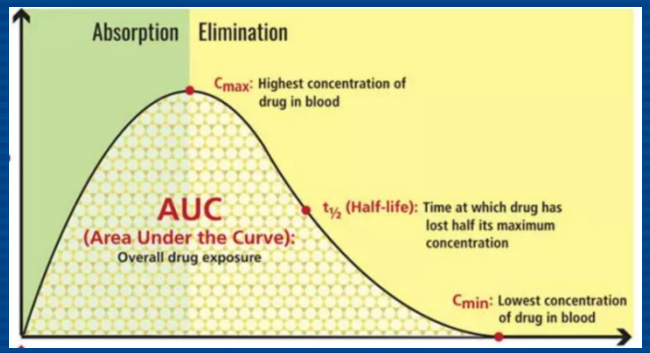
JOHNS HOPKINS
MEDICINE

# 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

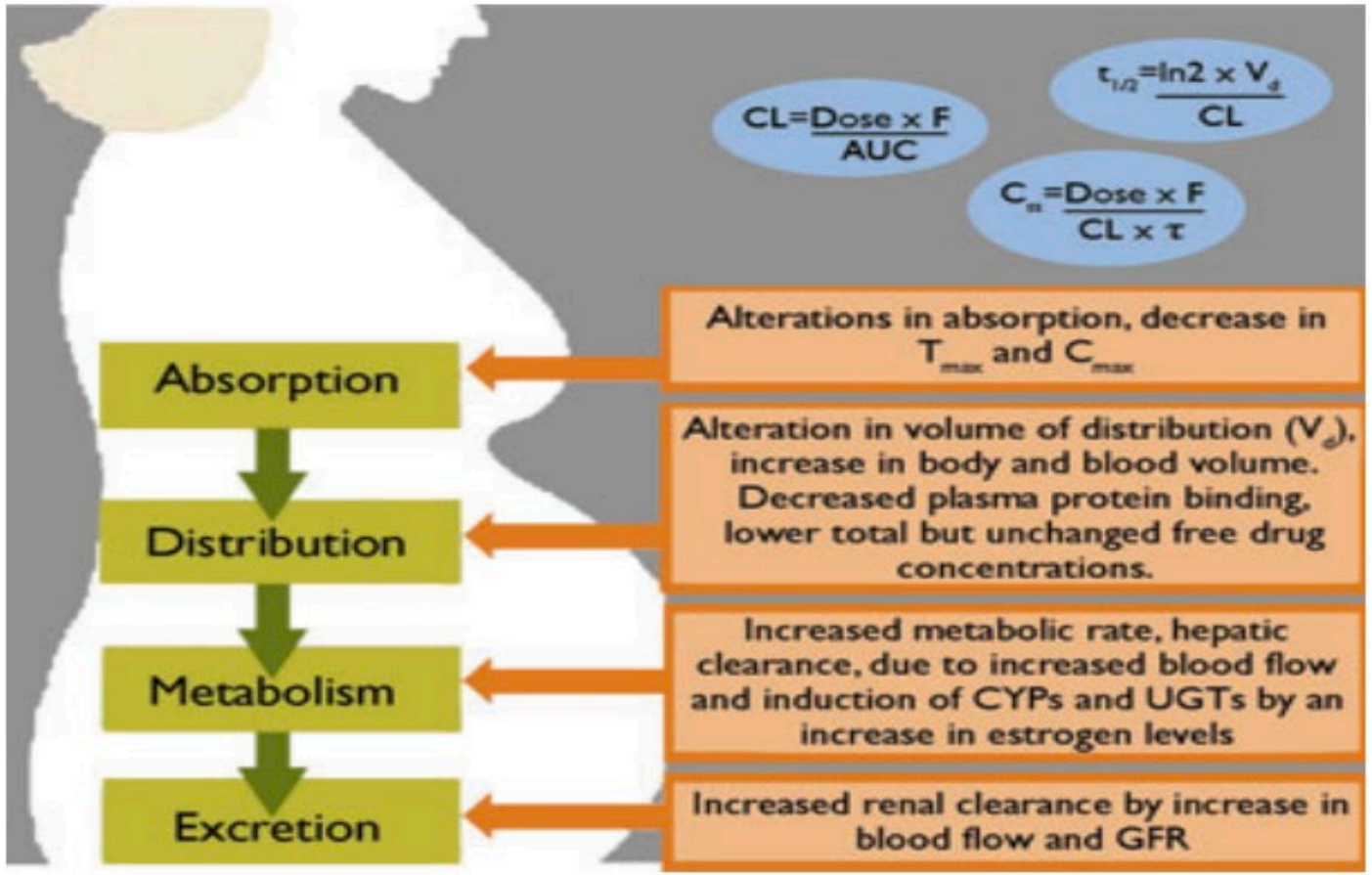
# Conflicts of Interest

- I have no conflicts of interest

# Outline

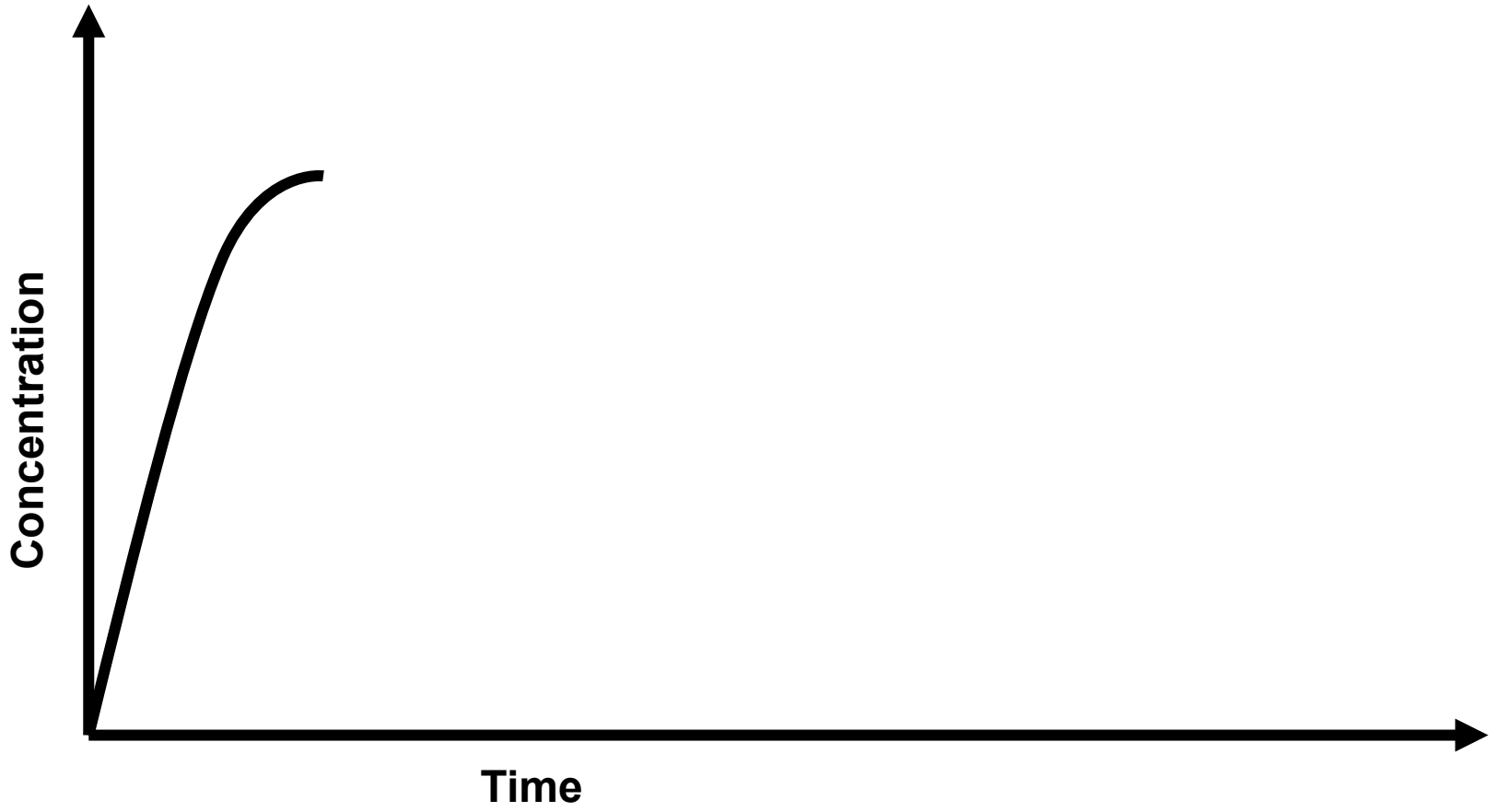
- Physiological changes in pregnancy
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Physiological changes as it affects drug disposition of biologics

# 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)



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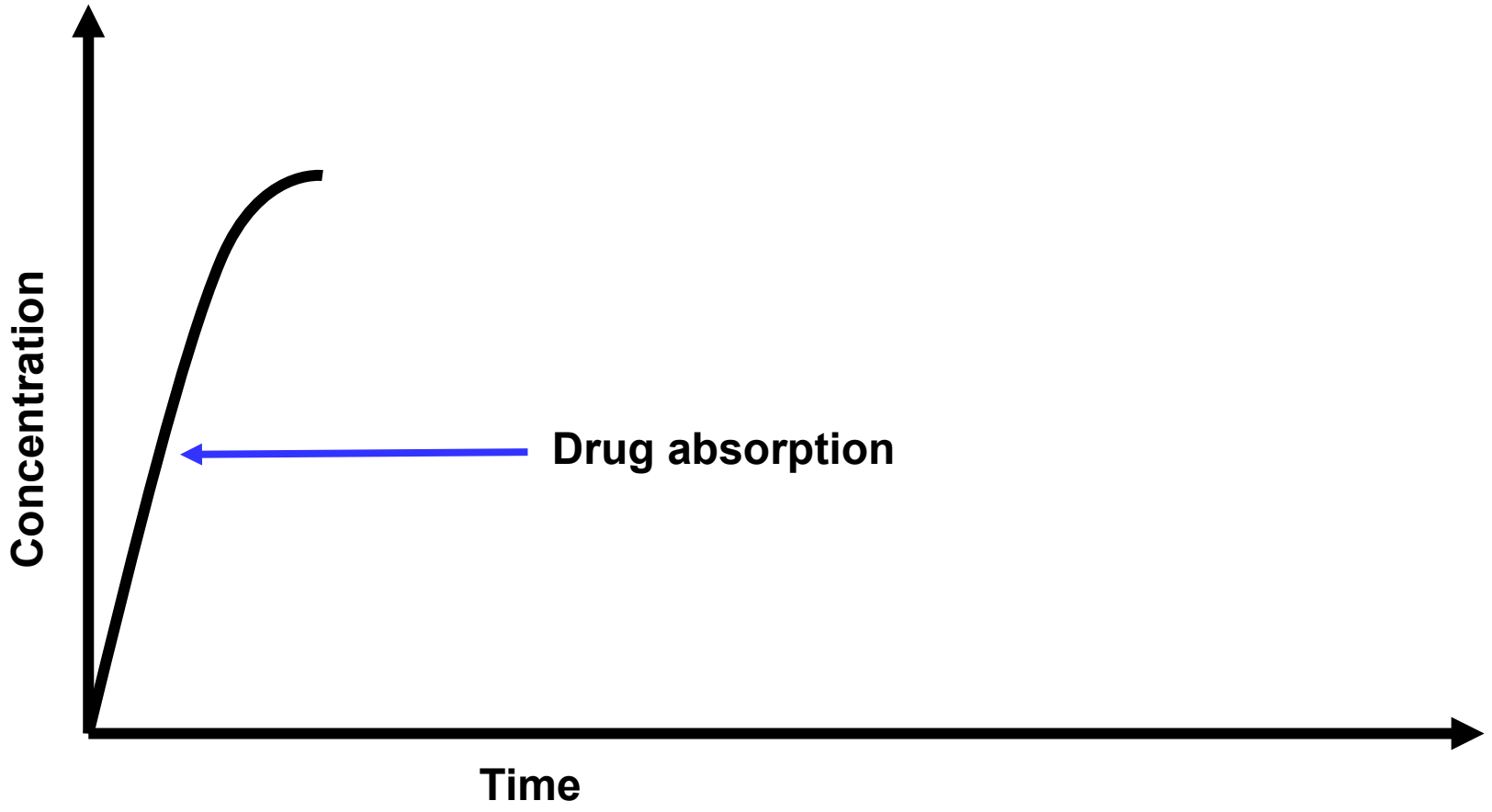

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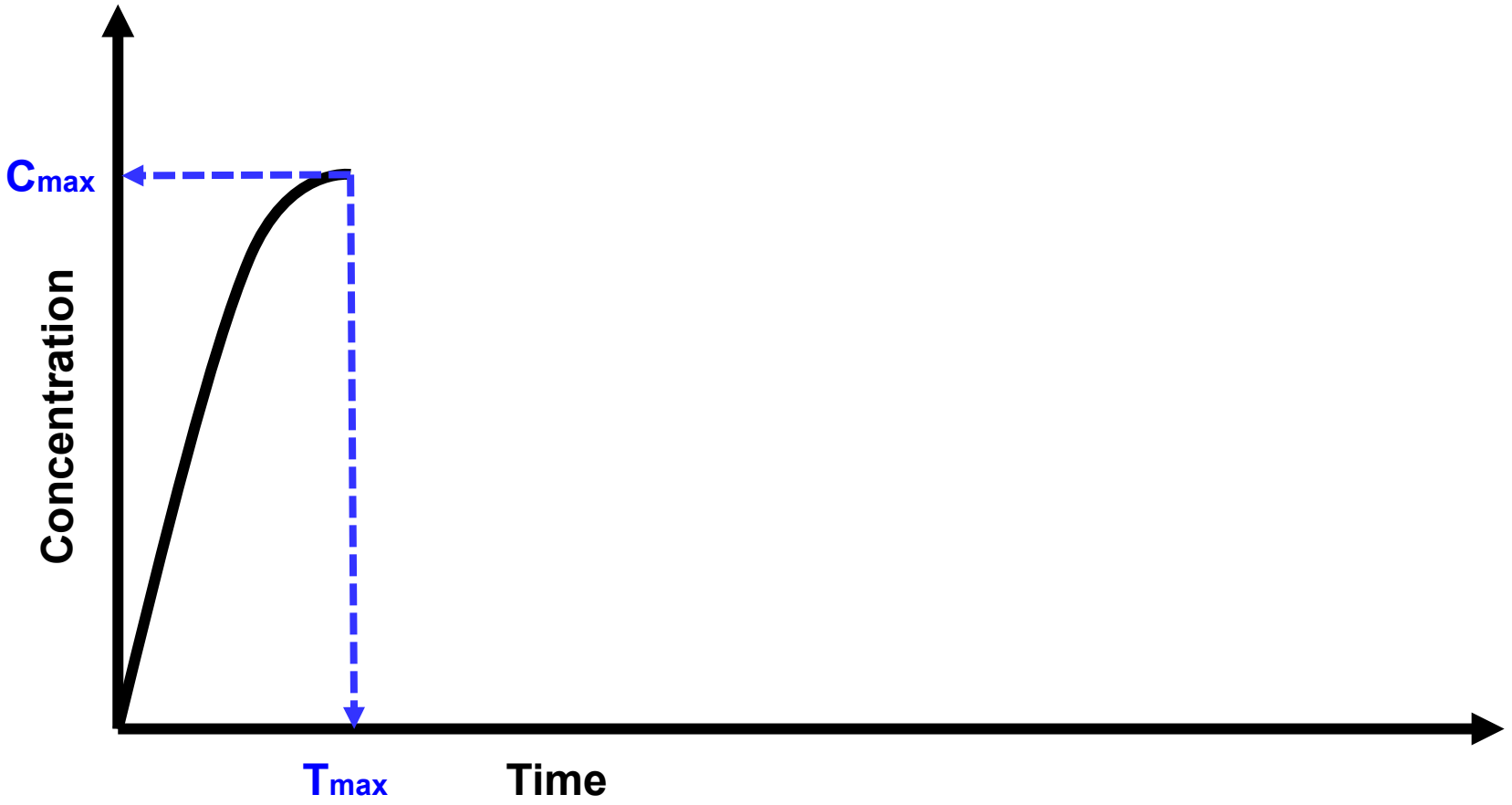

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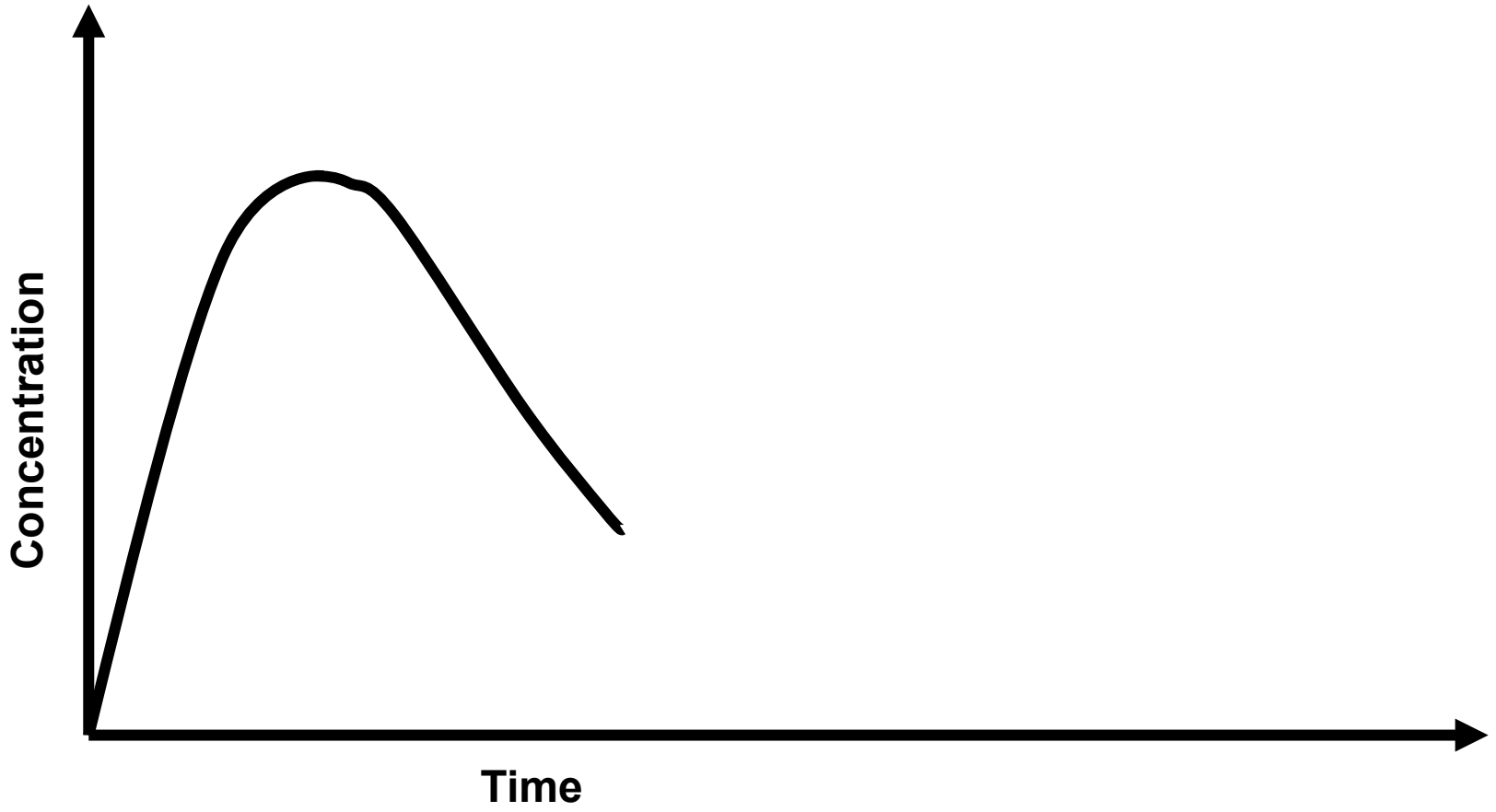

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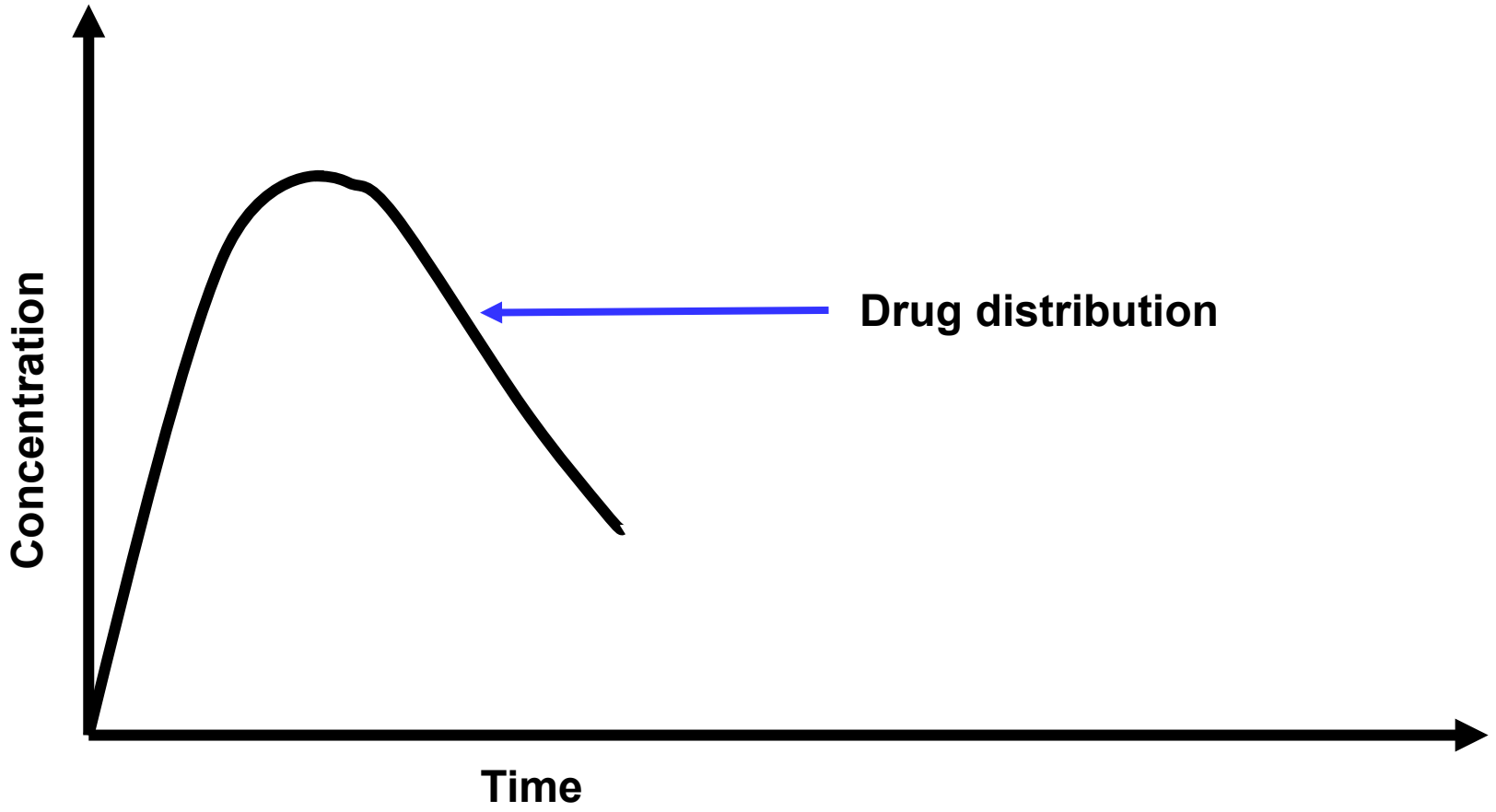

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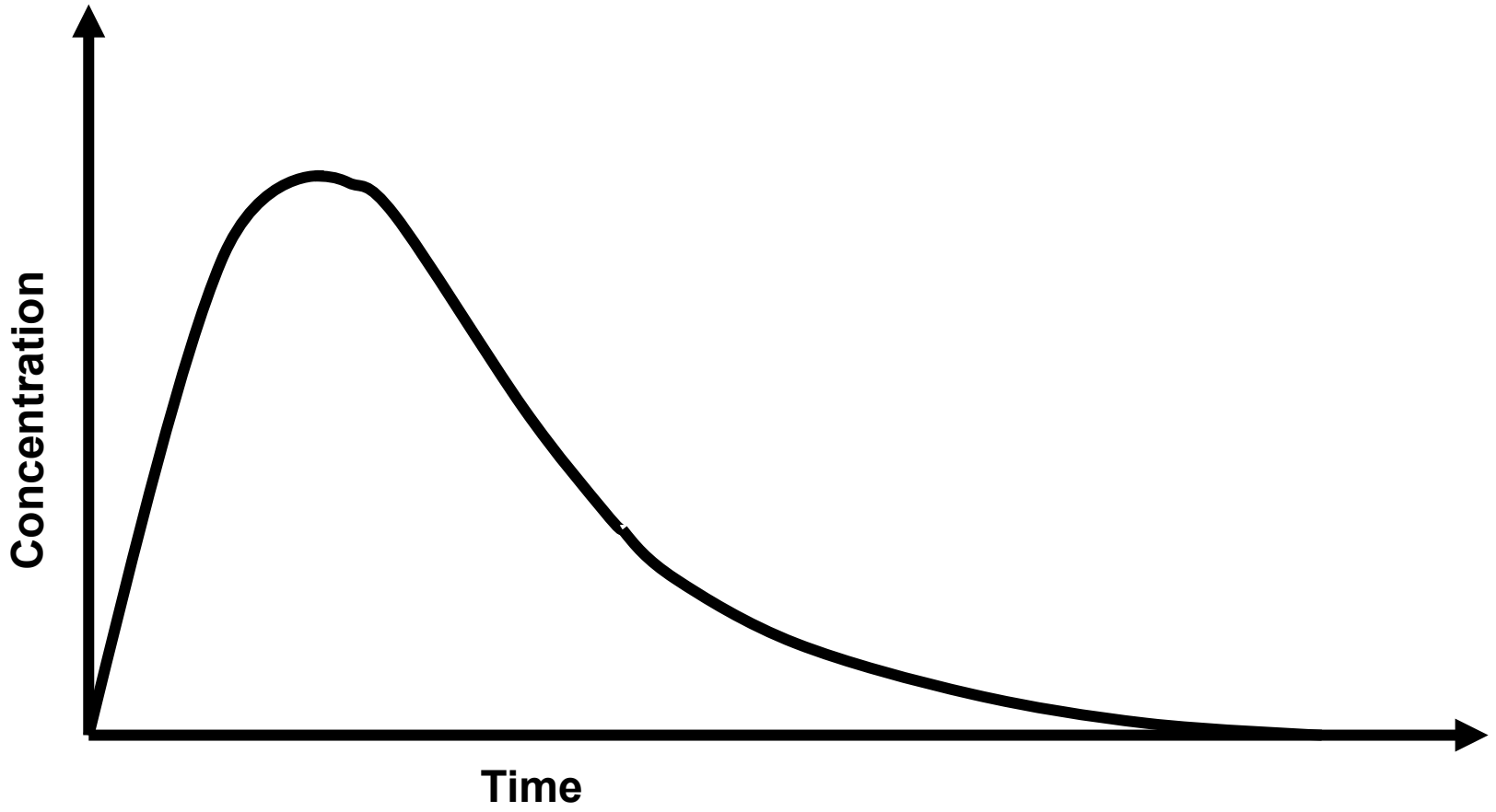

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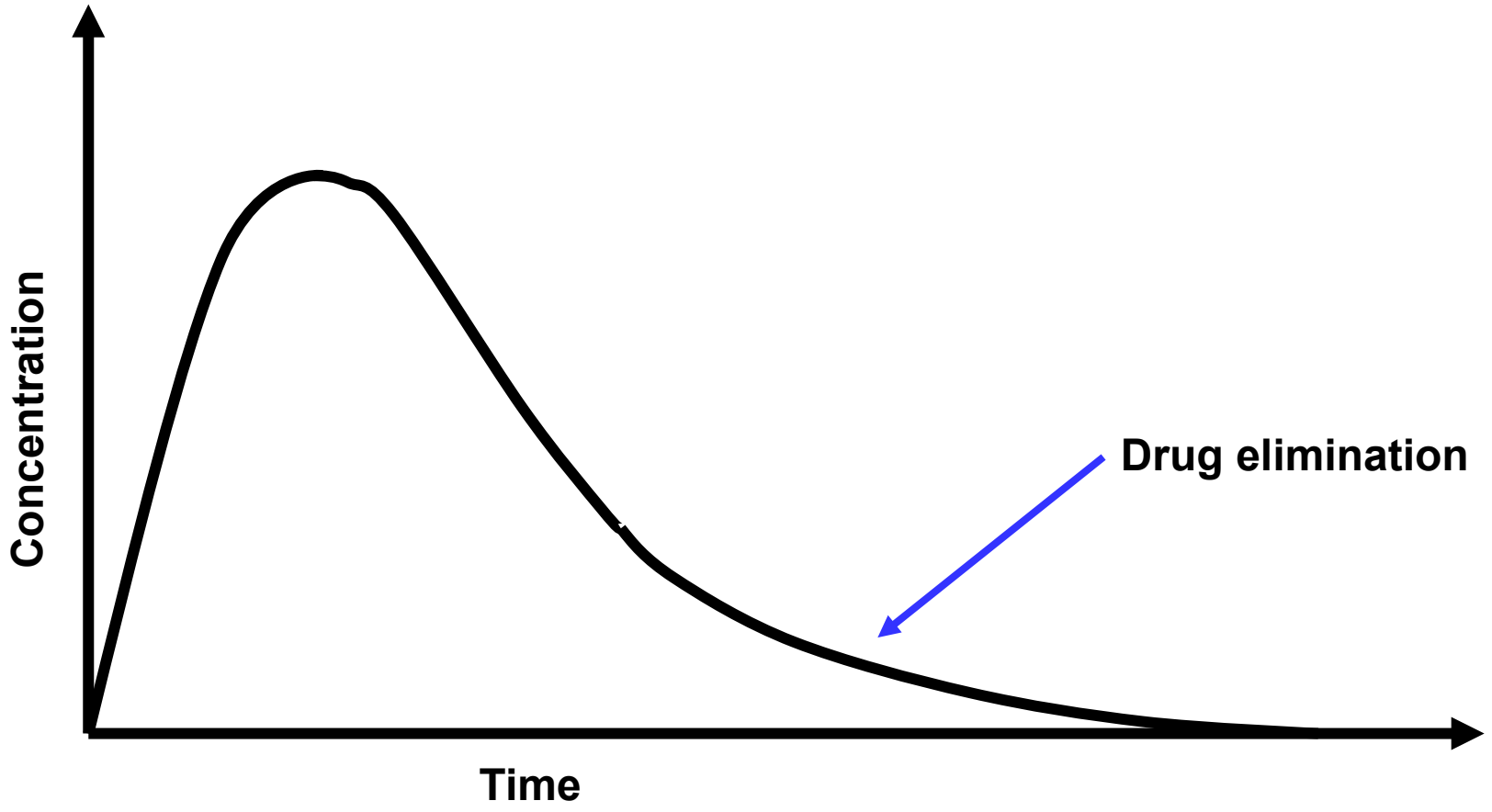

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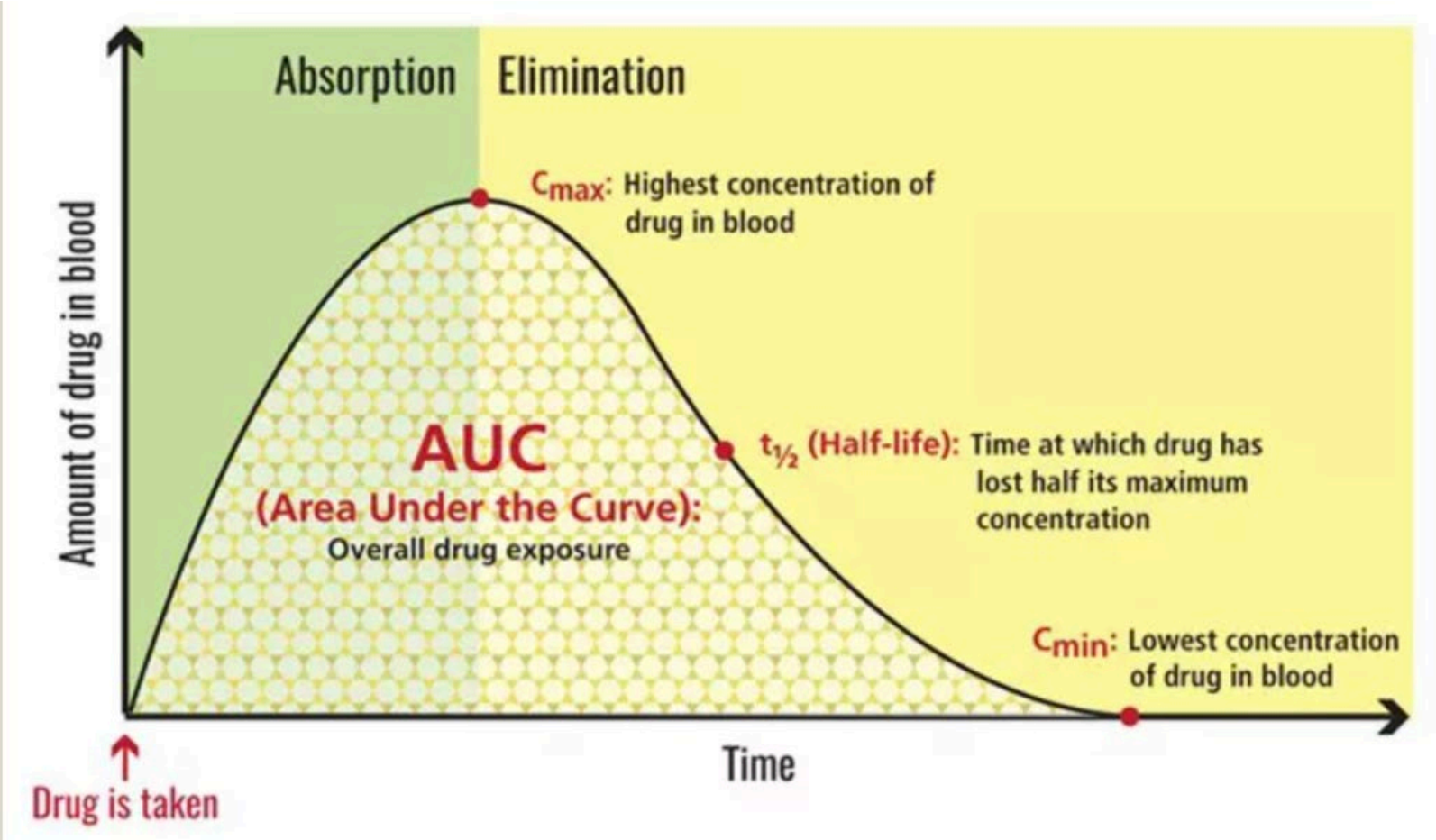


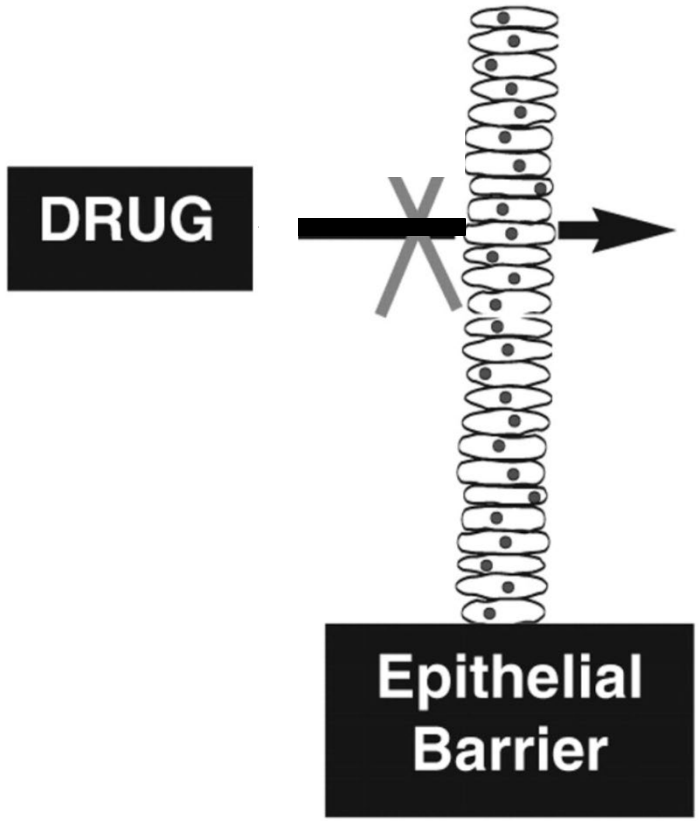

https://drgermophile.com/2020/06/26/pharmacokinetics-and-vancomycin/

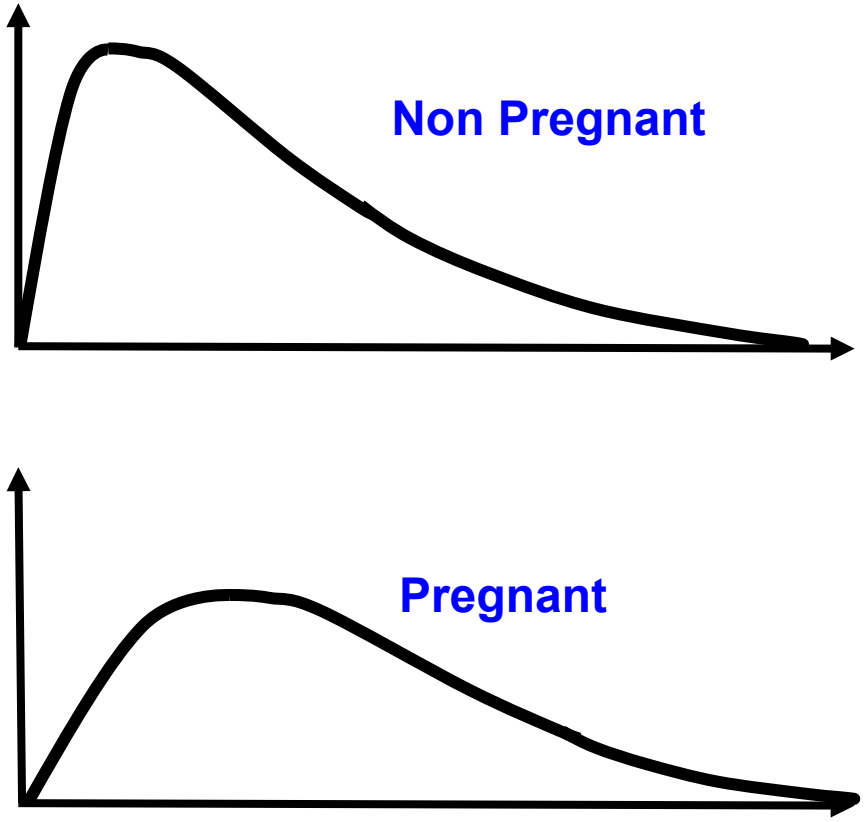
# PK parameters with greatest influence on pregnancy

- 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



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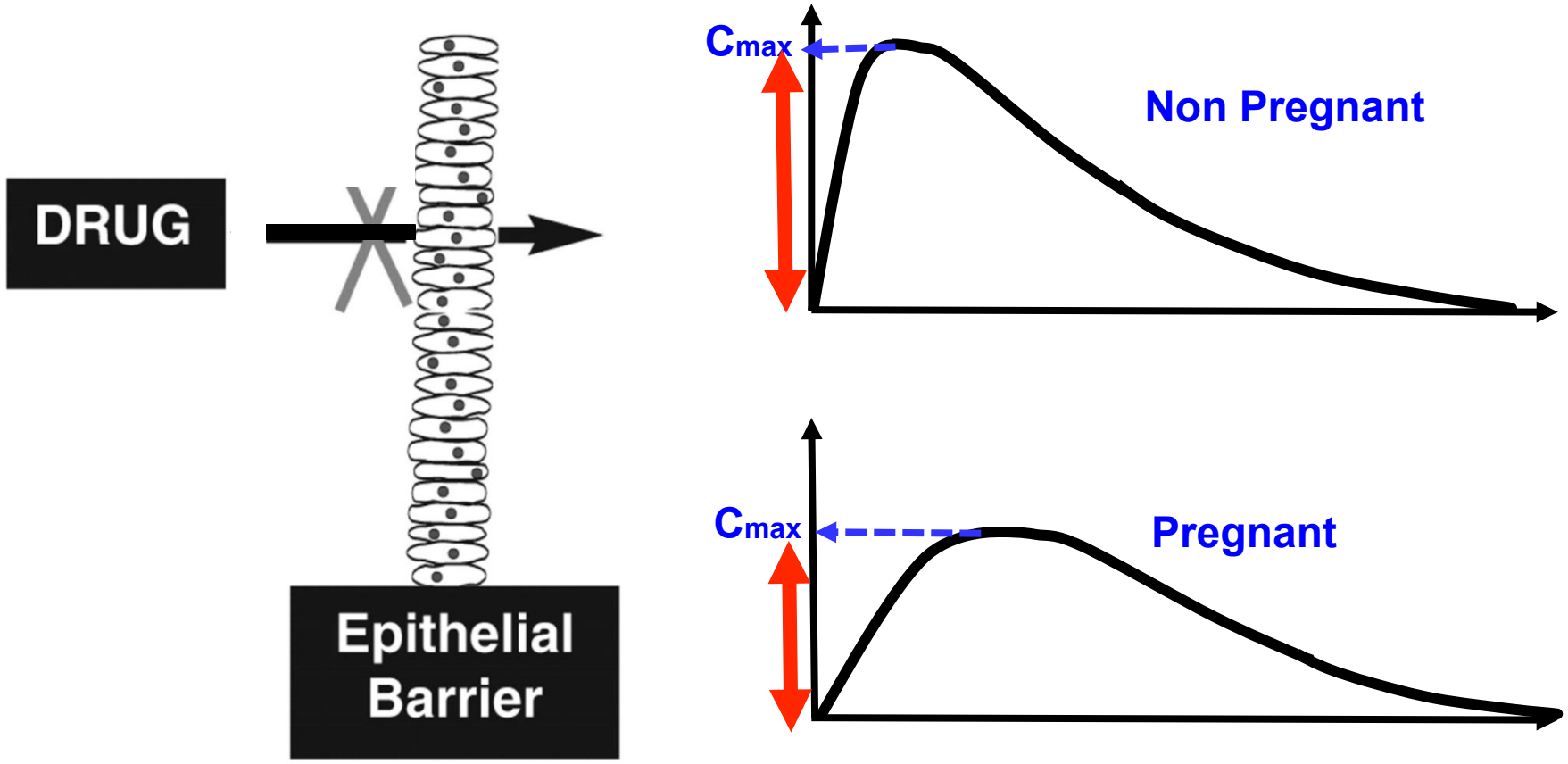

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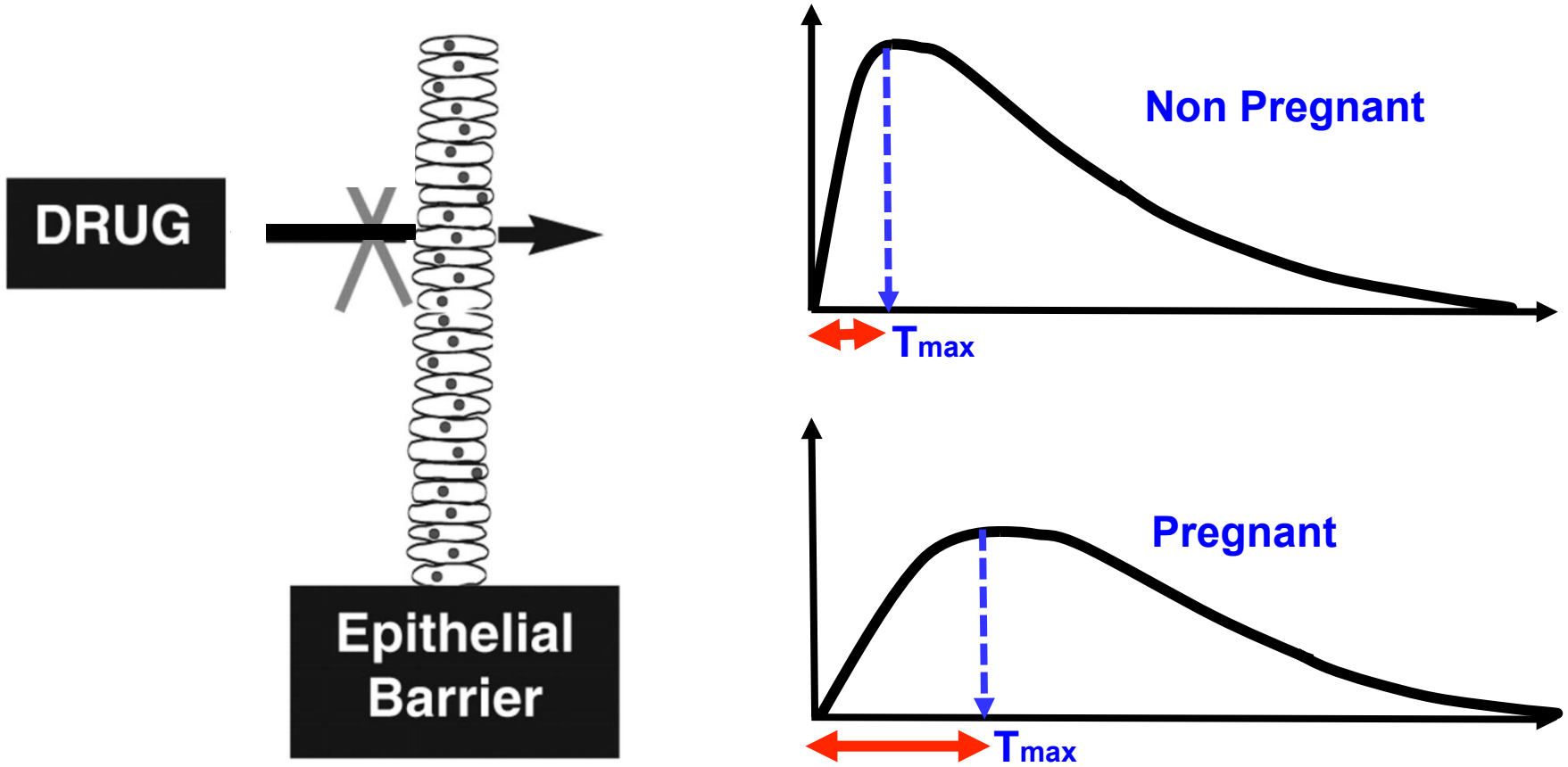

# Changes in GI transporter activity affecting drug absorption in pregnancy

| 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

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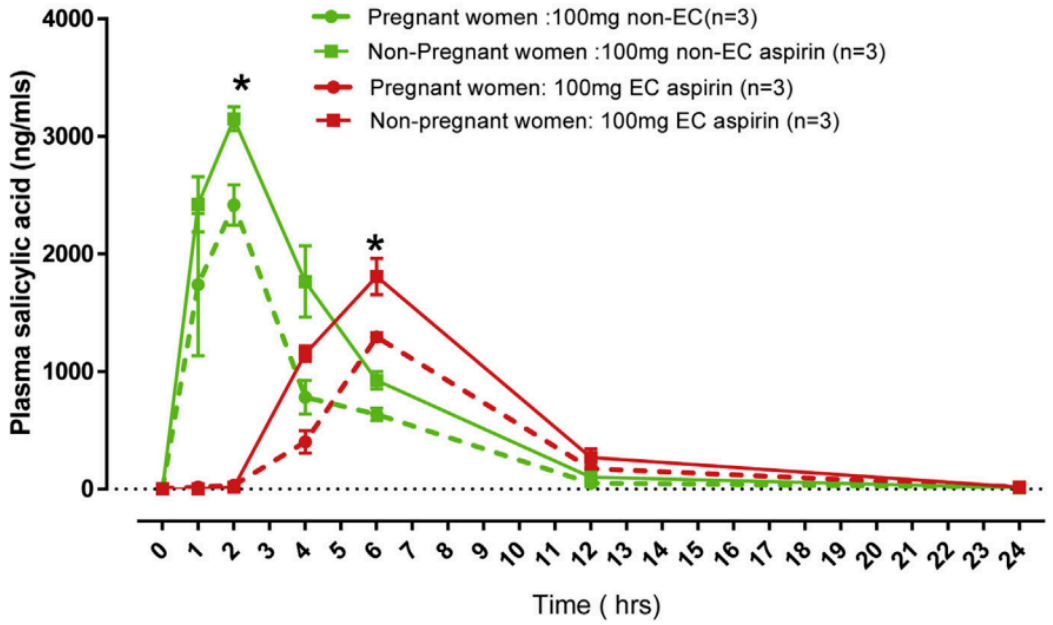
Original Research ajog.org

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.

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Original Research ajog.org

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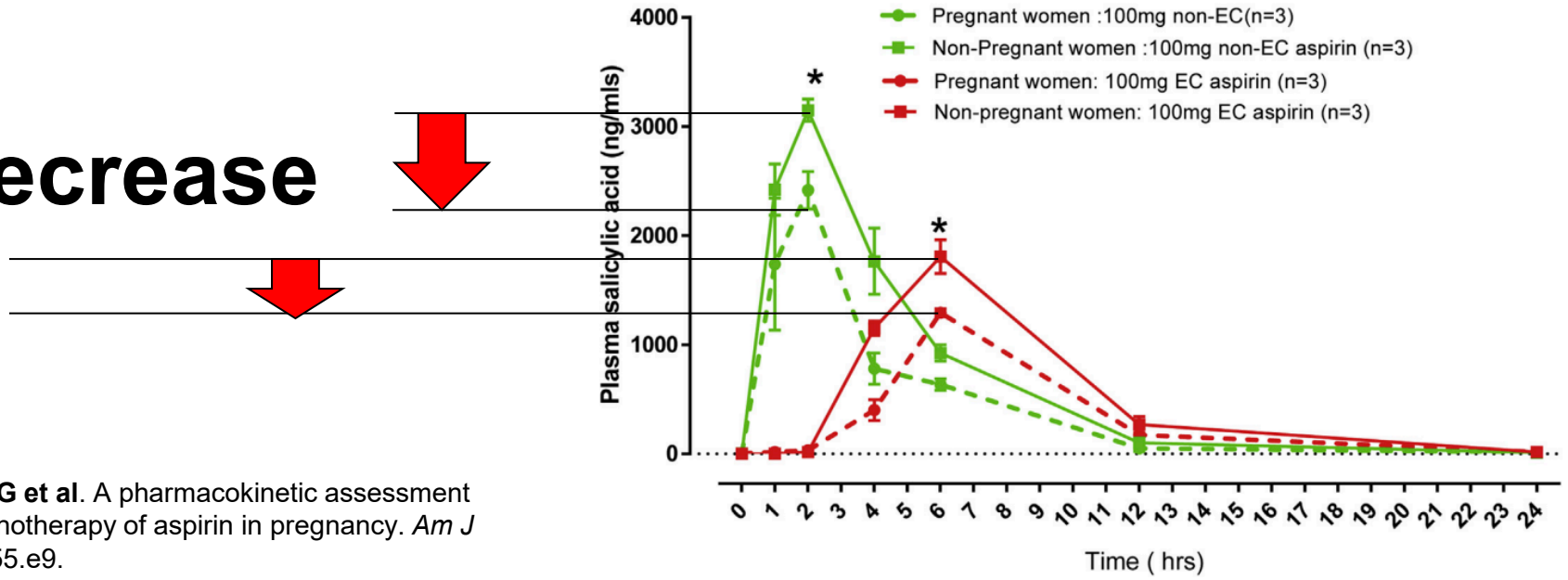
**29% decrease**

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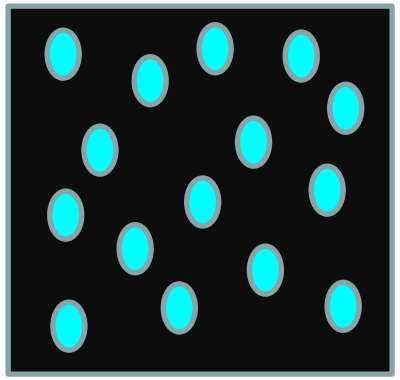
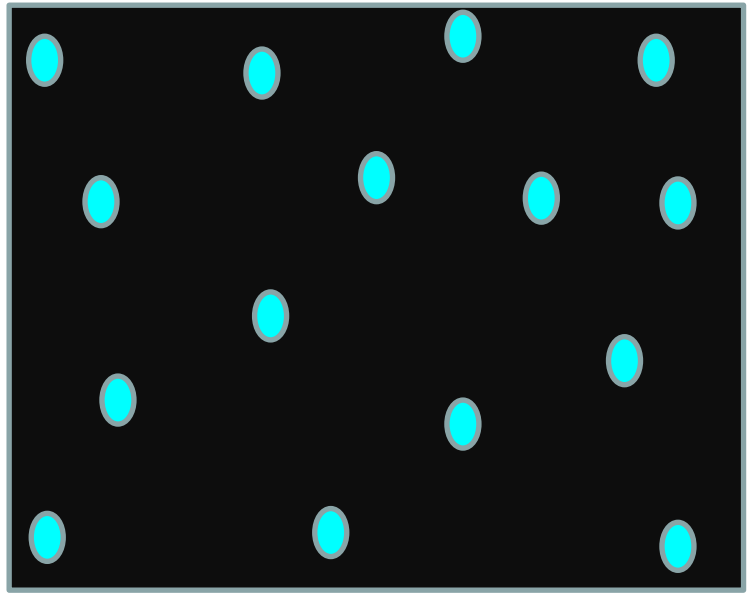
# Drug Distribution

# Volume of distribution



Non-pregnant

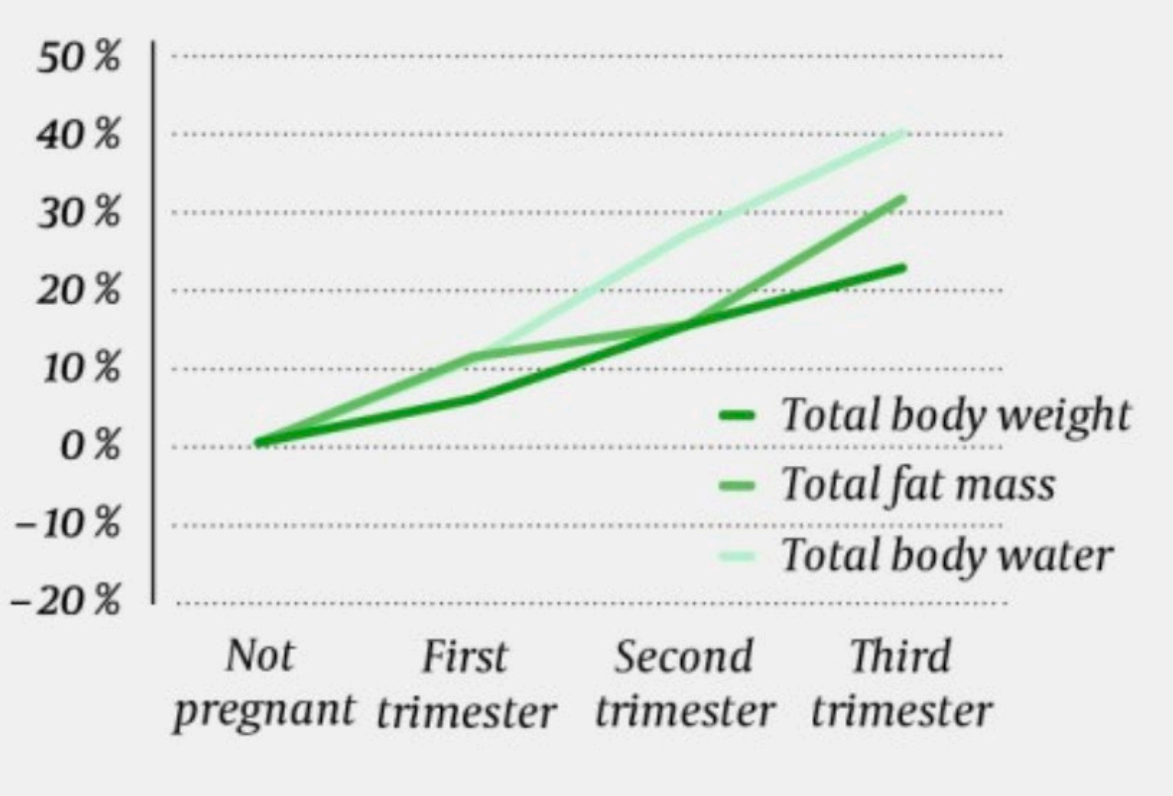


Pregnant

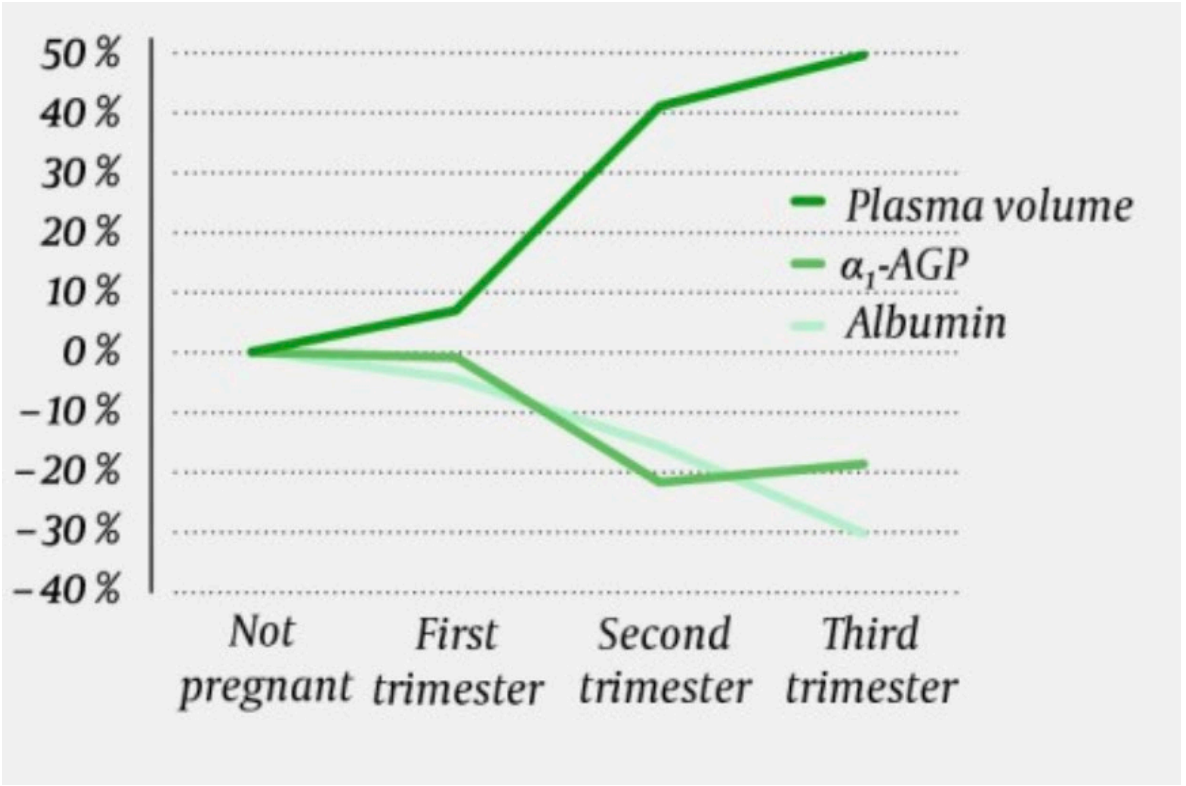
**Same amount of drug -> Increased volume of distribution**

***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

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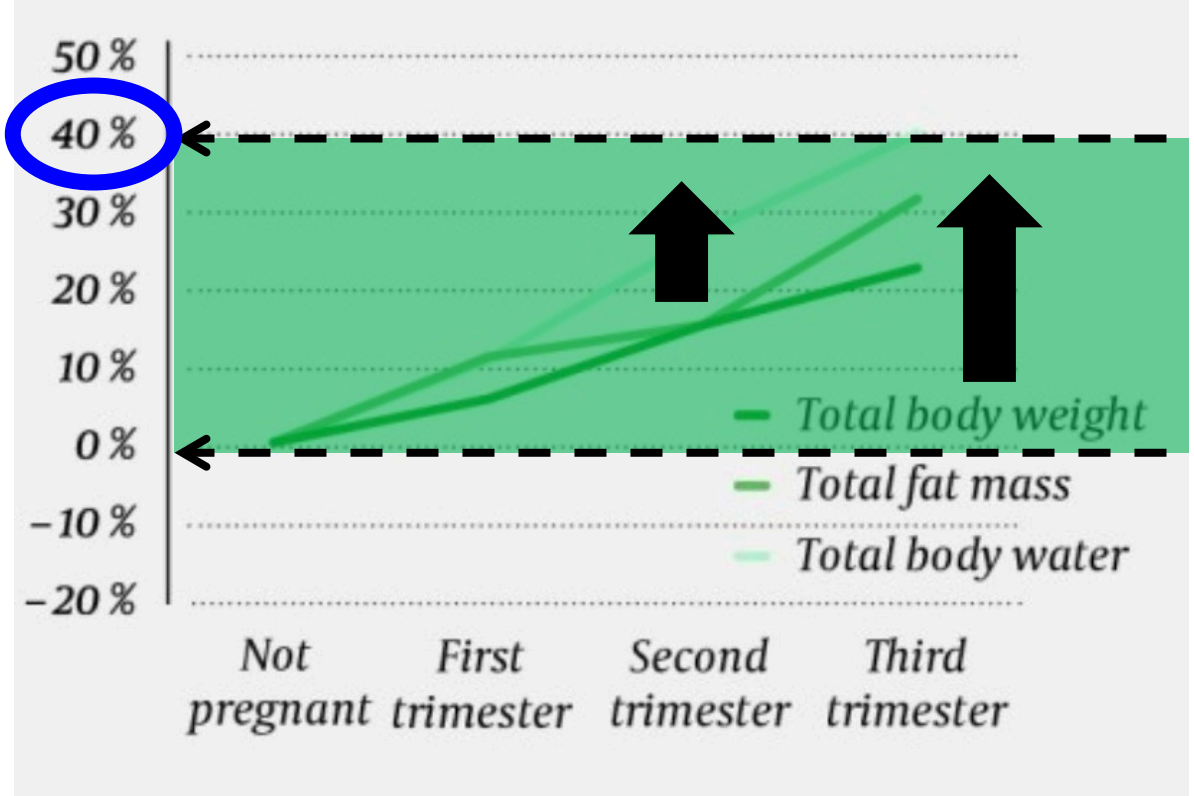


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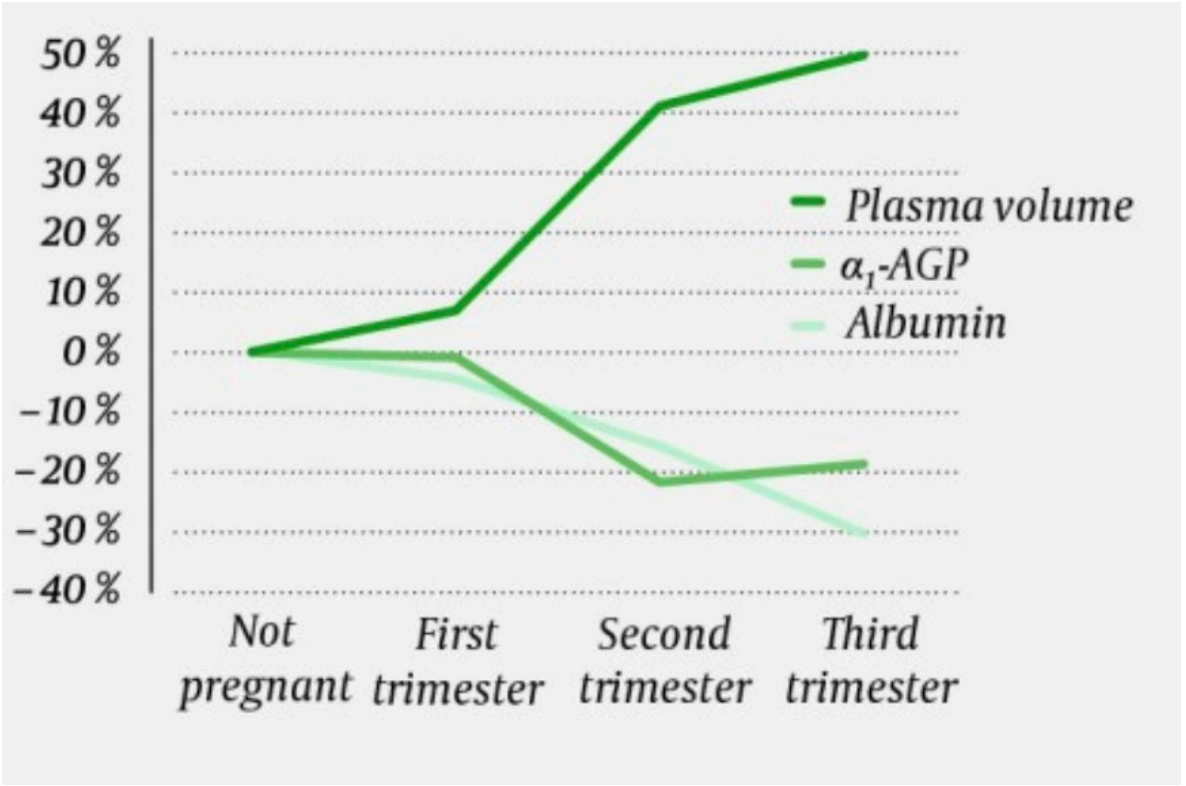


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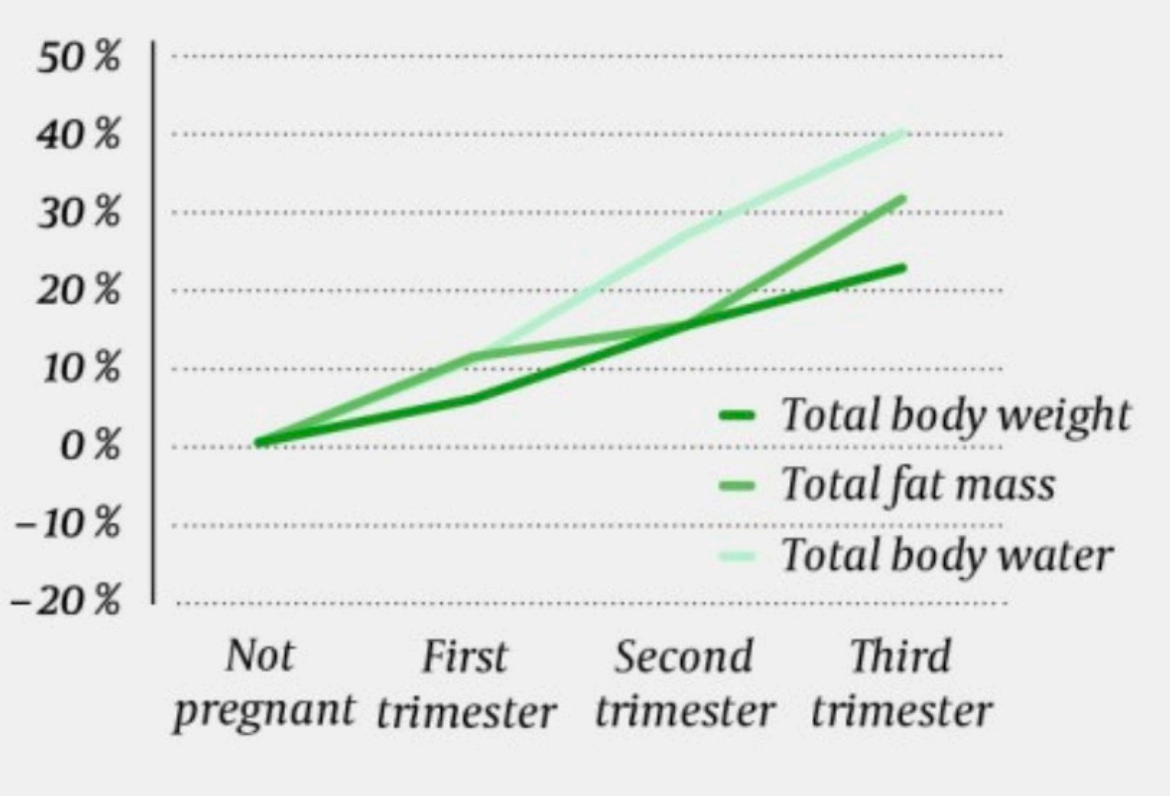


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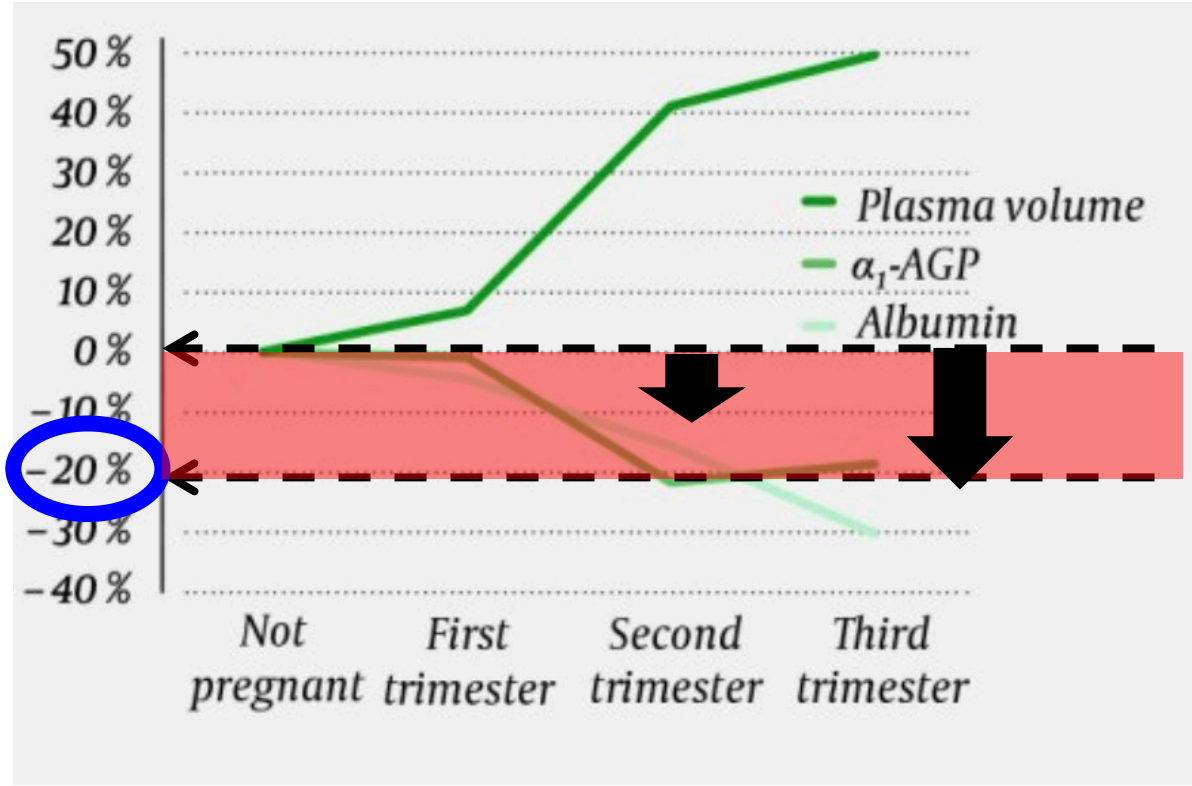


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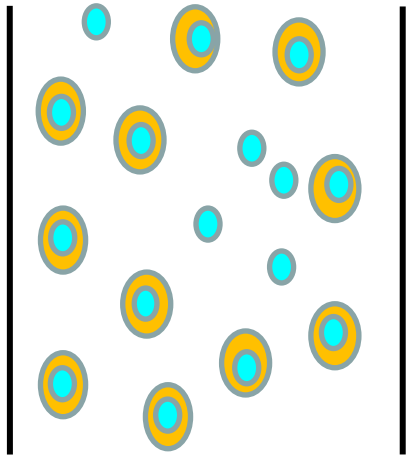
# Changes in Protein Binding

= protein

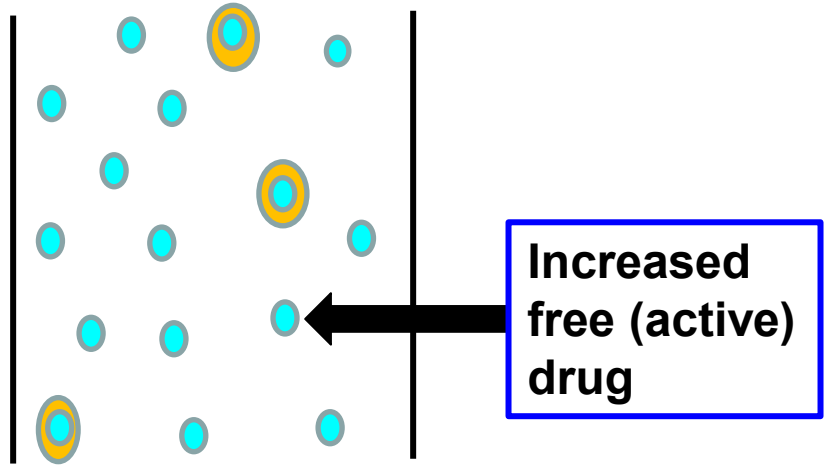
= drug

**More Protein Binding**



**Non Pregnant**

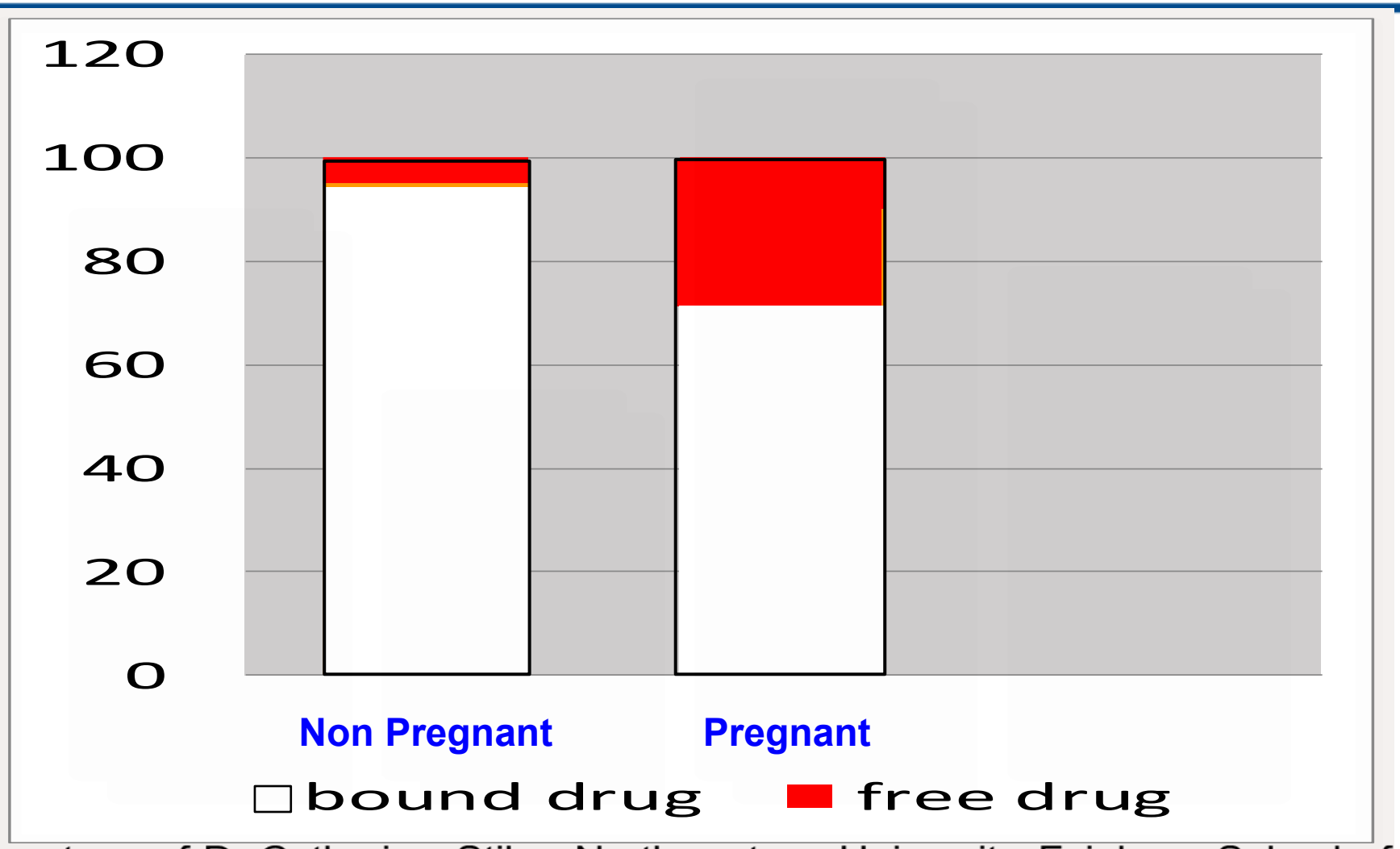
**Less Protein Binding**




**Pregnant**

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

# Changes in Protein Binding

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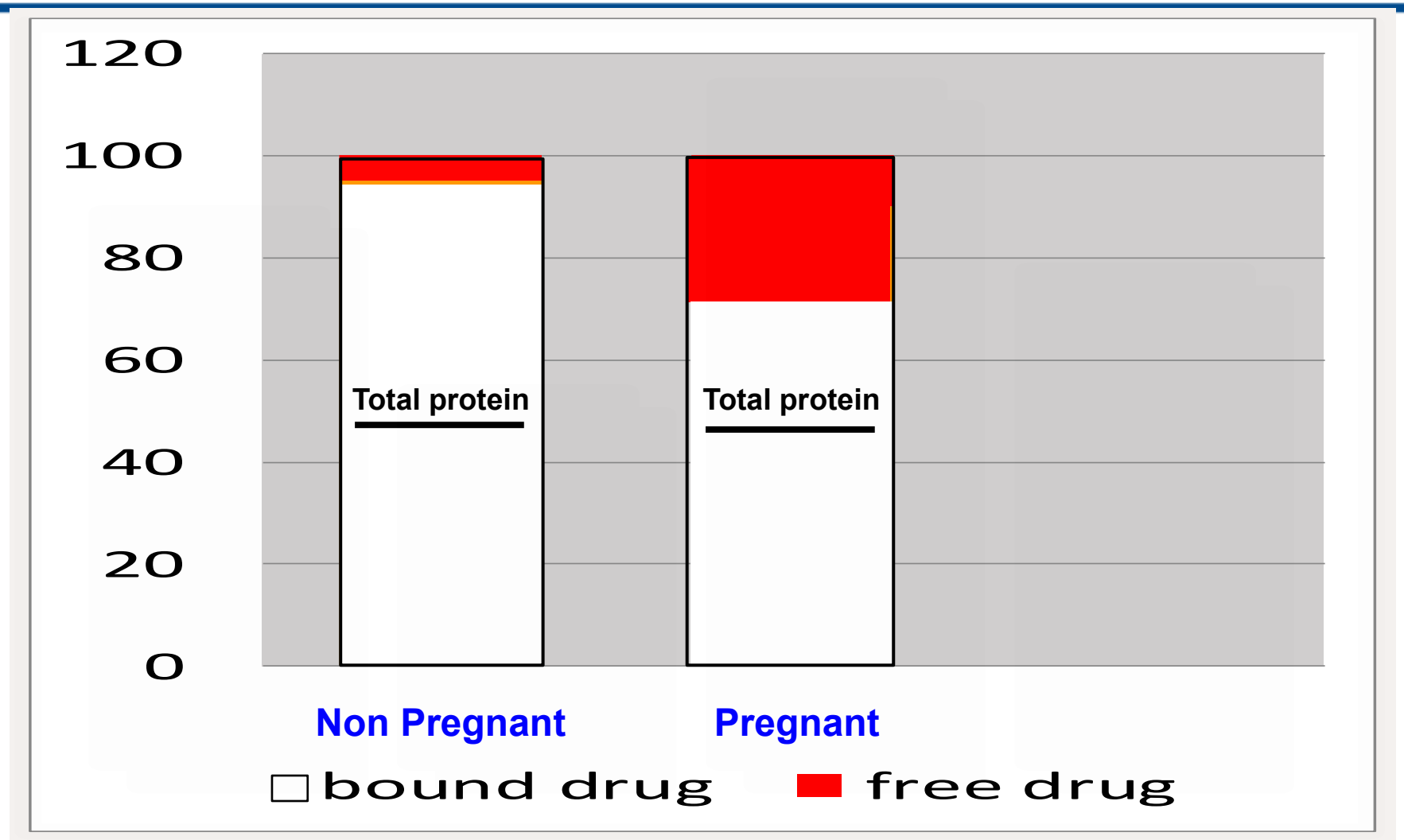


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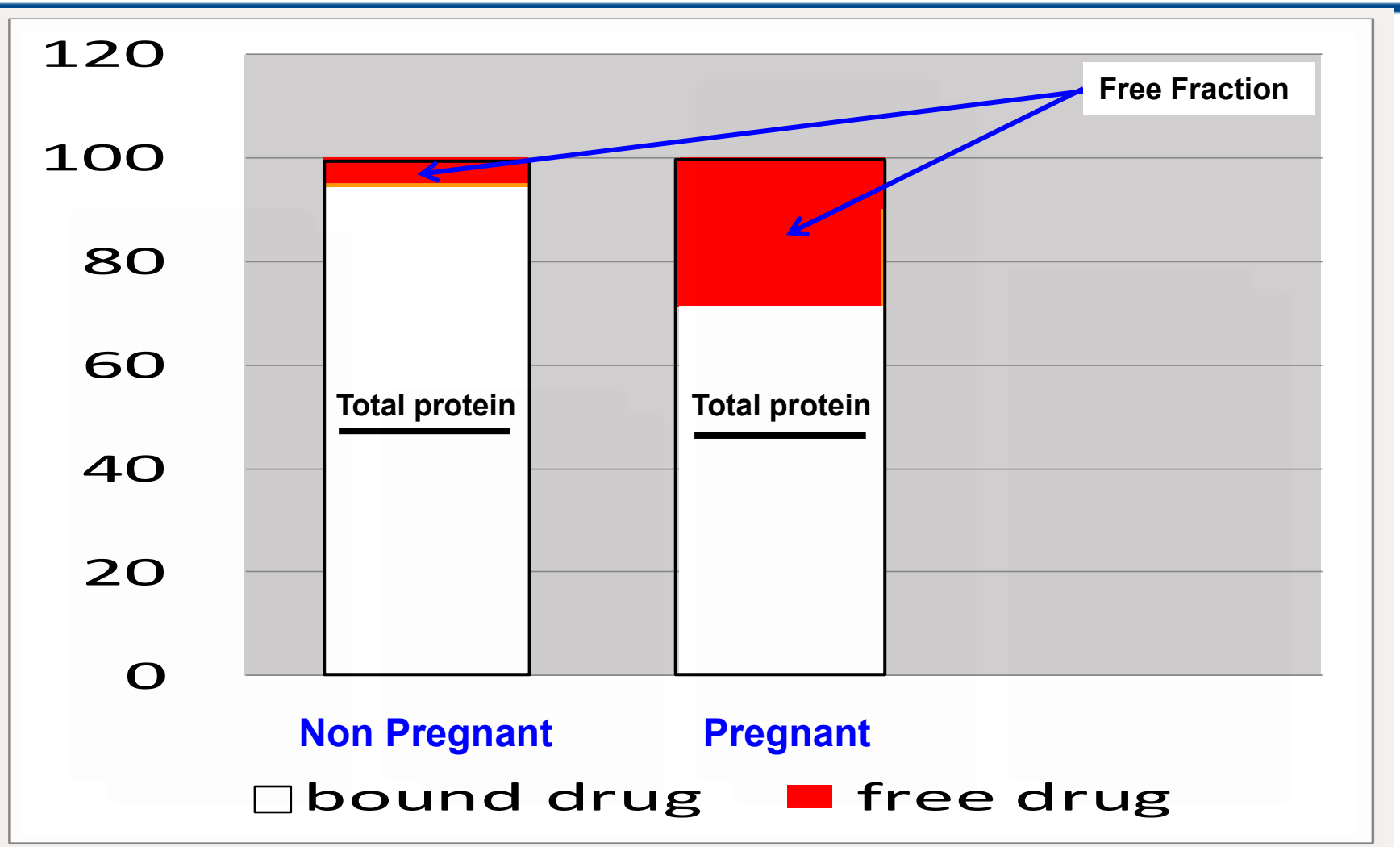


***Slide courtesy of Dr Catherine Stika, Northwestern University Feinberg School of Medicine

# 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

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# 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 |

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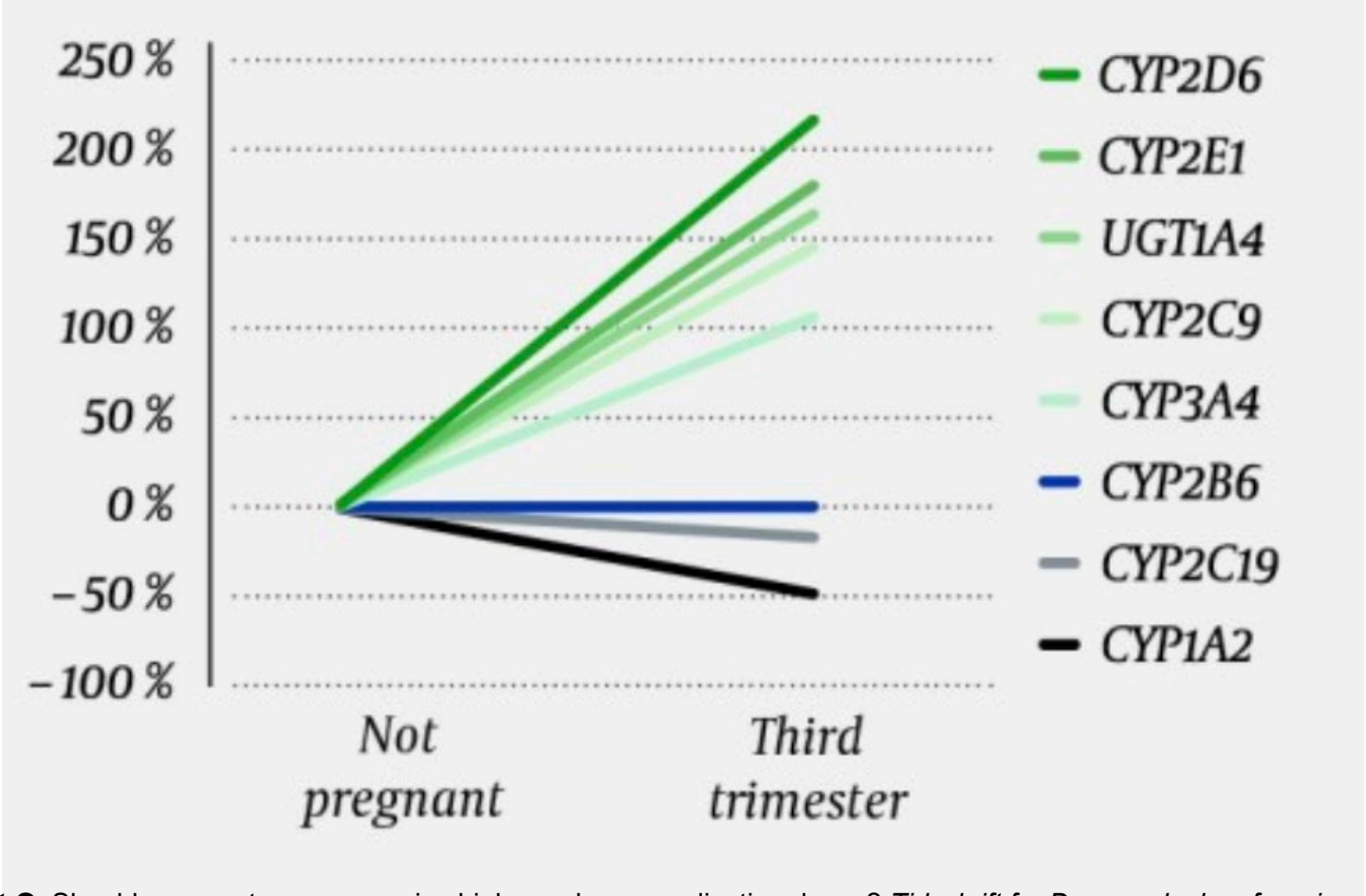
# Drug Metabolism

# 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

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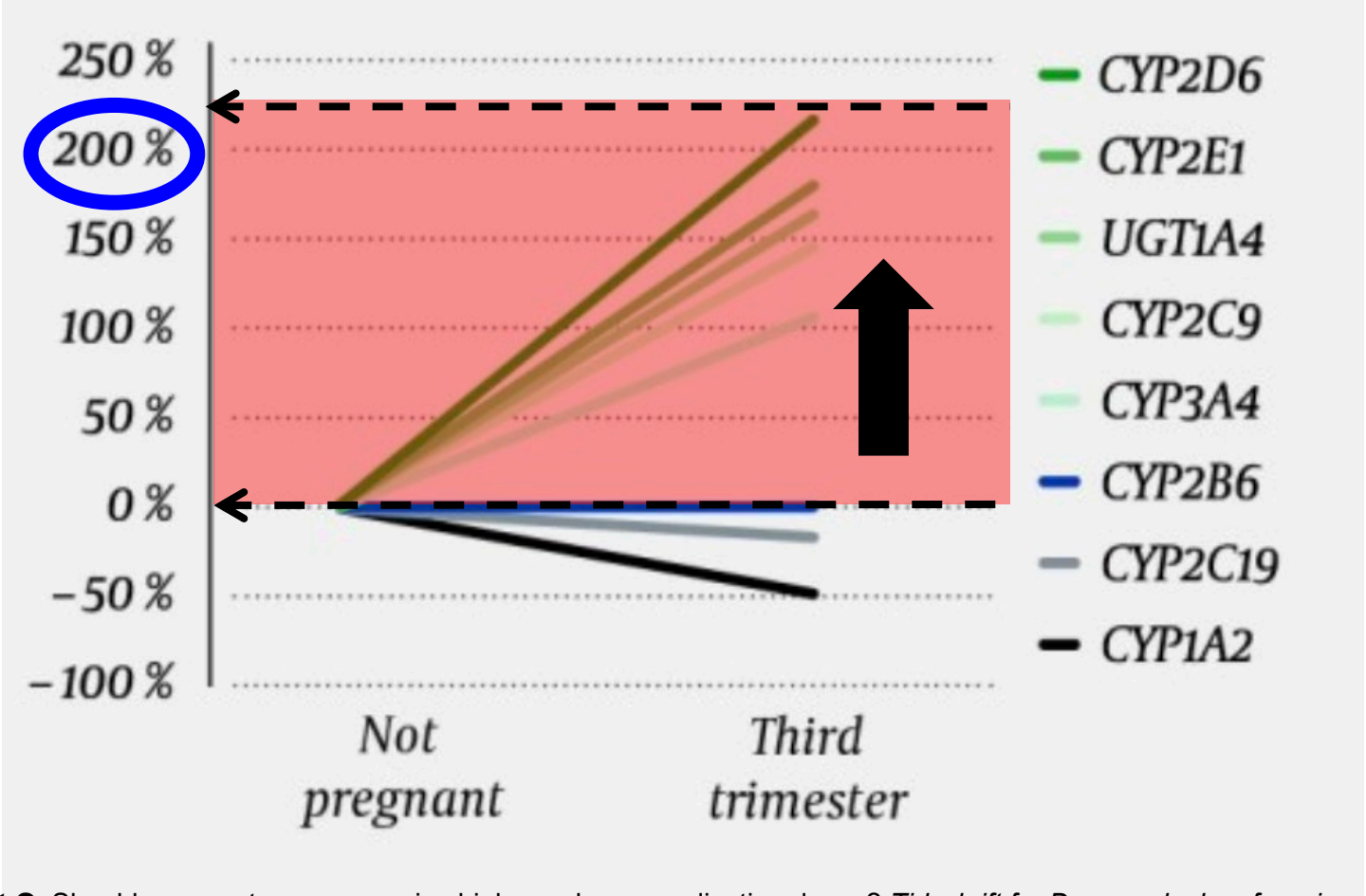


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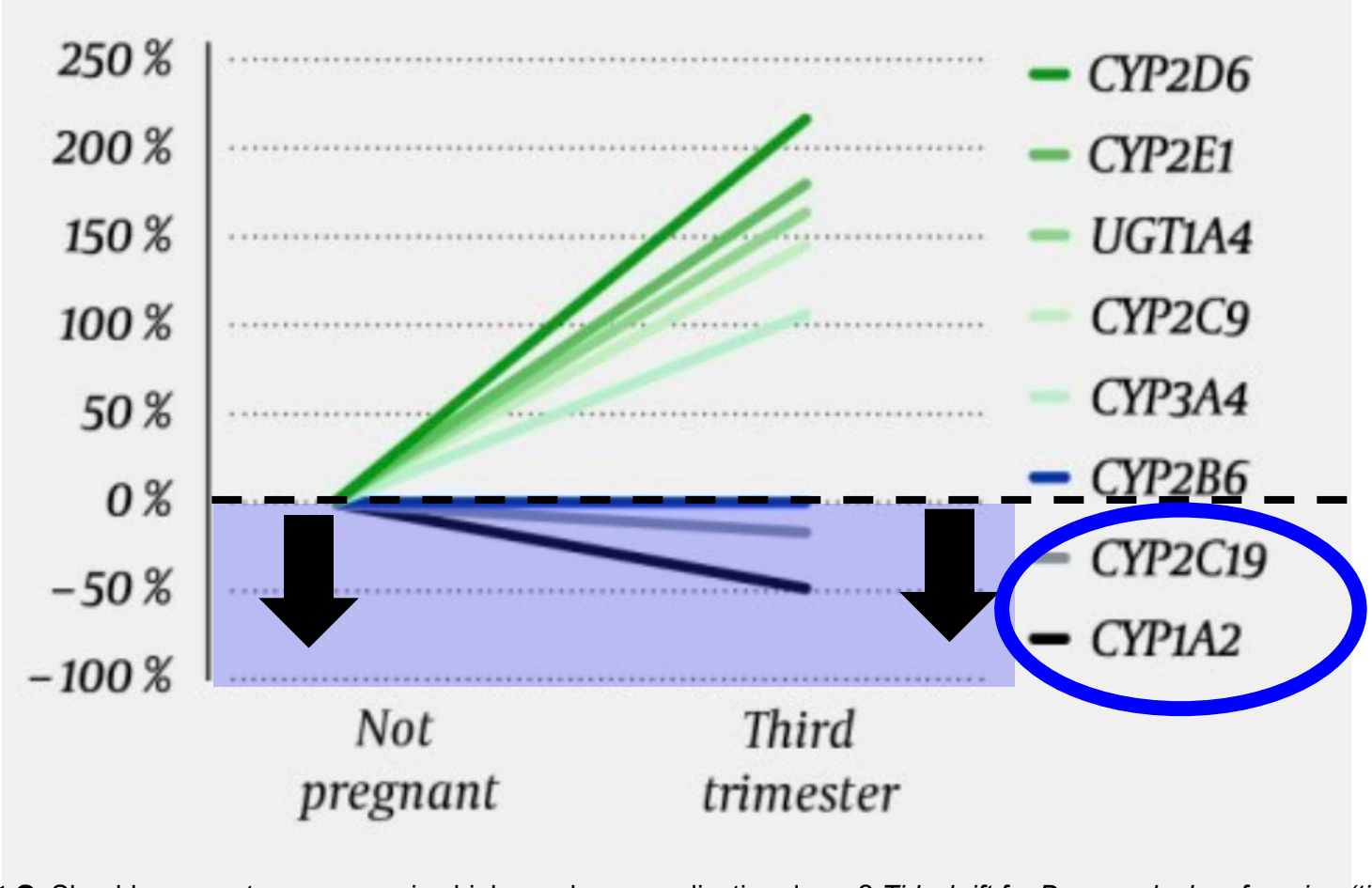


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# Metabolism – Change in liver enzyme activity

| 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

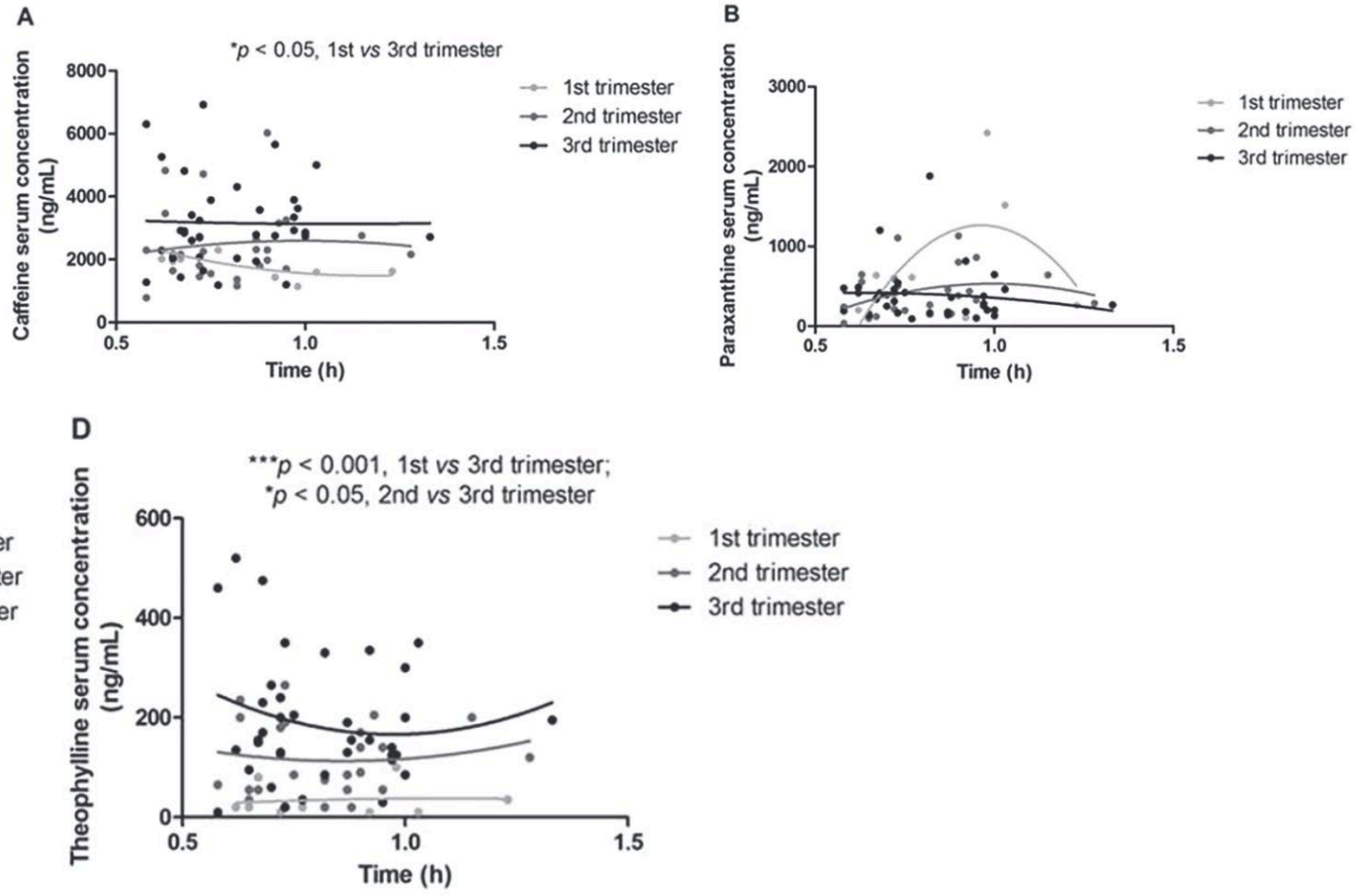
ACCP

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**

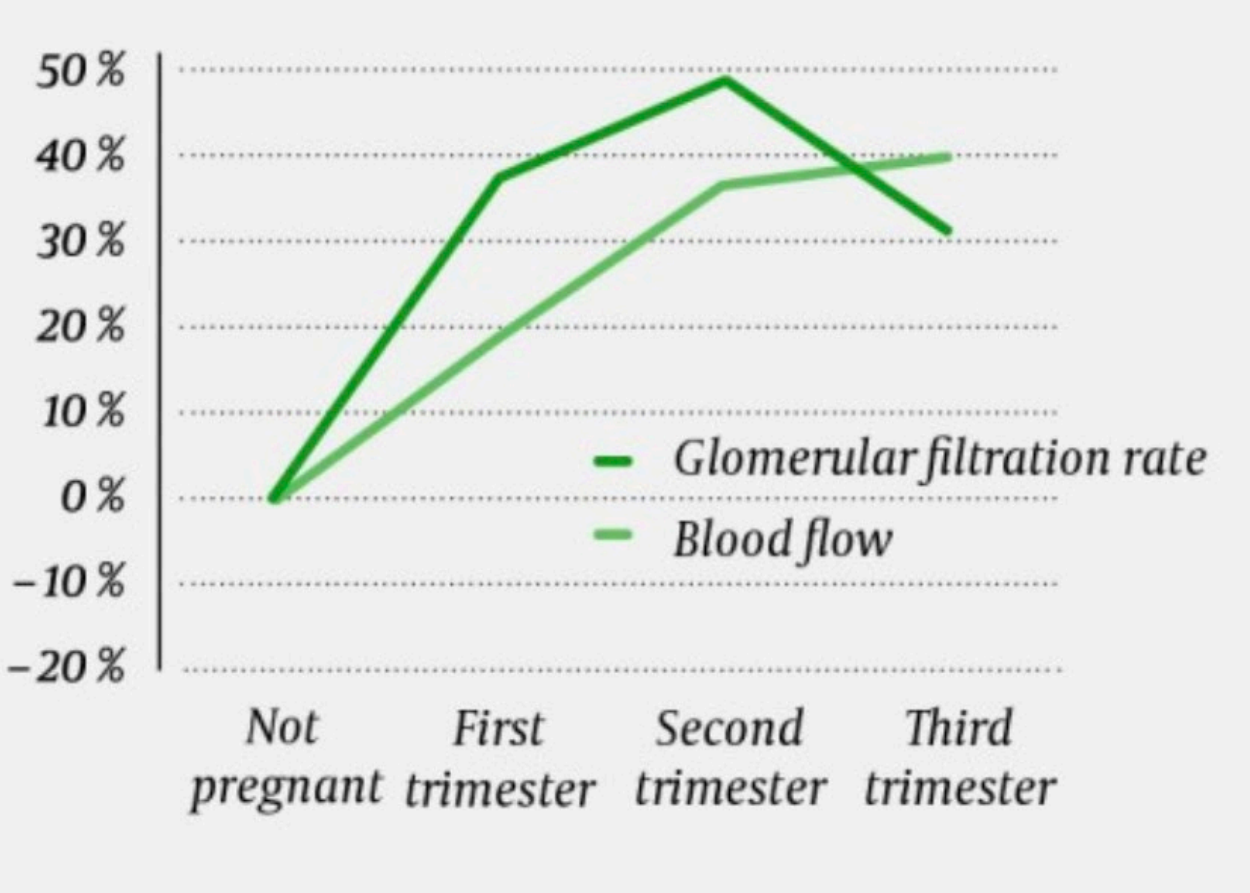
Tian Yu, PhD[1], Sarah C. Campbell, PhD[1], Chris Stockmann, MSc[1], Casey Tak, MPH[2*], Katherine Schoen[1], Erin A. S. Clark, MD[3], Michael W. Varner, MD[3,4], Michael G. Spigarelli, MD, PhD, FCP[1,2], and Catherine M. T. Sherwin, PhD, FCP[1,2]




**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

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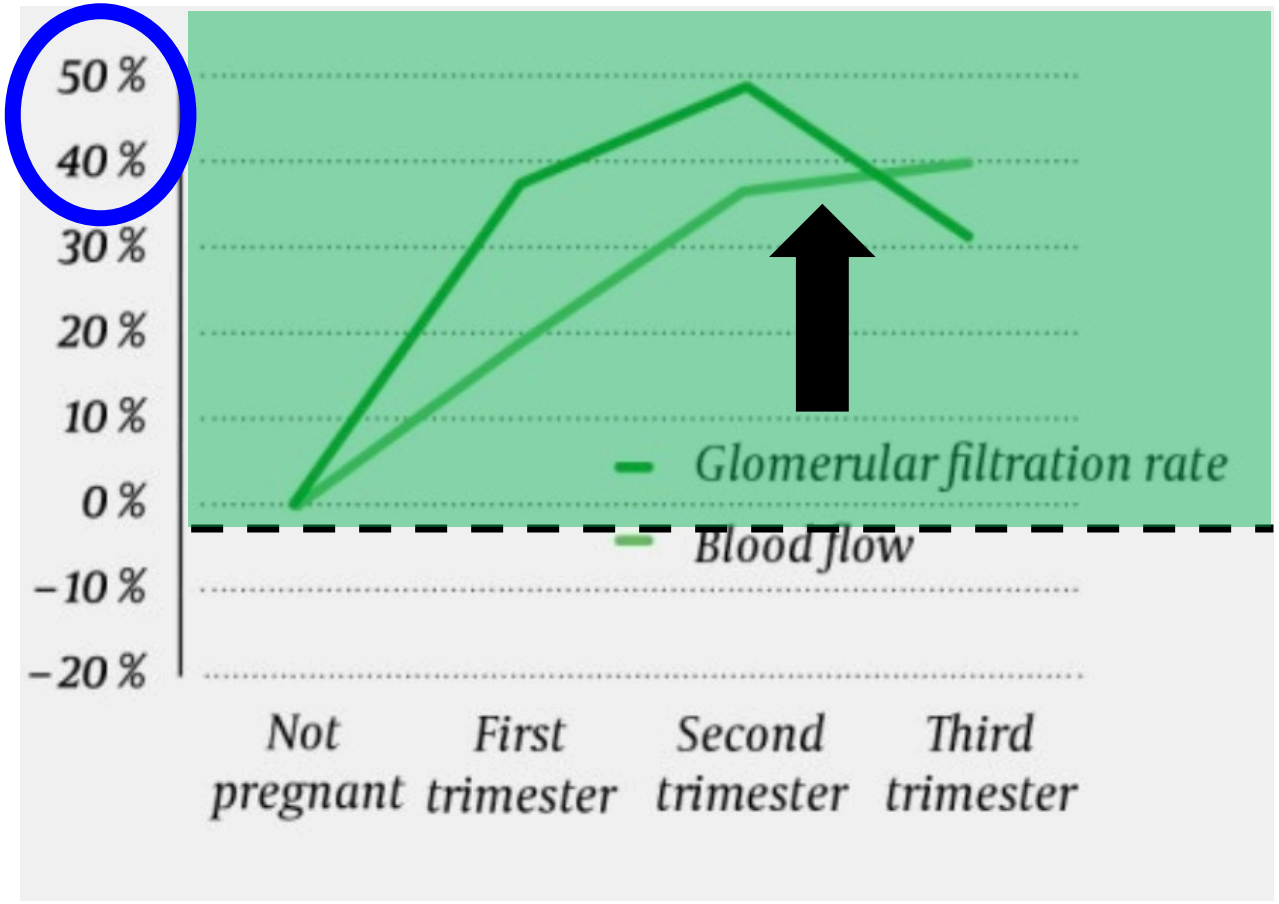
# Elimination – Changes in renal function

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# 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

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| | | | | Second trimester ($n$ = 7) versus postpartum ($n$ = 6) | Third trimester ($n$ = 6) versus postpartum ($n$ = 6) |
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| 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 |
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| $C_{max}$ (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**

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**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**

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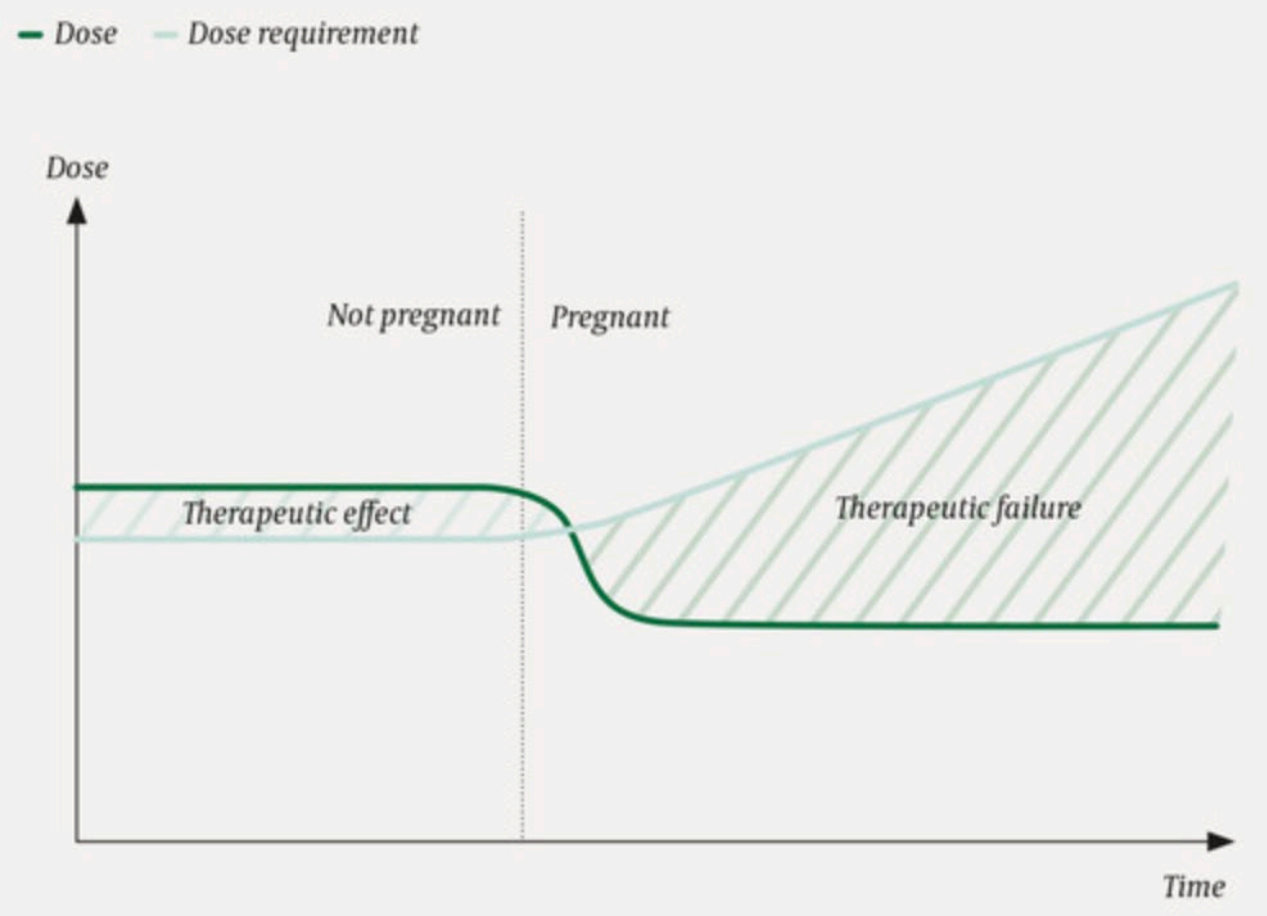
**Pharmacokinetics of darunavir and cobicistat in pregnant and postpartum women with HIV**

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**

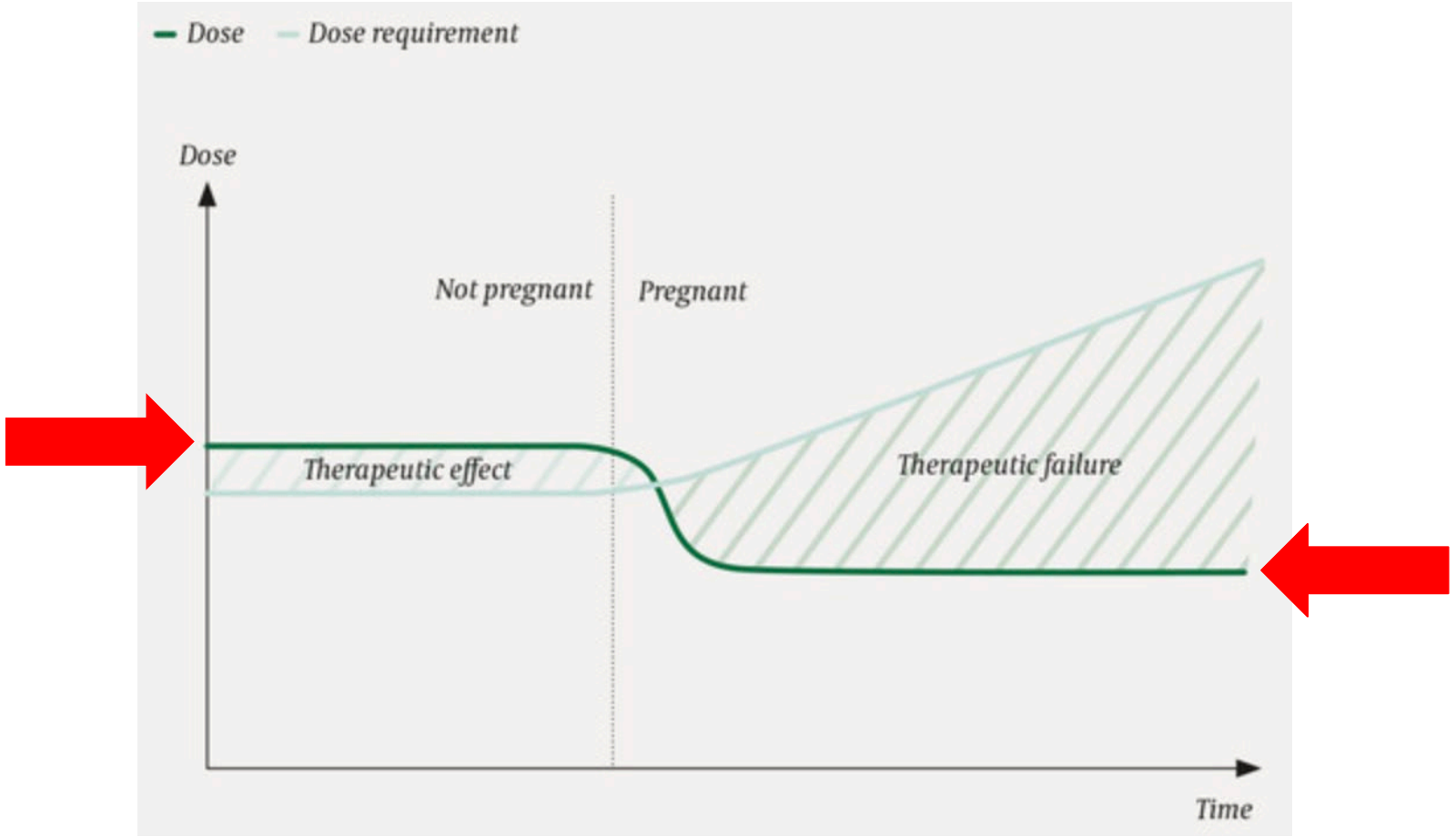
*Jeremiah D. Momper, PharmD, PhD,[a] Jiajia Wang, MS,[b] Alice Stek, MD,[c] David E. Shapiro, PhD,[b] Kathleen M. Powis, MD,[d] Mary E. Paul, MD,[e] Martina L. Badell, MD,[f] Renee Browning, RN, MSN,[g] Nahida Chakhtoura, MD,[h] Kayla Denson, PhD,[i] Kittipong Rungruengthanakit, MD,[j] Kathleen George, 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

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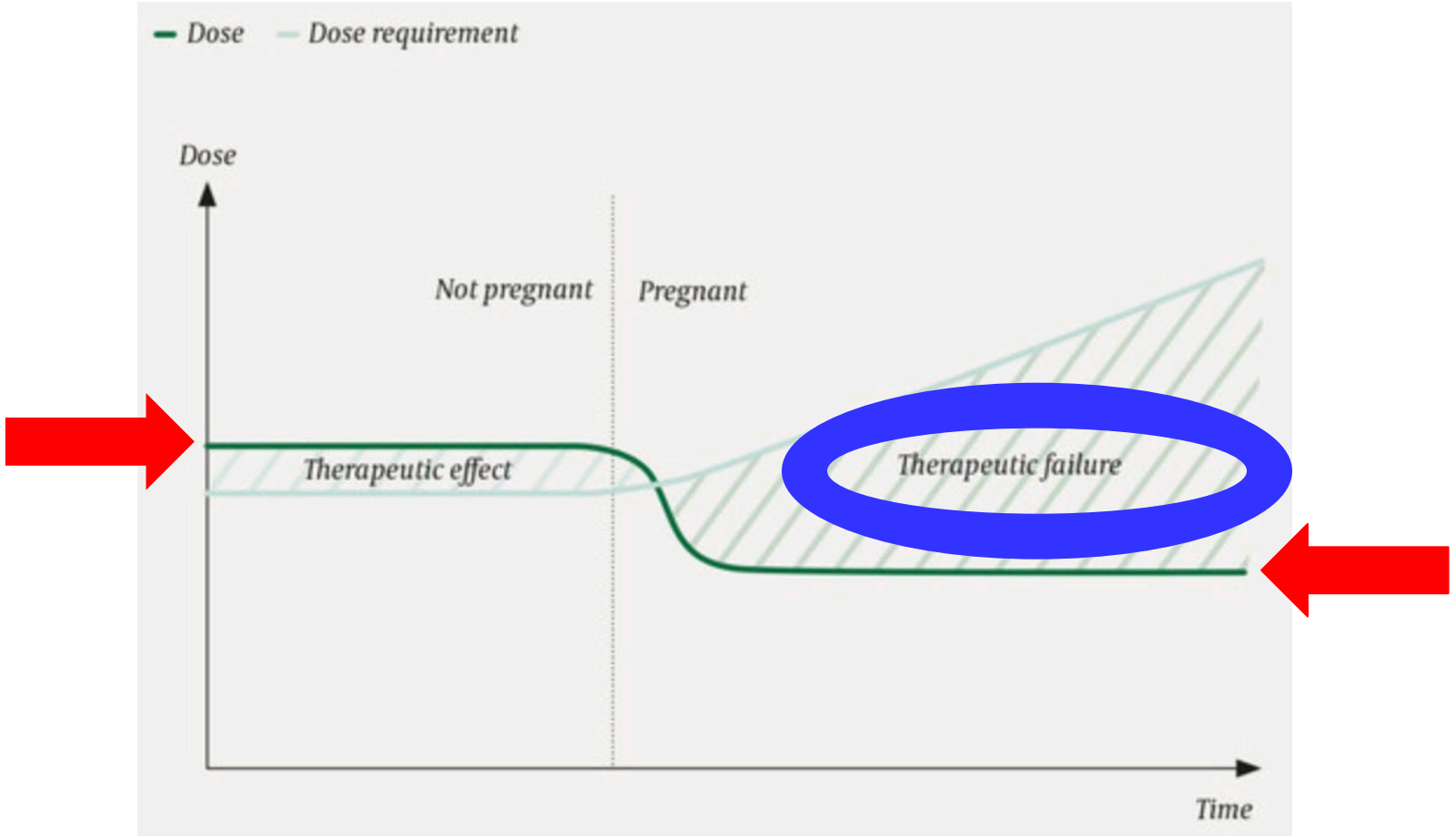
# Therapeutic failure during pregnancy

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# 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]**

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* 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

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| 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

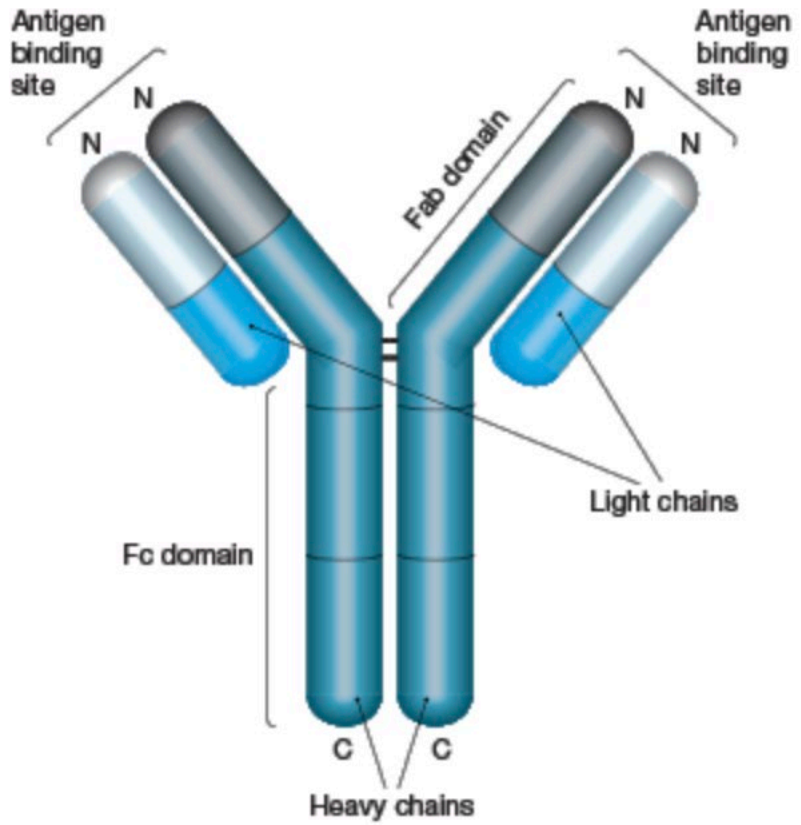
# Additional physiologic changes affecting mAb disposition

- 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



JOHNS HOPKINS MEDICINE

# 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 |
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# Distribution of monoclonal antibodies

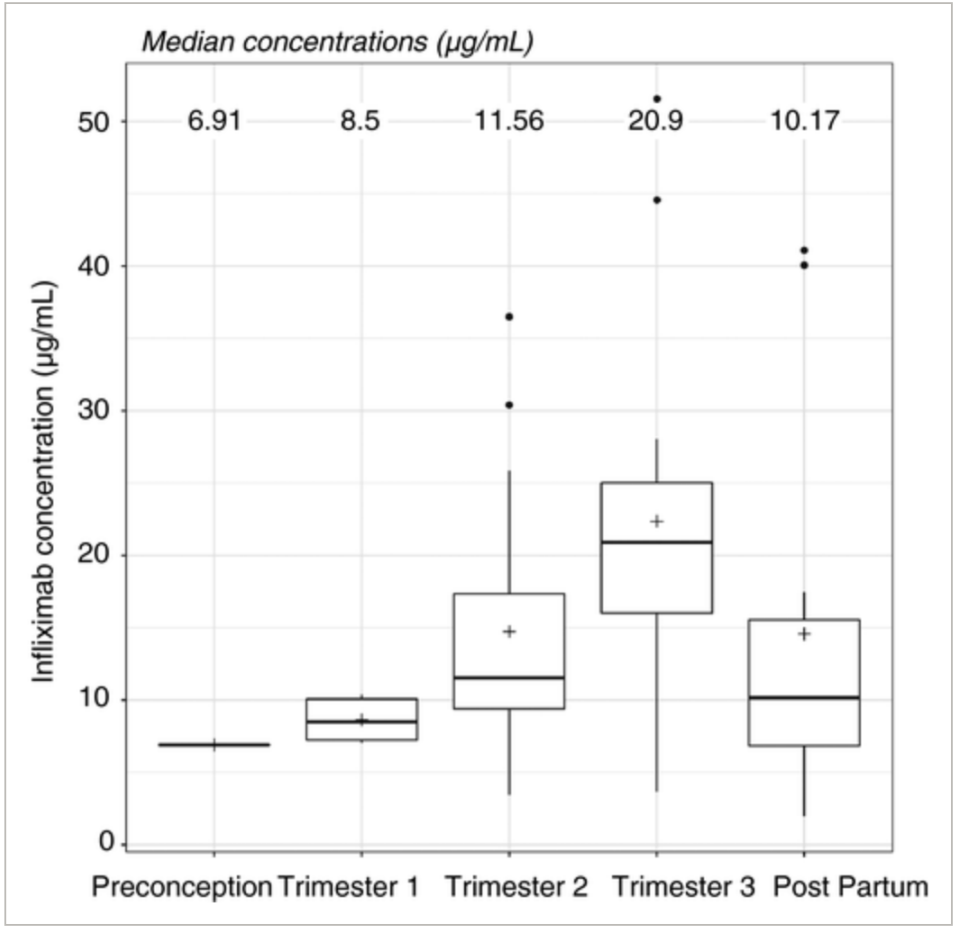
AP&T Alimentary Pharmacology and Therapeutics

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

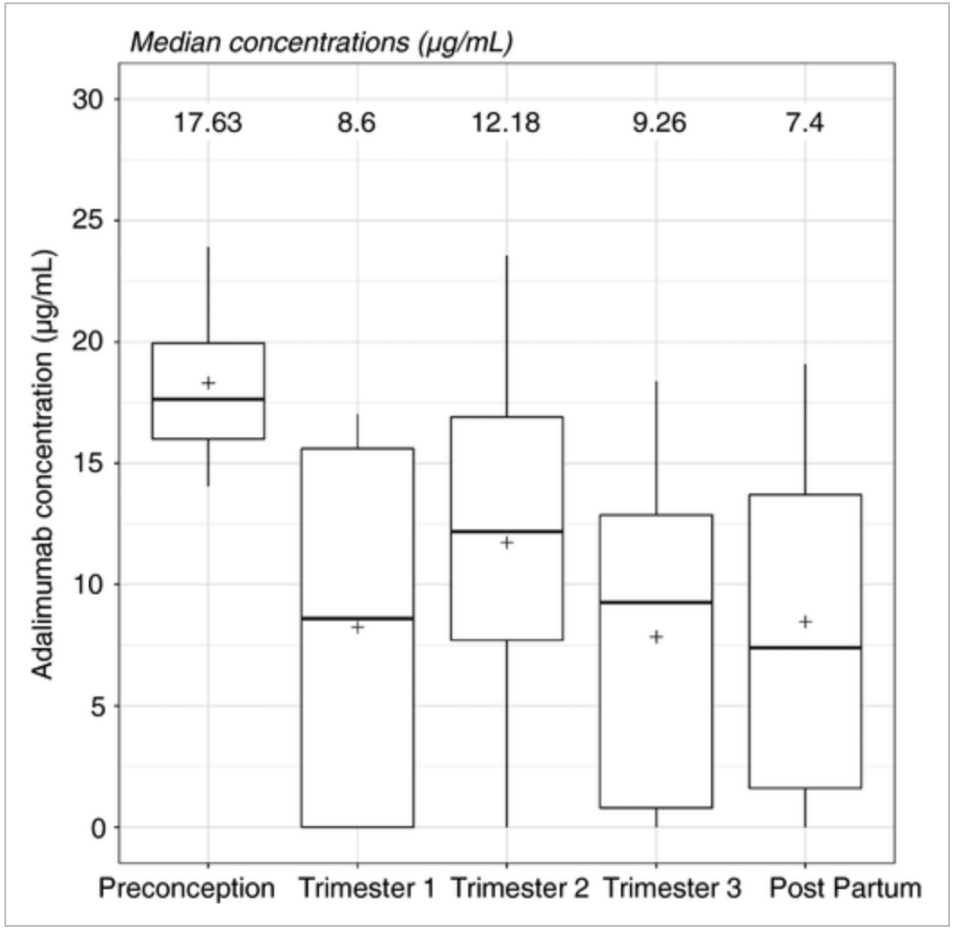
C. H. Seow*,† iD, Y. Leung*, N. Vande Casteele‡, E. Ehteshami Afshar*, D. Tanyingoh*, G. Bindra*, M. J. Stewart*, P. L. Beck*, G. G. Kaplan*,† iD, S. Ghosh* & R. Panaccione*

**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**

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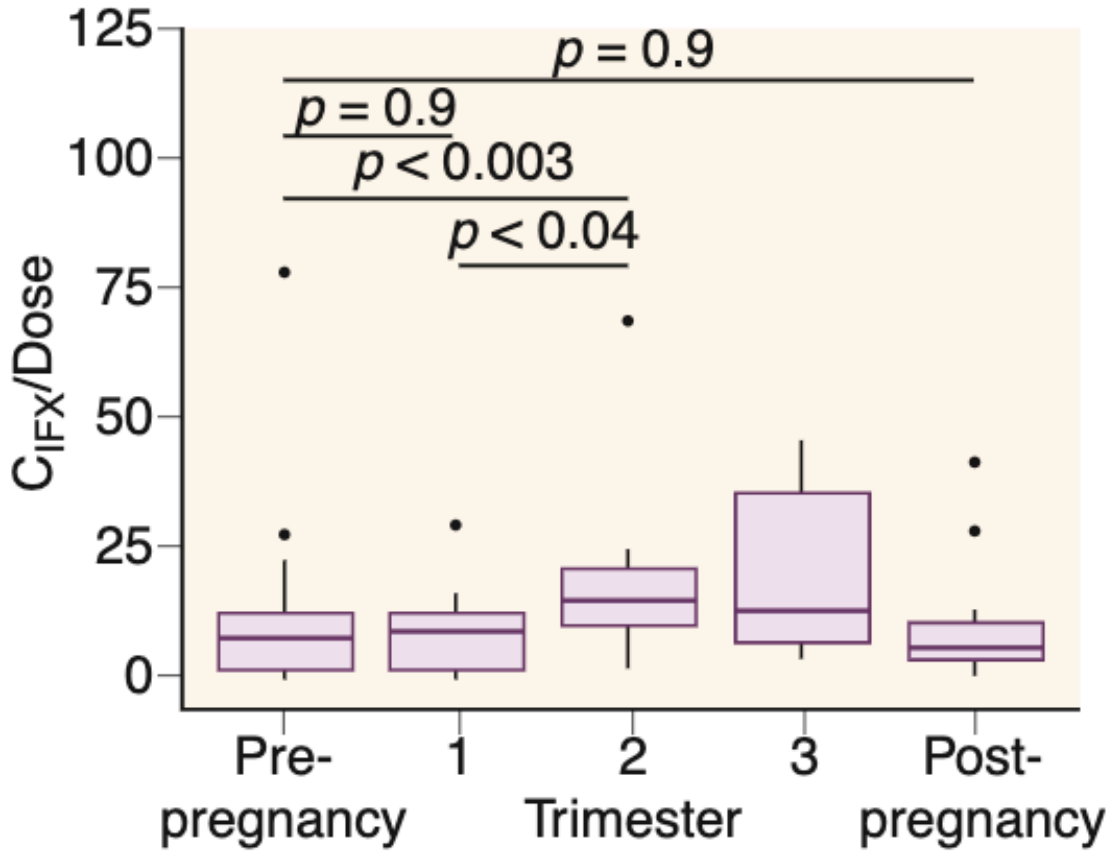
# Distribution of monoclonal antibodies

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

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# 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

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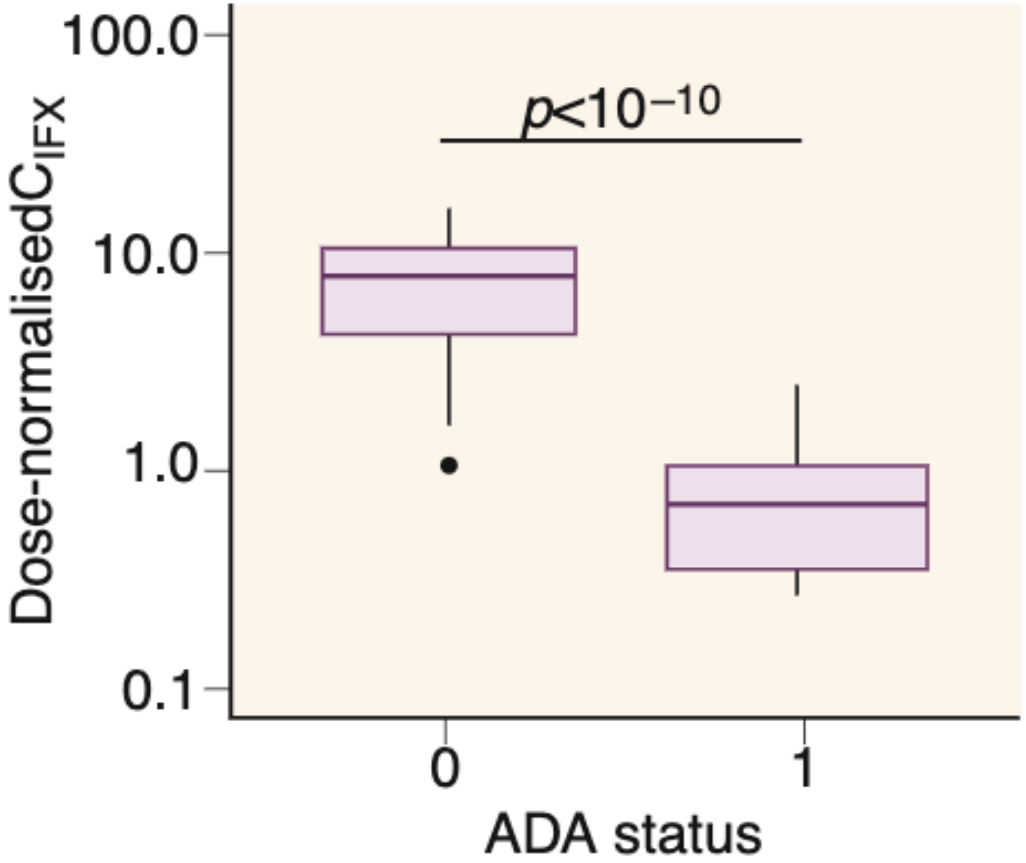
**Maintenance phase IFX concentrations (CIFX) by ADA status in pregnancy

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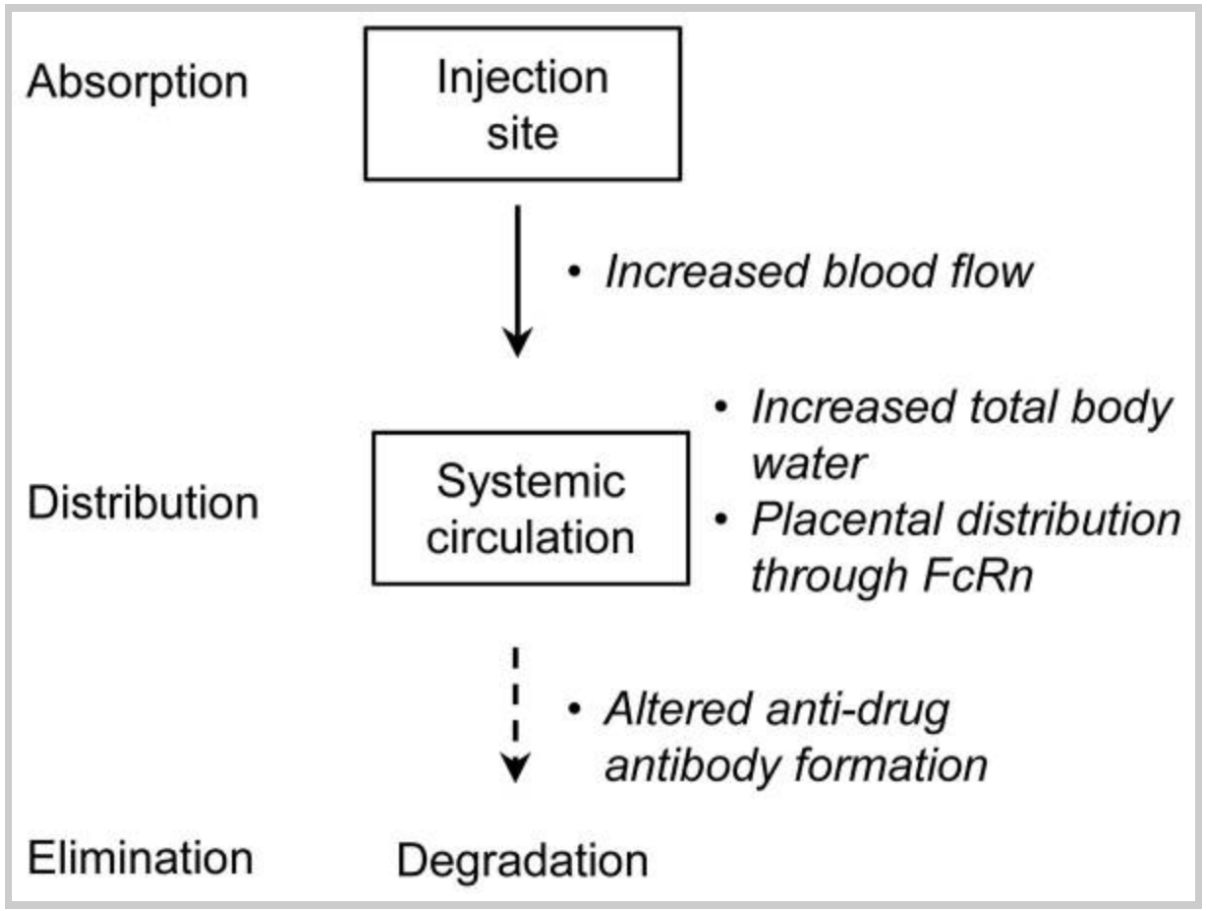
# Summary PK of monoclonal antibodies

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# 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