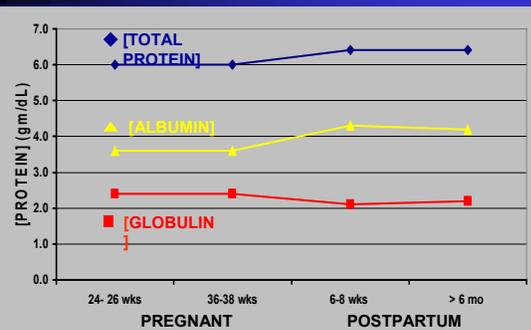
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## PROTEIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM



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

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### 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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### Pregnancy Physiology Potentially Affecting Pharmacokinetics

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- Enzymatic activity changes

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### Enzymatic Activity Changes

- Thought to be related to pregnancy hormonal changes
- N-demethylation inhibited by progesterone, not by estrogen

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## CYP3A4

- Hydroxylation
- Increased activity during pregnancy

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## CYP1A2

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

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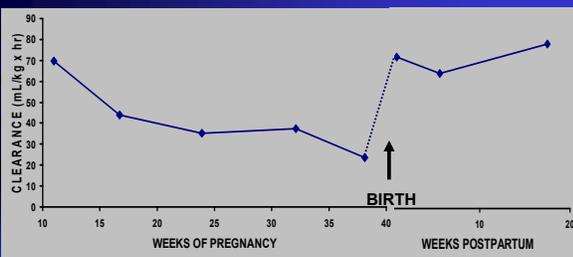
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## Caffeine Clearance – CYP 1A2



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

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## CYP2C9

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

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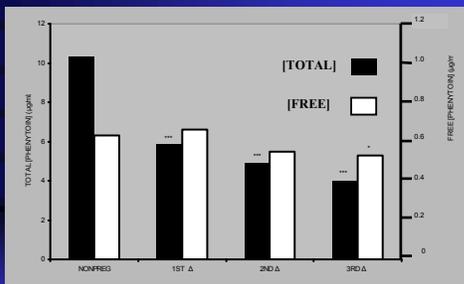
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## Phenytoin Plasma Concentrations during and after Pregnancy – CYP 2C9



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

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## 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.

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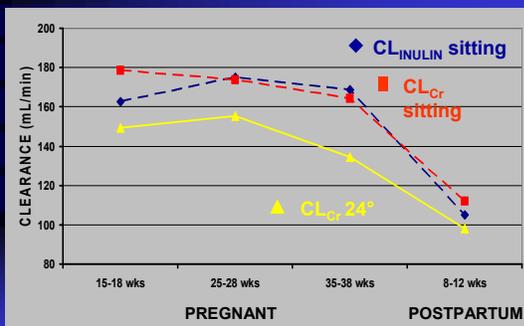
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## GFR DURING PREGNANCY AND POSTPARTUM



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

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## 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

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## Maternal Physiologic Changes Altering PK of Drugs

- Volume Expansion

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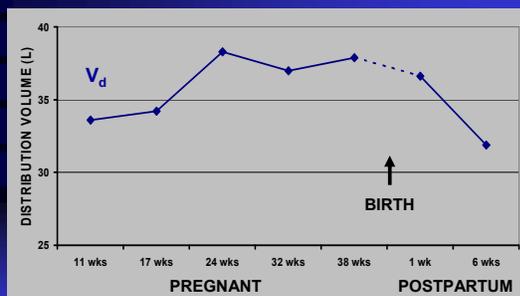
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## CAFFEINE $V_d$ (MARKER FOR TBW) DURING PREGNANCY AND POSTPARTUM



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

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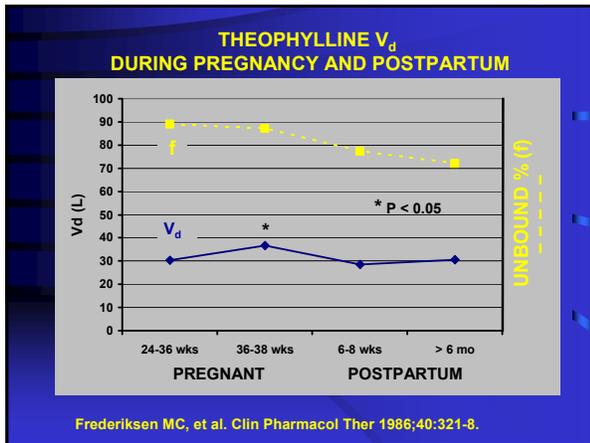
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- ### Maternal Physiologic Changes Altering PK of Drugs
- Volume expansion
  - Protein binding-increase in free fraction of drugs bound to albumin

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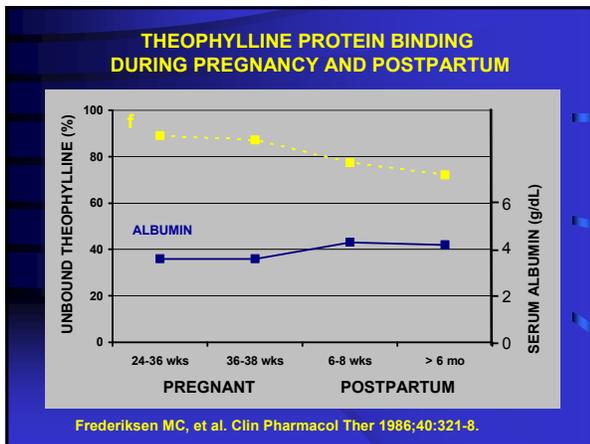
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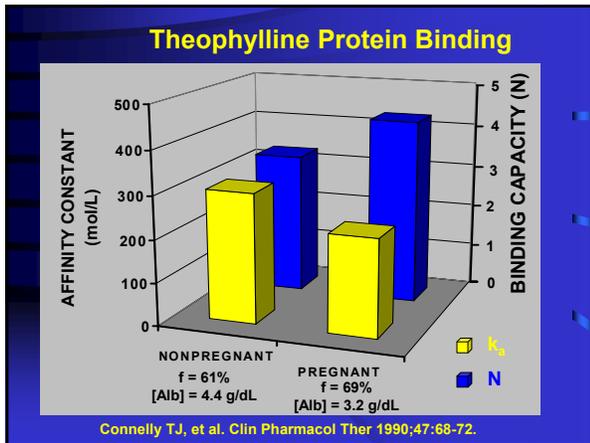
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- ### Maternal Physiologic Changes Altering PK of Drugs
- Volume expansion
  - Protein binding
  - Clearance changes

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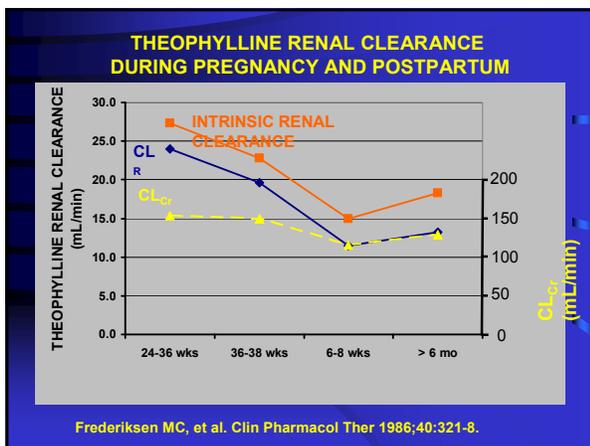
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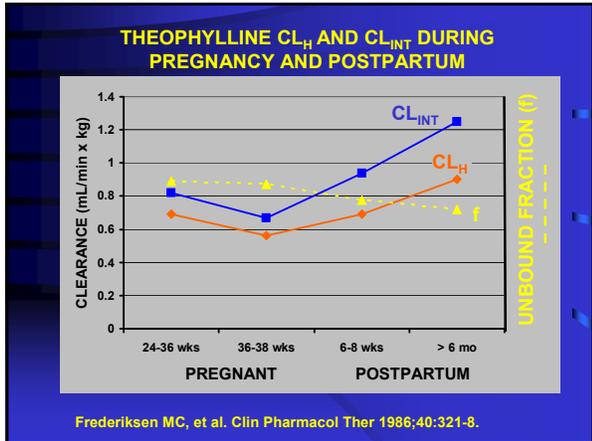
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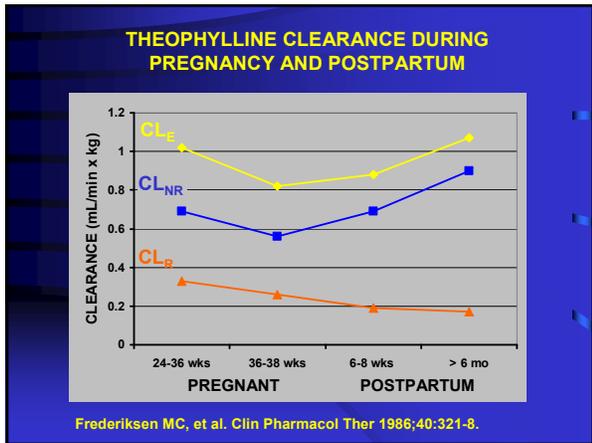
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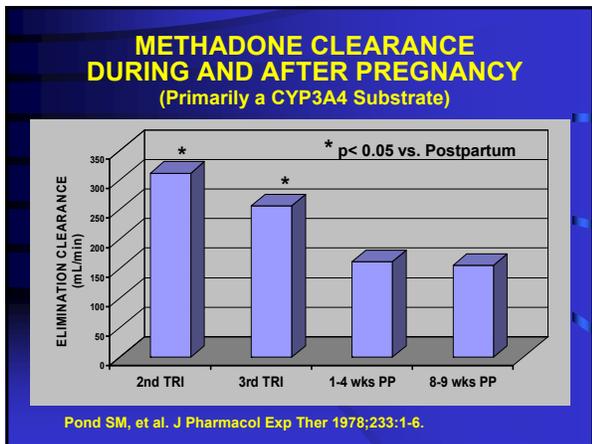
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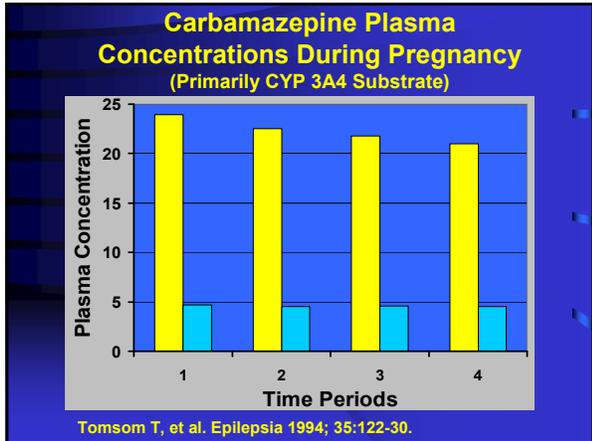
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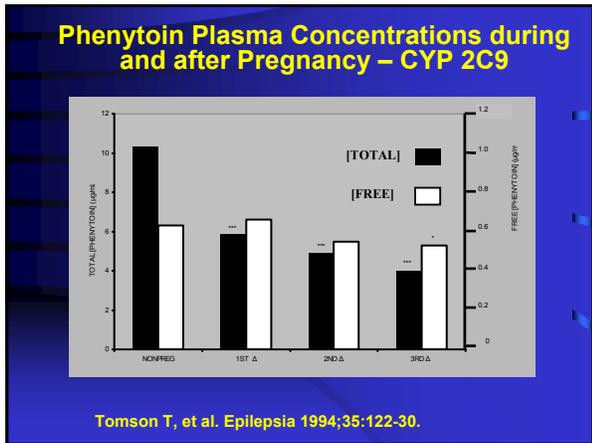
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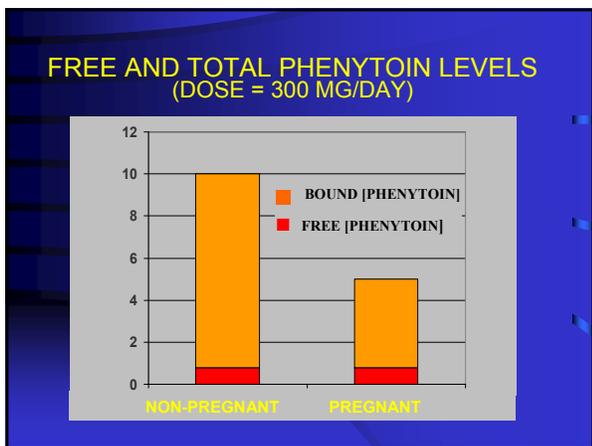
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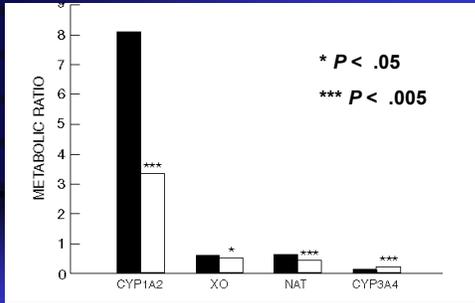
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**CAFFEINE METABOLITE / PARENT DRUG RATIOS IN PREGNANT AND NON-PREGNANT EPILEPTIC WOMEN**



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

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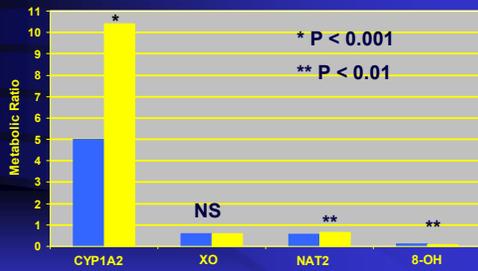
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**CAFFEINE METABOLITE / PARENT DRUG RATIOS IN HEALTHY PREGNANT AND NON-PREGNANT WOMEN**



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

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**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.

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### 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.

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### Pharmacokinetics of Cefuroxime in Pregnancy

Pt Category	V <sub>D</sub> (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

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### 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

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### 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.

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### 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.

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### 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.

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### Maternal Physiologic Changes Altering PK of Drugs

- Volume expansion
- Protein binding
- Clearance changes
- Gastrointestinal changes

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### 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.

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### 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

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### Peripartum Pharmacologic Considerations

- Increased cardiac output
- Blood flow changes
- Uterine contractions
- ? Pharmacodynamic changes

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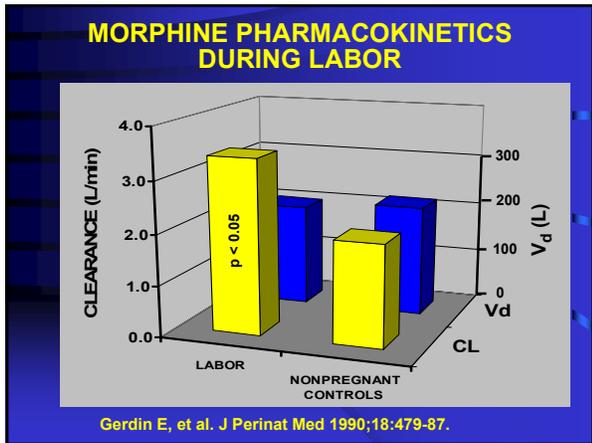
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\*p<0.05 on comparison to PP

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## Postpartum PK Considerations

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

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## Postpartum Clindamycin Pharmacokinetics



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

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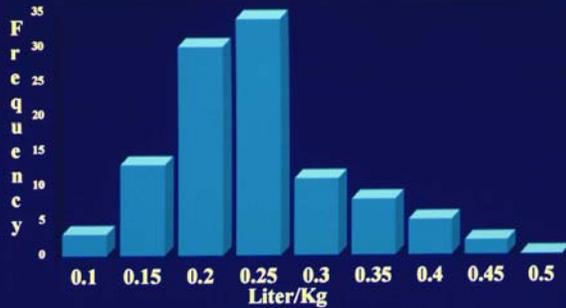
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## Postpartum Gentamicin Distribution Volume



Del Priore Obstet Gynecol 1996; 87: 994

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## Drug Studies for Pregnancy

- **Pregnancy Specific Drugs**
  - Tocolytic agents
  - Oxytocic agents
  - Eclampsia agents
- **Drugs commonly used by women of childbearing potential**
  - Antidepressants
  - Asthma drugs

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## Technical Considerations

- **Ethical and IRB concerns**
- **Serial studies**
  - Spanning pregnancy
  - Specific to peripartum period
  - Controls

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## 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**

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# Teratogenesis

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- ## 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

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- ## General Principles of Teratology
- Teratogens act with specificity

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## PHOCOMELIA DUE TO THALIDOMIDE



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## General Principles of Teratology

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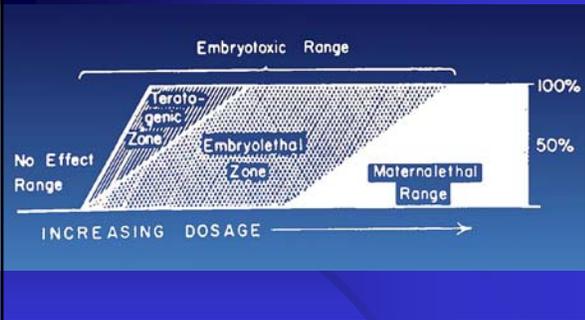
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## DOSE-RESPONSE RELATIONSHIP



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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

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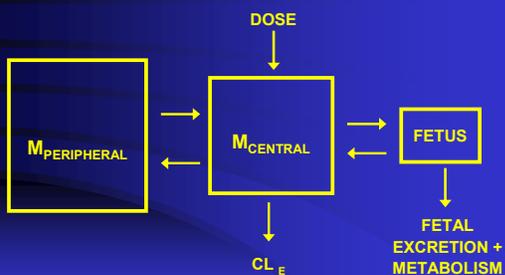
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## PHARMACOKINETIC MODEL OF MATERNAL-FETAL TRANSPORT



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- Effects depend upon the development stage when exposed

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## All or Nothing Period

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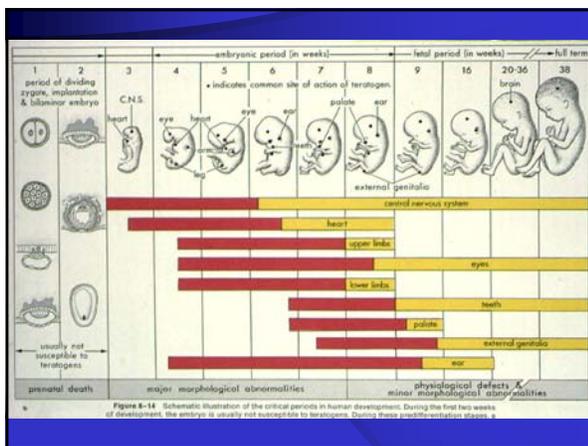
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- Effects depend upon the development stage when exposed
- Genotype of mother and fetus effect susceptibility

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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

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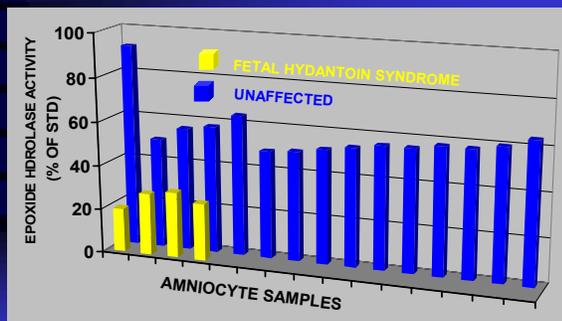
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## Prenatal Diagnosis of the Fetus at Risk



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

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### Genetic Polymorphisms

- Increased risk of clefting in fetuses carrying atypical allele for transforming growth factor  $\beta$  whose mothers smoke
- Decreased risk for fetal alcohol syndrome in African American women carrying alcohol dehydrogenase isoform 2

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### Mechanisms of Teratogenesis

- All theoretical
- Most not understood well
- Implications of a genetic component

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### 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

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## 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?

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## Evaluation of Drugs in Breast Milk

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

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## Drugs in Breast Milk

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

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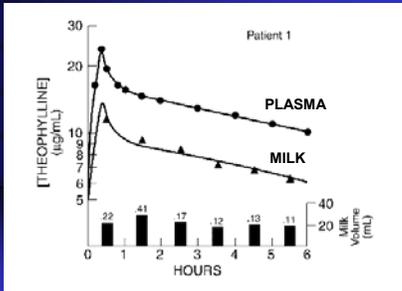
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**KINETIC ANALYSIS OF THEOPHYLLINE  
PLASMA AND MILK CONCENTRATIONS**




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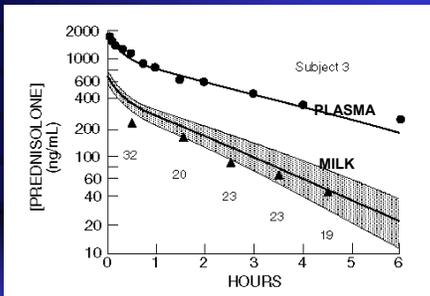
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**KINETIC ANALYSIS OF PREDNISOLONE  
PLASMA AND MILK CONCENTRATIONS**



SHADED AREA IS EXPECTED RANGE OF UNBOUND PLASMA CONC.

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**Factors Effecting the Milk / Plasma  
Concentration Ratio**

- Maternal protein binding
- Protein binding in milk
- Lipid solubility of drug
- Physiochemical factors of drug effecting diffusion

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## Drugs Generally Contraindicated during Lactation

- Antineoplastics
- Immune suppressants
- Ergot Alkaloids
- Gold
- Iodine
- Lithium carbonate
- Radiopharmaceuticals
- Social drugs & drugs of abuse
- Certain antibiotics

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## 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

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