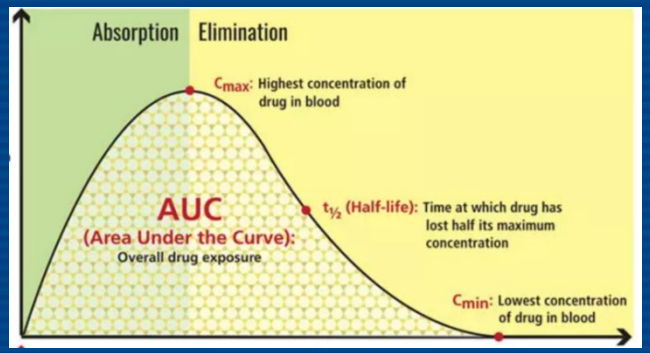
JOHNS HOPKINS
MEDICINE

Physiology changes during pregnancy and Impact on drug and biologics disposition and response.



Ahizechukwu Eke, MD PhD
Associate Professor,
Maternal Fetal Medicine,
Johns Hopkins University

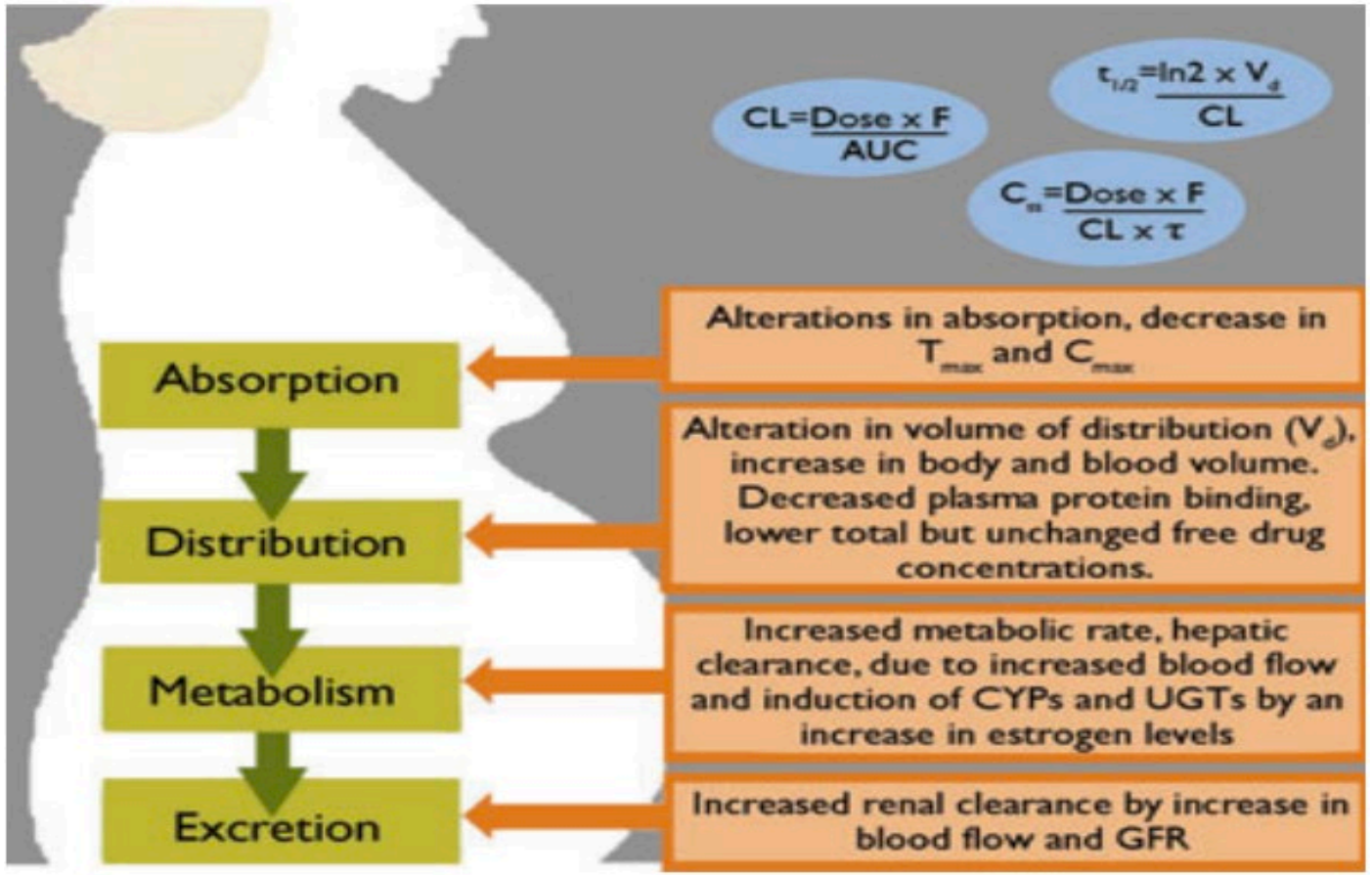
Conflicts of Interest

- I have no conflicts of interest

Outline

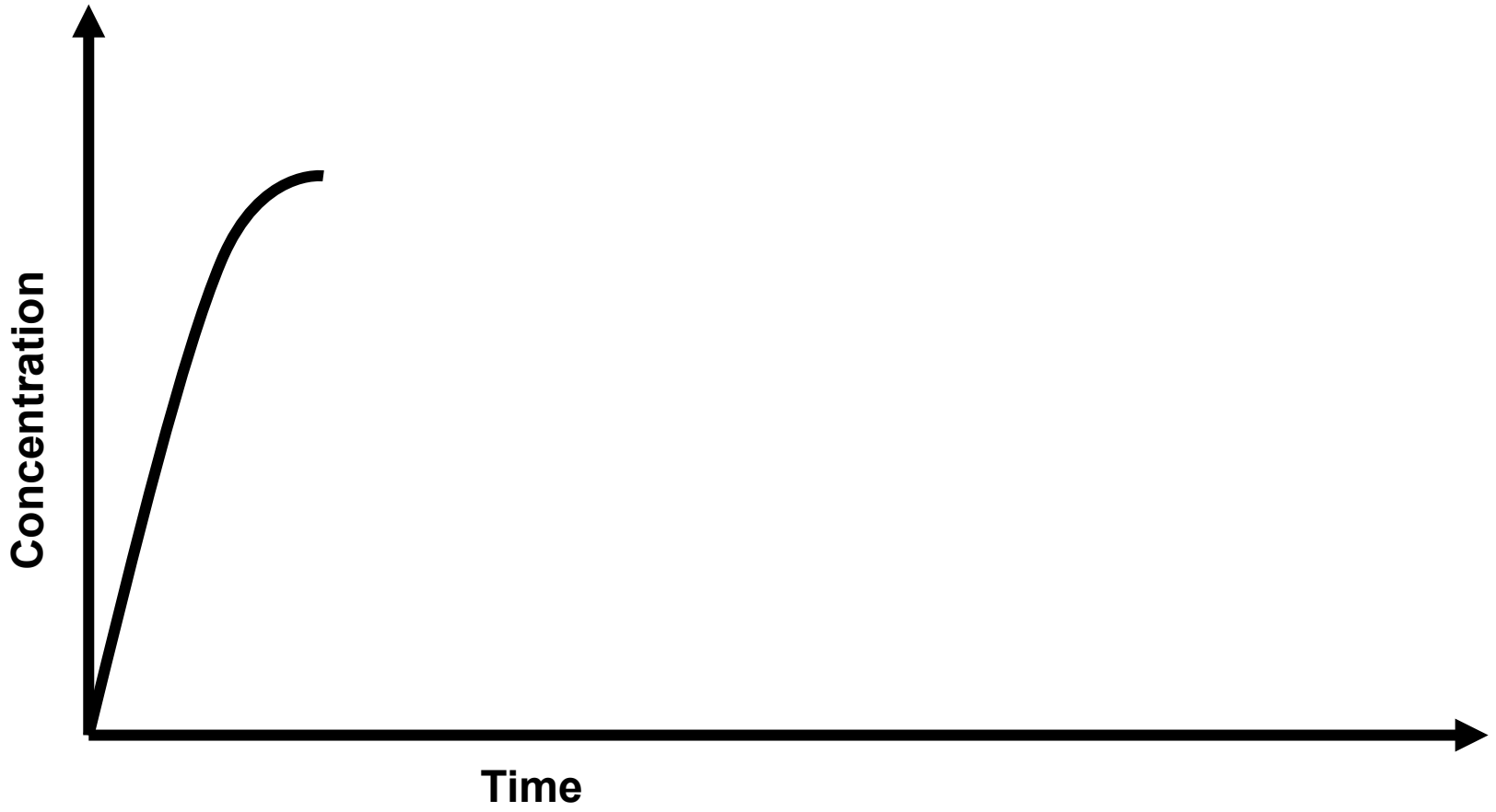
- Physiological changes in pregnancy
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Physiological changes as it affects drug disposition of biologics

Pregnancy affects drug disposition

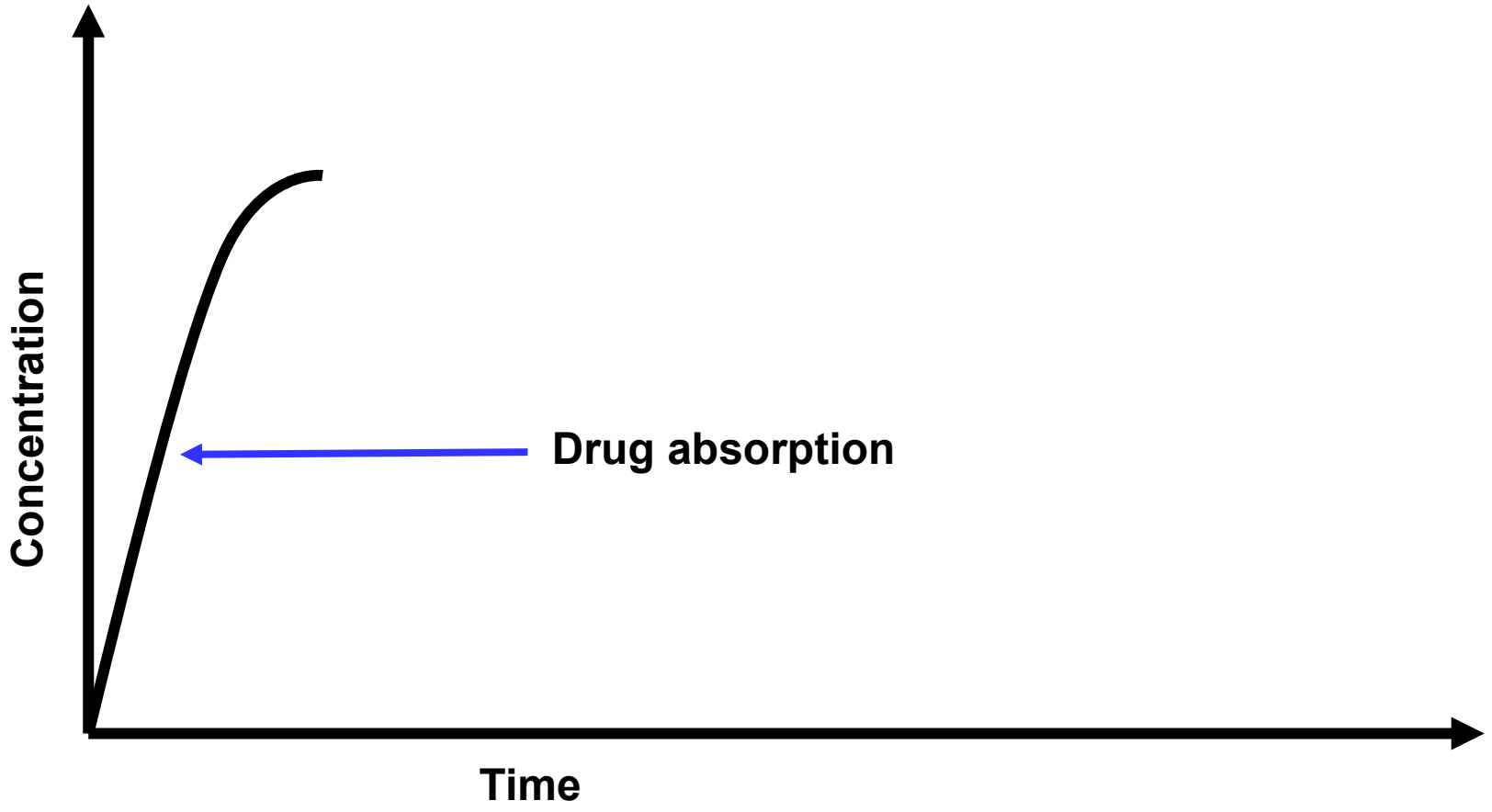


Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: Changes in drug disposition and their clinical implications. Epilepsia 2013; 54(3): 405-414.

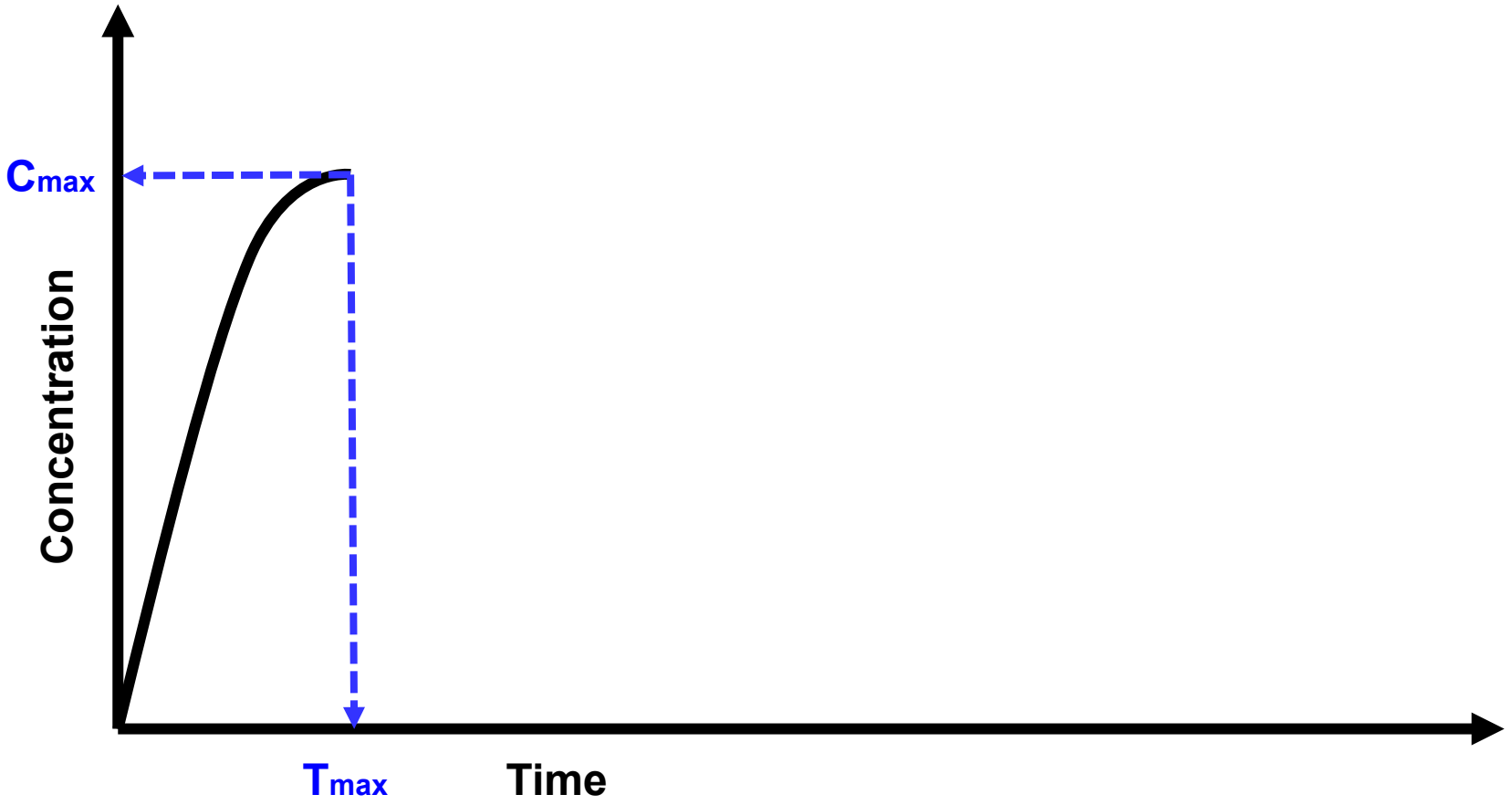
Concentration-time curve (Pharmacokinetics)



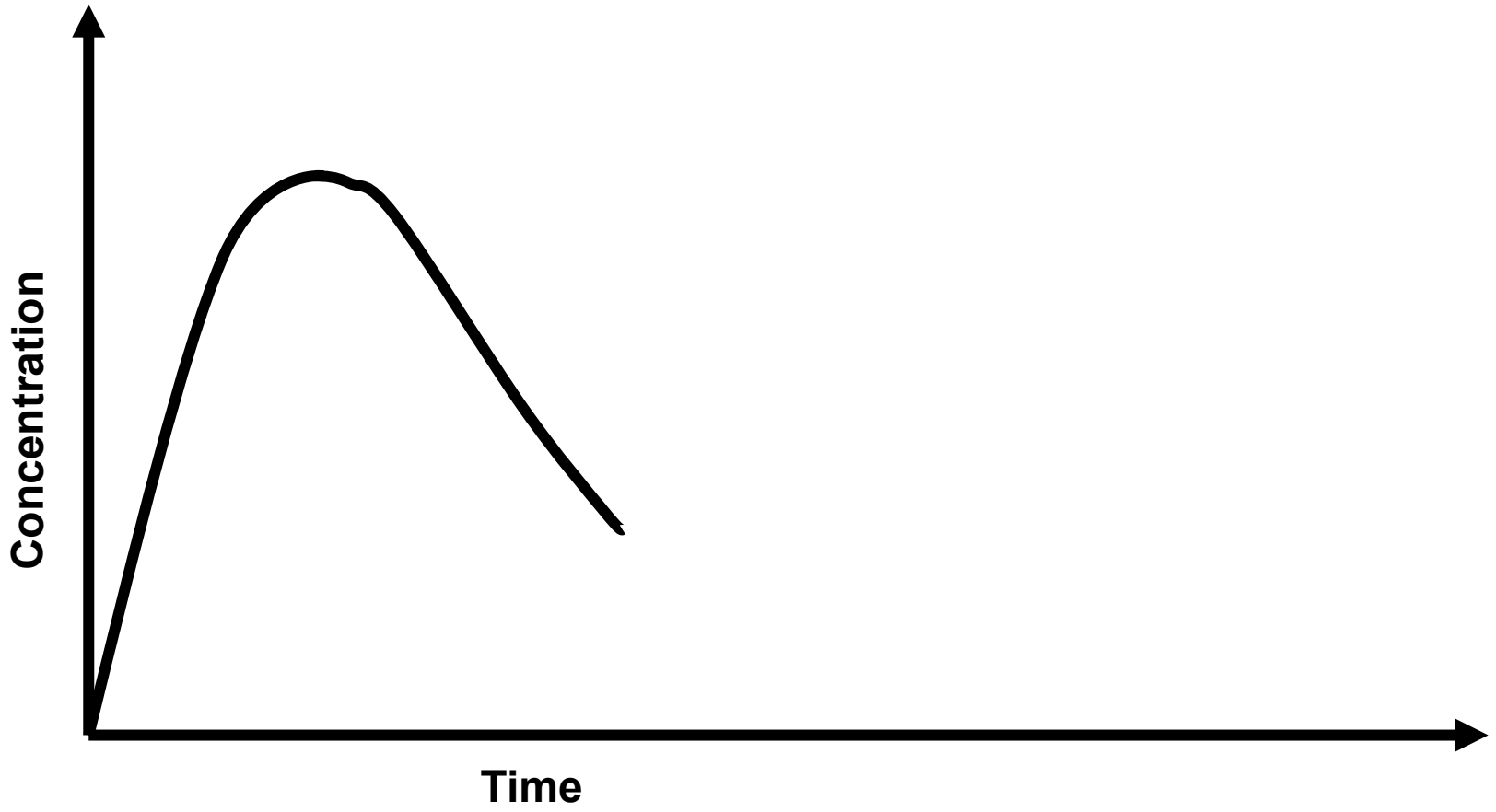
Concentration-time curve



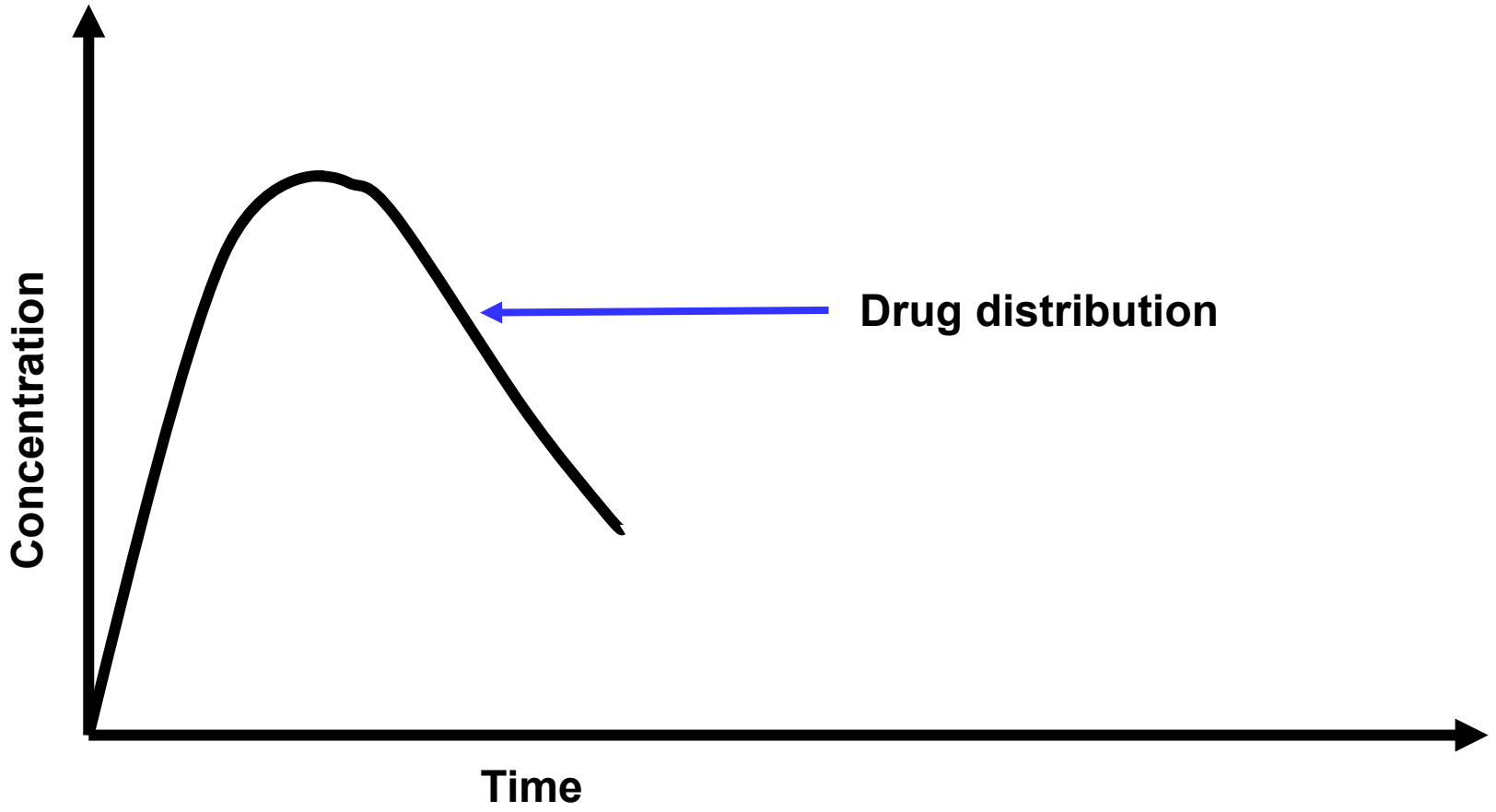
Concentration-time curve



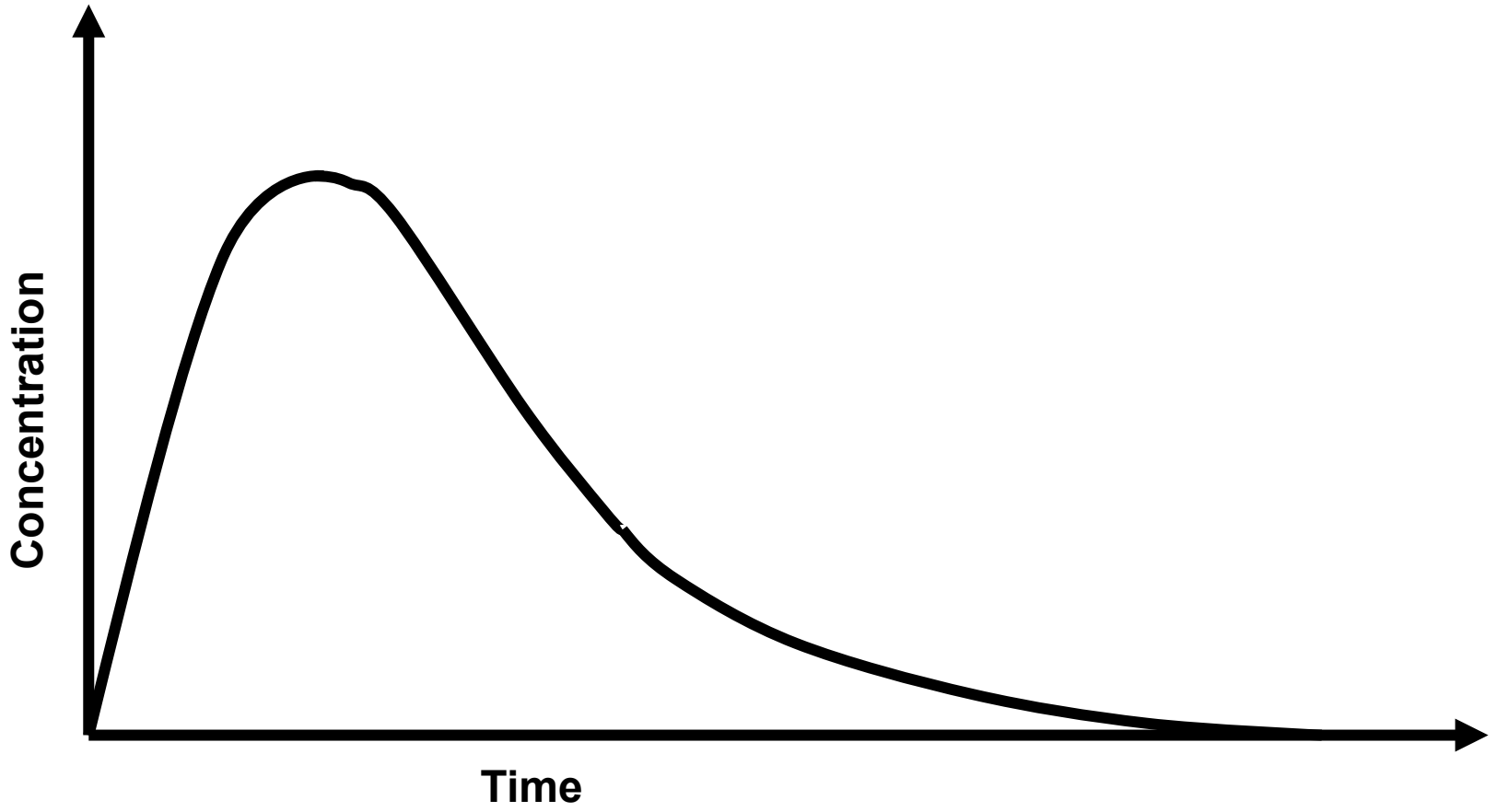
Concentration-time curve



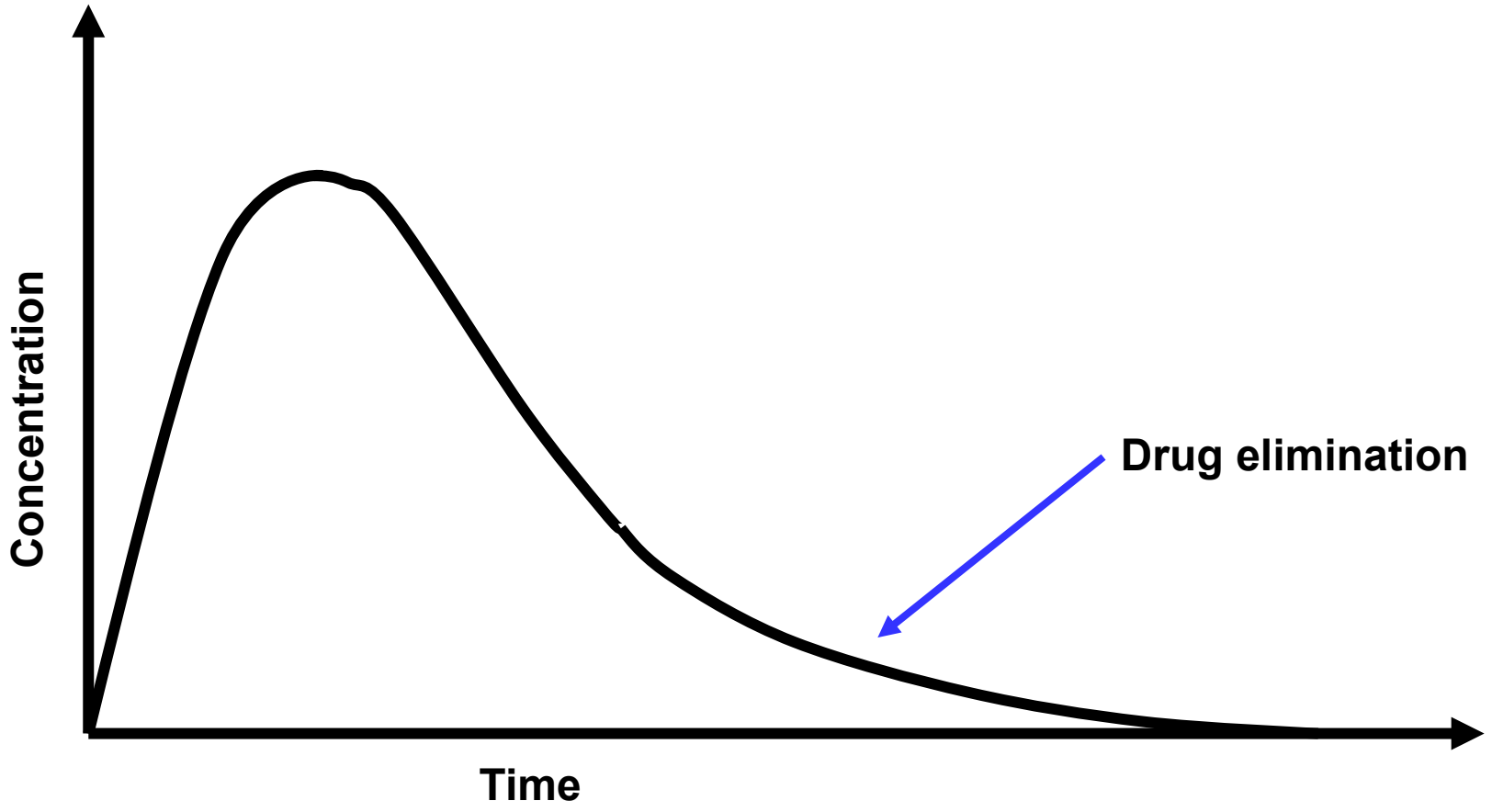
Concentration-time curve



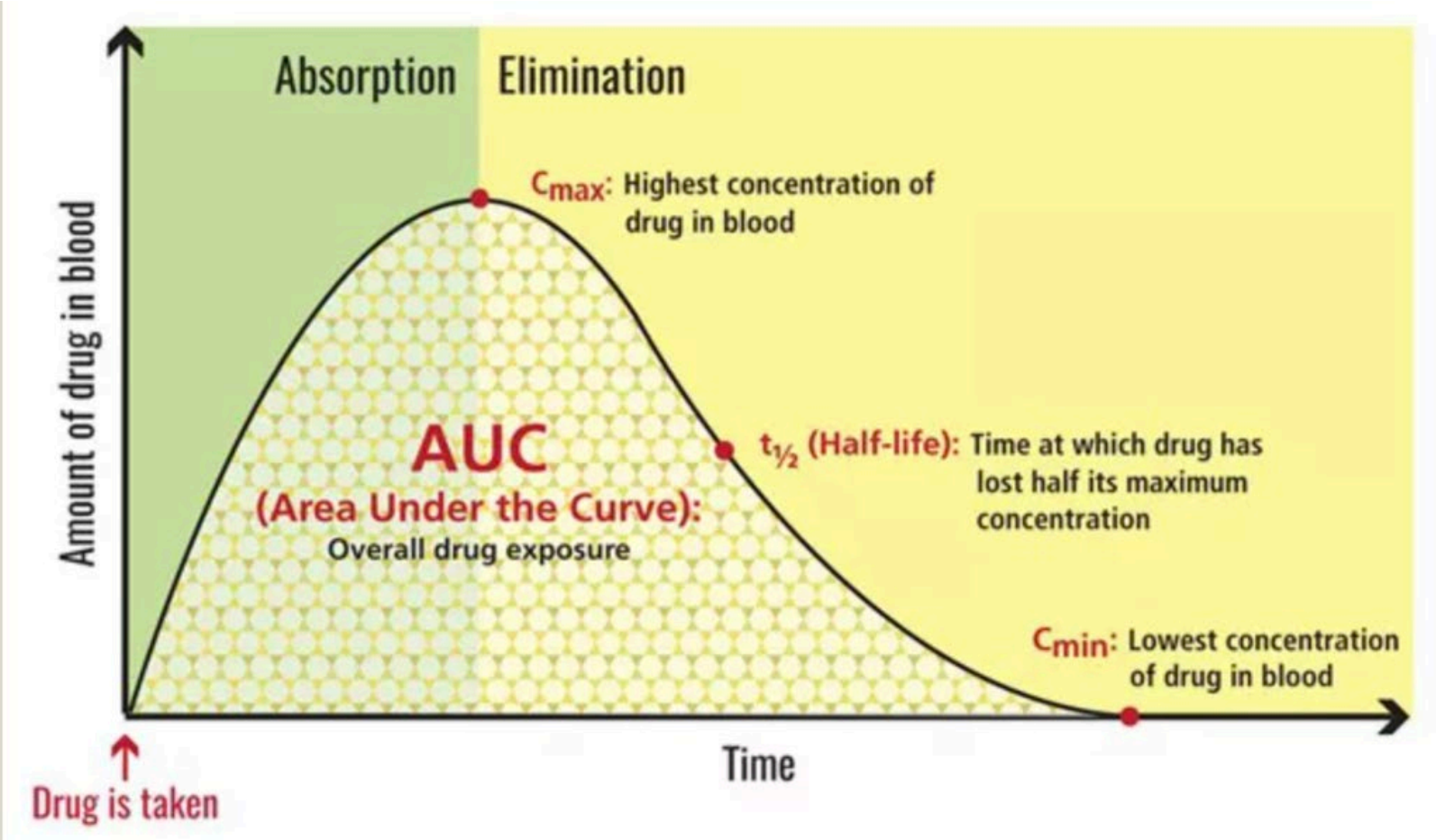
Concentration-time curve



Concentration-time curve



Concentration-time curve



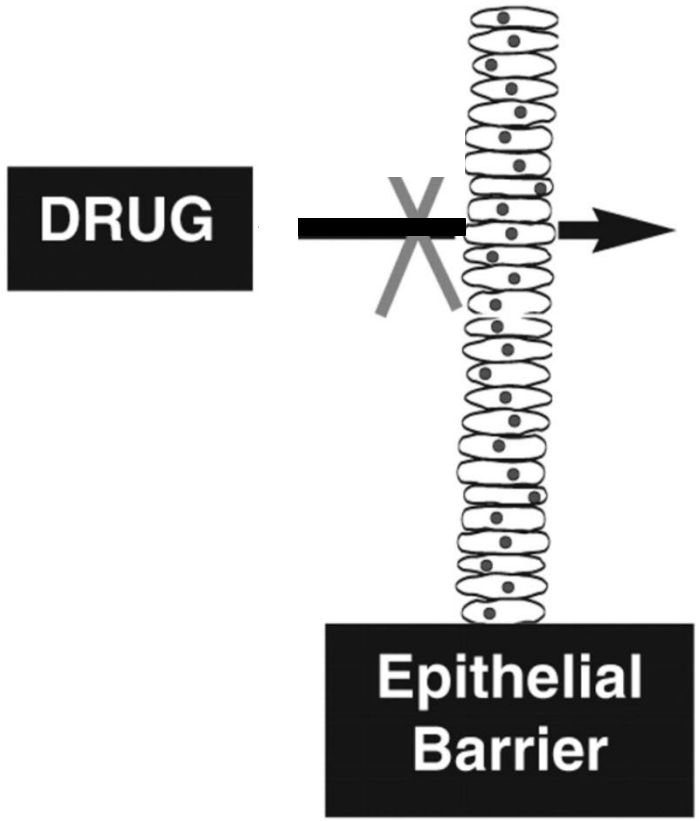
https://drgermophile.com/2020/06/26/pharmacokinetics-and-vancomycin/

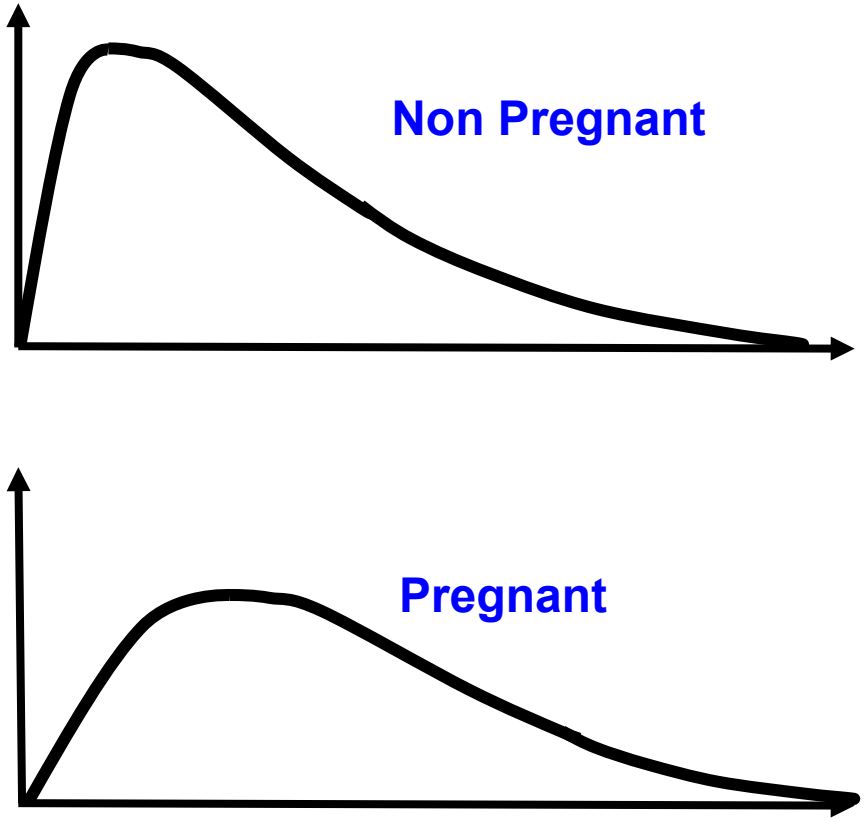
PK parameters with greatest influence on pregnancy

- Changes in drug absorption → Changes in drug concentration
- Volume of distribution → Changes in blood volume
- Changes in protein binding → Changes in blood volume
- Increased renal clearance → Increased CO, GFR
- Changes in metabolizing enzymes → Changes in drug concentration

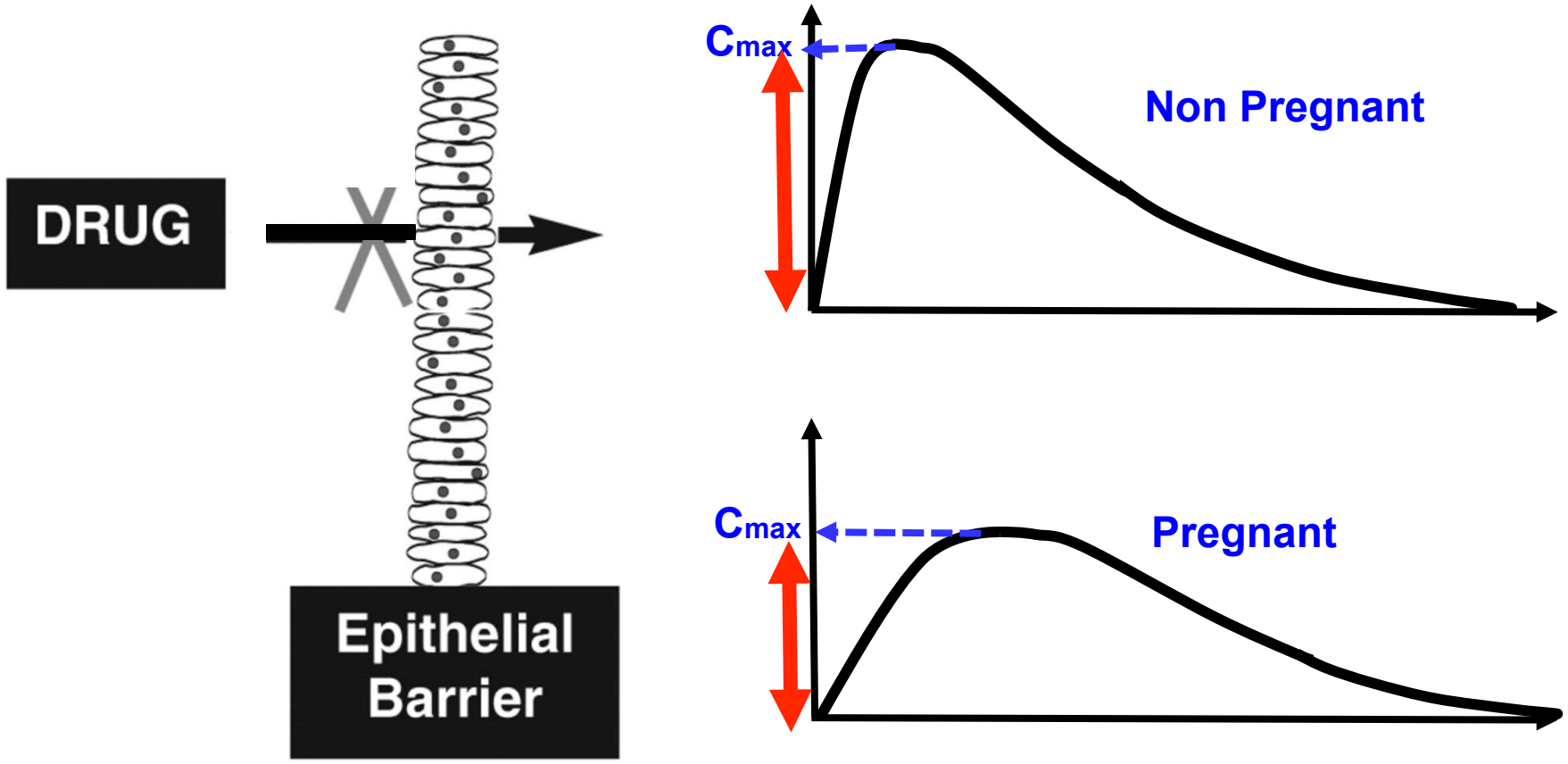
Drug Absorption

Absorption – Intestinal transfer

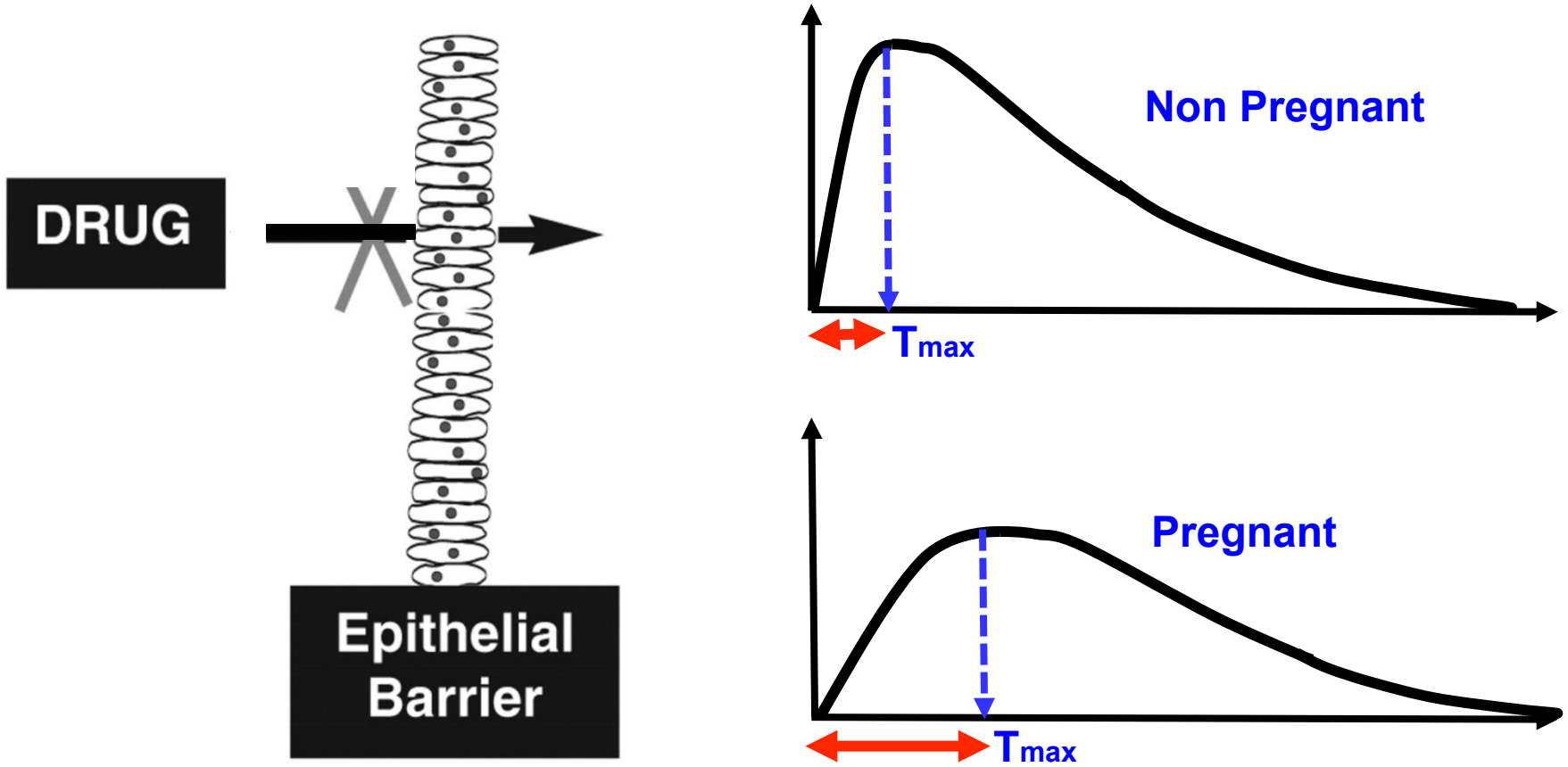




Absorption – Intestinal transfer



Absorption – Intestinal transfer



Changes in GI transporter activity affecting drug absorption in pregnancy

Gastrointestinal changes	Direction and magnitude of change in pregnancy
Transporter changes in the gut	Decreased [122]
ABC	Increased BRCP expression in pregnant mice (30–55%) [123]
BCRP	GLUT2 is increased during pregnancy
GLUT2	Increased expression of P-gp in pregnant mice [120]
MDR1 (P-gp)	Decreased MRP1 expression in pregnant mice (30–40%) [123]
MRP1	Decreased MRP2 expression in pregnant mice (30–40%) [123]
MRP2	Decreased expression of MRP3 in pregnant mice
MRP3	No change in OSTα expression [123]
OST alpha	No change/minimal increase in OSTβ expression [123]
OST beta	No change in expression of intestinal CYP3A4 [120, 124]
CYP3A4	No change in expression of intestinal CYP3A5 [120, 124]
CYP3A5	

Eke AC. An update on the physiologic changes during pregnancy and their impact on drug pharmacokinetics and pharmacogenomics. *J Basic Clin Physiol Pharmacol*, 2021 Dec 8. doi: 10.1515/jbcpp-2021-0312

Changes in GI transporter activity affecting drug absorption in pregnancy

DE GRUYTER J Basic Clin Physiol Pharmacol 2021; aop

Review

Ahizechukwu C. Eke*

An update on the physiologic changes during pregnancy and their impact on drug pharmacokinetics and pharmacogenomics

Eke AC. An update on the physiologic changes during pregnancy and their impact on drug pharmacokinetics and pharmacogenomics. *J Basic Clin Physiol Pharmacol*, 2021 Dec 8. doi: 10.1515/jbcpp-2021-0312

Aspirin absorption during pregnancy compared to non-pregnant state

JOHNS HOPKINS MEDICINE

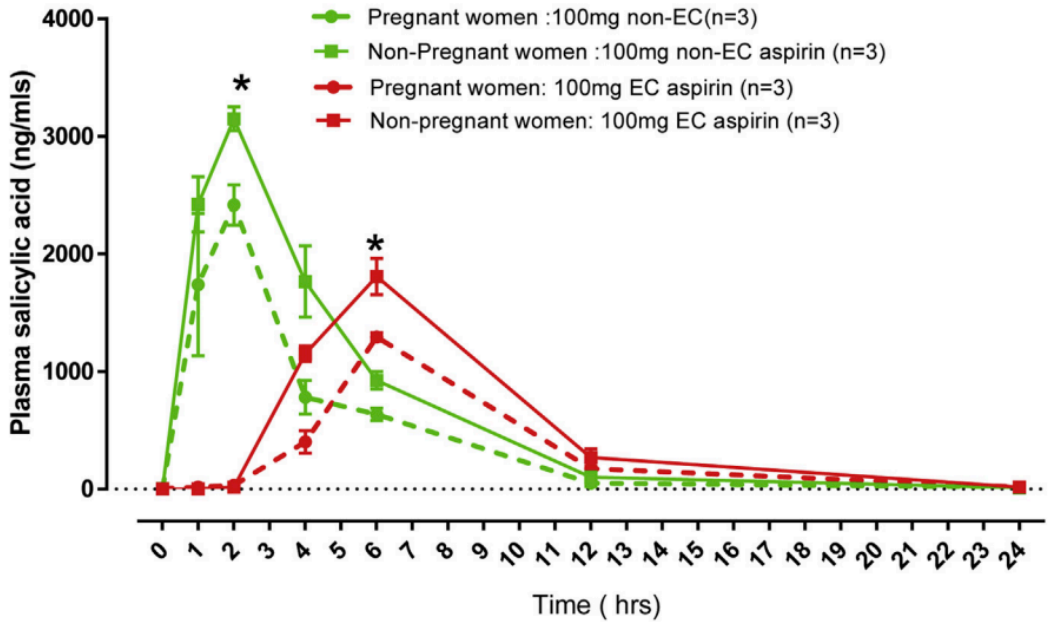
Original Research ajog.org

OBSTETRICS

A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy

Check for updates

Renuka Shanmugalingam, FRACP; XiaoSuo Wang, PhD; Gerald Münch, PhD; Ian Fulcher, RANZCOG; Gaksoo Lee, RN; Katrina Chau, PhD; Bei Xu, MBBS; Roshika Kumar, RN; Annemarie Hennessy, PhD; Angela Makris, PhD



Shanmugalingam R, Wang X, Munch G et al. A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy. *Am J Obstet Gynecol*, 2019;221(3):255.e1-255.e9.

Aspirin absorption during pregnancy compared to non-pregnant state

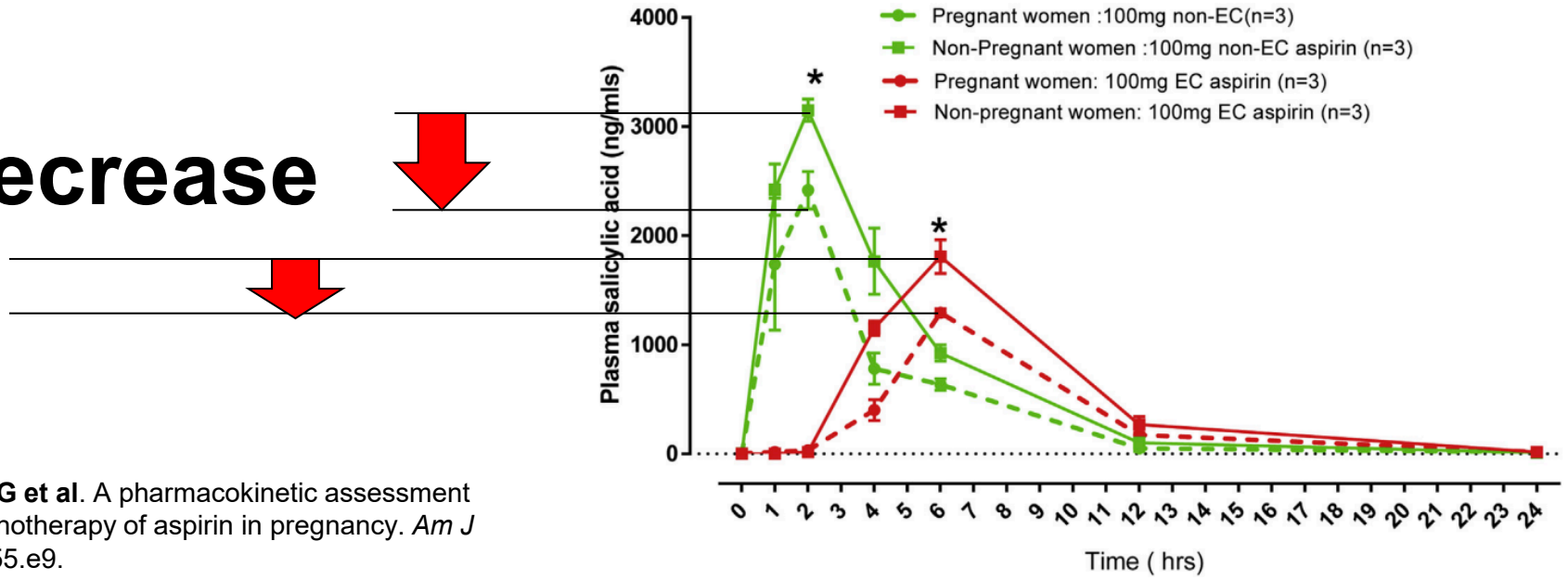
Original Research ajog.org

OBSTETRICS

A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy

Renuka Shanmugalingam, FRACP; XiaoSuo Wang, PhD; Gerald Münch, PhD; Ian Fulcher, RANZCOG; Gaksoo Lee, RN; Katrina Chau, PhD; Bei Xu, MBBS; Roshika Kumar, RN; Annemarie Hennessy, PhD; Angela Makris, PhD

29% decrease

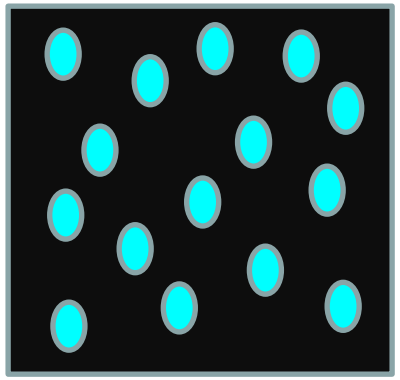


Shanmugalingam R, Wang X, Munch G et al. A pharmacokinetic assessment of optimal dosing, preparation, and chronotherapy of aspirin in pregnancy. *Am J Obstet Gynecol*, 2019;221(3):255.e1-255.e9.

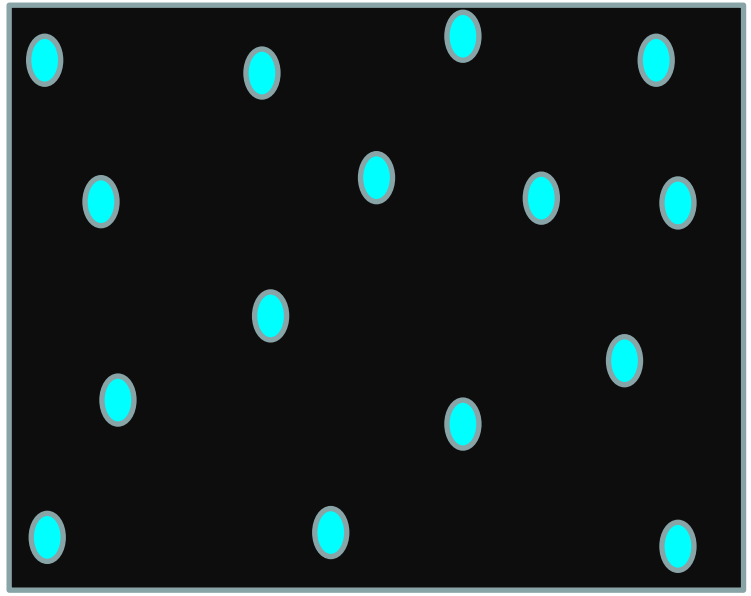
JOHNS HOPKINS MEDICINE

Drug Distribution

Volume of distribution



Non-pregnant

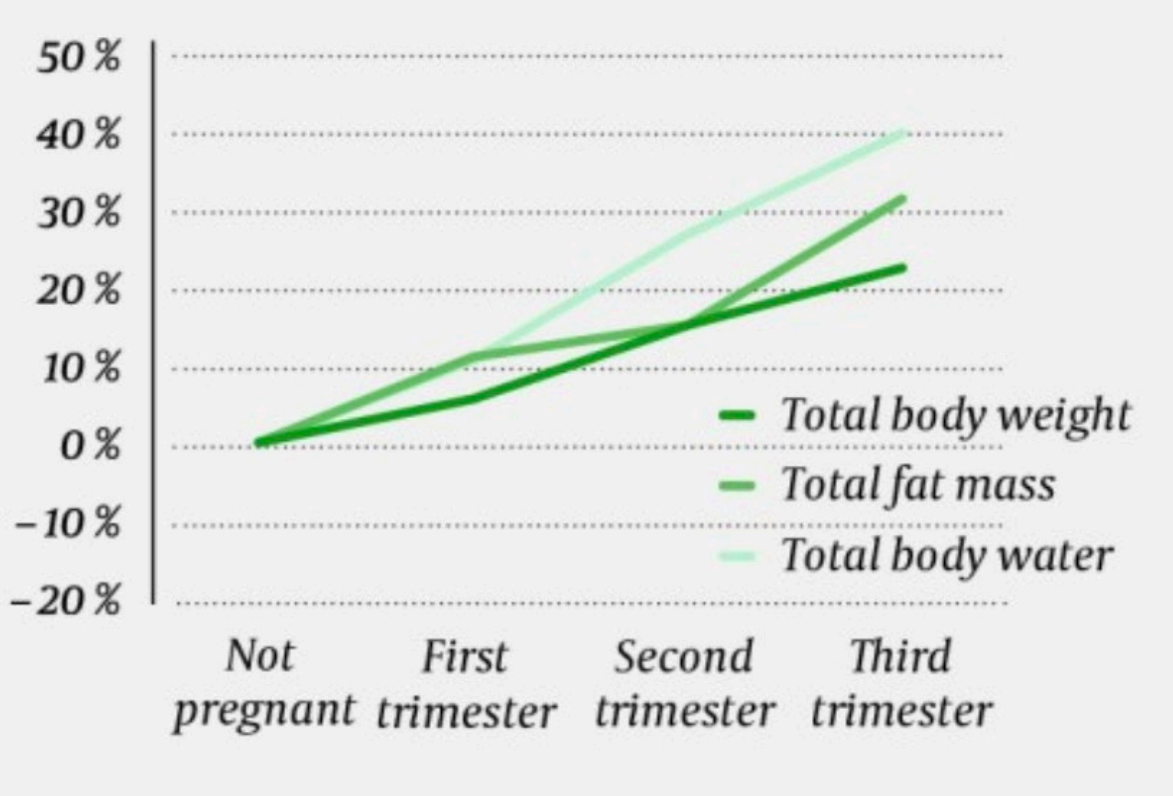


Pregnant

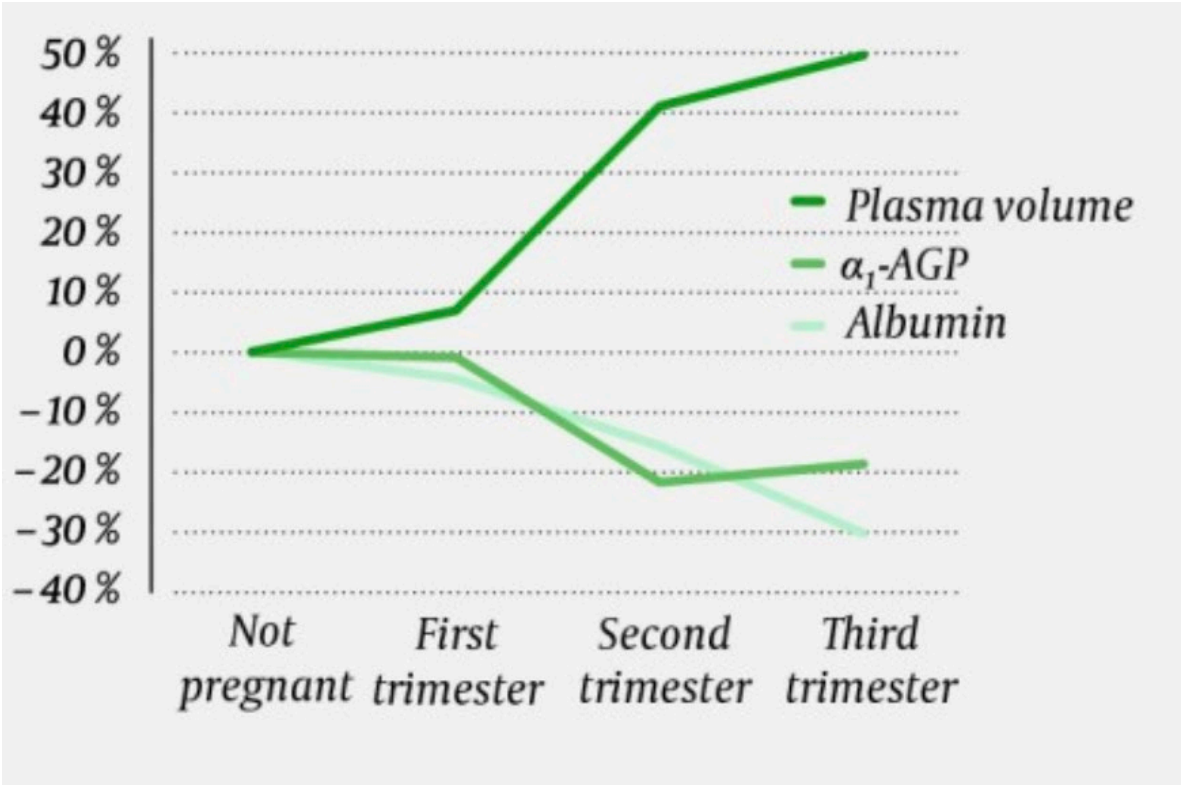
Same amount of drug -> Increased volume of distribution

***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

Distribution – Volume of distribution



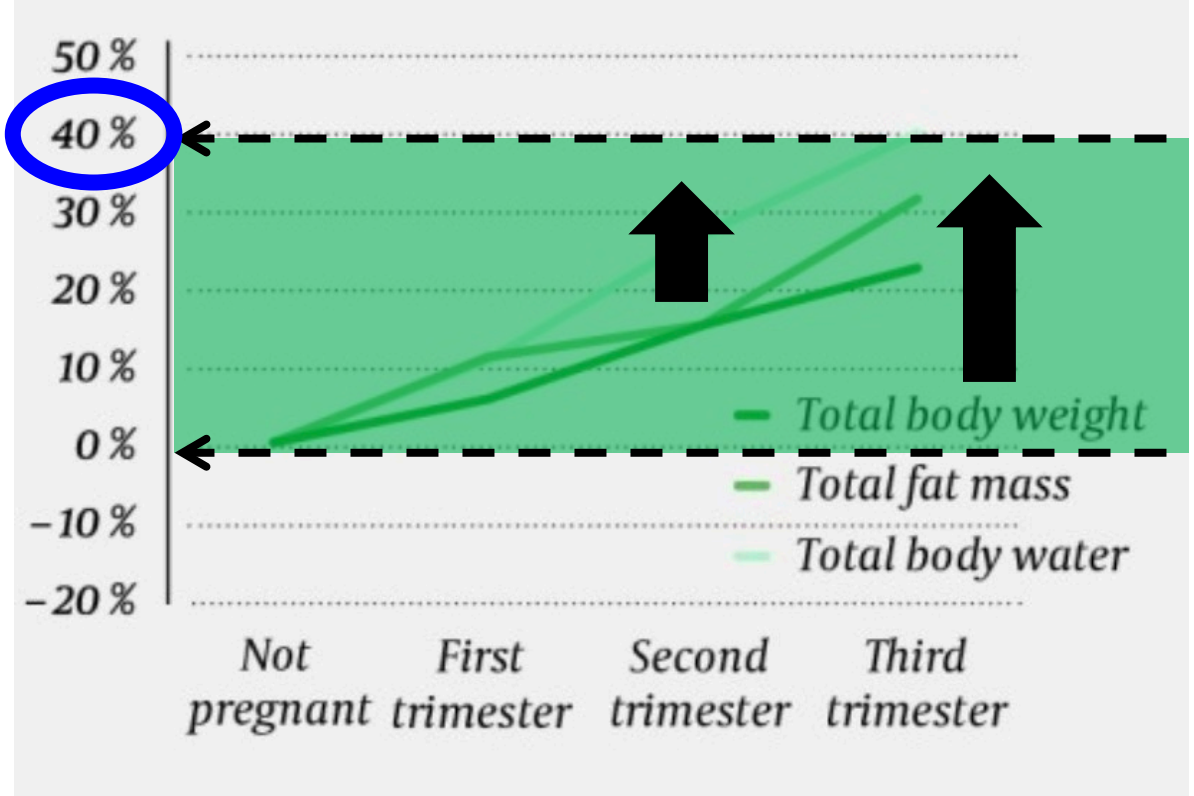
Changes in body composition



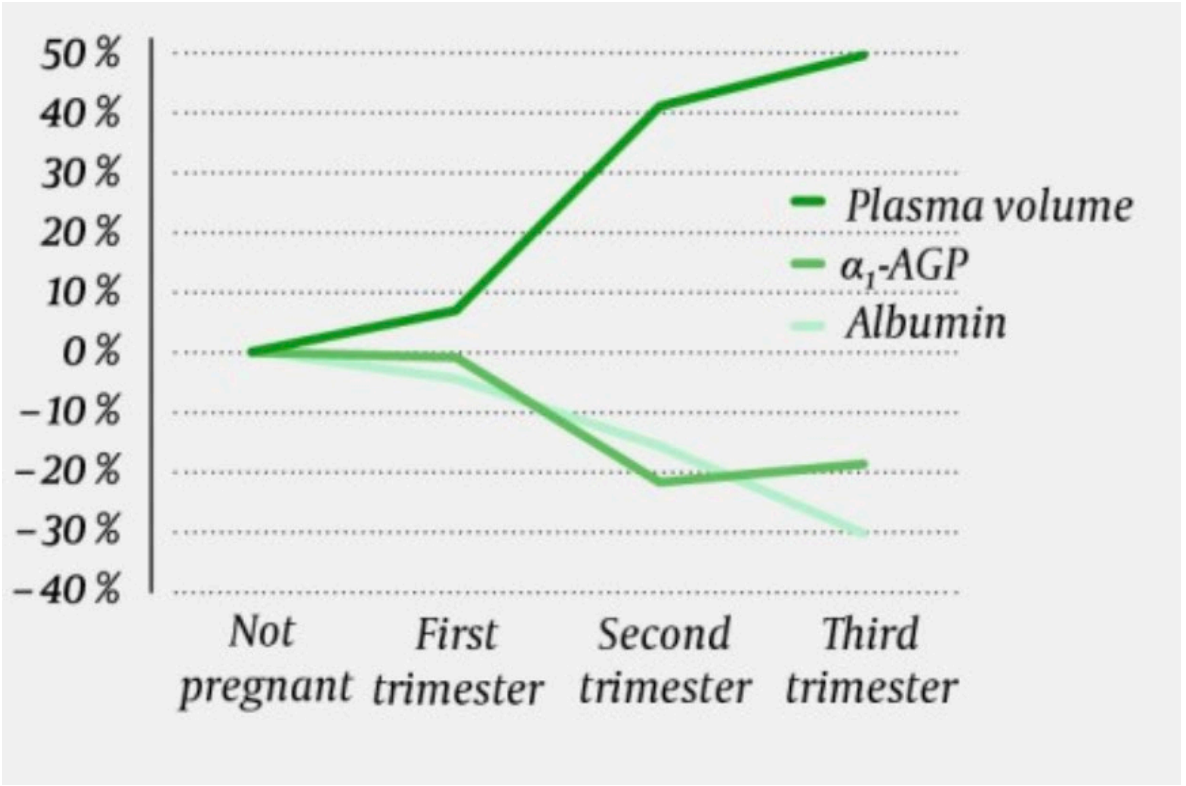
Changes in plasma protein during pregnancy versus postpartum

Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Distribution – Volume of distribution



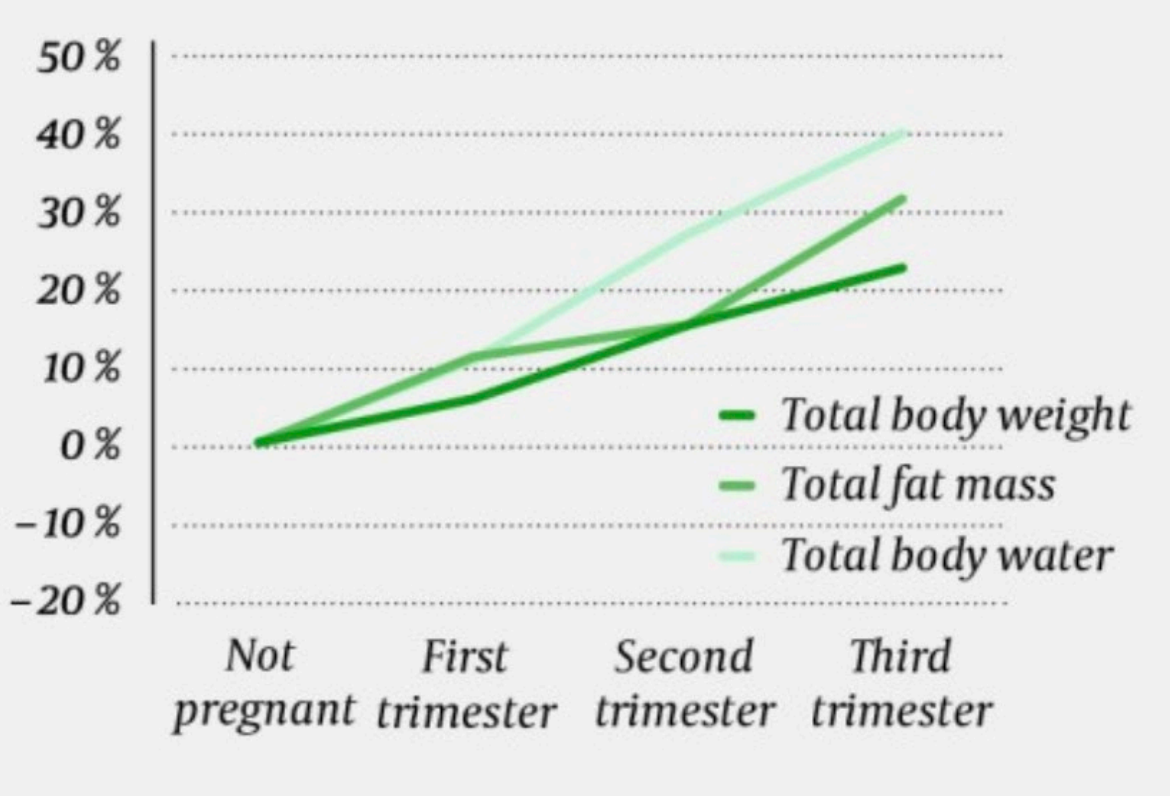
Changes in body composition



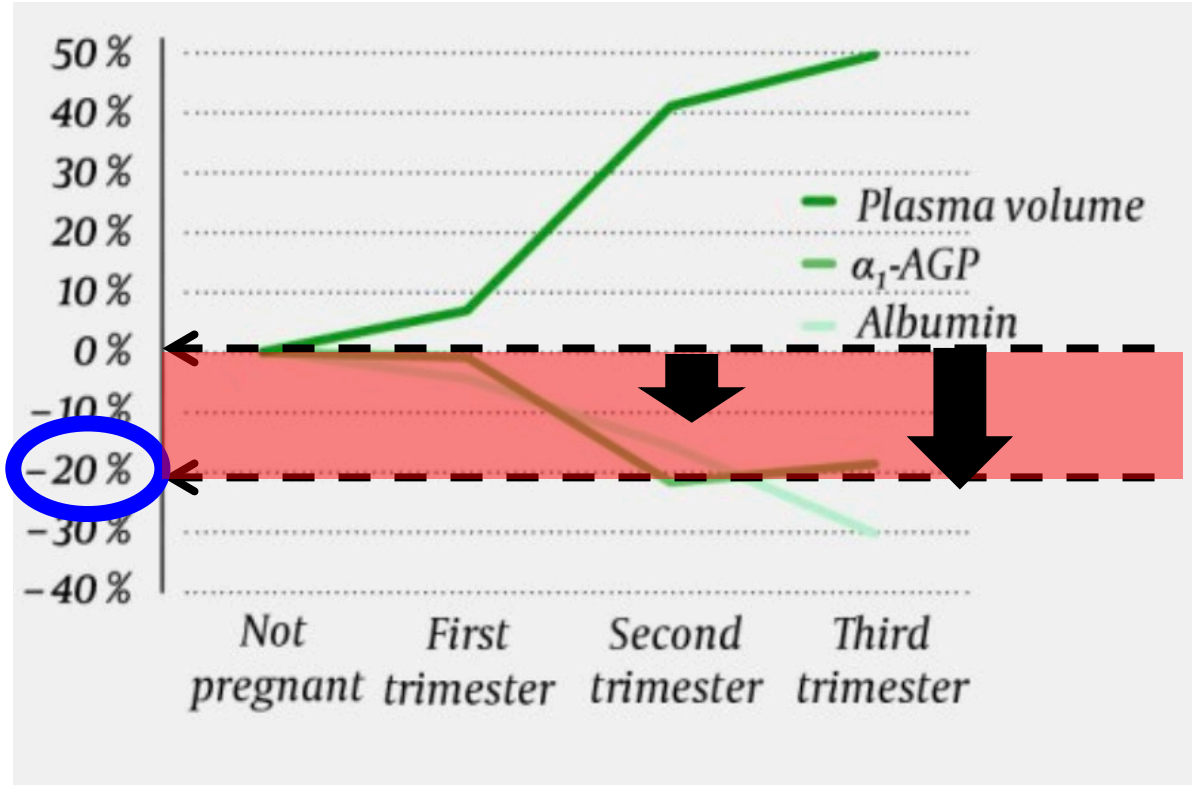
Changes in plasma protein during pregnancy versus postpartum

Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Distribution – Volume of distribution



Changes in body composition



Changes in plasma protein during pregnancy versus postpartum

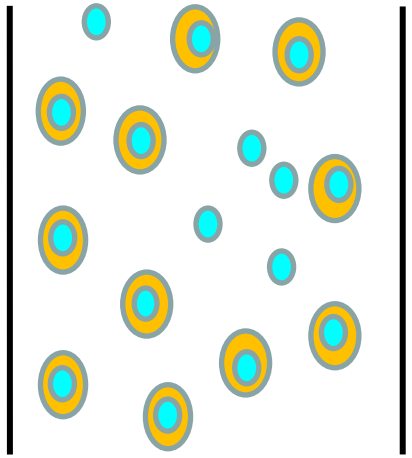
Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Changes in Protein Binding

= protein

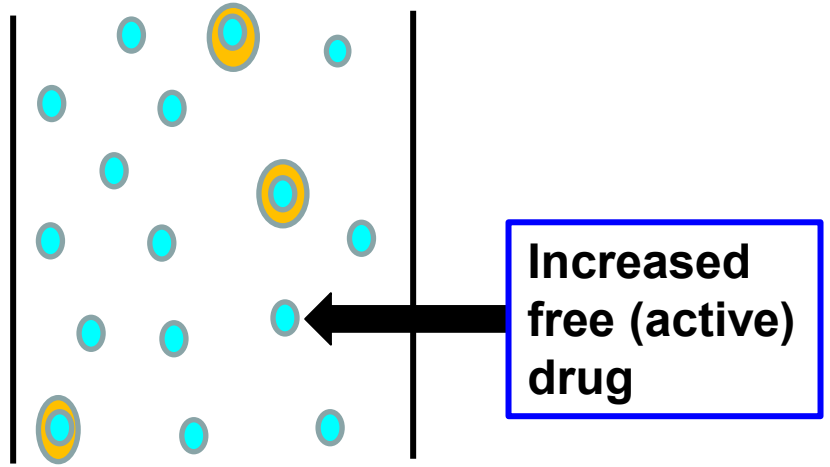
= drug

More Protein Binding



Non Pregnant

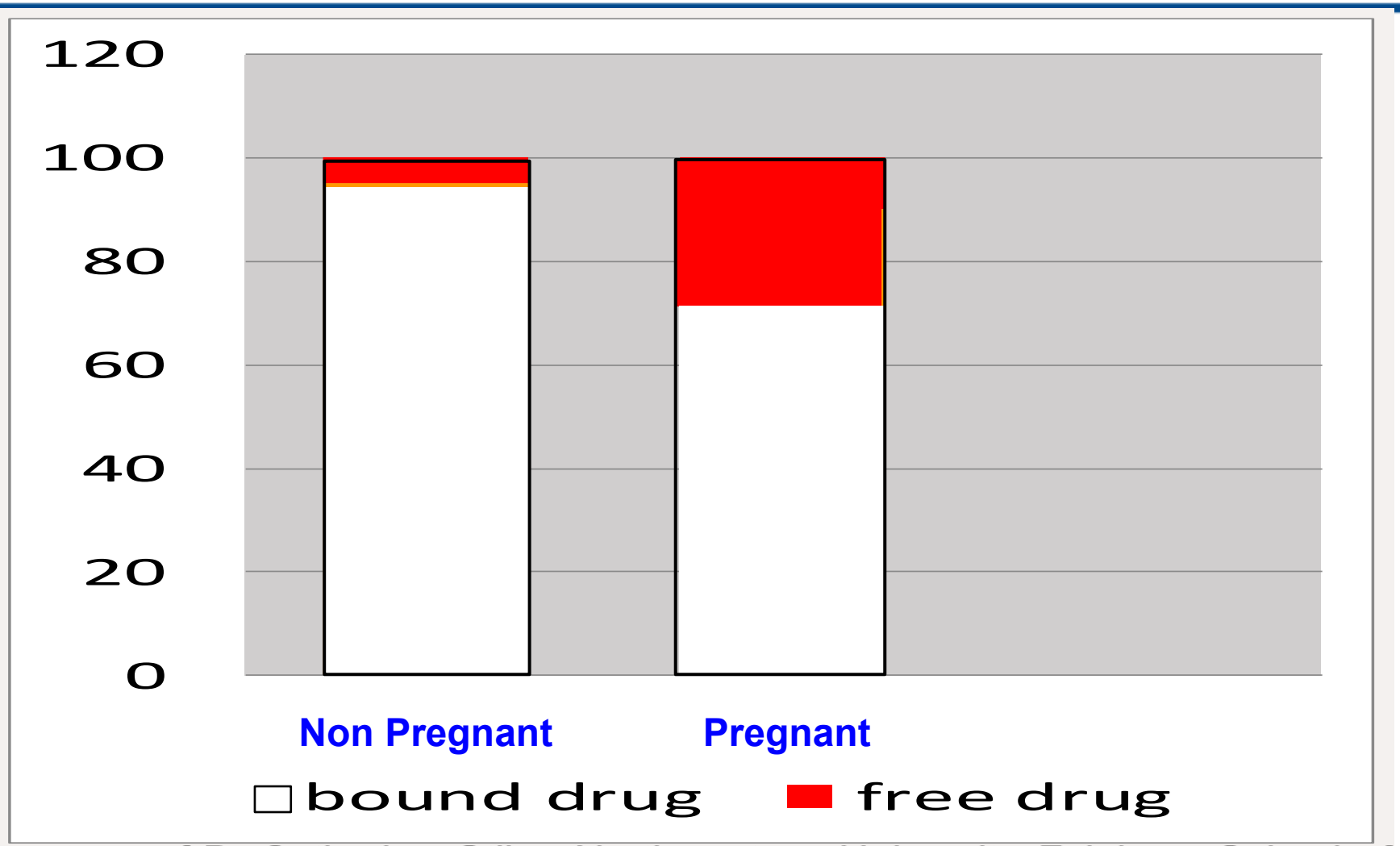
Less Protein Binding



Pregnant

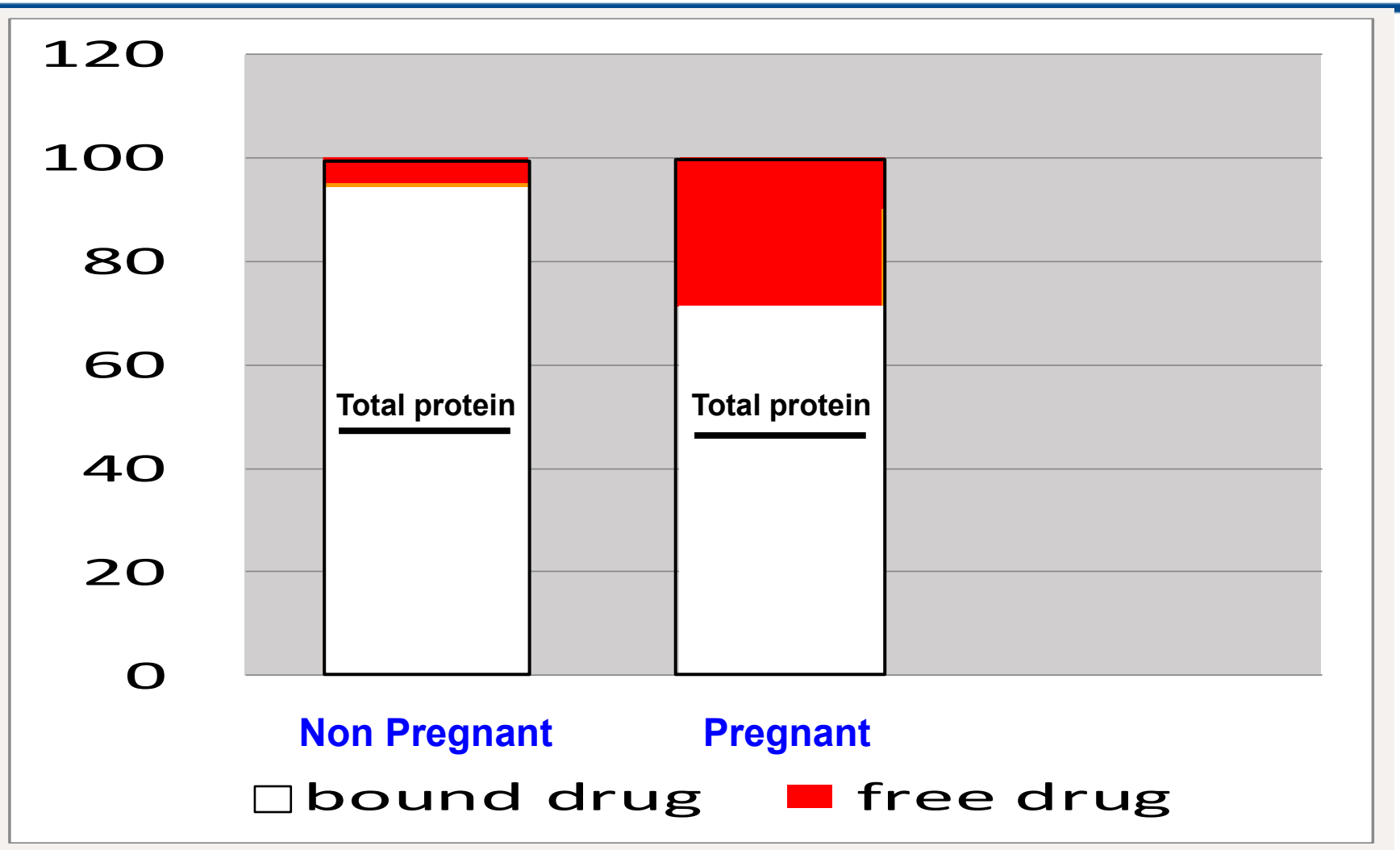
***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

Changes in Protein Binding



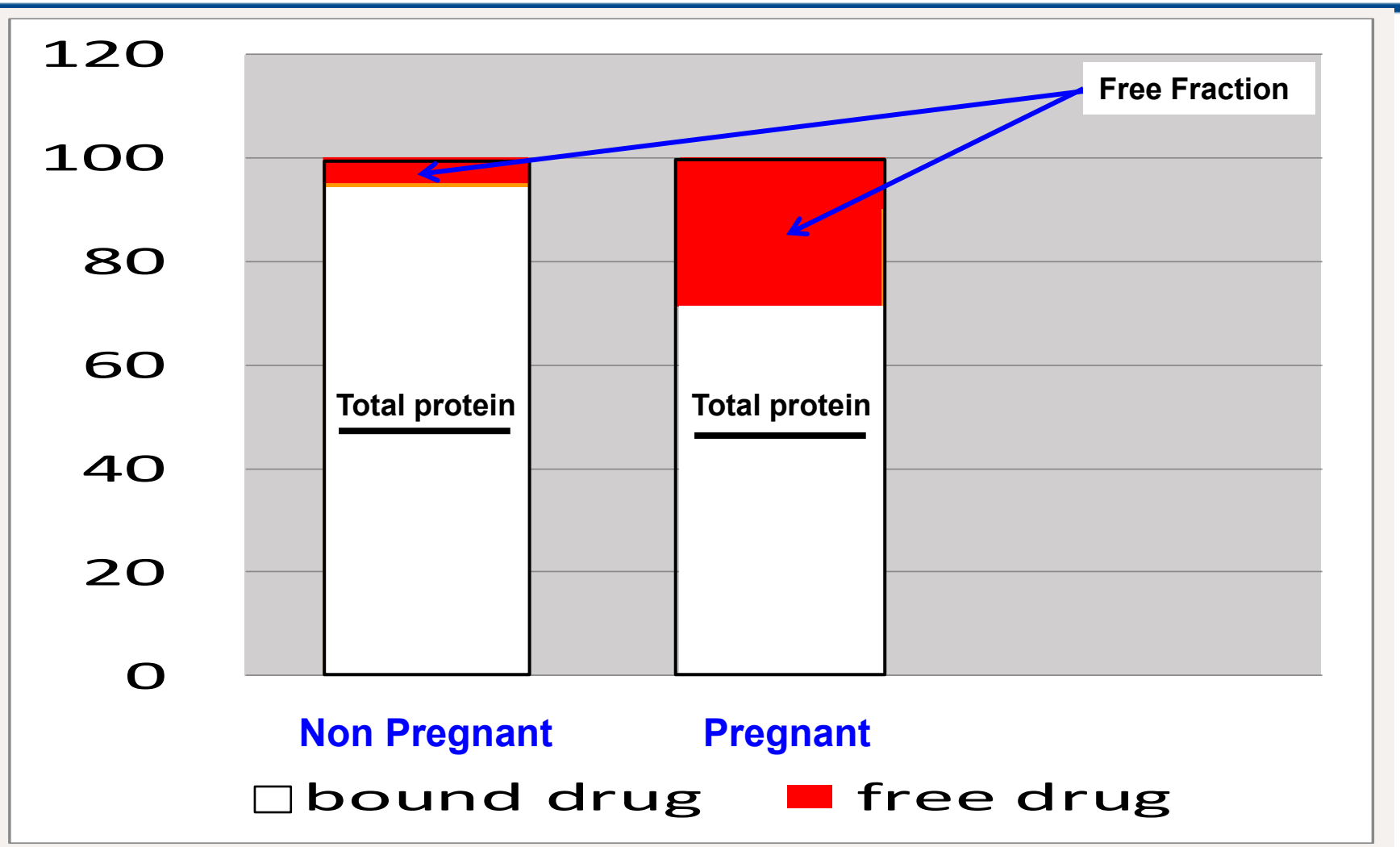
***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

Changes in Protein Binding



***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

Changes in Protein Binding



***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

Pregnancy associated changes affect drug PK

JOHNS HOPKINS MEDICINE

PLOS | MEDICINE

RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

How V_d and plasma protein changes affect drug PK

JOHNS HOPKINS MEDICINE

Antibiotics

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Amoxicillin [43]	1	16/16	22	NR	NR	**Cl 140%, $t_{1/2}$ 81%**	3rd
Azithromycin [47,51]	2	54/84	19.5	**V_d 121%**[&]	AUC 90%[&]	$t_{1/2}$ 101%[&]	1st–3rd
Cefatrizine [52]	1	20/20	19	NR	**C_{max} 55%, AUC 57%**	**$t_{1/2}$ 163%**	2nd
Cefazolin [39,53,54]	3	10[$]/54	18.6	V_d 80% (72%–89%)[&], **free fraction 131%**[&]	AUC 68%[&]	Cl 102% (65%–140%)[&], **$t_{1/2}$ 65%**[&], $t_{1/2}$ 131%[&]	2nd–3rd
Cefoperazone [55]	1	9/11	13	**Free fraction 208%**	NR	NR	3rd
Cefradine [54]	1	12/12	19	V_d 113%	**AUC 62%**	**Cl 154%, $t_{1/2}$ 73%**	1st–3rd
Ceftazidime [56]	1	12/12	16	NR	NR	**Cl 165%**	3rd
Cefuroxime [57]	1	7/7	13	V_d 109%	**AUC 69%**	**Cl 142%, $t_{1/2}$ 75%**	1st–3rd
Cloxacillin [48,58]	2	14/33	13.5	**Free fraction 154% (146%–162%)**	NR	NR	3rd
Flucloxacillin [58]	1	7/22	11	**Free fraction 148%**	NR	NR	3rd
Imipenem [59]	1	6/7	15	**V_d 249%**	**C_{max} 34%, AUC 41%**	**Cl 287%,** $t_{1/2}$ 87%	3rd
Mecillinam [60]	1	6/10	17	**V_d 224%**	C_{max} 85%, AUC 85%	Cl 103%, **$t_{1/2}$ 142%**	3rd
Moxifloxacin [61]	1	9/6	11	**V_d 329%**	**C_{max} 31%, AUC 21%**	**$t_{1/2}$ 63%**	3rd
Penicillin V [62]	1	6/6	16	NR	C_{max} 96%, **AUC 60%**	Cl 118%, **$t_{1/2}$ 30%**	3rd
Piperacillin [63–65]	3	11/18	12.3	**V_d 161%**, V_d 145% (136%–155%)	**C_{max} 50%**[&], C_{max} 57%[&], **AUC 61%**[&], AUC 110%[&]	**Cl 284%**, Cl 130% (96%–165%), $t_{1/2}$ 86% (70%–135%)	3rd
Trimethoprim [66]	1	8/10	11	**V_d 407%**	NR	**Cl 346%,** $t_{1/2}$ 100%	2nd–3rd
Tazobactam [64]	1	6/5	13	**V_d 150%**	C_{max} 75%, AUC 106%	**$t_{1/2}$ 156%**	3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How V_d and plasma protein changes affect drug PK

JOHNS HOPKINS MEDICINE

Antibiotics

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Amoxicillin [43]	1	16/16	22	NR	NR	**Cl 140%, $t_{1/2}$ 81%**	3rd
Azithromycin [47,51]	2	54/84	19.5	**V_d 121%**[&]	AUC 90%[&]	$t_{1/2}$ 101%[&]	1st–3rd
Cefatrizine [52]	1	20/20	19	NR	**C_{max} 55%, AUC 57%**	**$t_{1/2}$ 163%**	2nd
Cefazolin [39,53,54]	3	10[$]/54	18.6	V_d 80% (72%–89%)[&], **free fraction 131%**[&]	AUC 68%[&]	Cl 102% (65%–140%)[&], **$t_{1/2}$ 65%**[&], $t_{1/2}$ 131%[&]	2nd–3rd
Cefoperazone [55]	1	9/11	13	**Free fraction 208%**	NR	NR	3rd
Cefradine [54]	1	12/12	19	V_d 113%	**AUC 62%**	**Cl 154%, $t_{1/2}$ 73%**	1st–3rd
Ceftazidime [56]	1	12/12	16	NR	NR	**Cl 165%**	3rd
Cefuroxime [57]	1	7/7	13	V_d 109%	**AUC 69%**	**Cl 142%, $t_{1/2}$ 75%**	1st–3rd
Cloxacillin [48,58]	2	14/33	13.5	**Free fraction 154% (146%–162%)**	NR	NR	3rd
Flucloxacillin [58]	1	7/22	11	**Free fraction 148%**	NR	NR	3rd
Imipenem [59]	1	6/7	15	**V_d 249%**	**C_{max} 34%, AUC 41%**	**Cl 287%,** $t_{1/2}$ 87%	3rd
Mecillinam [60]	1	6/10	17	**V_d 224%**	C_{max} 85%, AUC 85%	Cl 103%, **$t_{1/2}$ 142%**	3rd
Moxifloxacin [61]	1	9/6	11	**V_d 329%**	**C_{max} 31%, AUC 21%**	**$t_{1/2}$ 63%**	3rd
Penicillin V [62]	1	6/6	16	NR	C_{max} 96%, **AUC 60%**	Cl 118%, **$t_{1/2}$ 30%**	3rd
Piperacillin [63–65]	3	11/18	12.3	**V_d 161%**, V_d 145% (136%–155%)	**C_{max} 50%**[&], C_{max} 57%[&], **AUC 61%**[&], AUC 110%[&]	**Cl 284%**, Cl 130% (96%–165%), $t_{1/2}$ 86% (70%–135%)	3rd
Trimethoprim [66]	1	8/10	11	**V_d 407%**	NR	**Cl 346%,** $t_{1/2}$ 100%	2nd–3rd
Tazobactam [64]	1	6/5	13	**V_d 150%**	C_{max} 75%, AUC 106%	**$t_{1/2}$ 156%**	3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How V_d and plasma protein changes affect drug PK

JOHNS HOPKINS MEDICINE

Antibiotics

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Amoxicillin [43]	1	16/16	22	NR	NR	**Cl 140%, $t_{1/2}$ 81%**	3rd
Azithromycin [47,51]	2	54/84	19.5	**V_d 121%**[&]	AUC 90%[&]	$t_{1/2}$ 101%[&]	1st–3rd
Cefatrizine [52]	1	20/20	19	NR	**C_{max} 55%, AUC 57%**	**$t_{1/2}$ 163%**	2nd
Cefazolin [39,53,54]	3	10[$]/54	18.6	V_d 80% (72%–89%)[&], **free fraction 131%**[&]	AUC 68%[&]	Cl 102% (65%–140%)[&], **$t_{1/2}$ 65%**[&], $t_{1/2}$ 131%[&]	2nd–3rd
Cefoperazone [55]	1	9/11	13	**Free fraction 208%**	NR	NR	3rd
Cefradine [54]	1	12/12	19	V_d 113%	**AUC 62%**	**Cl 154%, $t_{1/2}$ 73%**	1st–3rd
Ceftazidime [56]	1	12/12	16	NR	NR	**Cl 165%**	3rd
Cefuroxime [57]	1	7/7	13	V_d 109%	**AUC 69%**	**Cl 142%, $t_{1/2}$ 75%**	1st–3rd
Cloxacillin [48,58]	2	14/33	13.5	**Free fraction 154% (146%–162%)**	NR	NR	3rd
Flucloxacillin [58]	1	7/22	11	**Free fraction 148%**	NR	NR	3rd
Imipenem [59]	1	6/7	15	**V_d 249%**	**C_{max} 34%, AUC 41%**	**Cl 287%,** $t_{1/2}$ 87%	3rd
Mecillinam [60]	1	6/10	17	**V_d 224%**	C_{max} 85%, AUC 85%	Cl 103%, **$t_{1/2}$ 142%**	3rd
Moxifloxacin [61]	1	9/6	11	**V_d 329%**	**C_{max} 31%, AUC 21%**	**$t_{1/2}$ 63%**	3rd
Penicillin V [62]	1	6/6	16	NR	C_{max} 96%, **AUC 60%**	Cl 118%, **$t_{1/2}$ 30%**	3rd
Piperacillin [63–65]	3	11/18	12.3	**V_d 161%,** V_d 145% (136%–155%)	**C_{max} 50%**[&], C_{max} 57%[&], **AUC 61%**[&], AUC 110%[&]	**Cl 284%,** Cl 130% (96%–165%), $t_{1/2}$ 86% (70%–135%)	3rd
Trimethoprim [66]	1	8/10	11	**V_d 407%**	NR	**Cl 346%,** $t_{1/2}$ 100%	2nd–3rd
Tazobactam [64]	1	6/5	13	**V_d 150%**	C_{max} 75%, AUC 106%	**$t_{1/2}$ 156%**	3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How V_d and plasma protein changes affect drug PK

JOHNS HOPKINS MEDICINE

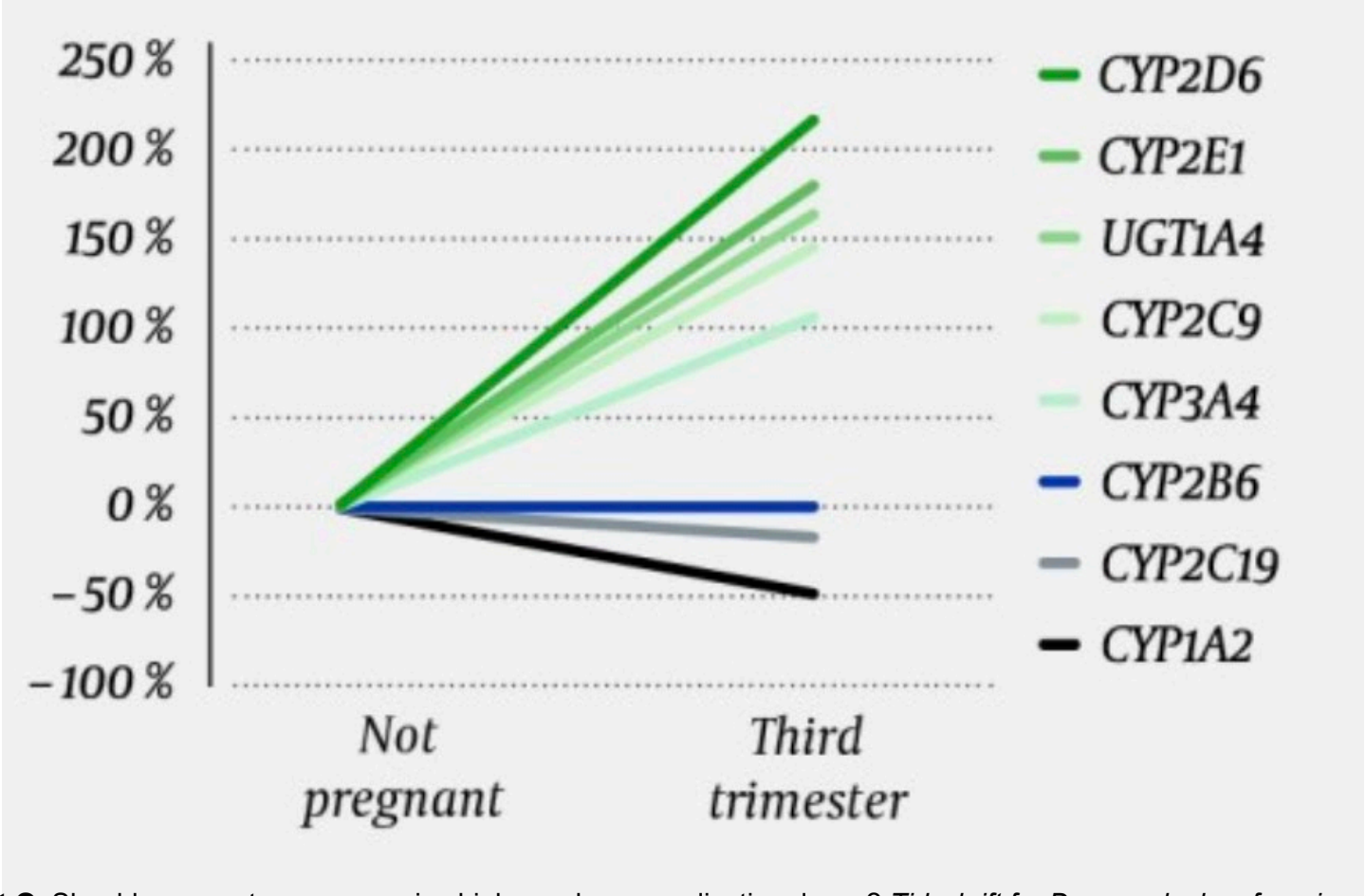
Antimalarials

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Artemeter [181,182]	2	22/46	19	NR	**C_{max} 52%[&], AUC 31%[&]**	NR	2nd–3rd
Atovaquone [183]	1	0[!]/9	18	**V_d 217%**	**C_{trough} 22%, C_{max} 37%, AUC 21%**	**Cl 821%**	2nd–3rd
Chloroquine [184–187]	4	50/70	18.7	**V_d 106%[&]**	C_{max} 106% (76%–137%), **AUC 74%[&]**, AUC 81% (72%–91%)[&]	**Cl 138% (133%–144%)[&]**, Cl 110%[&], **$t_{1/2}$ 91%[&]**, $t_{1/2}$ 86%[&]	2nd–3rd
Lumefantrine [181,182,188,189]	4	56/188	19.2	V_d 90%[&]	**Lower concentration[&,β]**, C_{max} 101% (100%–103%)[&], AUC 97% (90%114%)[&]	**Higher Cl[&,β]**, Cl 88%[&], **$t_{1/2}$ 81%[&]**, $t_{1/2}$ 151%[&]	2nd–3rd
Mefloquine [190–192]	3	32/53	17.6	**V_d 108%[&]**, V_d 121%[&]	**C_{max} 77%[&]**, C_{max} 103%[&], AUC 112%	**Cl 162%,** Cl 104% (100–109%), **$t_{1/2}$ 134%,** $t_{1/2}$ 78% (68%–88%)	1st–3rd
Piperaquine [193–195]	3	81/80	19	**V_d 66% (63%–68%),** V_d 93%	**C_{max} 134%[&]**, C_{max} 126%[&], **AUC 66%,** AUC 103% (110%–117%)[&]	**Cl 137%,** Cl 93% (90%–96%), **$t_{1/2}$ 72% (69%–90%)**	2nd–3rd
Proguanil [183,196]	2	4[!]/19	16.5	**V_d 109%**	C_{trough} 101%[&], C_{max} 80% (65%–95%), AUC 77% (60%–95%)	Cl 116% (73%–160%), **$t_{1/2}$ 71%,** $t_{1/2}$ 123%	2nd–3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

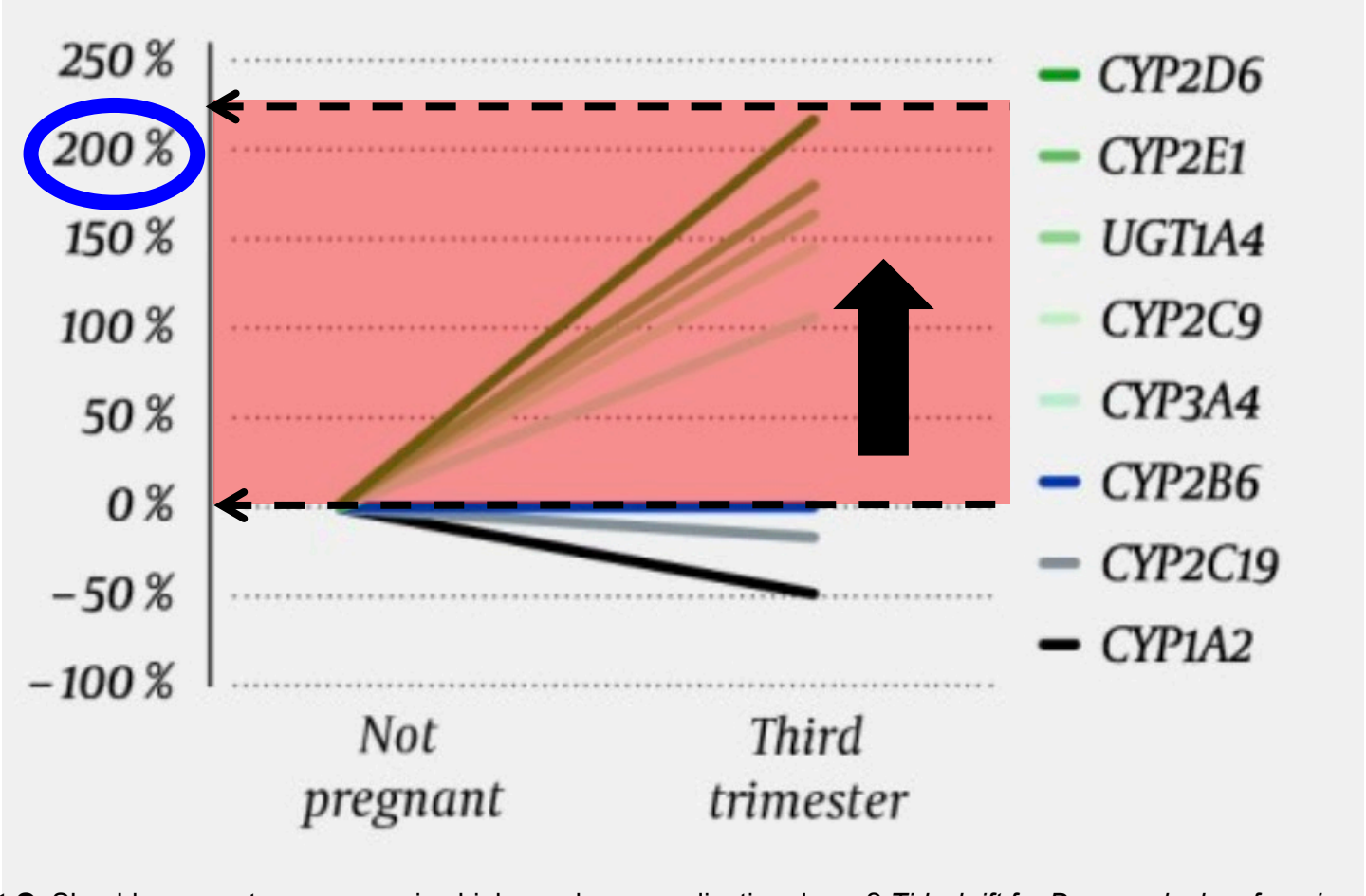
Drug Metabolism

Metabolism – Change in liver enzyme activity



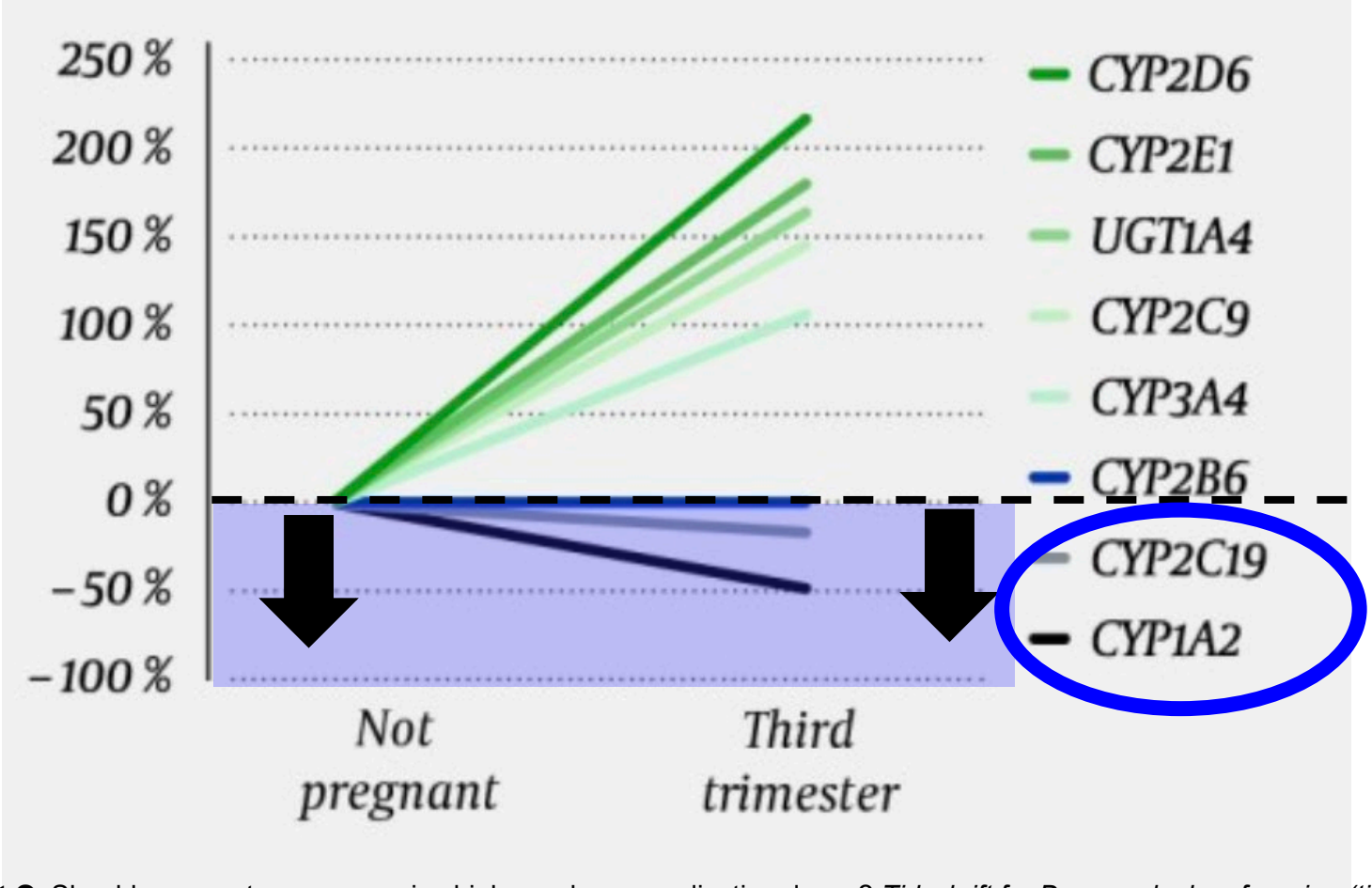
Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Metabolism – Change in liver enzyme activity



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Metabolism – Change in liver enzyme activity



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Metabolism – Change in liver enzyme activity

Enzyme	Substrate Examples
CYP1A2	Paracetamol, propranolol, theophylline
CYP2B6	Methadone, efavirenz, sertraline
CYP2C8	Verapamil, fluvastatin
CYP2C9	Glyburide, phenytoin
CYP2C19	Proguanil, indomethacin, citalopram, escitalopram
CYP2D6	Alprenolol, codeine, fluoxetine
CYP2E1	Disulfiram, theophylline
CYP3A4	Darunavir, citalopram
Uridine 5′-diphospho-glucuronosyltransferases	Lamotrigine, morphine

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

Metabolism – Decreased liver enzyme activity

JOHNS HOPKINS MEDICINE

Women's Health

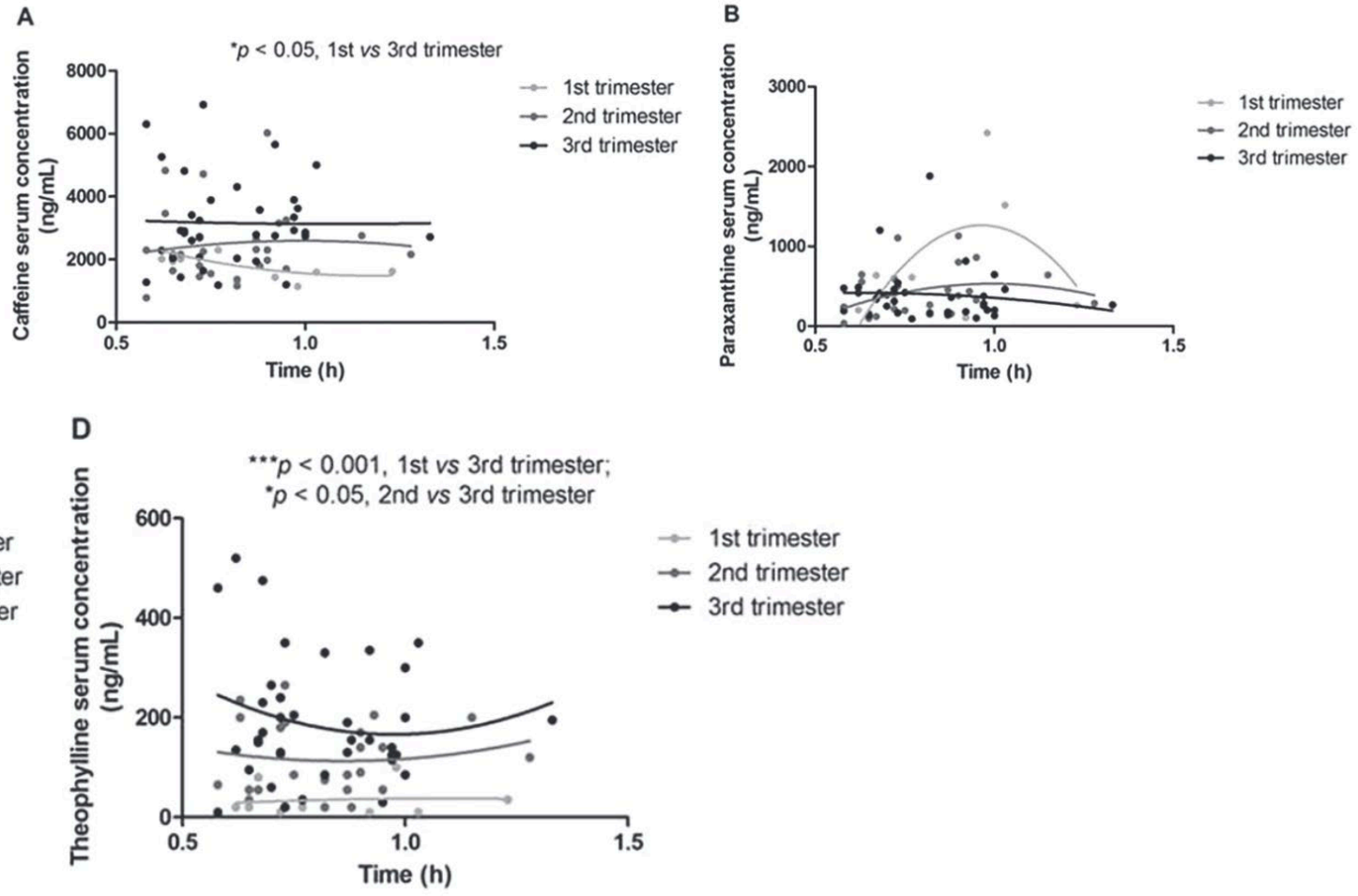
ACCP

The Journal of Clinical Pharmacology
2016, 56(5) 590–596

DOI: 10.1002/jcph.632

Pregnancy-Induced Changes in the Pharmacokinetics of Caffeine and Its Metabolites

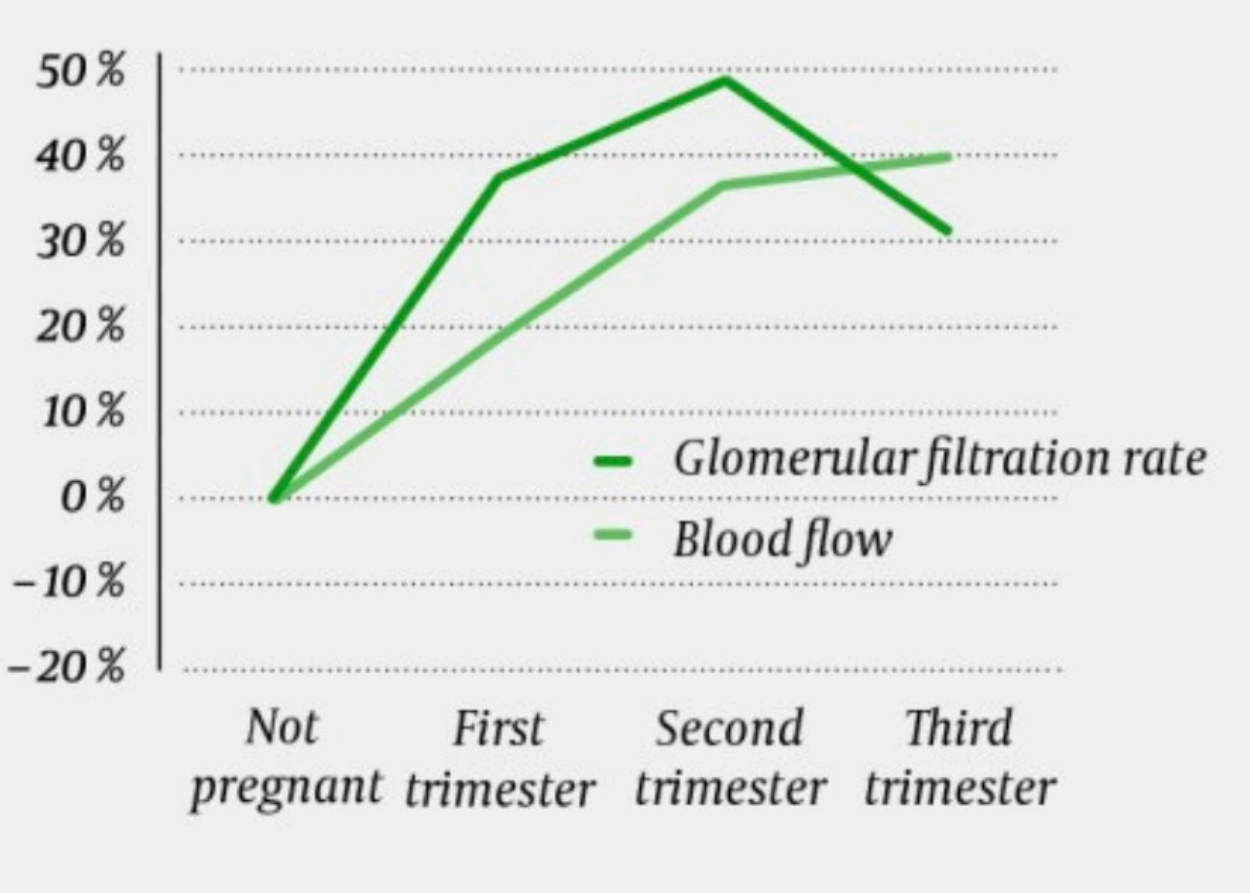
Tian Yu, PhD[1], Sarah C. Campbell, PhD[1], Chris Stockmann, MSc[1], Casey Tak, MPH[2*], Katherine Schoen[1], Erin A. S. Clark, MD[3], Michael W. Varner, MD[3,4], Michael G. Spigarelli, MD, PhD, FCP[1,2], and Catherine M. T. Sherwin, PhD, FCP[1,2]



Yu T, Campbell SC, Stockmann C et al. Pregnancy-Induced changes in the pharmacokinetics of caffeine and its metabolites. J Clin Pharmacol 2016; 56(5): 590-6.

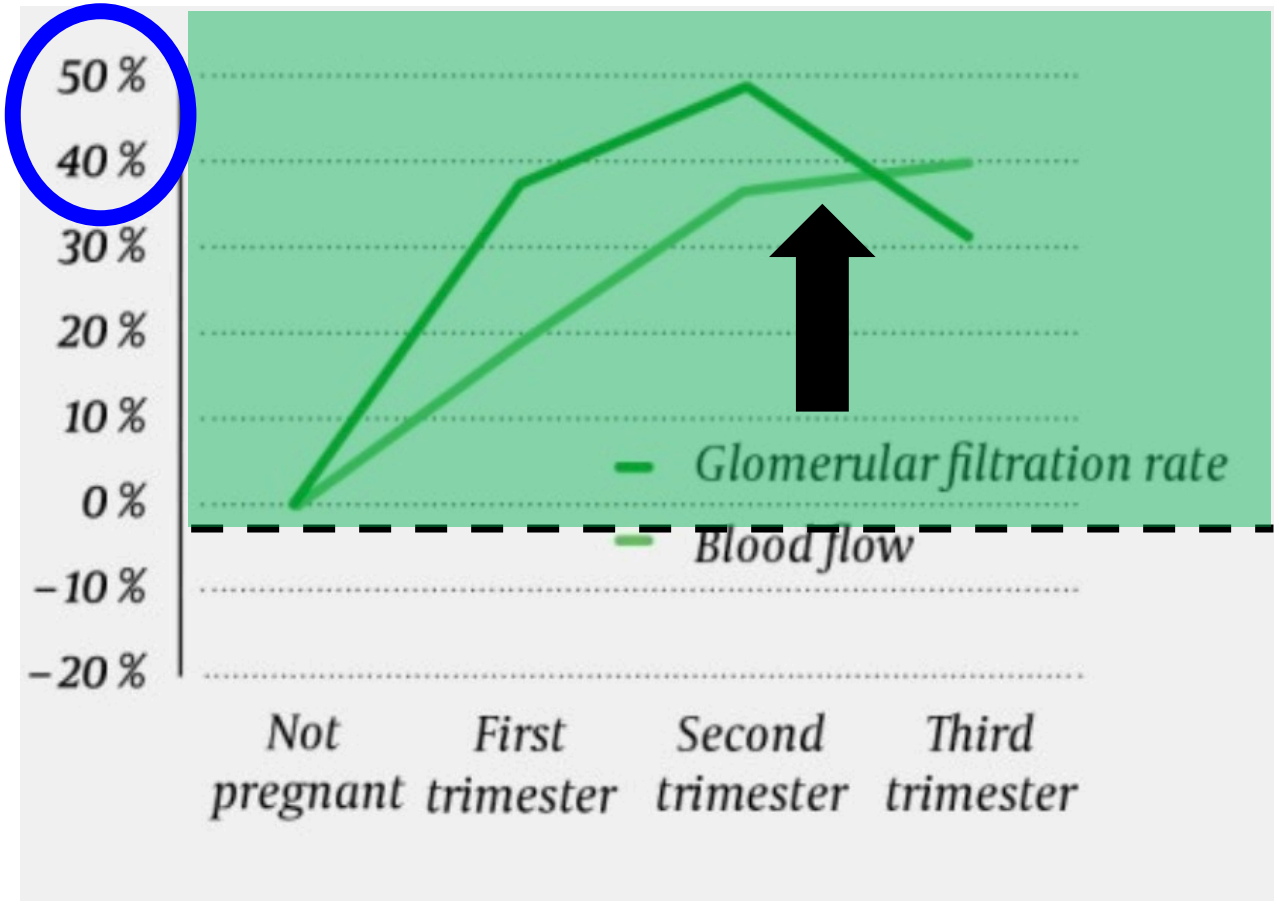
Drug Elimination

Elimination – Changes in renal function



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Elimination – Changes in renal function



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Darunavir/cobicistat drug combination in pregnancy

Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen

HM Crauwels,[1] O Osiyemi,[2] C Zorrilla,[3] C Bicer[4] and K Brown[5]

[1]Janssen Research & Development, Beerse, Belgium, [2]Triple O Research Institute PA, West Palm Beach, FL, USA, [3]University of Puerto Rico School of Medicine, San Juan, Puerto Rico, [4]BICER Consulting & Research, Antwerp, Belgium and [5]Janssen Research & Development, LLC, Titusville, NJ, USA

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Darunavir/cobicistat drug combination in pregnancy

	Second trimester (24–28 weeks of gestation) (n = 7)	Third trimester (34–38 weeks of gestation) (n = 6)	Postpartum (6–12 weeks postpartum) (n = 6)	LSM ratio (95% CI)	
				Second trimester (n = 7) versus postpartum (n = 6)	Third trimester (n = 6) versus postpartum (n = 6)
Total daruanvir*					
$C_{0\ h}$ (ng/mL)	435 (BLQ-2300)	624 (247–1850)	2625 (BLQ–5820)	ND	ND
C_{min} (ng/mL)†	134 (BLQ–369)	162 (50.9–304)	1381 (BLQ–3220)	0.08 (0.01–0.50)	0.11 (0.04–0.30)
C_{max} (ng/mL)	4710 (1050–5760)	4855 (3530–6210)	7445 (5880–12 000)	0.51 (0.30–0.86)	0.63 (0.50–0.79)
t_{max} (h)	4.00 (3.00–6.00)	3.50 (2.00–6.00)	4.00 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	52 009 (10 547–71 497)	50 214 (34 068–57 509)	91 644 (64 573–157 934)	0.44 (0.24–0.80)	0.50 (0.37–0.66)
Unbound darunavir					
$C_{0\ h}$ (ng/mL)	56.5 (BLQ–361)	89.2 (56.7–439)	399 (BLQ–826)	ND	ND
C_{min} (ng/mL)‡	17.5 (BLQ–54.1)	31.2 (9.35–57.3)	229 (BLQ–420)	0.08 (0.02–0.42)	0.12 (0.05–0.27)
C_{max} (ng/mL)	945 (168–1110)	1058 (777–1109)	1199 (866–2065)	0.59 (0.34–1.02)	0.77 (0.59–1.00)
t_{max} (h)	4.05 (1.03–6.00)	4.00 (2.00–4.00)	3.50 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	9725 (1885–12 310)	8883 (6132–11 883)	15 429 (6958–23 792)	0.55 (0.28–1.06)	0.60 (0.44–0.83)
Cobicistat					
C_{min} (ng/mL)	BLQ (BLQ–10.0)	BLQ (BLQ–7.02)	29.1 (BLQ–134)	0.17 (0.05–0.61)	0.17 (0.04–0.74)
C_{max} (ng/mL)§	523 (173–1190)	671 (365–1430)	971 (629–1460)	0.50 (0.28–0.91)	0.73 (0.52–1.02)
t_{max} (h)	4.03 (2.00–6.00)	3.50 (2.00–4.00)	4.00 (2.00–4.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	3654 (1088–8892)	4072 (1963–10 379)	9424 (4801–11 989)	0.37 (0.17–0.79)	0.51 (0.33–0.80)

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Darunavir/cobicistat drug combination in pregnancy

	Second trimester (24–28 weeks of gestation) (n = 7)	Third trimester (34–38 weeks of gestation) (n = 6)	Postpartum (6–12 weeks postpartum) (n = 6)	LSM ratio (95% CI)	
				Second trimester (n = 7) versus postpartum (n = 6)	Third trimester (n = 6) versus postpartum (n = 6)
Total daruanvir*					
$C_{0\ h}$ (ng/mL)	435 (BLQ-2300)	624 (247–1850)	2625 (BLQ–5820)	ND	ND
C_{min} (ng/mL)†	134 (BLQ–369)	162 (50.9–304)	1381 (BLQ–3220)	0.08 (0.01–0.50)	0.11 (0.04–0.30)
C_{max} (ng/mL)	4710 (1050–5760)	4855 (3530–6210)	7445 (5880–12 000)	0.51 (0.30–0.86)	0.63 (0.50–0.79)
t_{max} (h)	4.00 (3.00–6.00)	3.50 (2.00–6.00)	4.00 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	52 009 (10 547–71 497)	50 214 (34 068–57 509)	91 644 (64 573–157 934)	0.44 (0.24–0.80)	0.50 (0.37–0.66)
Unbound darunavir					
$C_{0\ h}$ (ng/mL)	56.5 (BLQ–361)	89.2 (56.7–439)	399 (BLQ–826)	ND	ND
C_{min} (ng/mL)‡	17.5 (BLQ–54.1)	31.2 (9.35–57.3)	229 (BLQ–420)	0.08 (0.02–0.42)	0.12 (0.05–0.27)
C_{max} (ng/mL)	945 (168–1110)	1058 (777–1109)	1199 (866–2065)	0.59 (0.34–1.02)	0.77 (0.59–1.00)
t_{max} (h)	4.05 (1.03–6.00)	4.00 (2.00–4.00)	3.50 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	9725 (1885–12 310)	8883 (6132–11 883)	15 429 (6958–23 792)	0.55 (0.28–1.06)	0.60 (0.44–0.83)
Cobicistat					
C_{min} (ng/mL)	BLQ (BLQ–10.0)	BLQ (BLQ–7.02)	29.1 (BLQ–134)	0.17 (0.05–0.61)	0.17 (0.04–0.74)
C_{max} (ng/mL)§	523 (173–1190)	671 (365–1430)	971 (629–1460)	0.50 (0.28–0.91)	0.73 (0.52–1.02)
t_{max} (h)	4.03 (2.00–6.00)	3.50 (2.00–4.00)	4.00 (2.00–4.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	3654 (1088–8892)	4072 (1963–10 379)	9424 (4801–11 989)	0.37 (0.17–0.79)	0.51 (0.33–0.80)

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Darunavir/cobicistat drug combination in pregnancy

				LSM ratio (95% CI)	
	Second trimester (24–28 weeks of gestation) (n = 7)	Third trimester (34–38 weeks of gestation) (n = 6)	Postpartum (6–12 weeks postpartum) (n = 6)	Second trimester (n = 7) versus postpartum (n = 6)	Third trimester (n = 6) versus postpartum (n = 6)
Total daruanvir*					
$C_{0\ h}$ (ng/mL)	435 (BLQ-2300)	624 (247–1850)	2625 (BLQ–5820)	ND	ND
C_{min} (ng/mL)†	134 (BLQ–369)	162 (50.9–304)	1381 (BLQ–3220)	0.08 (0.01–0.50)	0.11 (0.04–0.30)
C_{max} (ng/mL)	4710 (1050–5760)	4855 (3530–6210)	7445 (5880–12 000)	0.51 (0.30–0.86)	0.63 (0.50–0.79)
t_{max} (h)	4.00 (3.00–6.00)	3.50 (2.00–6.00)	4.00 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	52 009 (10 547–71 497)	50 214 (34 068–57 509)	91 644 (64 573–157 934)	0.44 (0.24–0.80)	0.50 (0.37–0.66)
Unbound darunavir					
$C_{0\ h}$ (ng/mL)	56.5 (BLQ–361)	89.2 (56.7–439)	399 (BLQ–826)	ND	ND
C_{min} (ng/mL)‡	17.5 (BLQ–54.1)	31.2 (9.35–57.3)	229 (BLQ–420)	0.08 (0.02–0.42)	0.12 (0.05–0.27)
C_{max} (ng/mL)	945 (168–1110)	1058 (777–1109)	1199 (866–2065)	0.59 (0.34–1.02)	0.77 (0.59–1.00)
t_{max} (h)	4.05 (1.03–6.00)	4.00 (2.00–4.00)	3.50 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	9725 (1885–12 310)	8883 (6132–11 883)	15 429 (6958–23 792)	0.55 (0.28–1.06)	0.60 (0.44–0.83)
Cobicistat					
C_{min} (ng/mL)	BLQ (BLQ–10.0)	BLQ (BLQ–7.02)	29.1 (BLQ–134)	0.17 (0.05–0.61)	0.17 (0.04–0.74)
C_{max} (ng/mL)§	523 (173–1190)	671 (365–1430)	971 (629–1460)	0.50 (0.28–0.91)	0.73 (0.52–1.02)
t_{max} (h)	4.03 (2.00–6.00)	3.50 (2.00–4.00)	4.00 (2.00–4.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	3654 (1088–8892)	4072 (1963–10 379)	9424 (4801–11 989)	0.37 (0.17–0.79)	0.51 (0.33–0.80)

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Darunavir/cobicistat drug combination in pregnancy

	Second trimester (24–28 weeks of gestation) (n = 7)	Third trimester (34–38 weeks of gestation) (n = 6)	Postpartum (6–12 weeks postpartum) (n = 6)	LSM ratio (95% CI) Second trimester (n = 7) versus postpartum (n = 6)	LSM ratio (95% CI) Third trimester (n = 6) versus postpartum (n = 6)
Total daruanvir*					
$C_{0\ h}$ (ng/mL)	435 (BLQ-2300)	624 (247–1850)	2625 (BLQ–5820)	ND	ND
C_{min} (ng/mL)†	134 (BLQ–369)	162 (50.9–304)	1381 (BLQ–3220)	0.08 (0.01–0.50)	0.11 (0.04–0.30)
C_{max} (ng/mL)	4710 (1050–5760)	4855 (3530–6210)	7445 (5880–12 000)	0.51 (0.30–0.86)	0.63 (0.50–0.79)
t_{max} (h)	4.00 (3.00–6.00)	3.50 (2.00–6.00)	4.00 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	52 009 (10 547–71 497)	50 214 (34 068–57 509)	91 644 (64 573–157 934)	0.44 (0.24–0.80)	0.50 (0.37–0.66)
Unbound darunavir					
$C_{0\ h}$ (ng/mL)	56.5 (BLQ–361)	89.2 (56.7–439)	399 (BLQ–826)	ND	ND
C_{min} (ng/mL)‡	17.5 (BLQ–54.1)	31.2 (9.35–57.3)	229 (BLQ–420)	0.08 (0.02–0.42)	0.12 (0.05–0.27)
C_{max} (ng/mL)	945 (168–1110)	1058 (777–1109)	1199 (866–2065)	0.59 (0.34–1.02)	0.77 (0.59–1.00)
t_{max} (h)	4.05 (1.03–6.00)	4.00 (2.00–4.00)	3.50 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	9725 (1885–12 310)	8883 (6132–11 883)	15 429 (6958–23 792)	0.55 (0.28–1.06)	0.60 (0.44–0.83)
Cobicistat					
C_{min} (ng/mL)	BLQ (BLQ–10.0)	BLQ (BLQ–7.02)	29.1 (BLQ–134)	0.17 (0.05–0.61)	0.17 (0.04–0.74)
C_{max} (ng/mL)§	523 (173–1190)	671 (365–1430)	971 (629–1460)	0.50 (0.28–0.91)	0.73 (0.52–1.02)
t_{max} (h)	4.03 (2.00–6.00)	3.50 (2.00–4.00)	4.00 (2.00–4.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	3654 (1088–8892)	4072 (1963–10 379)	9424 (4801–11 989)	0.37 (0.17–0.79)	0.51 (0.33–0.80)

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Darunavir/cobicistat drug combination in pregnancy

	Second trimester (24–28 weeks of gestation) (n = 7)	Third trimester (34–38 weeks of gestation) (n = 6)	Postpartum (6–12 weeks postpartum) (n = 6)	LSM ratio (95% CI) Second trimester (n = 7) versus postpartum (n = 6)	LSM ratio (95% CI) Third trimester (n = 6) versus postpartum (n = 6)
Total daruanvir*					
$C_{0\ h}$ (ng/mL)	435 (BLQ-2300)	624 (247–1850)	2625 (BLQ–5820)	ND	ND
C_{min} (ng/mL)†	134 (BLQ–369)	162 (50.9–304)	1381 (BLQ–3220)	0.08 (0.01–0.50)	0.11 (0.04–0.30)
C_{max} (ng/mL)	4710 (1050–5760)	4855 (3530–6210)	7445 (5880–12 000)	0.51 (0.30–0.86)	0.63 (0.50–0.79)
t_{max} (h)	4.00 (3.00–6.00)	3.50 (2.00–6.00)	4.00 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	52 009 (10 547–71 497)	50 214 (34 068–57 509)	91 644 (64 573–157 934)	0.44 (0.24–0.80)	0.50 (0.37–0.66)
Unbound darunavir					
$C_{0\ h}$ (ng/mL)	56.5 (BLQ–361)	89.2 (56.7–439)	399 (BLQ–826)	ND	ND
C_{min} (ng/mL)‡	17.5 (BLQ–54.1)	31.2 (9.35–57.3)	229 (BLQ–420)	0.08 (0.02–0.42)	0.12 (0.05–0.27)
C_{max} (ng/mL)	945 (168–1110)	1058 (777–1109)	1199 (866–2065)	0.59 (0.34–1.02)	0.77 (0.59–1.00)
t_{max} (h)	4.05 (1.03–6.00)	4.00 (2.00–4.00)	3.50 (2.00–6.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	9725 (1885–12 310)	8883 (6132–11 883)	15 429 (6958–23 792)	0.55 (0.28–1.06)	0.60 (0.44–0.83)
Cobicistat					
C_{min} (ng/mL)	BLQ (BLQ–10.0)	BLQ (BLQ–7.02)	29.1 (BLQ–134)	0.17 (0.05–0.61)	0.17 (0.04–0.74)
C_{max} (ng/mL)§	523 (173–1190)	671 (365–1430)	971 (629–1460)	0.50 (0.28–0.91)	0.73 (0.52–1.02)
t_{max} (h)	4.03 (2.00–6.00)	3.50 (2.00–4.00)	4.00 (2.00–4.00)	ND	ND
$AUC_{24\ h}$ (ng h/mL)	3654 (1088–8892)	4072 (1963–10 379)	9424 (4801–11 989)	0.37 (0.17–0.79)	0.51 (0.33–0.80)

Crauwels HM, Osiyemi O, Zorrilla C et al. Reduced exposure to darunavir and cobicistat in HIV-1 infected pregnant women receiving a darunavir/cobicistat-based regimen. HIV Med. 2019;20(5):337-343.

Cobicistat drug combinations in pregnancy

JOHNS HOPKINS MEDICINE

Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Jeremiah D. Momper[a], Brookie M. Best[a], Jiajia Wang[b], Edmund V. Capparelli[a], Alice Stek[c], Emily Barr[d], Martina L. Badell[e], Edward P. Acosta[f], Murli Purswani[g], Elizabeth Smith[h], Nahida Chakhtoura[i], Kyunghun Park[a], Sandra Burchett[j], David E. Shapiro[b], Mark Mirochnick[k], for the IMPAACT P1026s Protocol Team

Cobicistat drug combinations in pregnancy

JOHNS HOPKINS MEDICINE

Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Je
Edmund
Ed
Na
Da

Pharmacokinetics of darunavir and cobicistat in pregnant and postpartum women with HIV

Jeremiah D. Momper[a], Jiajia Wang[b], Alice Stek[c], David E. Shapiro[b], Gwendolyn B. Scott[d], Mary E. Paul[e], Irma L. Febo[f], Sandra Burchett[g], Elizabeth Smith[h], Nahida Chakhtoura[i], Kayla Denson[j], Kittipong Rungruengthanakit[k], Kathleen George[l], Derek Z. Yang[a], Edmund V. Capparelli[a], Mark Mirochnick[m], Brookie M. Best[a], for the IMPAACT P1026s Protocol Team

Cobicistat drug combinations in pregnancy

JOHNS HOPKINS MEDICINE

Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Je
Edmund
Ed
Na
Da

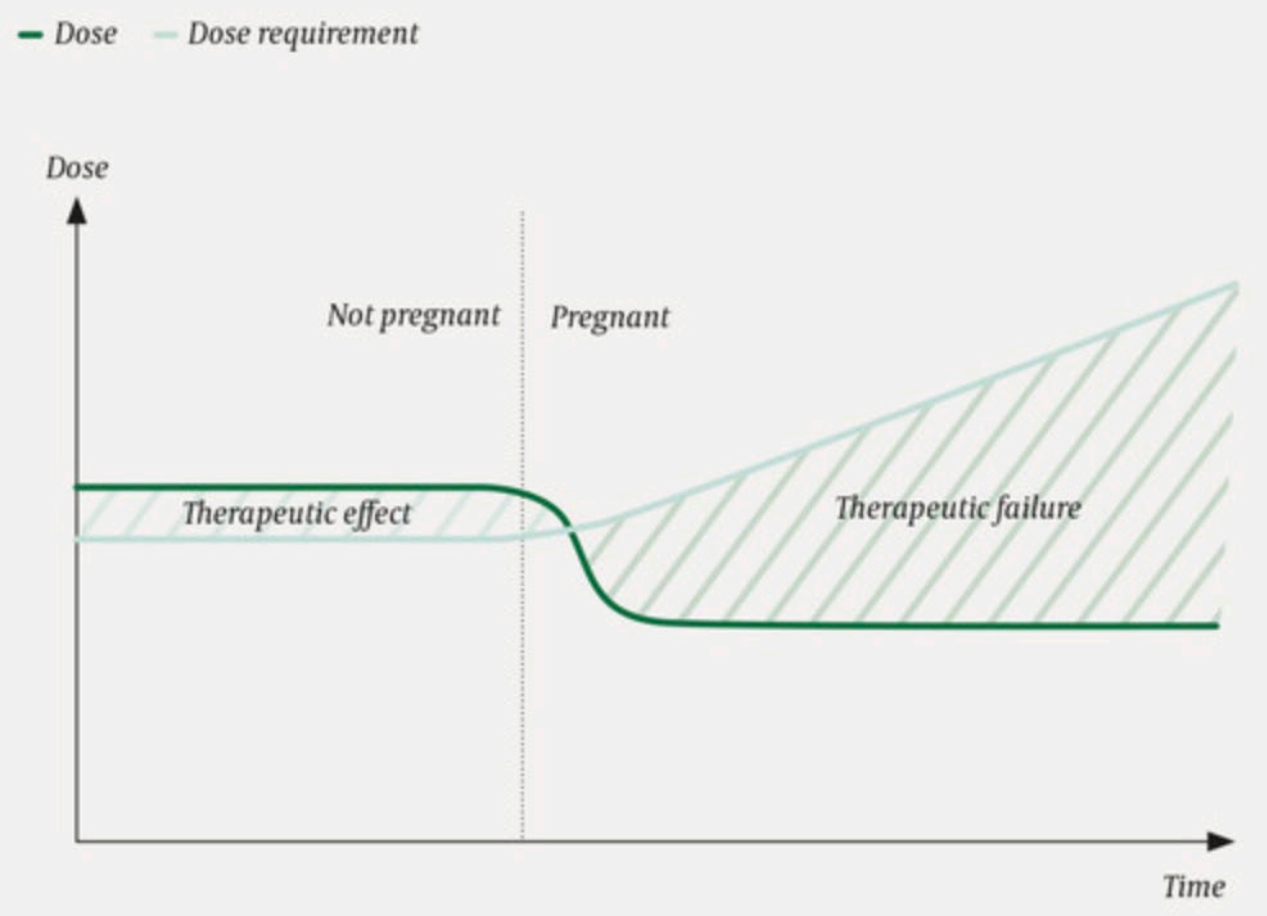
Pharmacokinetics of darunavir and cobicistat in pregnant and postpartum women with HIV

Jeremiah D. Momper[a], Jiajia Wang[b], Alice Stek[c], David E. Shapiro[b],
Gwendolyn
Eliza
Kittipong
Edmund

Pharmacokinetics of Atazanavir Boosted With Cobicistat in Pregnant and Postpartum Women With HIV

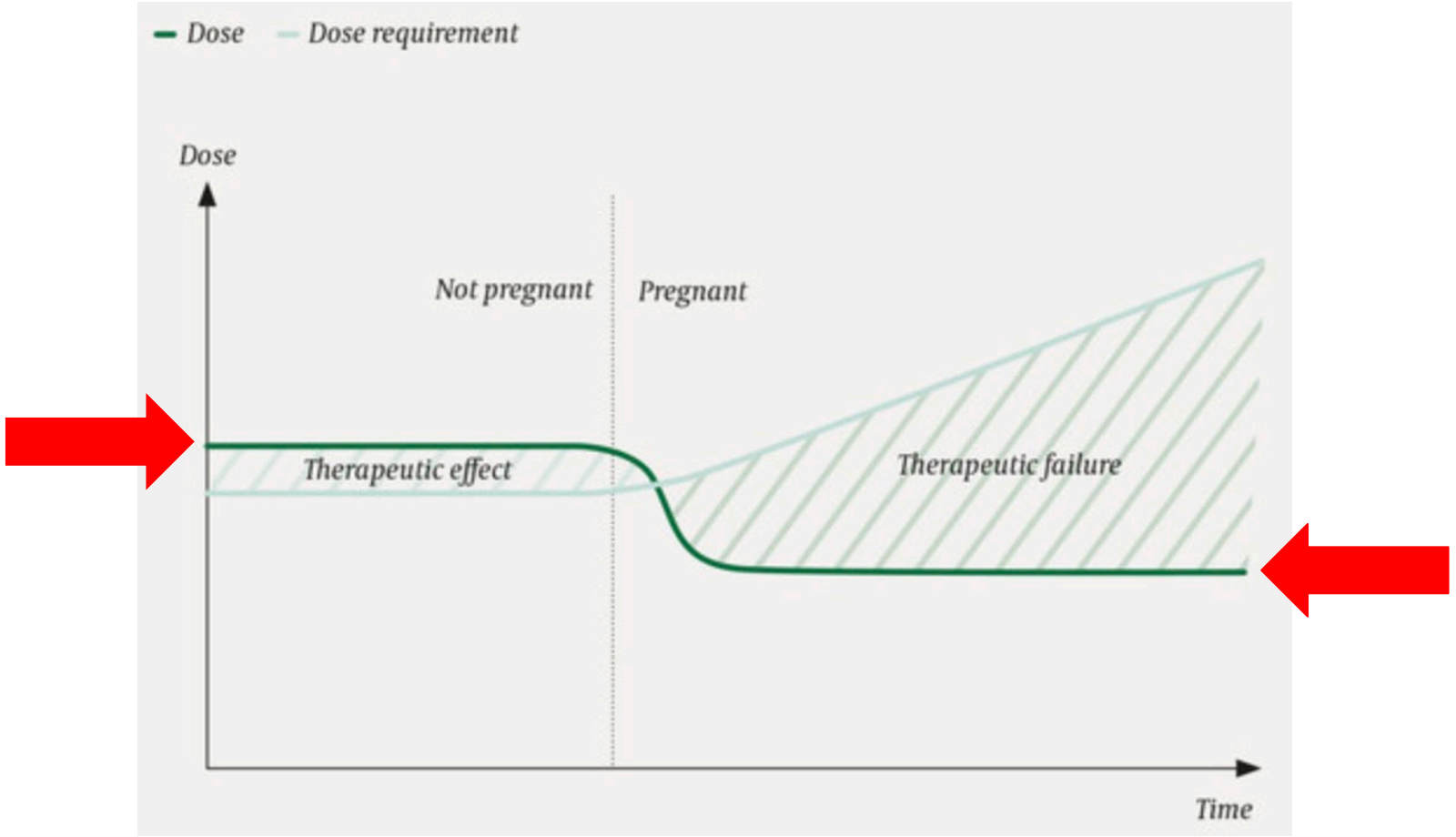
Jeremiah D. Momper, PharmD, PhD,[a] Jiajia Wang, MS,[b] Alice Stek, MD,[c] David E. Shapiro, PhD,[b] Kathleen M. Powis, MD,[d] Mary E. Paul, MD,[e] Martina L. Badell, MD,[f] Renee Browning, RN, MSN,[g] Nahida Chakhtoura, MD,[h] Kayla Denson, PhD,[i] Kittipong Rungruengthanakit, MD,[j] Kathleen George, MPH,[k] Edmund V. Capparelli, PharmD,[a] Mark Mirochnick, MD,[l] and Brookie M. Best, PharmD, MAS,[a] for the IMPAACT P1026s Protocol Team

Therapeutic failure during pregnancy



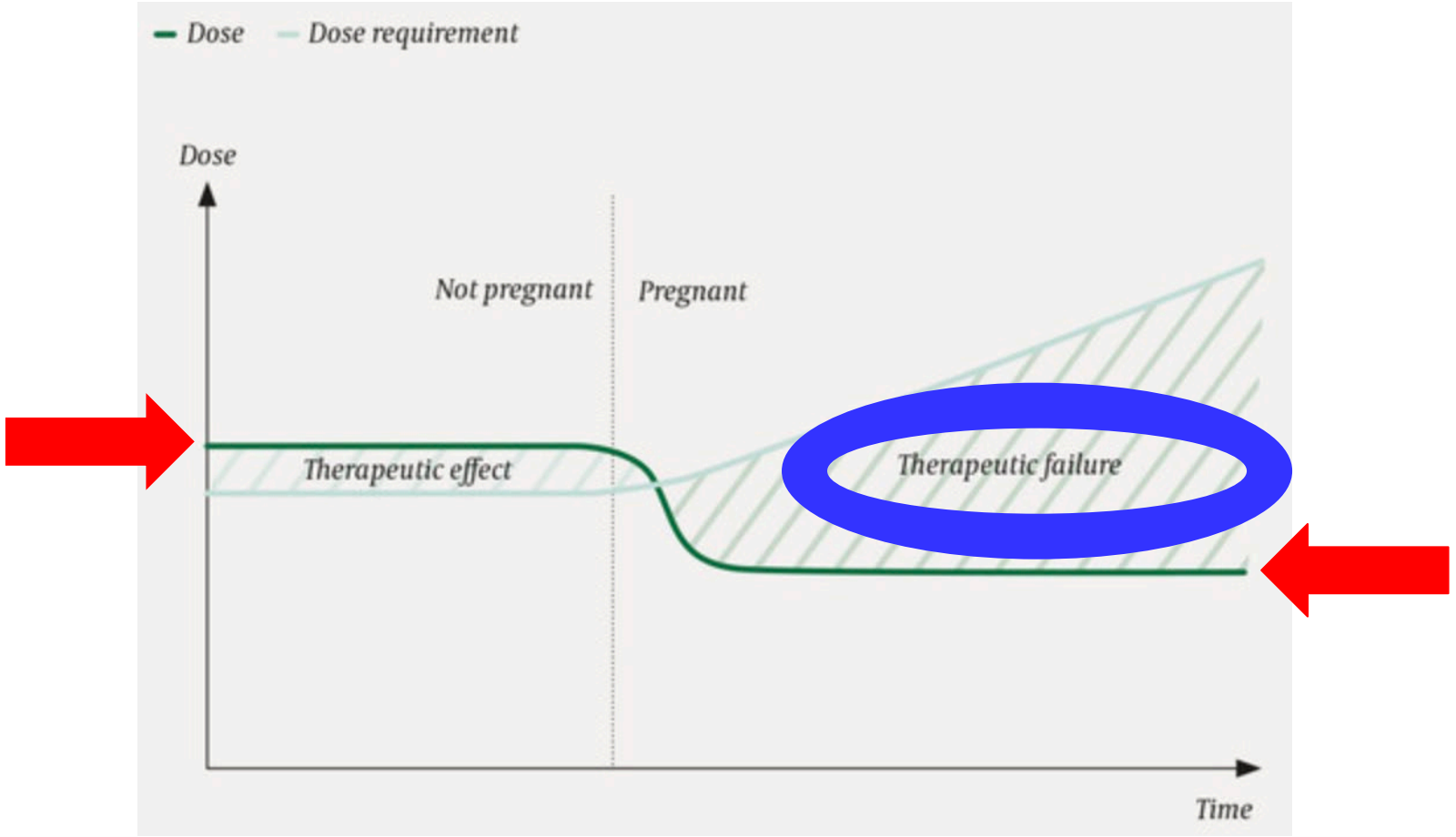
Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Therapeutic failure during pregnancy



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Therapeutic failure during pregnancy



Westin AA, Reimers A, Spigset O. Should pregnant women receive higher or lower medication doses? *Tidsskrift for Den norske legeforening (tidsskriftet.no*. https://tidsskriftet.no/en/2018/10/klinisk-oversikt/should-pregnant-women-receive-lower-or-higher-medication-doses

Cobicistat drug combinations in pregnancy

JOHNS HOPKINS MEDICINE

FDA Revises Certain Antiretroviral Drug Labeling to Not Recommend Cobicistat During Pregnancy

Cobicistat drug combinations in pregnancy

Stribild

Prezcobix

Evotaz

Symtuza

Genvoya

How changes in clearance affect drug PK

Anticonvulsants
Antidepressants

RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

Drug Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Carbamazepine [77–85]	9	128/130	11.7	**Free fraction 116% (113%–119%)[&], free** fraction 101% (95%–107%)[&]	**Total concentration 79%[&]**	**Cl 127% (116%–140%)[&]**, Cl 110% (108%–112%)[&]	1st–3rd
Lamotrigine [83,86–93]	9	208/241	15.7	NR	**C/D ratio 34%[&]**	**Cl 212% (185%–240%)[&]**	3rd
Levetiracetam [16,83,94,95]	4	47/47	14	NR	**C/D ratio 45% (39%–52%)[&]**	**Cl 269% (197%–342%)[&]**	3rd
Oxcarbazepine [83,96–98]	4	28/28	13.7	NR	**Lower concentration and C/D ratio[&,β]**	Cl 237%[&]	3rd
Phenytoin [81,82,84,99]	4	82/78	12.5	**Free fraction 126%[&]**	**Total concentration 67% (51%–84%)[&]**	**Cl 145% (130%–160%)[&]**	1st–3rd
Phenobarbital [81]	1	11/11	9	**Free fraction 112%**	**Total concentration 53%**	**Cl 125%**	3rd
Topiramate [83,100,101]	3	21/25	16	NR	**C/D ratio 60% (57%–64%)[&]**	Cl 110%[&]	3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How changes in clearance affect drug PK

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Ketorolac [102]	1	8/8	16	**V_d 134%**	NR	**Cl 150%, $t_{1/2}$** 108%	3rd
Morphine [103]	1	6/8	19	V_d 92%	**AUC 96%**	**Cl 169%, $t_{1/2}$51%**	3rd
Paracetamol [49,102,104–107]	6	52/85	18.1	**V_d 182%**[&]	**C_{trough} 56%**[&], C_{max} 87% (42%–96%)[&], **AUC 72%**[&], AUC 83%[&]	**Cl 142% (132%–196%), $t_{1/2}$ 80%**[&], $t_{1/2}$ 95% (72%–119%[&]	1st + 3rd

Analgesics and anesthetic agents

RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How changes in clearance affect drug PK

Antibiotics

RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Amoxicillin [43]	1	16/16	22	NR	NR	**Cl 140%, $t_{1/2}$ 81%**	3rd
Azithromycin [47,51]	2	54/84	19.5	**V_d 121%**[&]	AUC 90%[&]	$t_{1/2}$ 101%[&]	1st–3rd
Cefatrizine [52]	1	20/20	19	NR	**C_{max} 55%, AUC 57%**	**$t_{1/2}$ 163%**	2nd
Cefazolin [39,53,54]	3	10[$]/54	18.6	V_d 80% (72%–89%)[&], **free fraction 131%**[&]	AUC 68%[&]	Cl 102% (65%–140%)[&], **$t_{1/2}$ 65%**[&], $t_{1/2}$ 131%[&]	2nd–3rd
Cefoperazone [55]	1	9/11	13	**Free fraction 208%**	NR	NR	3rd
Cefradine [54]	1	12/12	19	V_d 113%	**AUC 62%**	**Cl 154%, $t_{1/2}$ 73%**	1st–3rd
Ceftazidime [56]	1	12/12	16	NR	NR	**Cl 165%**	3rd
Cefuroxime [57]	1	7/7	13	V_d 109%	**AUC 69%**	**Cl 142%, $t_{1/2}$ 75%**	1st–3rd
Cloxacillin [48,58]	2	14/33	13.5	**Free fraction 154% (146%–162%)**	NR	NR	3rd
Flucloxacillin [58]	1	7/22	11	**Free fraction 148%**	NR	NR	3rd
Imipenem [59]	1	6/7	15	**V_d 249%**	**C_{max} 34%, AUC 41%**	**Cl 287%**, $t_{1/2}$ 87%	3rd
Mecillinam [60]	1	6/10	17	**V_d 224%**	C_{max} 85%, AUC 85%	Cl 103%, **$t_{1/2}$ 142%**	3rd
Moxifloxacin [61]	1	9/6	11	**V_d 329%**	**C_{max} 31%, AUC 21%**	**$t_{1/2}$ 63%**	3rd
Penicillin V [62]	1	6/6	16	NR	C_{max} 96%, **AUC 60%**	Cl 118%, **$t_{1/2}$ 30%**	3rd
Piperacillin [63–65]	3	11/18	12.3	**V_d 161%**, V_d 145% (136%–155%)	**C_{max} 50%**[&], C_{max} 57%[&], **AUC 61%**[&], AUC 110%[&]	**Cl 284%**, Cl 130% (96%–165%), $t_{1/2}$ 86% (70%–135%)	3rd
Trimethoprim [66]	1	8/10	11	**V_d 407%**	NR	**Cl 346%**, $t_{1/2}$ 100%	2nd–3rd
Tazobactam [64]	1	6/5	13	**V_d 150%**	C_{max} 75%, AUC 106%	**$t_{1/2}$ 156%**	3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

How V_d and plasma protein changes affect drug PK

Antimalarials

RESEARCH ARTICLE

Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

Gali Pariente[1], Tom Leibson[1], Alexandra Carls[1], Thomasin Adams-Webber[2], Shinya Ito[1,3,4,5]*, Gideon Koren[6]

1 Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada, **2** Hospital Library, Hospital for Sick Children, Toronto, Ontario, Canada, **3** Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada, **4** Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, **5** Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada, **6** Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

* Shinya.ito@sickkids.ca

Drug [Reference]	Number of Studies	Total Number of Women (Nonpregnant/ Pregnant)	Average Quality (24 Items)	Distribution Parameters	Exposure Parameters	Elimination Parameters	Trimester
Artemeter [181,182]	2	22/46	19	NR	**C_{max} 52%[&], AUC 31%[&]**	NR	2nd–3rd
Atovaquone [183]	1	0[!]/9	18	**V_d 217%**	**C_{trough} 22%, C_{max} 37%, AUC 21%**	**Cl 821%**	2nd–3rd
Chloroquine [184–187]	4	50/70	18.7	**V_d 106%[&]**	C_{max} 106% (76%–137%), **AUC 74%[&]**, AUC 81% (72%–91%)[&]	**Cl 138% (133%–144%)[&]**, Cl 110%[&], **$t_{1/2}$ 91%[&]**, $t_{1/2}$ 86%[&]	2nd–3rd
Lumefantrine [181,182,188,189]	4	56/188	19.2	V_d 90%[&]	**Lower concentration[&,β]**, C_{max} 101% (100%–103%)[&], AUC 97% (90%114%)[&]	**Higher Cl[&,β]**, Cl 88%[&], **$t_{1/2}$ 81%[&]**, $t_{1/2}$ 151%[&]	2nd–3rd
Mefloquine [190–192]	3	32/53	17.6	**V_d 108%[&]**, V_d 121%[&]	**C_{max} 77%[&]**, C_{max} 103%[&], AUC 112%	**Cl 162%,** Cl 104% (100–109%), **$t_{1/2}$ 134%,** $t_{1/2}$ 78% (68%–88%)	1st–3rd
Piperaquine [193–195]	3	81/80	19	**V_d 66% (63%–68%),** V_d 93%	**C_{max} 134%[&]**, C_{max} 126%[&], **AUC 66%,** AUC 103% (110%–117%)[&]	**Cl 137%,** Cl 93% (90%–96%), **$t_{1/2}$ 72% (69%–90%)**	2nd–3rd
Proguanil [183,196]	2	4[!]/19	16.5	**V_d 109%**	C_{trough} 101%[&], C_{max} 80% (65%–95%), AUC 77% (60%–95%)	Cl 116% (73%–160%), **$t_{1/2}$ 71%,** $t_{1/2}$ 123%	2nd–3rd

Pariente G, Leibson T, Carls A et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med 2016; 13 (11): e1002160

Effect of pregnancy on the PK and PD of Monoclonal antibodies

Monoclonal antibodies

Biologic	Drug transfer to fetus	Estimated drug clearance in the infant	Level of clinical experience*
Infliximab	High	3–7 mo	++++
Adalimumab	Moderate	3–5 mo	++++
Golimumab	Moderate	Unknown	+
Certolizumab pegol	Minimal (passive diffusion)	NA	+++
Etanercept	Low	0–3 mo	+++
Ustekinumab	Moderate	Unknown	+
Vedolizumab	Low-moderate	Likely < 3 mo	+
Natalizumab	Low-moderate	Unknown	+
Rituximab	Moderate-high	Unknown	+
Belimumab	Unknown	Unknown	+

Pham-Huy A, Top KA, Constantinescu C et al. The use and impact of monoclonal antibody biologics during pregnancy. CMAJ 2021 Jul 26; 193(29): E1129–E1136

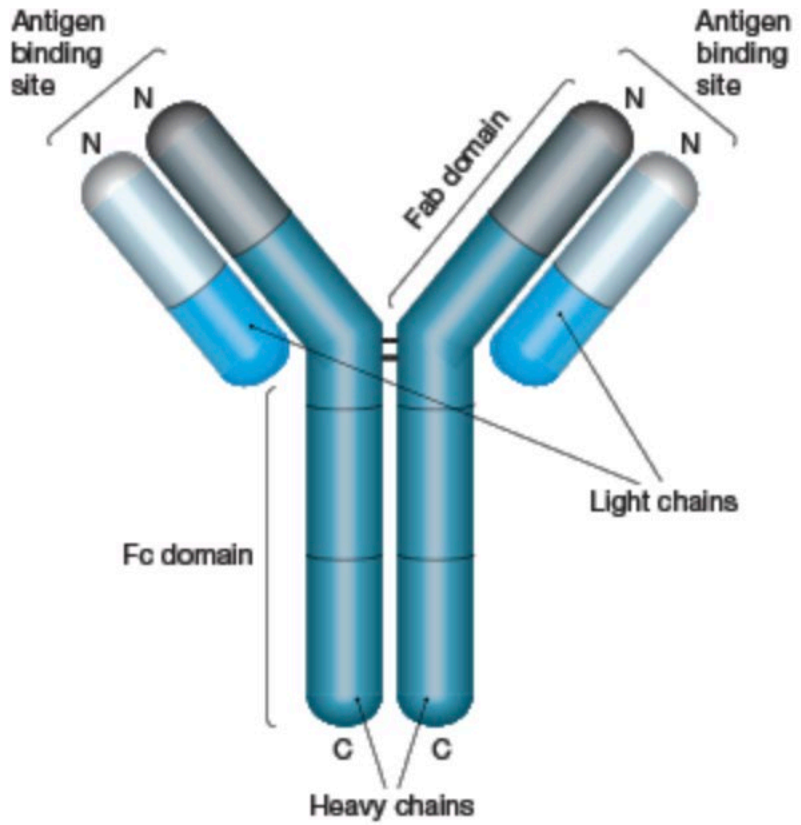
Additional physiologic changes affecting mAb disposition

- Monoclonal antibody structure
- Antigen properties
- Increased anti-drug antibody (ADA) formation to mAb
- Increased complement activity
- Flip flop kinetics

Absorption of Biologics

Absorption of monoclonal antibodies

- Distinct from small-molecule drugs
- Most mAb are administered parenterally
  - Large molecular size (>150kD)
  - Poor lipophilicity
  - Increased GI degradation
- Bioavailability (50-100%)
  - Protein degradation in pregnancy?
  - Increased blood flow



Distribution of Biologics

Distribution of monoclonal antibodies

- Relatively low volume of distribution (plasma)
  - High molecular weight
  - Hydrophilic profile
- Volume of distribution approximate the size of blood and extracellular space (3-8L)

Distribution of monoclonal antibodies

Drug Name	Target	Source	Route of administration	FDA-approved indication	FDA pregnancy category	Bioavailability	Elimination half-life (days)	Volume of distribution
Adalimumab (AbbVie, 2013)	TNFα	Human[a]	SC	IBD, RA[d], psoriasis, ankylosing spondylitis	B	64%	14	4.7–6 L
Certolizumab pegol (UBC, 2013)	TNFα	Humanized[b]	SC	IBD	B	76–88%	14	6–8 L
Golimumab (Janssen, 2014)	TNFα	Human[a]	SC	UC, RA, psoriatic arthritis, ankylosing spondylitis	B	53%	14	58–126 ml/kg
Infliximab (Janssen, 2013)	TNFα	Chimeric[c]	IV	IBD, RA, psoriasis, ankylosing spondylitis	B	-	7–12	3–6 L
Natalizumab (Biogen, 2013)	α4-integrin	Humanized[b]	IV	CD, multiple sclerosis	C	-	3–17	~5 L

Stone RH, Hong J, Jeong H. Pharmacokinetics of monoclonal antibodies used for inflammatory bowel diseases in pregnant women. J Clin Toxicol 2014; 4(4): 209

Distribution of monoclonal antibodies

Drug Name	Target	Source	Route of administration	FDA-approved indication	FDA pregnancy category	Bioavailability	Elimination half-life (days)	Volume of distribution
Adalimumab (AbbVie, 2013)	TNFα	Human[a]	SC	IBD, RA[d], psoriasis, ankylosing spondylitis	B	64%	14	4.7–6 L
Certolizumab pegol (UBC, 2013)	TNFα	Humanized[b]	SC	IBD	B	76–88%	14	6–8 L
Golimumab (Janssen, 2014)	TNFα	Human[a]	SC	UC, RA, psoriatic arthritis, ankylosing spondylitis	B	53%	14	58–126 ml/kg
Infliximab (Janssen, 2013)	TNFα	Chimeric[c]	IV	IBD, RA, psoriasis, ankylosing spondylitis	B	-	7–12	3–6 L
Natalizumab (Biogen, 2013)	α4-integrin	Humanized[b]	IV	CD, multiple sclerosis	C	-	3–17	~5 L

Stone RH, Hong J, Jeong H. Pharmacokinetics of monoclonal antibodies used for inflammatory bowel diseases in pregnant women. J Clin Toxicol 2014; 4(4): 209

Distribution of monoclonal antibodies

Drug Name	Target	Source	Route of administration	FDA-approved indication	FDA pregnancy category	Bioavailability	Elimination half-life (days)	Volume of distribution
Adalimumab (AbbVie, 2013)	TNFα	Human[a]	SC	IBD, RA[d], psoriasis, ankylosing spondylitis	B	64%	14	4.7–6 L
Certolizumab pegol (UBC, 2013)	TNFα	Humanized[b]	SC	IBD	B	76–88%	14	6–8 L
Golimumab (Janssen, 2014)	TNFα	Human[a]	SC	UC, RA, psoriatic arthritis, ankylosing spondylitis	B	53%	14	58–126 ml/kg
Infliximab (Janssen, 2013)	TNFα	Chimeric[c]	IV	IBD, RA, psoriasis, ankylosing spondylitis	B	-	7–12	3–6 L
Natalizumab (Biogen, 2013)	α4-integrin	Humanized[b]	IV	CD, multiple sclerosis	C	-	3–17	~5 L

Stone RH, Hong J, Jeong H. Pharmacokinetics of monoclonal antibodies used for inflammatory bowel diseases in pregnant women. J Clin Toxicol 2014; 4(4): 209

Distribution of monoclonal antibodies

Drug Name	Target	Source	Route of administration	FDA-approved indication	FDA pregnancy category	Bioavailability	Elimination half-life (days)	Volume of distribution
Adalimumab (AbbVie, 2013)	TNFα	Human[a]	SC	IBD, RA[d], psoriasis, ankylosing spondylitis	B	64%	14	4.7–6 L
Certolizumab pegol (UBC, 2013)	TNFα	Humanized[b]	SC	IBD	B	76–88%	14	6–8 L
Golimumab (Janssen, 2014)	TNFα	Human[a]	SC	UC, RA, psoriatic arthritis, ankylosing spondylitis	B	53%	14	58–126 ml/kg
Infliximab (Janssen, 2013)	TNFα	Chimeric[c]	IV	IBD, RA, psoriasis, ankylosing spondylitis	B	-	7–12	3–6 L
Natalizumab (Biogen, 2013)	α4-integrin	Humanized[b]	IV	CD, multiple sclerosis	C	-	3–17	~5 L

Stone RH, Hong J, Jeong H. Pharmacokinetics of monoclonal antibodies used for inflammatory bowel diseases in pregnant women. J Clin Toxicol 2014; 4(4): 209

Distribution of monoclonal antibodies

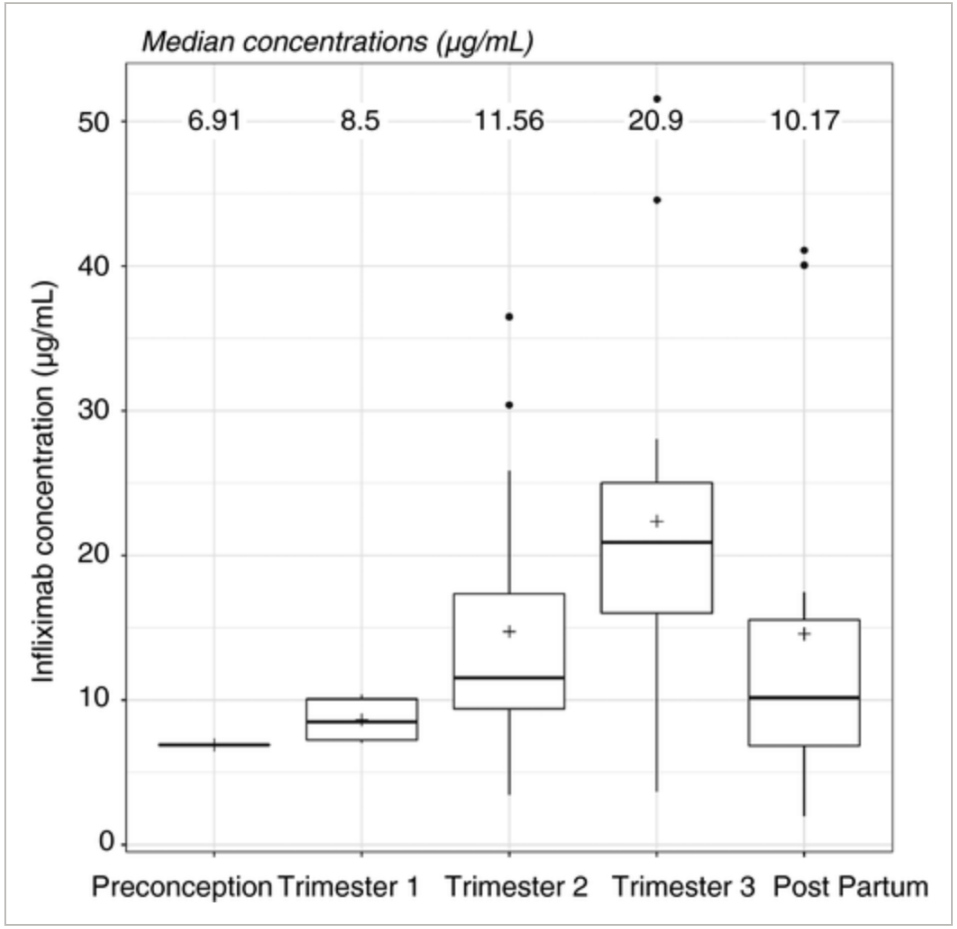
AP&T Alimentary Pharmacology and Therapeutics

The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease

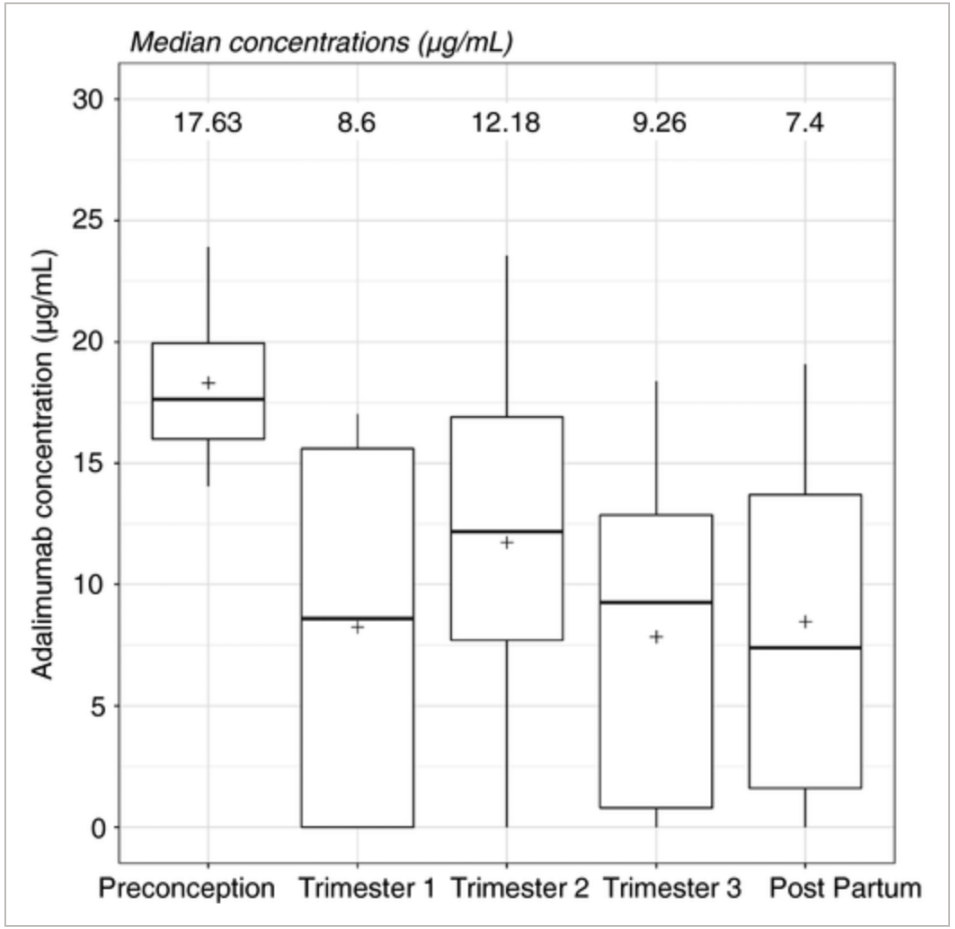
C. H. Seow*,† iD, Y. Leung*, N. Vande Casteele‡, E. Ehteshami Afshar*, D. Tanyingoh*, G. Bindra*, M. J. Stewart*, P. L. Beck*, G. G. Kaplan*,† iD, S. Ghosh* & R. Panaccione*

Seow CH, Leung Y, Casteele NV et al. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:1329–1338

Distribution of monoclonal antibodies



Median infliximab concentrations by trimester



Median adalimumab concentrations per trimester

Seow CH, Leung Y, Casteele NV et al. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:1329–1338

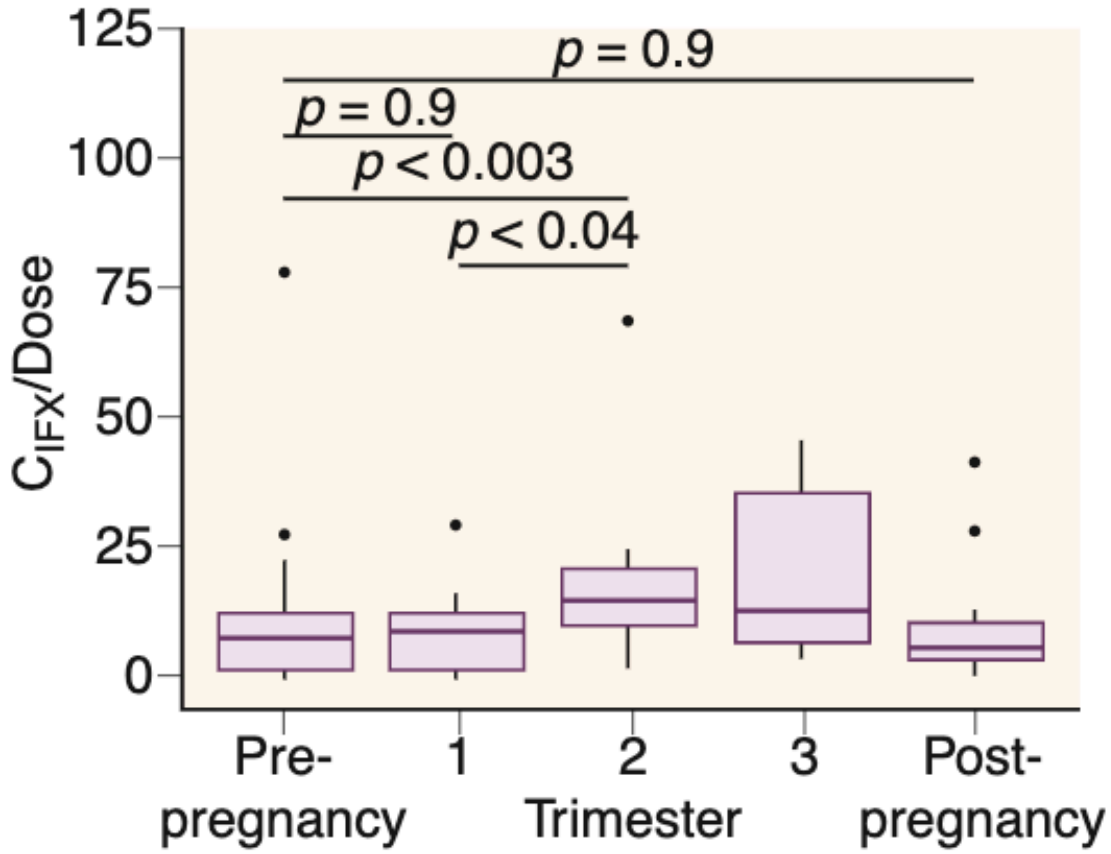
Distribution of monoclonal antibodies

ORIGINAL ARTICLE

ueg journal WILEY

Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease

Ana-Marija Grišić[1,2] | Maria Dorn-Rasmussen[3] | Bella Ungar[4] | Jørn Brynskov[3] | Johan F. K. F. Ilvemark[3] | Nils Bolstad[5] | David J. Warren[5] | Mark A. Ainsworth[3] | Wilhelm Huisinga[6] | Shomron Ben-Horin[4] | Charlotte Kloft[1] | Casper Steenholdt[3]



**Maintenance phase IFX concentrations (CIFX) per trimester

Grisic AM, Dorn-Rasmussen M, Ungar B et al. Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease. United European Gastroentrol J 2021; 9(1): 91-101.

Elimination of Biologics

Elimination of monoclonal antibodies

- FcRn- and target-mediated elimination pathways
- Renal excretion and hepatic metabolism are not primarily involved in elimination of mAbs
- The large size of mAbs prevents excretion into the urine

Clearance of Infliximab during pregnancy

ORIGINAL ARTICLE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease

Ana-Marija Grišić[1,2] | Maria Dorn-Rasmussen[3] | Bella Ungar[4] | Jørn Brynskov[3] | Johan F. K. F. Ilvemark[3] | Nils Bolstad[5] | David J. Warren[5] | Mark A. Ainsworth[3] | Wilhelm Huisinga[6] | Shomron Ben-Horin[4] | Charlotte Kloft[1] | Casper Steenholdt[3]

Grisic AM, Dorn-Rasmussen M, Ungar B et al. Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease. United European Gastroentrol J 2021; 9(1): 91-101.

Eculizumab use in pregnancy

JOHNS HOPKINS MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria

Richard J. Kelly, M.B., Ch.B., Ph.D., Britta Höchsmann, M.D., Jeff Szer, M.B., B.S., Austin Kulasekararaj, F.R.C.Path., Sophie de Guibert, M.D., Alexander Röth, M.D., Ilene C. Weitz, M.D., Elina Armstrong, M.D., Ph.D., Antonio M. Risitano, M.D., Ph.D., Christopher J. Patriquin, M.D., Louis Terriou, M.D., Petra Muus, M.D., Ph.D., Anita Hill, M.B., Ch.B., Ph.D., Michelle P. Turner, M.S., Hubert Schrezenmeier, M.D., and Regis Peffault de Latour, M.D., Ph.D.

Effect of anti-drug antibodies (ADA) on the PK of Biologics

ADA status in Elimination of monoclonal antibodies

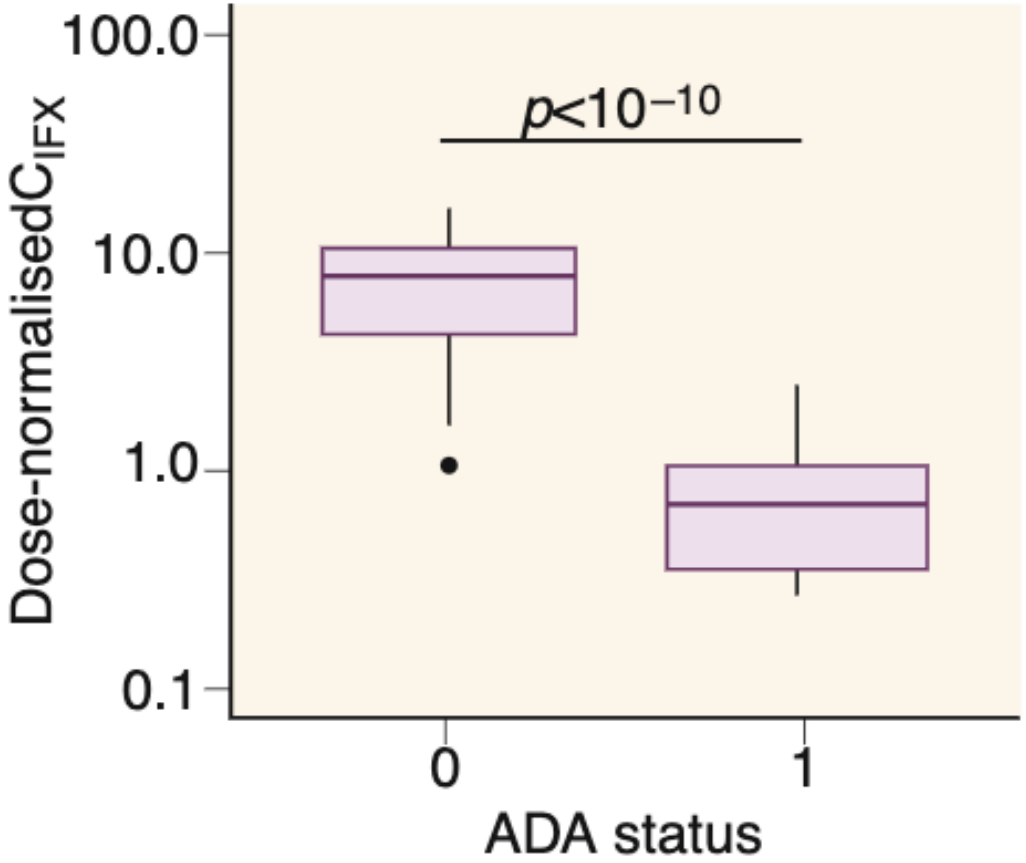
ORIGINAL ARTICLE

ueg journal WILEY

Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease

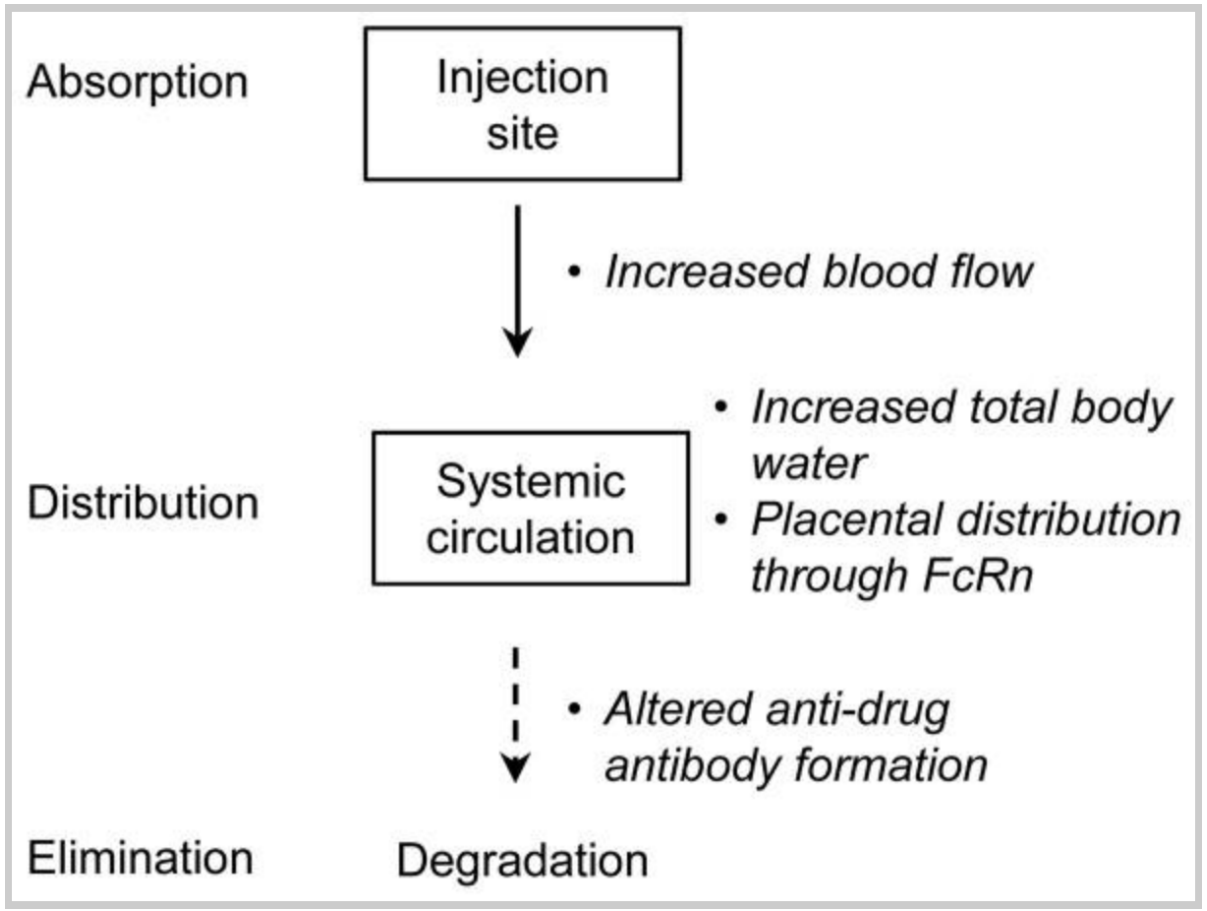
Ana-Marija Grišić[1,2] | Maria Dorn-Rasmussen[3] | Bella Ungar[4] | Jørn Brynskov[3] | Johan F. K. F. Ilvemark[3] | Nils Bolstad[5] | David J. Warren[5] | Mark A. Ainsworth[3] | Wilhelm Huisinga[6] | Shomron Ben-Horin[4] | Charlotte Kloft[1] | Casper Steenholdt[3]

**Maintenance phase IFX concentrations (CIFX) by ADA status in pregnancy



Grisic AM, Dorn-Rasmussen M, Ungar B et al. Infliximab clearance decreases in the second and third trimesters of pregnancy in inflammatory bowel disease. United European Gastroentrol J 2021; 9(1): 91-101.

Summary PK of monoclonal antibodies



Stone RH, Hong J, Jeong H. Pharmacokinetics of monoclonal antibodies used for inflammatory bowel diseases in pregnant women. J Clin Toxicol 2014; 4(4): 209

Net drug plasma concentration during pregnancy

- Complex relationship (net effect) between so many PK variables
  - Fraction of drug absorbed
  - The physicochemical properties governing diffusion across membranes
  - Drug bioavailability
  - Protein binding
  - Unbound fractions of drug
  - Volume of distribution
  - Intrinsic organ clearance
  - Organ extraction ratio (hepatic or renal)
  - Drug-drug interactions
  - Pharmacogenomic, pharmacomicrobiomic, and
  - Several other variables.

Areas for continuing research

- Drug transporters
- Free (unbound) fraction of drugs
- Pharmacodynamic data
- Pharmacogenomic data
- Pharmacomicrobiomic data
- PK of newer drugs
- Understanding the placenta

Thank you