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Dose / Concentração plasmática

- Medicamento
- Paciente
- Interação de fármacos

MATERNAL-FETAL Pharmacokinetics

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More than 50% of pregnant women receive some form of drug during pregnancy

~ 40% of drugs used has no evidence of safety in pregnant women

Pregnancy PBPK model components

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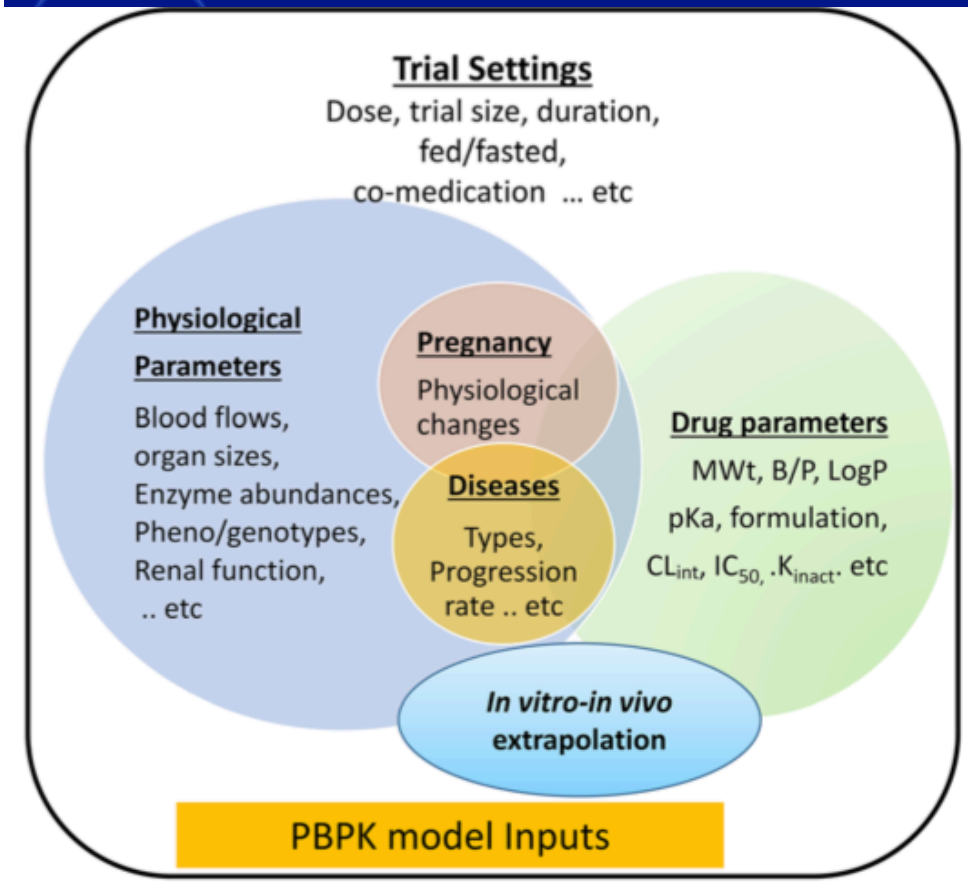
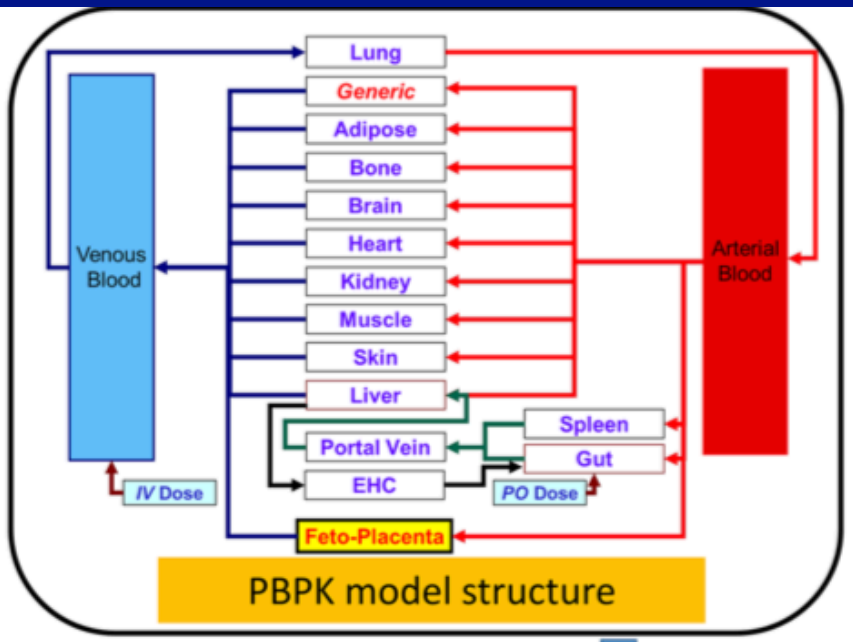
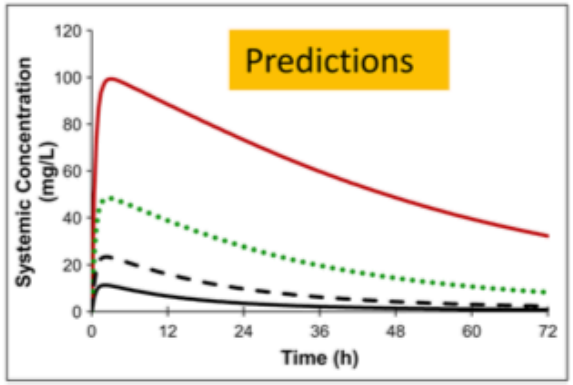
PBPK= Physiologically-based pharmacokinetic







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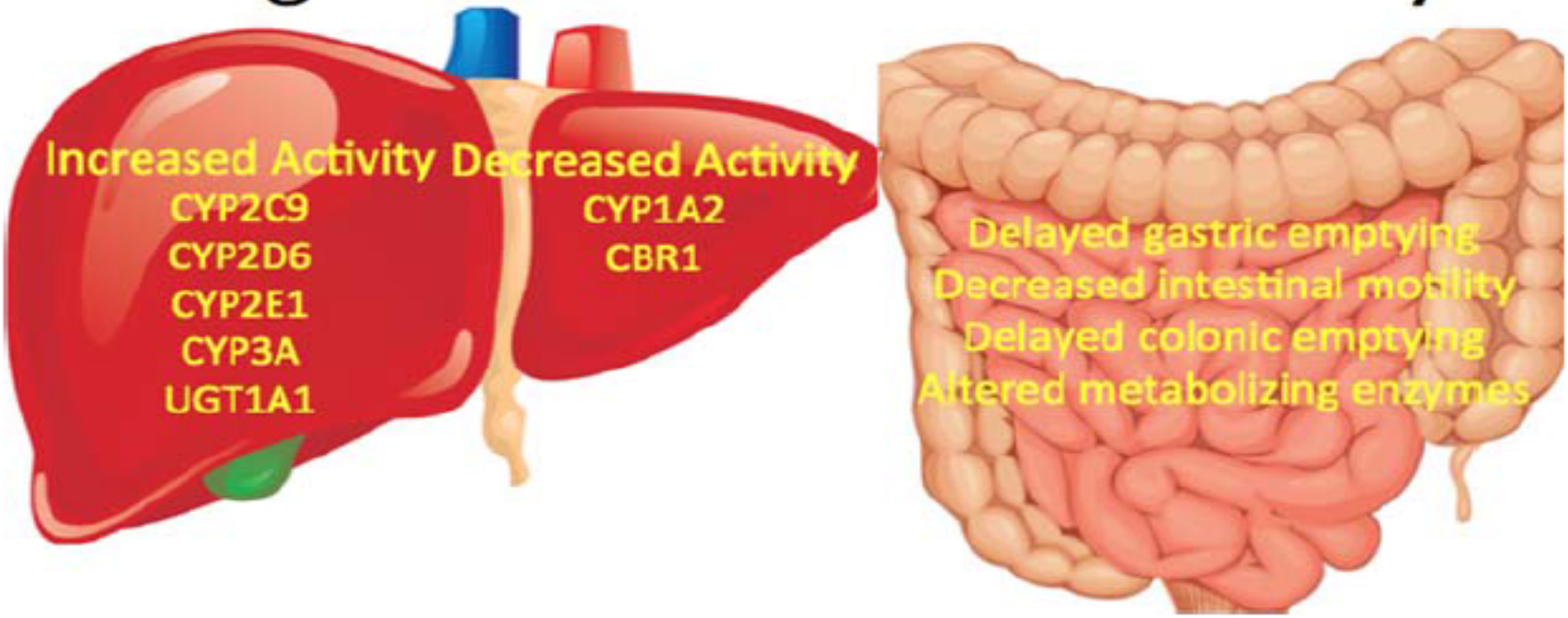
Pregnancy

Effects of Pregnancy on Drug Metabolism and GI Motility



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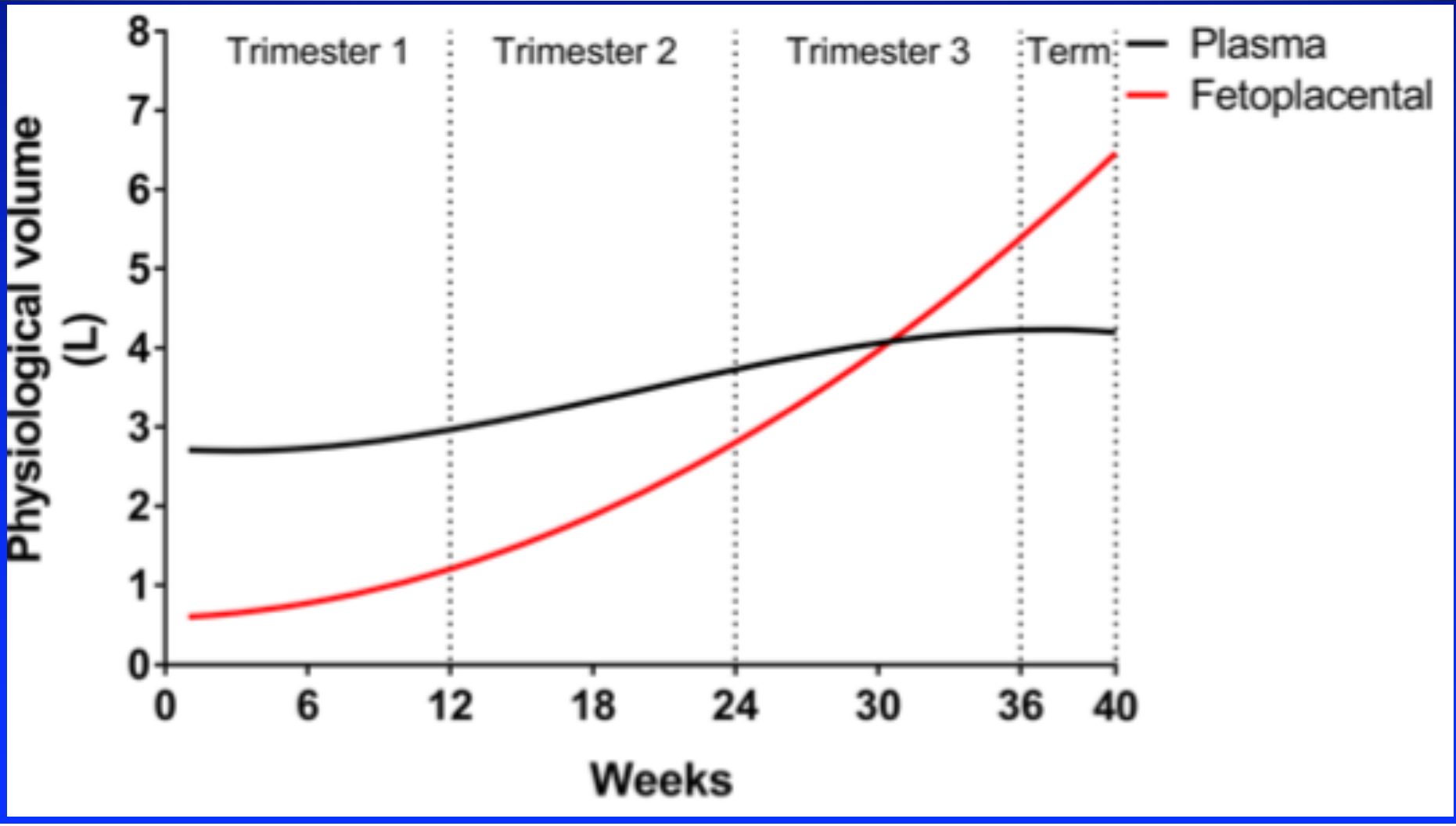
Expansion of plasma volume during gestation



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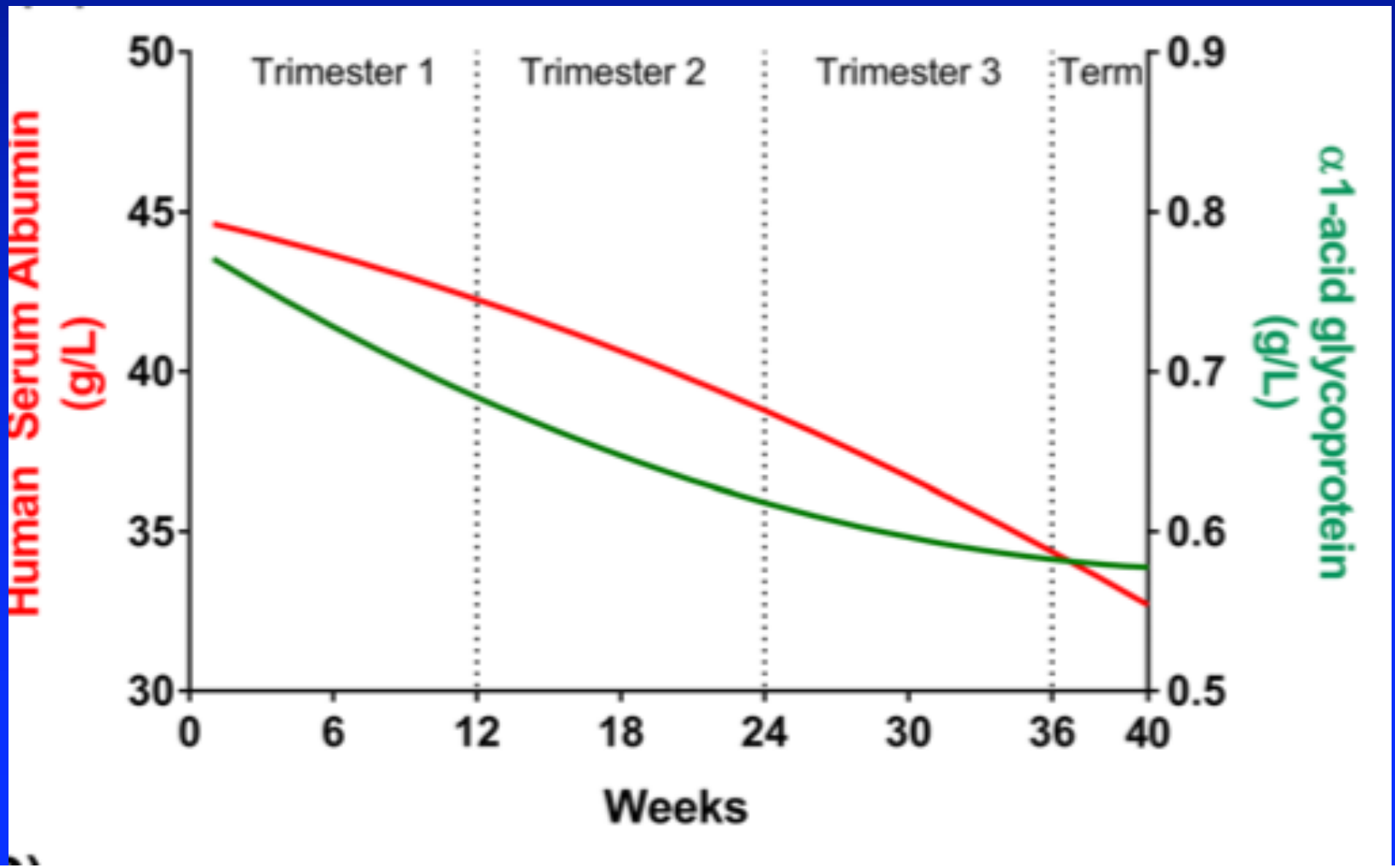
Plasma proteins and pregnancy



Changes in cardiac output during gestation

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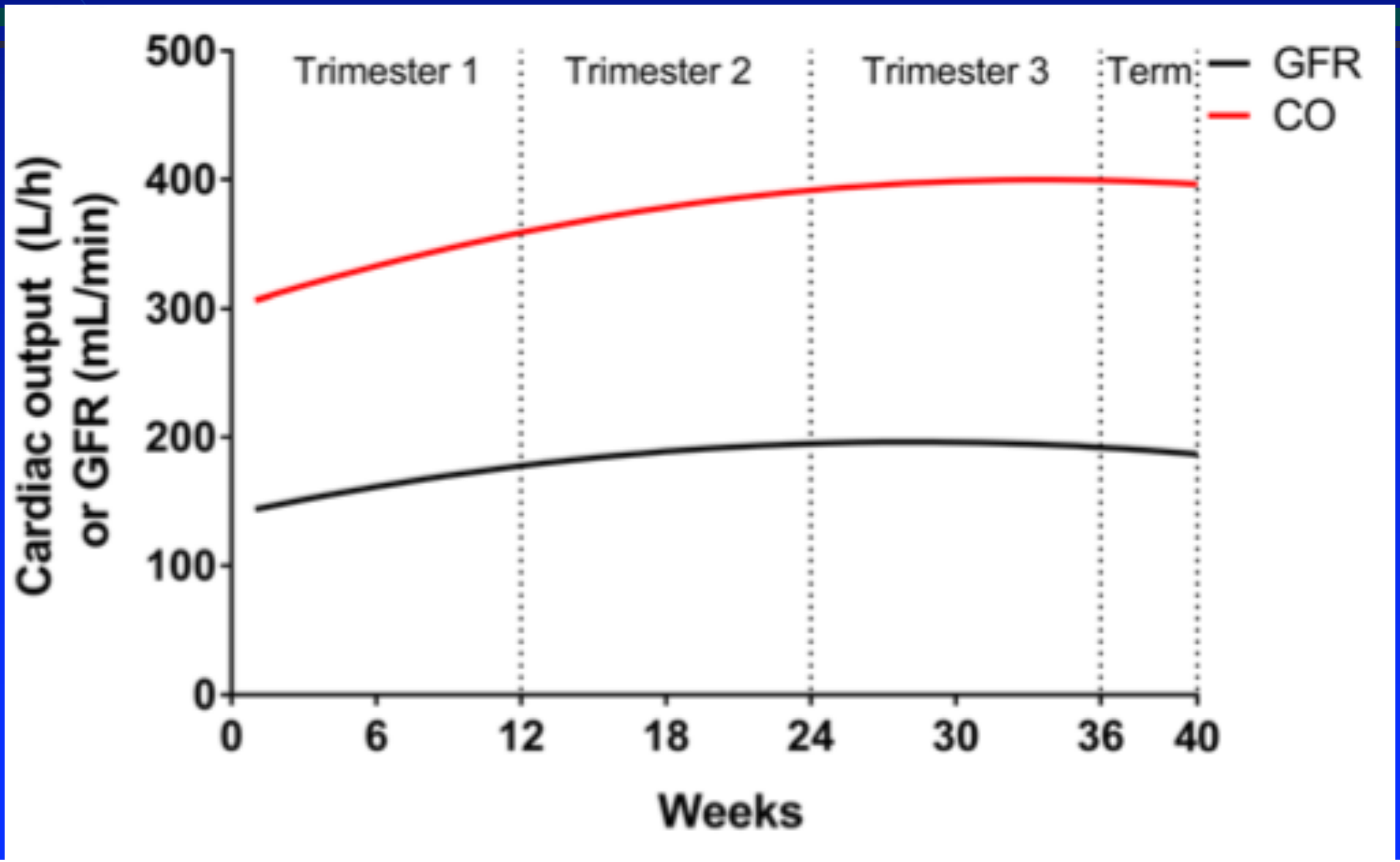

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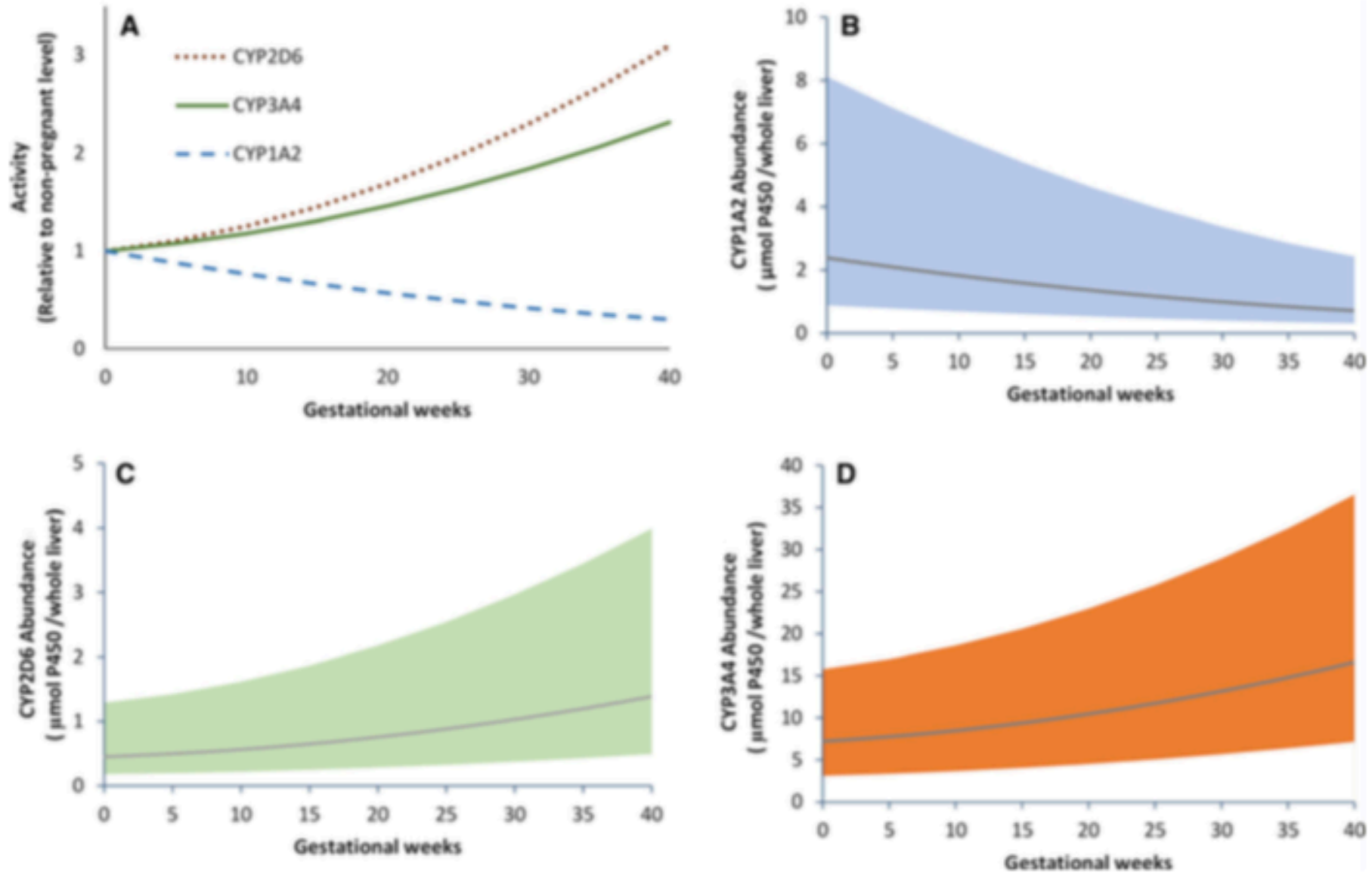
Activity and expression of CYP2D6, CYP3A4 and CYP1A2 during pregnancy



PHARMACOKINETICS CHANGES IN PREGNANCY

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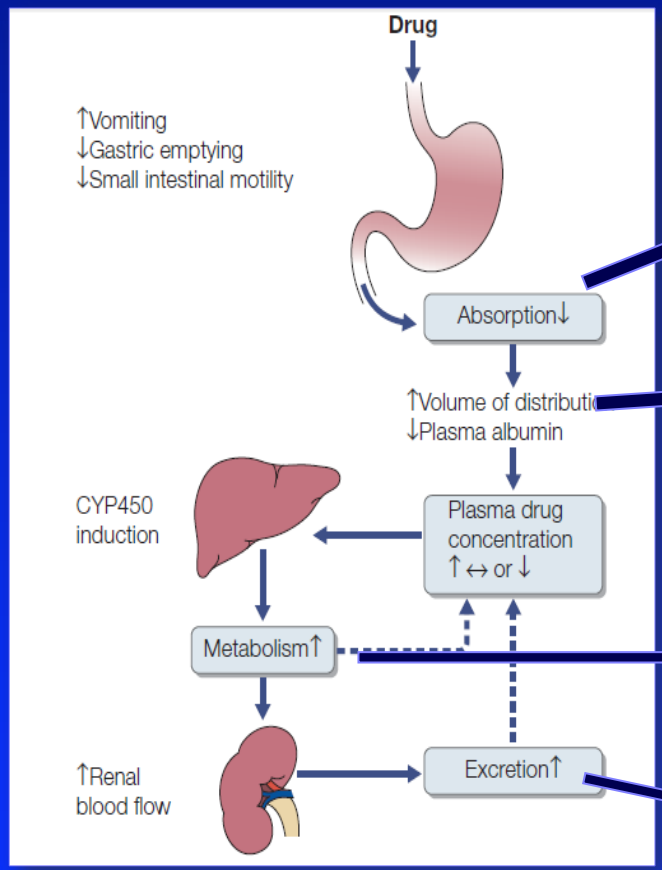

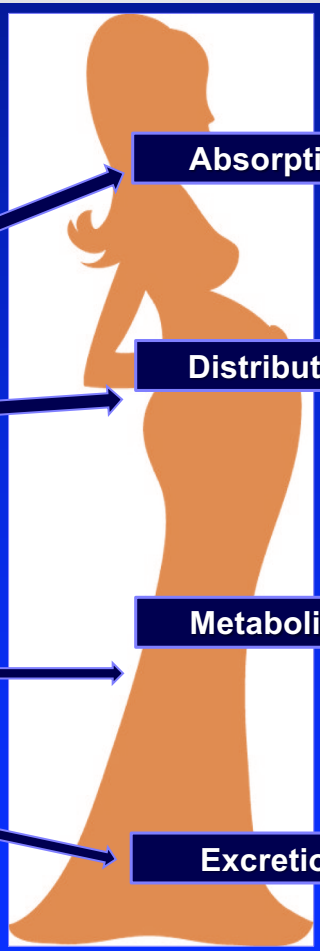

Absorption → T_{max} ↓ C_{max} ↓ F

Distribution → ↑ V_d ↓ C_{max}

Metabolism → ↑↓ hepatic clearance

Excretion → ↑ renal clearance

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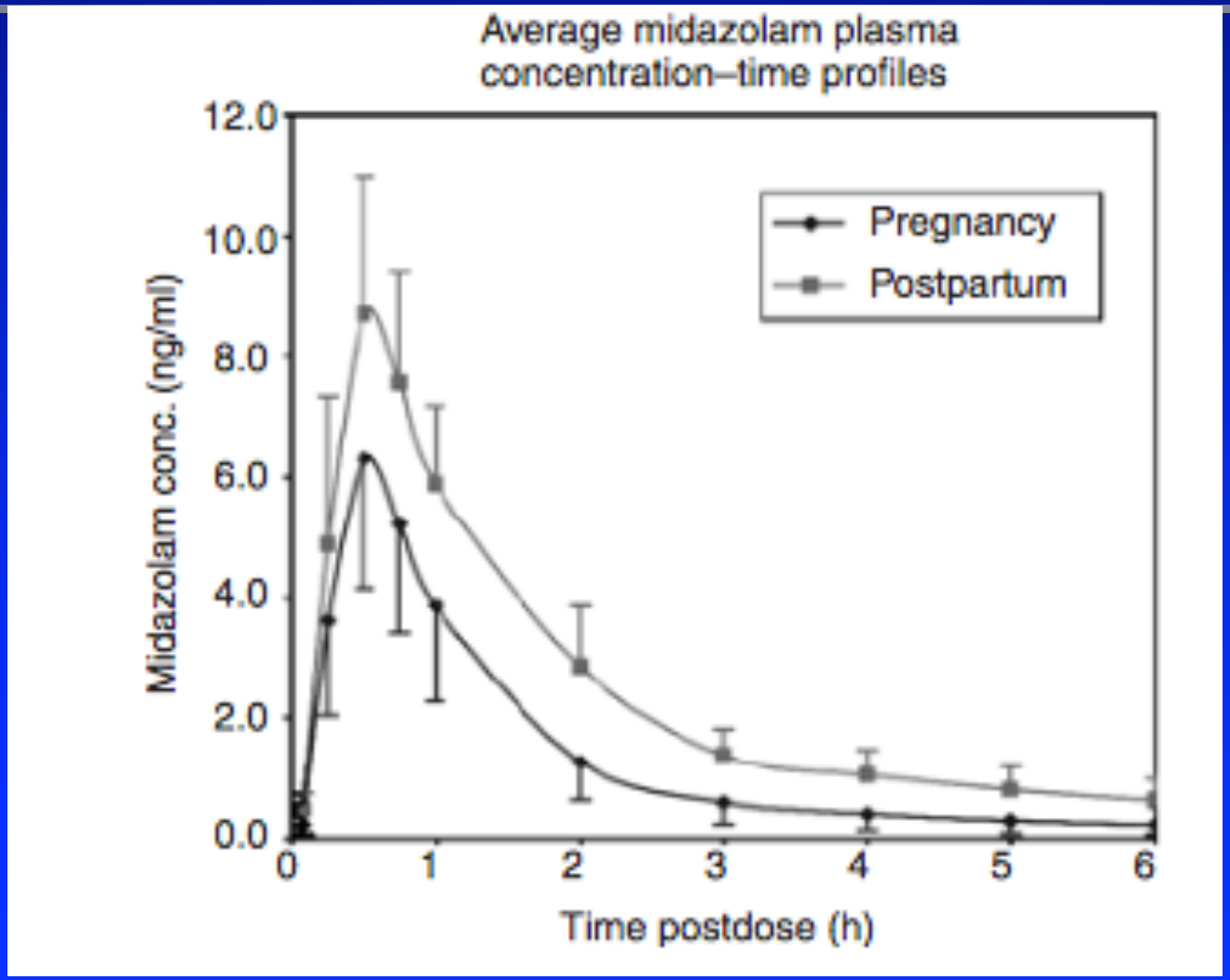
Midazolam (CYP3A) Pregnancy *vs* Postpartum



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Midazolam (CYP3A) PK parameters Pregnancy vs Postpartum

Parameter	Pregnancy	Postpartum	Percent difference	*P* value
$AUC_{0\rightarrow inf}$ (ng·h/ml)	9.5 ± 4.3	17.9 ± 6.0	–46 ± 26	<0.002
CL/F (l/min)	4.2 ± 1.8	2.0 ± 0.6	108 ± 62	0.002
$CL/F_{unbound}$ (l/min)	593 ± 237	343 ± 103	86 ± 79	0.007
1′OH-mid $CL_{formation}$ (l/min)	3.0 ± 1.1	1.4 ± 0.4	124 ± 63	<0.002
1′OH-mid $CL_{formation,unbound}$ (l/min)	418 ± 150	228 ± 67	99 ± 86	<0.005
f_u (%)	0.71 ± 0.11	0.61 ± 0.16	21 ± 26	<0.05
C_{max} (ng/ml)	6.4 ± 2.6	9.3 ± 2.0	–28 ± 32	0.01
T_{max} (h)	0.56 ± 0.15	0.54 ± 0.14	7 ± 31	0.8
Half-life (h)	2.4 ± 0.7	2.5 ± 1.3	2 ± 26	0.6

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Effect of pregnancy on enzyme and transporter activities

Effects of pregnancy on apparent enzyme and transporter activities

	Probe	Pregnancy effect on activity	Reference
Enzymes			
CYP3A	Midazolam	86–124% increase	1
CYP2D6	Metoprolol	1.5- to 2.8-fold increase	2
CYP2C9	Phenytoin	1.4- to 1.5-fold increase	4
CYP2C19	Proguanil	Mixed results	3,31–33
CYP1A2	Caffeine	30–65% decrease	5
CYP2E1	Acetaminophen	1.8-fold increase	38
CYP2B6	Efavirenz	No significant change	8
Alcohol dehydrogenase	Abacavir	No significant change	25
UGT1A4	Lamotrigine	65–264% increase	6,42,43
CBR1	Doxorubicin	30–39% decrease	7
Transporters			
OCT2	Metformin	38–45% increase	11
P-gp	Digoxin	107% increase	1
OAT1	Amoxicillin	>50% increase	12

CBR1, carbonyl reductase 1; CYP, cytochrome P450; OAT1, organic anion transporter 1; OCT2, organic cation transporter 2; P-gp, P-glycoprotein; UGT1A4, uridine diphosphate-glucuronosyltransferase 1A4.

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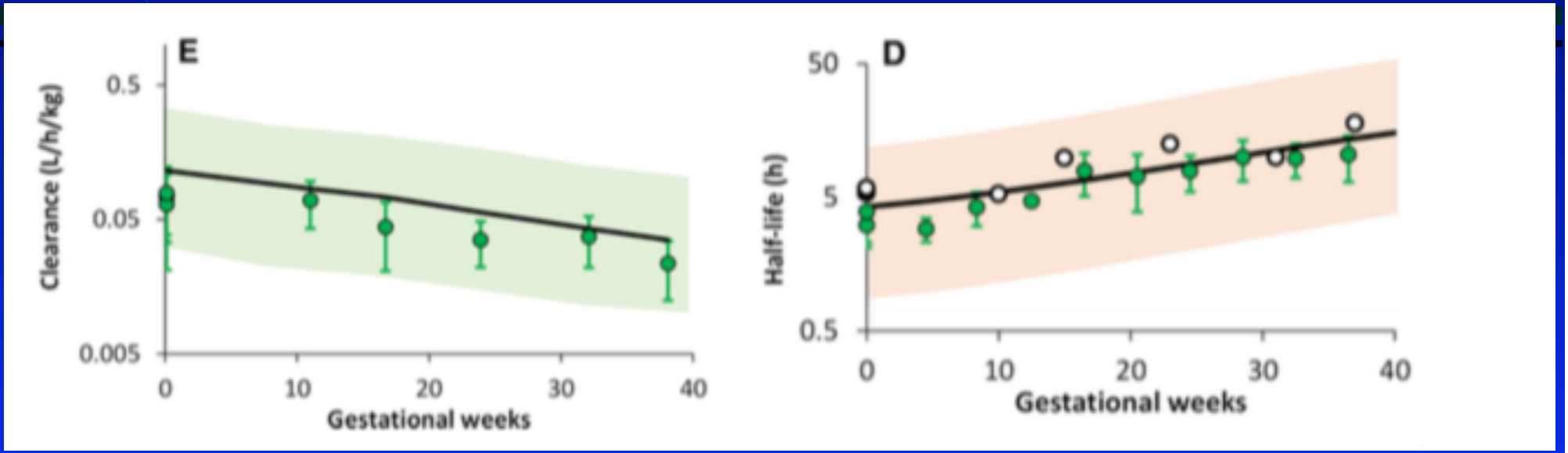
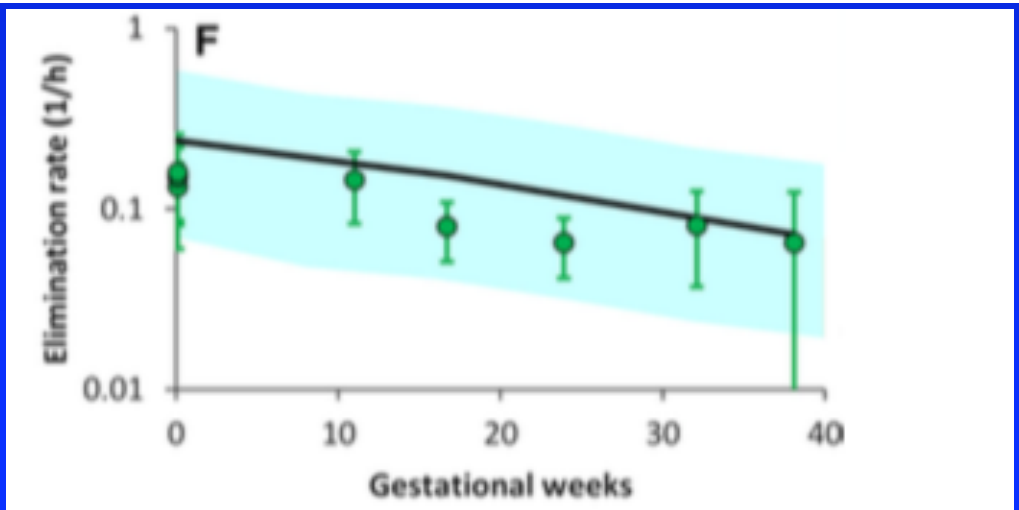
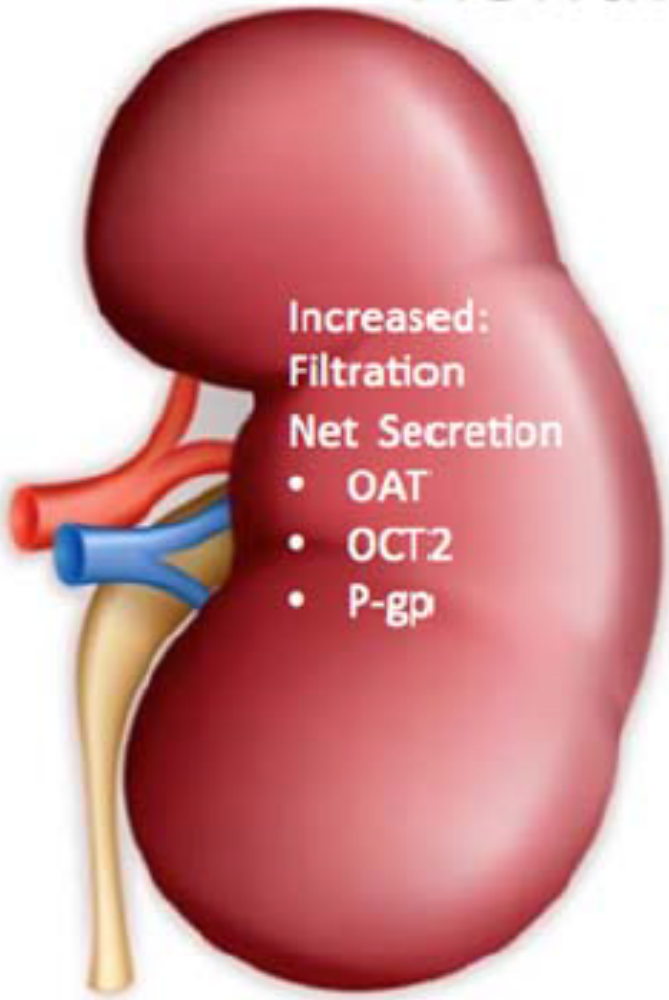
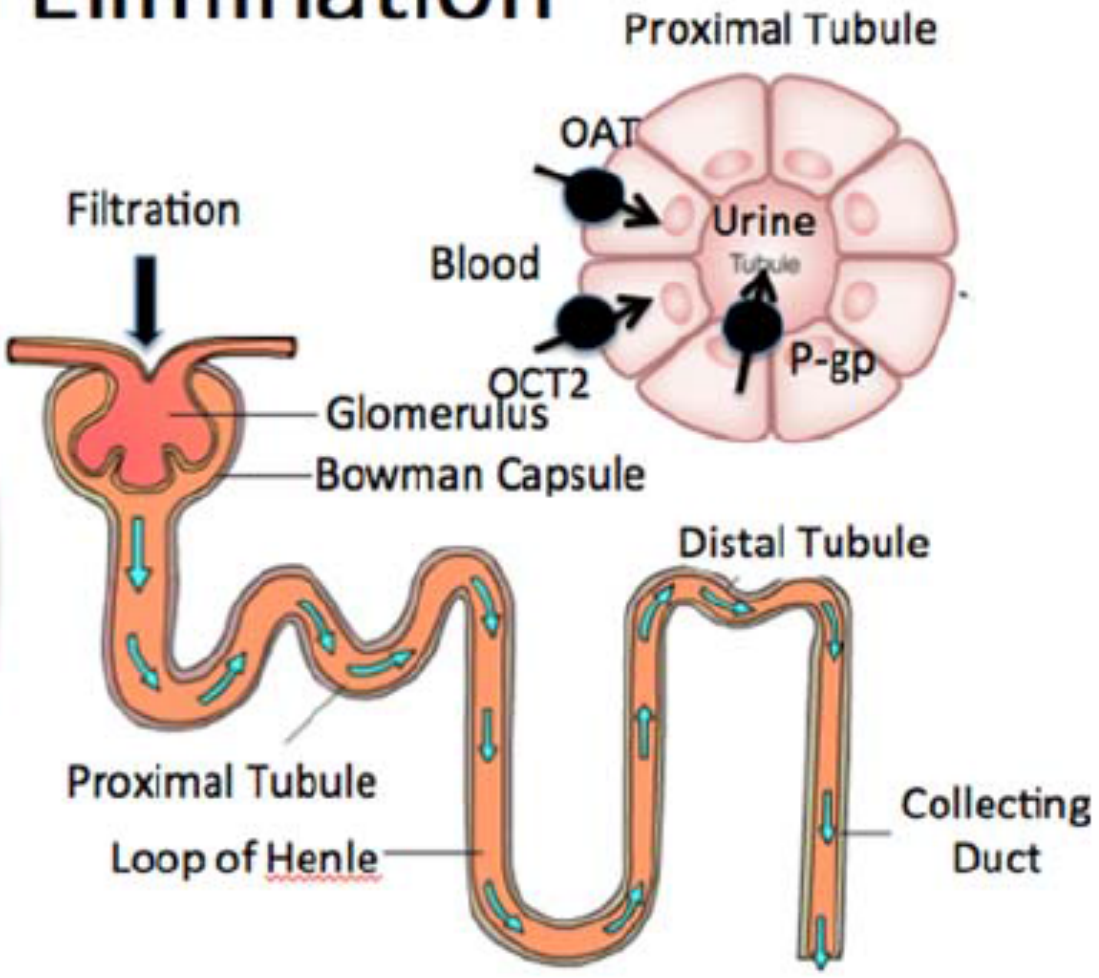
Caffeine (CYP1A2) pharmacokinetics in pregnant women





Effects of Pregnancy on Renal Elimination





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Digoxin (P-gp) PK parameters Pregnancy vs Postpartum

Parameter	Pregnancy	Postpartum	Percent difference	*P* value
$AUC_{0\rightarrow48}$ (ng·h/ml)	7.3 ± 1.6	9.3 ± 2.2	−19 ± 19	<0.006
$AUC_{0\rightarrow4}$ (ng·h/ml)	1.7 ± 0.5	2.3 ± 0.9	−15 ± 37	0.05
CL_{Renal} (ml/min)	181 ± 25	115 ± 25	61 ± 29	<0.002
$CL_{Renal,\ unbound}$ (ml/min)	272 ± 45	183 ± 37	52 ± 25	<0.002
$CL_{secretion}$ (ml/min)	73 ± 22	37 ± 14	120 ± 99	<0.002
$Cl_{secretion,\ unbound}$ (ml/min)	109 ± 34	58 ± 22	107 ± 99	<0.002
f_u (%)	67 ± 4	63 ± 5	5.8 ± 3.4	<0.002
C_{max} (ng/ml)	0.8 ± 0.4	1.1 ± 0.6	−10 ± 50	0.3
T_{max} (h)	1.6 ± 1.1	1.3 ± 0.9	62 ± 147	0.6
Half-life (h)	38.4 ± 8.7	46.5 ± 16.4	−6 ± 41	<0.09

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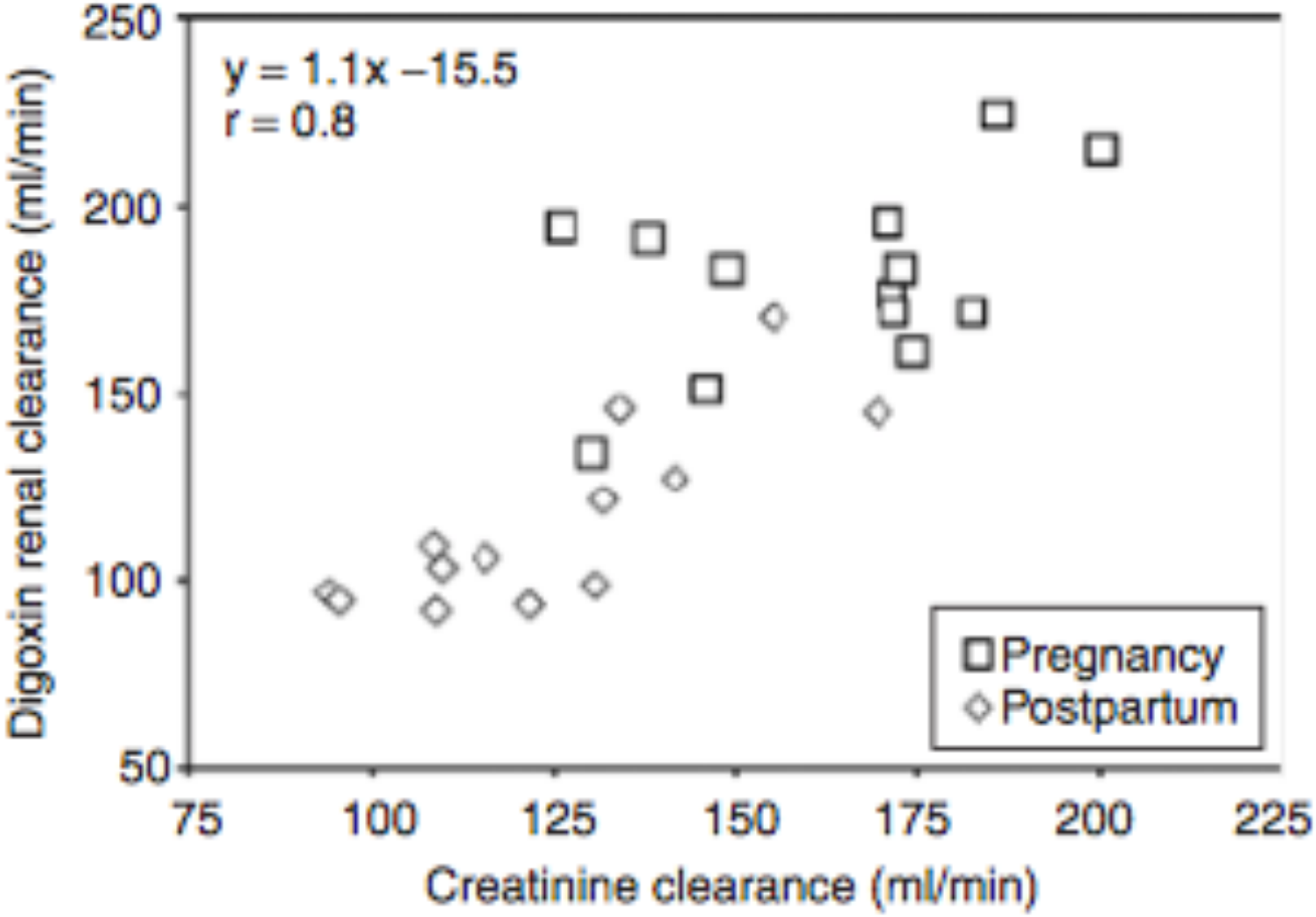
Digoxin renal clearance *vs* creatinine clearance



Farmacocinética em gestantes

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$$t_{1/2} = \frac{0{,}693 \times Vd}{CL}$$

CL ↑
Vd ↑
t½ ↑

↑ %pp

anticonvulsivantes
antidepressivos

↑ lipossolubilidade

↓ lipossolubilidade

aminoglicosídicos

CL ↑
Vd ↑
t½ ↓

↓ %pp

TRANSPORT SYSTEMS THAT CONTRIBUTE TO THE BARRIER FUNCTION OF THE PLACENTA

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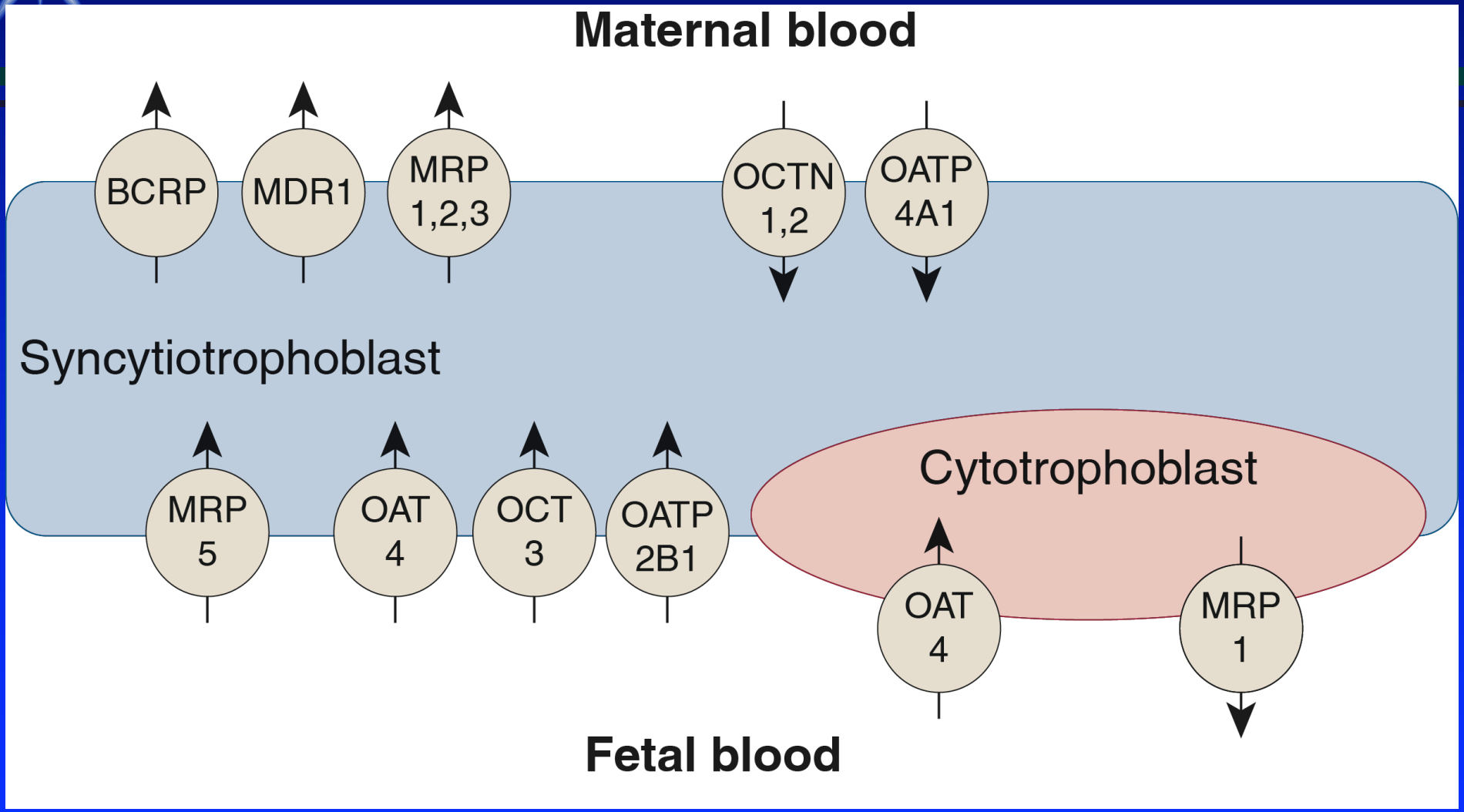

P-gp P-glycoprotein; MRP Multidrug resistance protein; BCRP Breast cancer resistance protein

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FENTANYL

Placental transfer of fentanyl indicates the need of caution regarding the doses of drug administration

To prevent deleterious effects on the fetus and/or newborn infant

Table 3 Fentanyl concentrations (in nanograms per milliliter) in maternal and fetal plasma determined by GC-MS, and fetal/maternal ratio

Parameter[a]	Parturients ($n = 8$) [Median (P25–P75)][b]
Latency (min)	28.50 (25.75–32.25)
Maternal concentration (ng/ml)	0.31 (0.28–0.32)
Fetal concentration (ng/ml)	0.25 (0.19–0.51)
Fetal/maternal ratio	0.89 (0.75–1.62)

[a]Latency, Time between drug administration and birth; fetal/maternal ratio, ratio between fetal and maternal fentanyl concentration in plasma at the time of birth

[b]P25, 25th percentile; P75, 75th percentile

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METFORMIN

CAUTION IS RECOMMENDED → **70% transplacental transfer**

Table 3 Maternal and umbilical cord plasma metformin concentrations in eight parturients with PCOS

Parameter	Median (minimum and maximum)
Maternal plasma (mg/L)	0.4 (0.1–2.4)
Umbilical cord plasma (mg/L)	0.3 (0.1–1.4)
Umbilical/maternal	0.7 (0.4–1.3)

Data are expressed as the median, with the minimum and maximum values given in parenthesis

Exercício 1

A administração de dose única oral de 100 mg de metoprolol a uma paciente gestante ou de 200 mg de metoprolol a uma paciente não gestante resultou nas concentrações plasmáticas em função do tempo abaixo apresentadas. Com base nos dados, responda:

Tempo (h)	Paciente não gestante ng/mL	Paciente gestante ng/mL
zero	zero	zero
0.25	31.31	3.44
0.5	66.53	30.38
0.75	180.47	129.69
1	286.01	151.49
1.5	235.78	93.05
2	195.06	72.62
2.5	160.3	55.4
3	135.81	42.3
4	109.32	32.5
5	80.02	20.28
6	63.03	14.46
8	31.88	7.58
10	27.23	5.09
12	23.36	3.47
16	15.51	1.47
20	9.62	1.41
24	4.75	1.2

a) Calcular o volume de distribuição aparente (Vd/F) do metoprolol nas pacientes gestante e não gestante.

b) Calcular o clearance total aparente (Cl/F) do metoprolol nas pacientes gestante e não gestante.

c) Discutir os valores encontrados de Vd/F e Cl/F com base nas alterações fisiológicas da gestação que alteram a farmacocinética.

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Dose / Concentração plasmática

- Medicamento
- Paciente
- Interação de fármacos

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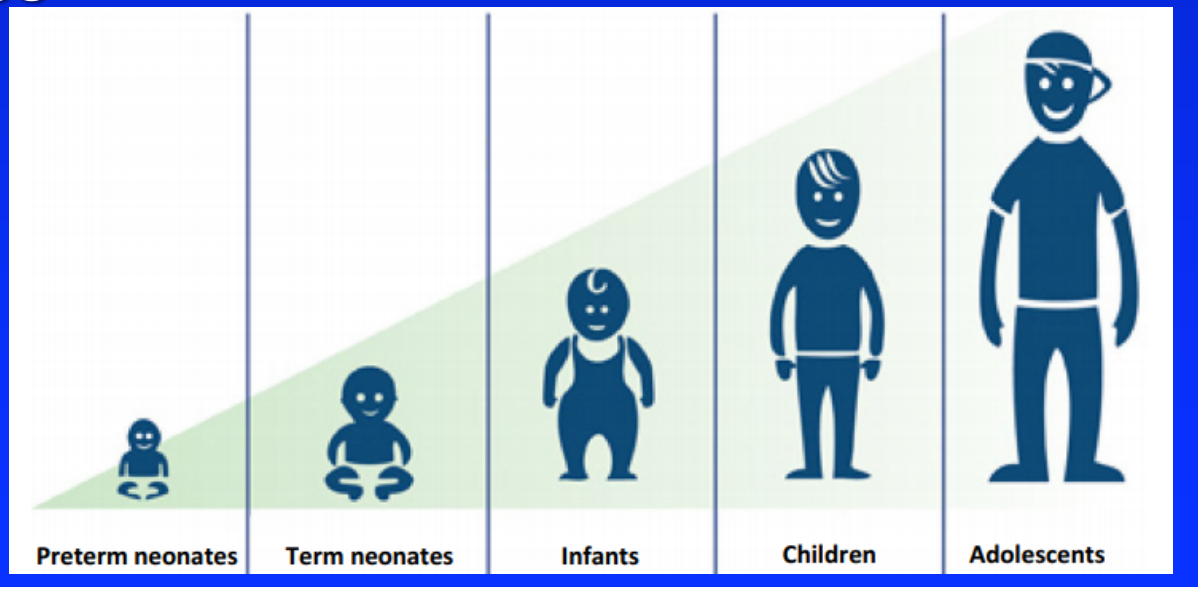
Pediatric pharmacokinetics

Neonates – até 1 mês (idade gestacional >= 36 semanas)

Infant – 1 mês até 2 anos

Children – 2 a 12 anos

Adolescents – 12 a 16 anos



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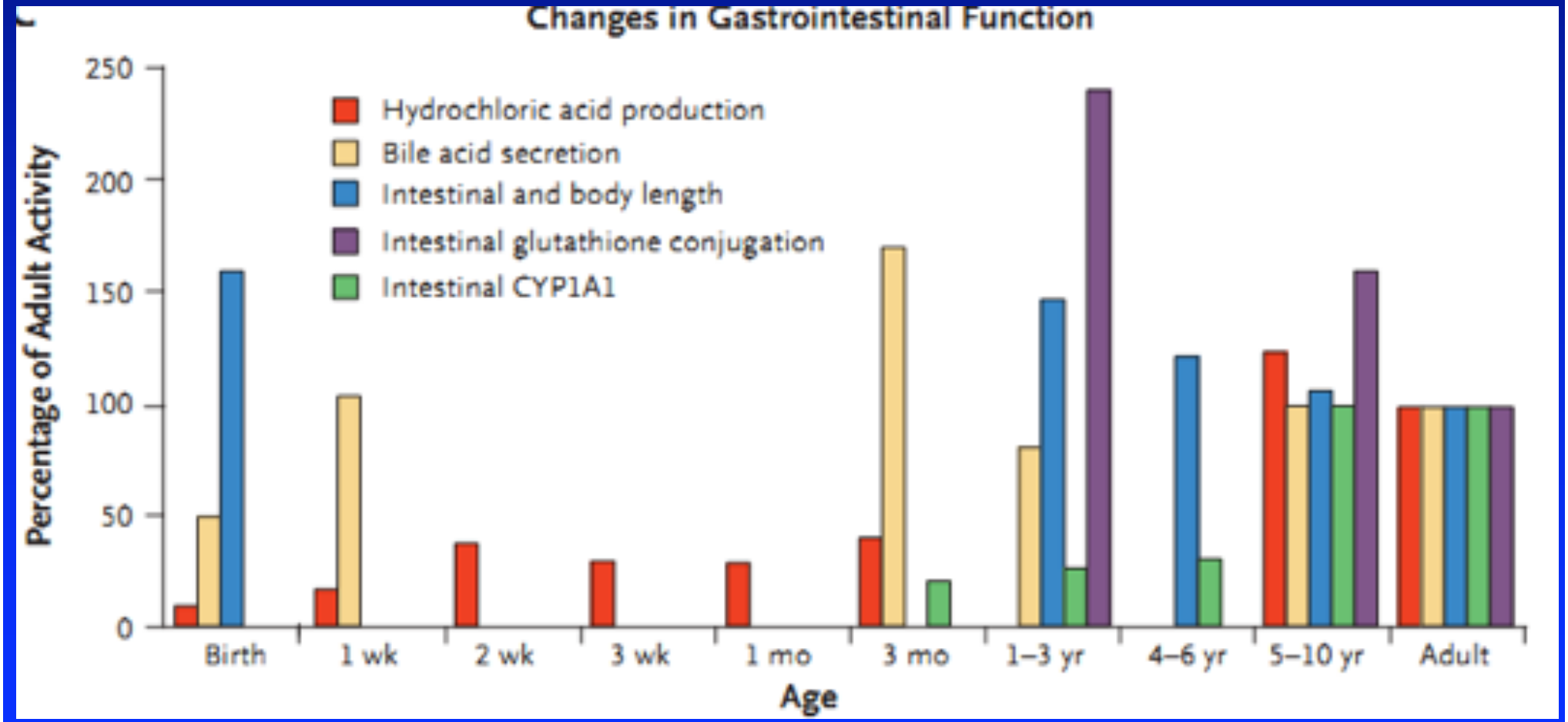
Changes in Gstrointestinal Function



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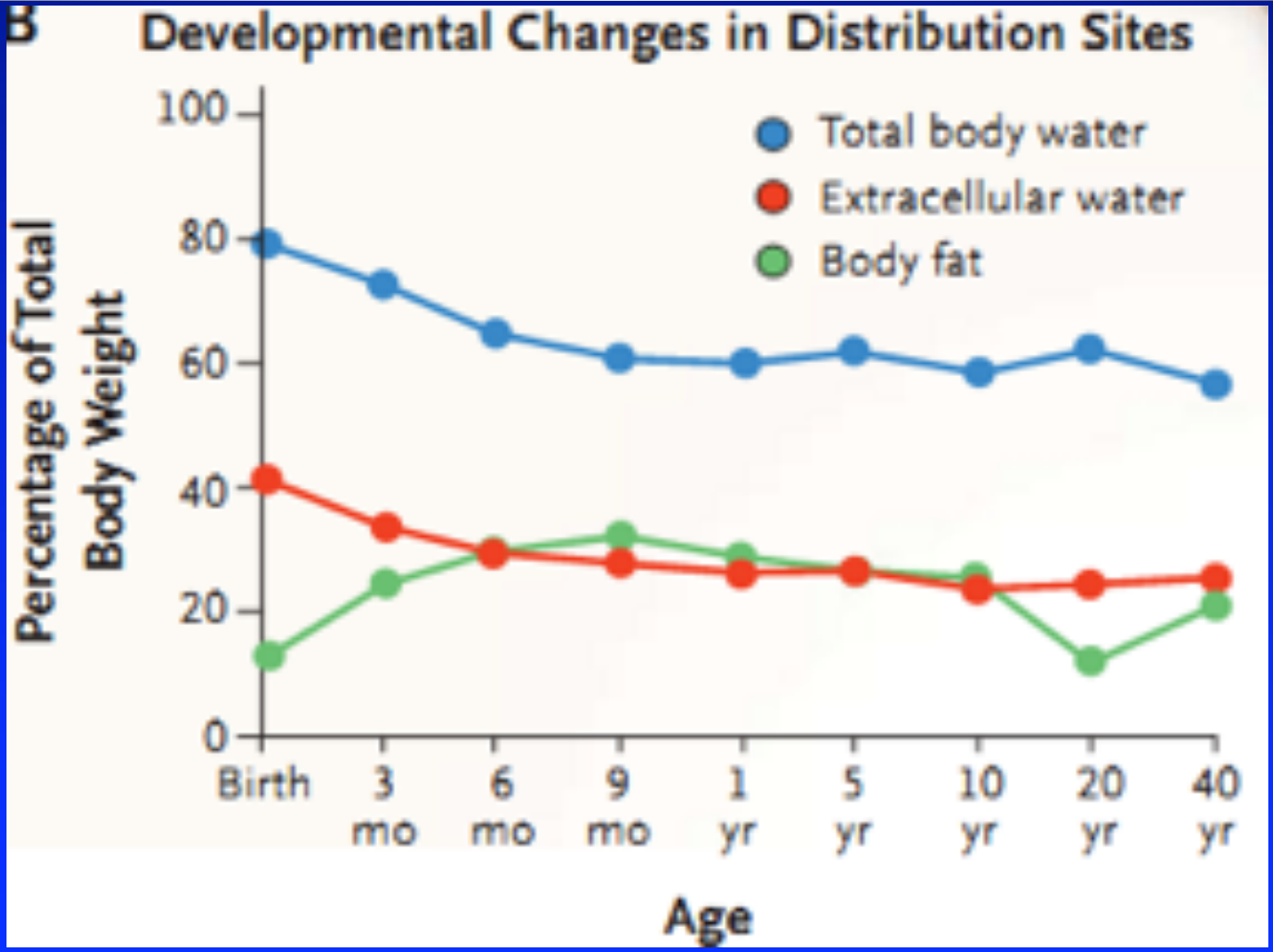
Developmental changes in distribution sites



Ligação às proteínas plasmáticas neonatos *vs* adultos

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	Fração livre		Vd (L/kg)	
	neonato	adulto	neonato	adulto
fenobarbital	0,68	0,53	1	0,55
sulfametoxipirazina	0,43	0,38	0,47	0,24
digoxina	0,8	0,7	10	7
fenitoina	0,2	0,1	1,3	0,63

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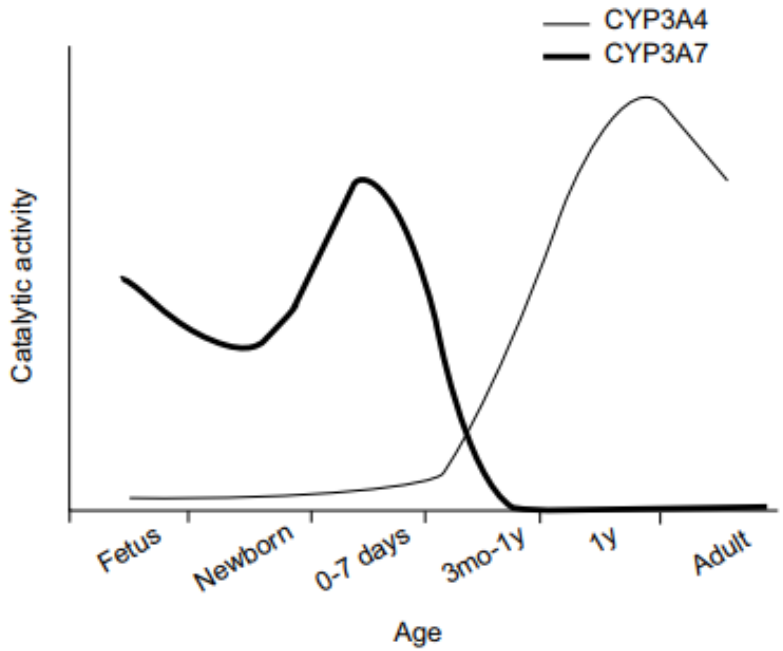
Ontogeny of CYP enzymes



Enzyme	Becomes active at	Substrates	Inhibitors	Inducers
CYP 1A2	1–3 months	Caffeine Paracetamol	Ciprofloxacin	Tobacco Insulin Omeprazole
CYP 2D6	Hours, days	Amphetamines Codeine Flecainide Lignocaine Metoclopramide	Cocaine Methadone Ranitidine	Phenobarbitone Phenytoin
CYP 2C9	First weeks	Ibuprofen Phenytoin	Fluconazole Sulfamethoxazole	Rifampicin
CYP 2C19	First weeks	Omeprazole Phenytoin Indomethacin	Omeprazole Indomethacin	Carbamazepine Prednisone
CYP 3A4	First weeks	Steroids Clarithromycin Midazolam	Fluconazole Grapefruit Juice	Phenobarbitone Phenytoin
CYP 2E1	Hours	Ethanol Paracetamol	disulfiram	Ethanol Isoniazid

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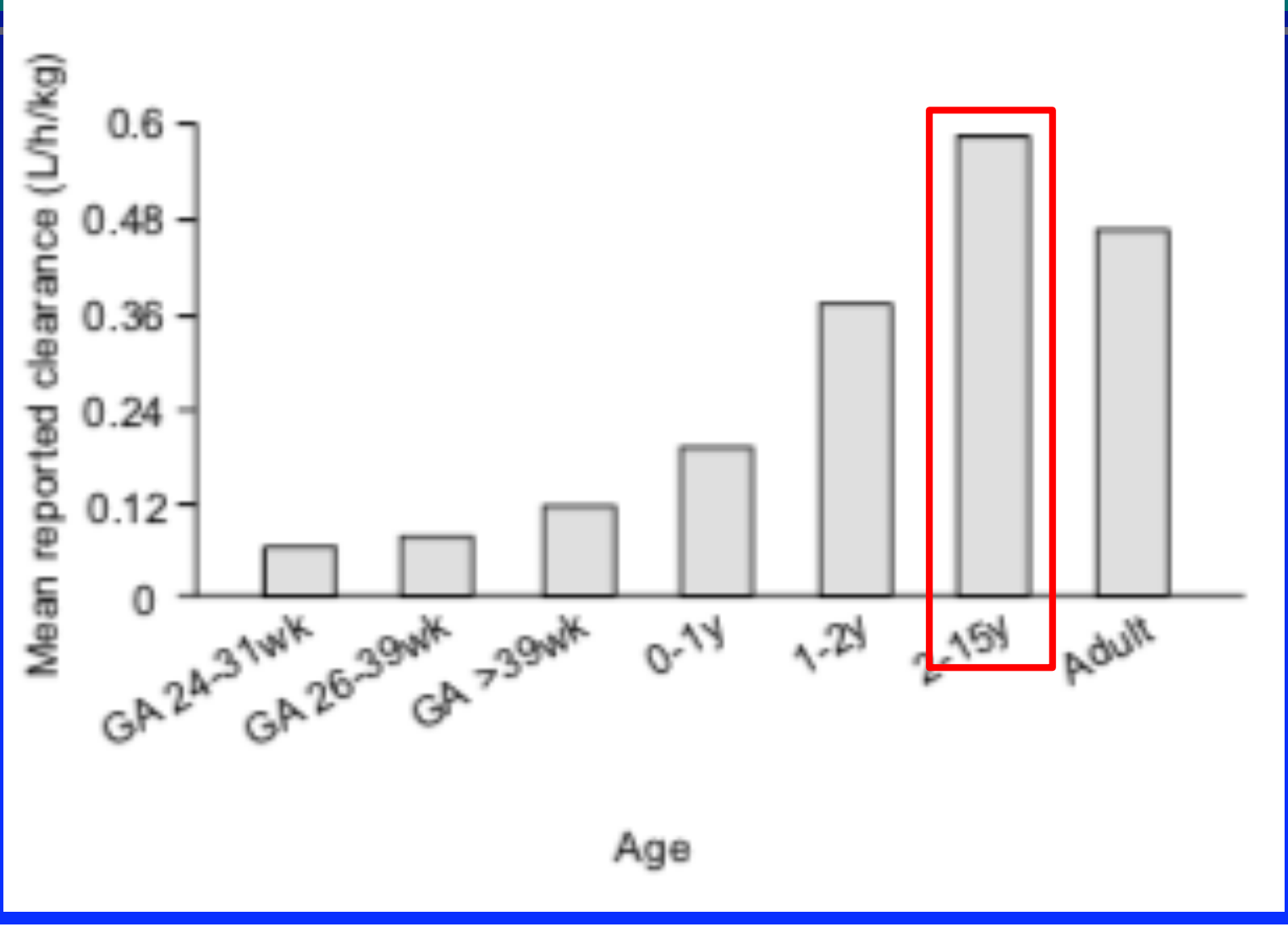
Effect of age on the clearance of midazolam (CYP3A)



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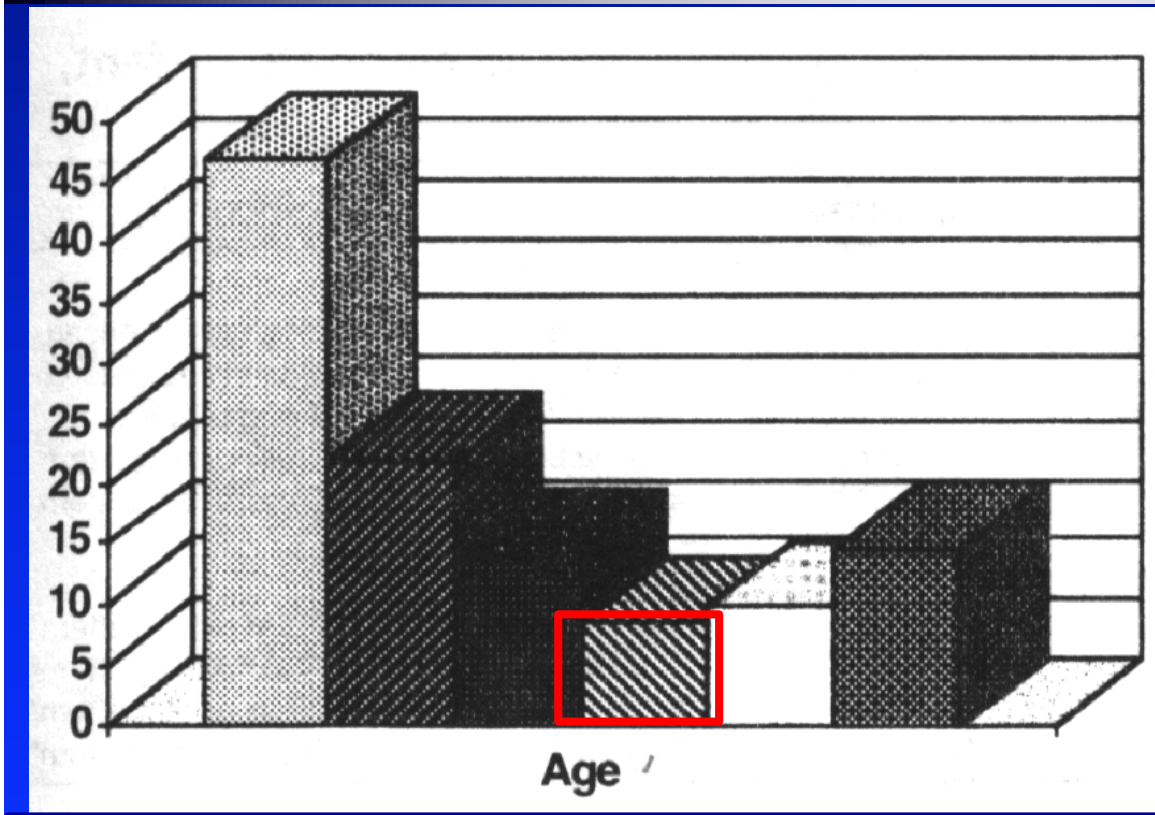
Impact of development on theophylline plasma concentrations



$$C_{ss} = \frac{\text{Dosing rate}}{\text{Clearance}}$$

- 3-15 d
- 25-57 d
- 3-23 mo
- 16 mo -4 yr
- 6-17 yr
- 23-79 yr

Steady state (Css) serum theophylline concentrations from a dose of 20mg/kg/day administered to patients of varying age

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Clearance (mL/min) of theophylline in diferente age groups

Age Groups	Observed CL
Premature neonates (n = 20)	0.69 ± 0.42
Infants (n = 10)	4.7 ± 2.3
Children (n = 10)	20 ± 8
Adults (n = 12)	49 ± 9

$$\text{Dosing rate} = CL \times C_{ss}$$

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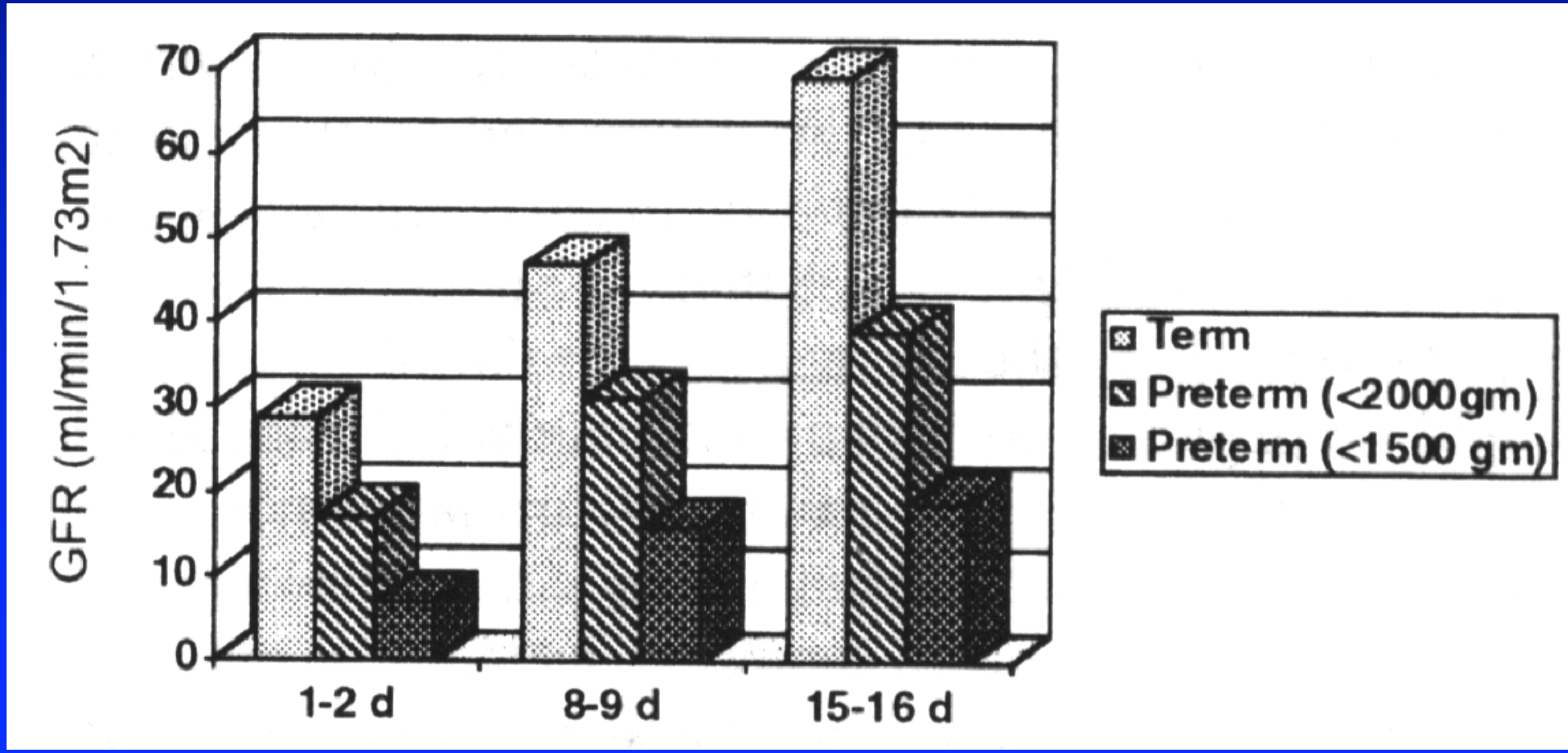
Ontogeny of glomerular filtration in the neonate



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Pediatric pharmacokinetics
Gentamicin dosing

Table 2. Pharmacokinetics and Nonsynergistic Gentamicin and Tobramycin Dosing across Different Age Groups[1]

Age Group	Volume of Distribution (L/kg)	Half-Life (hr)	Conventional Dose[a]	Extended-Interval Dose (mg/kg every 24 hr)[b]
Neonates	0.45–0.6	3–12	4–5 mg/kg every 24–48 hr depending on gestational age, postnatal age, and renal function for target peak of 8–10 mg/L and trough of <2 mg/L	…[d]
Infants	0.3–0.5	4	2.5 mg/kg every 8 hr	4–5
Children and adolescents	0.3–0.35	2	2.5 mg/kg every 8 hr	7–8
Children with cystic fibrosis[c]	0.2–0.35	1.2–2.2	3.3 mg/kg every 8 hr	10–12
Adults	0.2–0.3	2	1–1.6 mg/kg every 8 hr	5–7

FCFRP-USP

Pediatric pharmacokinetics
Vancomycin dosing

Table 3. Vancomycin Dosing across Different Age Groups

Age Group	Volume of Distribution (L/kg)	Half-Life (hr)	Dosing (mg/kg)
Neonates	0.4–0.6	6–10	10–20 every 12–24 hr depending on gestational age, postnatal age, and renal function
Infants	0.4–0.6	4	10–20 every 6–8 hr
Children and adolescents	0.5–0.76	2–3	10–20 every 6–8 hr
Children with cystic fibrosis	0.63	2–3	10–20 every 6–8 hr
Adults	0.4–1	4–6	15–20 every 8–12 hr

Neonates: ↓ Cl_{renal}

Children > 1 yr: ↑ Cl_{renal}

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Farmacocinética

neonatos *vs* adultos

	neonato *vs* adulto	farmacocinética	exemplo
Vd	↑	↓ C_{max}	penicilinas sulfonamidas
%pp	↓	↑ fração livre	teofilina
metabolismo	↓	↓Cl	teofilina
excreção	↓	↑AUC ↑ $t_{1/2}$	gentamicina

Prediction of drug clearance in children from adults:

Drugs/age	Body weight (kg)	Obs CL ($l\ h^{-1}$)	Pred CL (0.75)
Morphine			
<1 week	3.5	1.365	6.513
1 week to 2 months	3.9	2.106	7.064
2–6 months	6.2	7.936	10.001
0.5–2.5 years	7.2	9.360	11.188
Adult	70	61.600	
Fentanyl			
<1month	3.2	3.104	5.536
1–12 months	5.9	6.431	8.760
1–5 years	17.3	11.937	19.629
Adult	70	56.000	
Remifentanil			
2–12 years	18	63.360	62.435
Adult	70	172.900	
Bupivacine			
1–21 days	3.2	0.704	3.183
5.5–10 years	23	13.800	13.974
Adult	70	32.200	
Midazolam			
1–7 days (premature)	2	0.149	1.925
1–7 days term	3	0.300	2.609
34–41 weeks (gestational)	3.1	1.264	2.674
Mean 5.2 years	17.3	9.460	9.709
Adult	70	27.700	

CL in the child = adult CL

×

(weight of the child/70) $^{0.75}$

Children > 5 years

$$\text{Dosing rate} = \text{CL} \times C_{ss}$$

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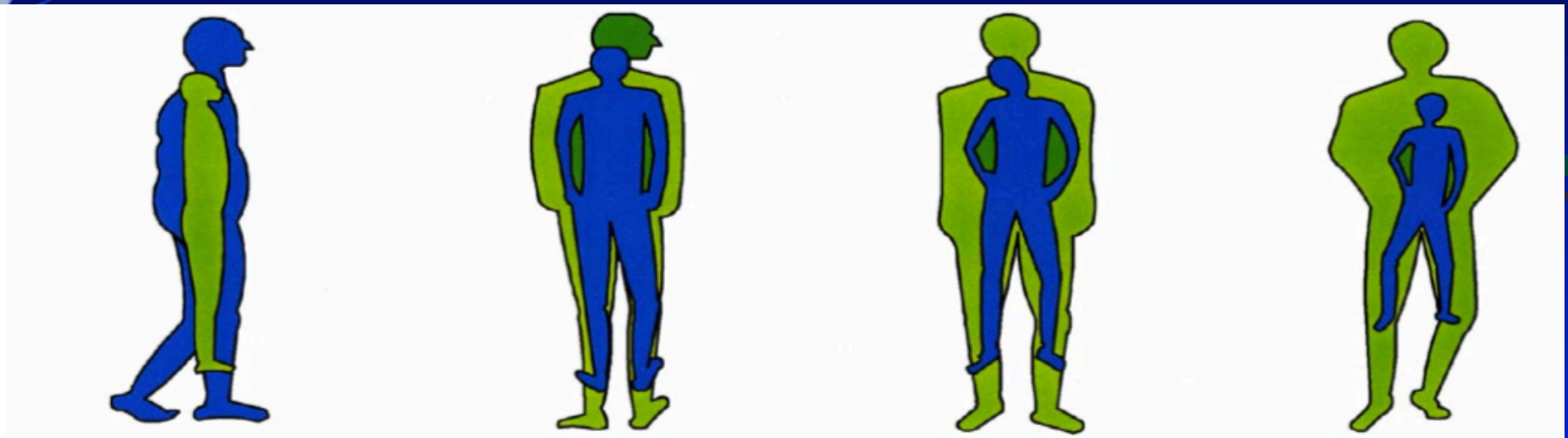
Use of medicines in older adults

- Older adults: > 65 years old

$$C_{ss} = \frac{\text{Dosing rate}}{\text{Clearance}}$$

“START LOW, GO SLOW”

Age-related pharmacokinetic changes



increase in body fat

↑ 35 %

decrease in plasma volume

↓ 8 %

decrease in total body water

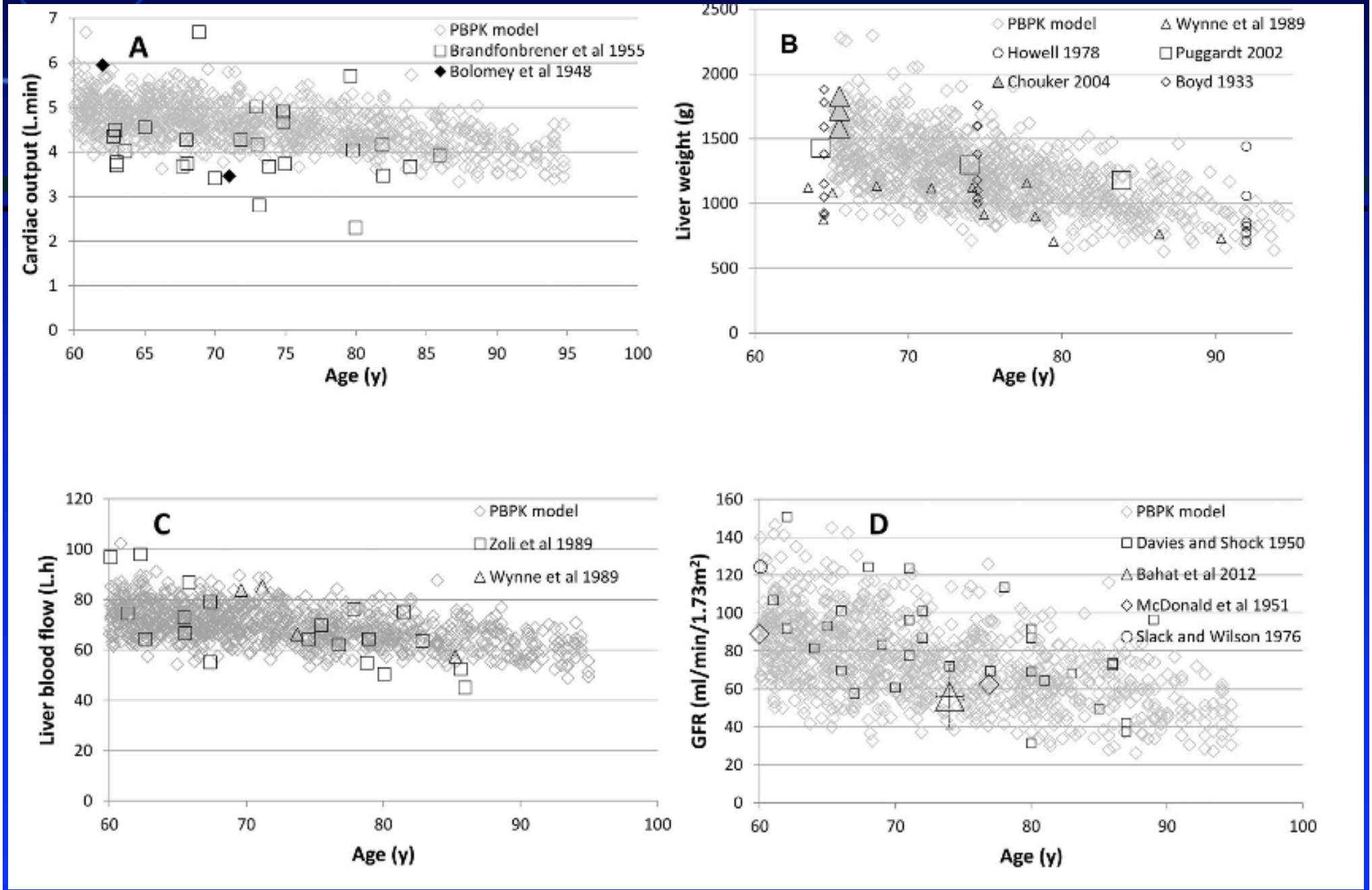
↓ 17 %

decrease in intracellular body fluid

↓ 40 %

20 years

65 – 80 years


A
PBPK model
Brandfonbrener et al 1955
Bolomey et al 1948
Cardiac output (L.min)
Age (y)
B
PBPK model
Wynne et al 1989
Howell 1978
Puggardt 2002
Chouker 2004
Boyd 1933
Liver weight (g)
Age (y)
C
PBPK model
Zoli et al 1989
Wynne et al 1989
Liver blood flow (L.h)
Age (y)
D
PBPK model
Davies and Shock 1950
Bahat et al 2012
McDonald et al 1951
Slack and Wilson 1976
GFR (ml/min/1.73m²)
Age (y)

Pharmacokinetics			
PK Process	***Age-related change***	***Impact***	***Clinical Consequences***
Absorption	Increased gastric pH	Slightly decreased absorption	May impact T_{max} and C_{max}
	Delayed gastric emptying		
	Reduced splanchnic blood flow		
	Decreased absorption surface area		
	Decreased gastrointestinal motility		
Distribution	Increased body fat	Altered volume of distribution	Increased V and $t_{1/2}$ of lipophilic drugs
	Reduced body lean mass		
	Reduced body total water		Increased plasma concentrations of water-soluble drugs
	Reduced serum albumin		Increased free-fraction of highly protein-bound acidic drugs
	Increased α1-acid glycoprotein		Decreased free-fraction of basic drugs
	Decreased cerebrovascular P-glycoprotein (P-gp) functionality	Altered blood-brain barrier permeability	Excessive levels and prolonged residence of drugs and xenobiotics in the brain
Metabolism	Reduced hepatic blood flow and overall liver mass	Less effective first-pass and phase I metabolism	Increased bioavailability of drugs undergoing extensive first-pass metabolism or reduced bioavailability of drug, which need to be activated in the liver
Excretion	Reduced renal blood flow	Impaired renal elimination of water-soluble drugs/ metabolites	Increased volume of distribution for water soluble drugs and enhanced risk of ADRs especially for drugs with a narrow therapeutic index (e.g. digoxin, aminoglycosides)
	Reduced glomerular filtration rate		
	Increased filtration fraction		

Darunavir pharmacokinetics according to age

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	Boosted darunavir	
	Younger ($n = 4$)	Aging ($n = 5$)
Age	63 (62–64)	73 (67–76)
C_{max} (ng/ml)	[a]7963 (7139–8787)	7809 (5695–10 652)
	[b]4651 (4558–4743)	
T_{max} (h)	1.6 (0.9–4)	3 (1–4)
$AUC_{0-\tau}$ (ng.h/ml)	[c]68 197	77 500
	(57 790–78 605)	(55 541–121 893)
	[d]34 658	
	(33 431–35 885)	
$t_{1/2}$ (h)	7.1 (4.9–9.7)	17.6 (4.4–44.4)
CL/*F* (l/h)	17.3 (15.3–20.8)	10.3 (6.6–21.6)
V/*F* (l)	170.3 (145.6–235.1)	371.5 (109.0–441.3)

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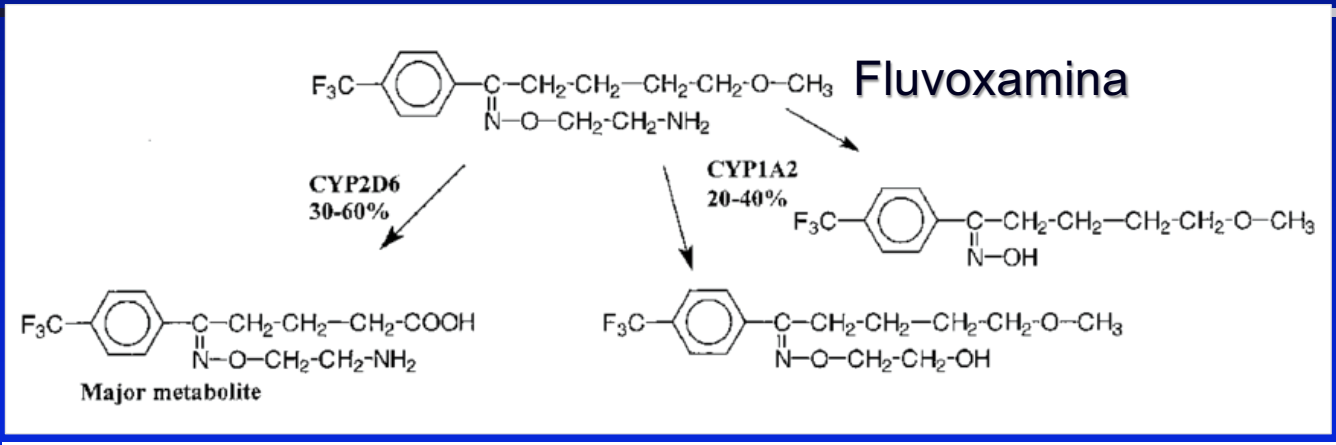
Influência da idade
Metabolismo



Pharmacokinetic Parameter	Young Subjects (Mean Age 35 Years) (*n*=10)	Elderly Subjects (Mean Age 73 Years) (*n*=10)
AUC (ng·h/mL)	304±84	885±560*
CL/F (L/h/kg)	2.25±0.66	1.12±0.77***
$t_{1/2}$ (h)	12.9±6.4	21.2±6.2**
C_{max} (ng/mL)	15±3	31±19*
t_{max} (h)	5(4-8)¶	4(2-8)¶

*P < 0.05; **P < 0.01; ***P < 0.001 vs. young subjects.

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Função renal

influência da idade

idade	clearance da creatinina (mL/min)	
	homens	mulheres
20	120	102
55	85	72
90	50	43

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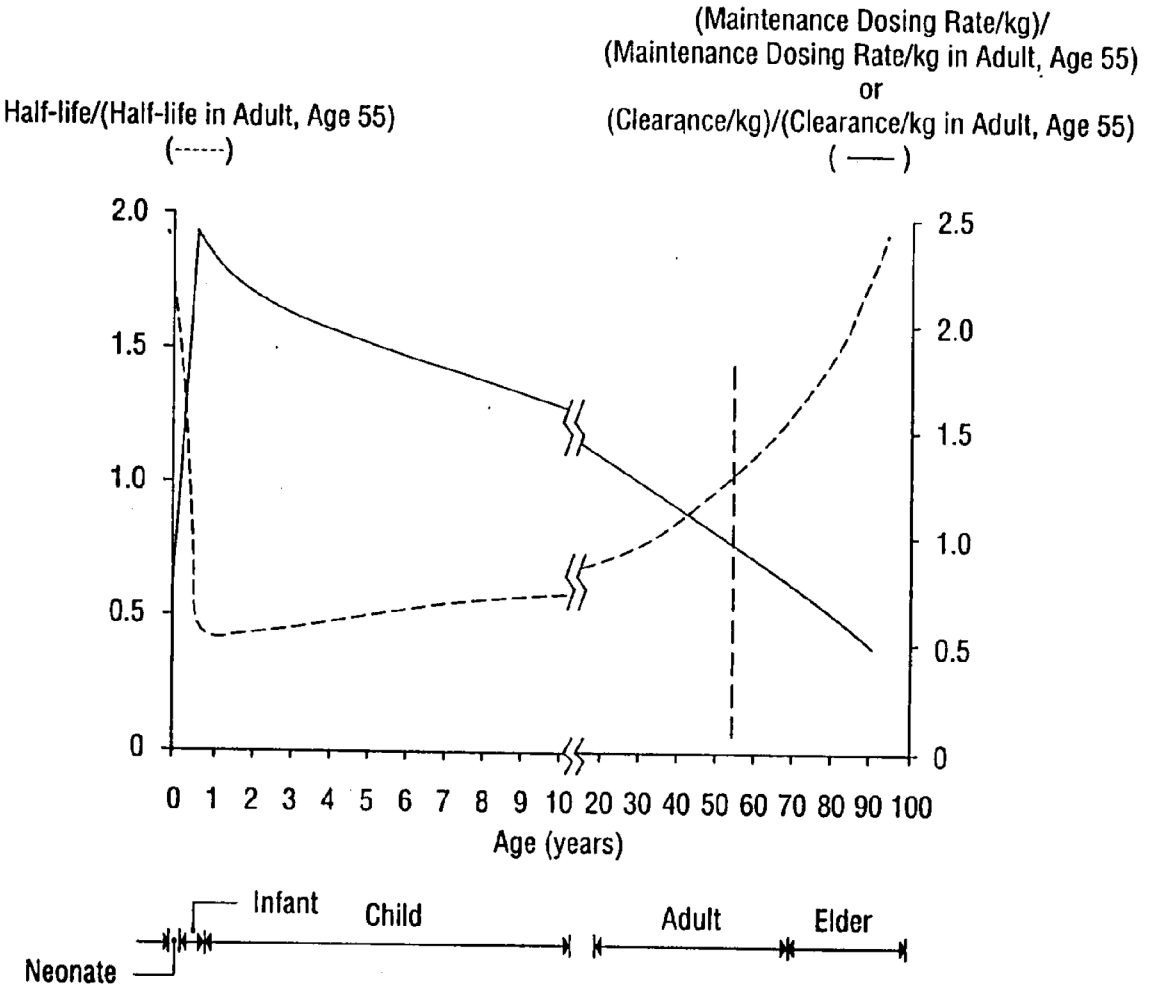
Influência da idade

Meia-vida, clearance e dose de manutenção



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EXERCÍCIO 2

A figura abaixo representa a variação do clearance do antibiótico ceftriaxone em pacientes de 1 dia a 92 anos de idade. Em pacientes adultos jovens o antibiótico é eliminado por excreção renal (50%) e por excreção biliar (50%). Discutir as alterações observadas em neonatos (< 1 mês), crianças de 1 a 5 anos e pacientes idosos (> 65 anos) assim como as possíveis implicações no regime de dosagem.

Sobrepor na figura as alterações esperadas na meia-vida de eliminação em função da idade considerando que a distribuição do antibiótico permanece inalterada.