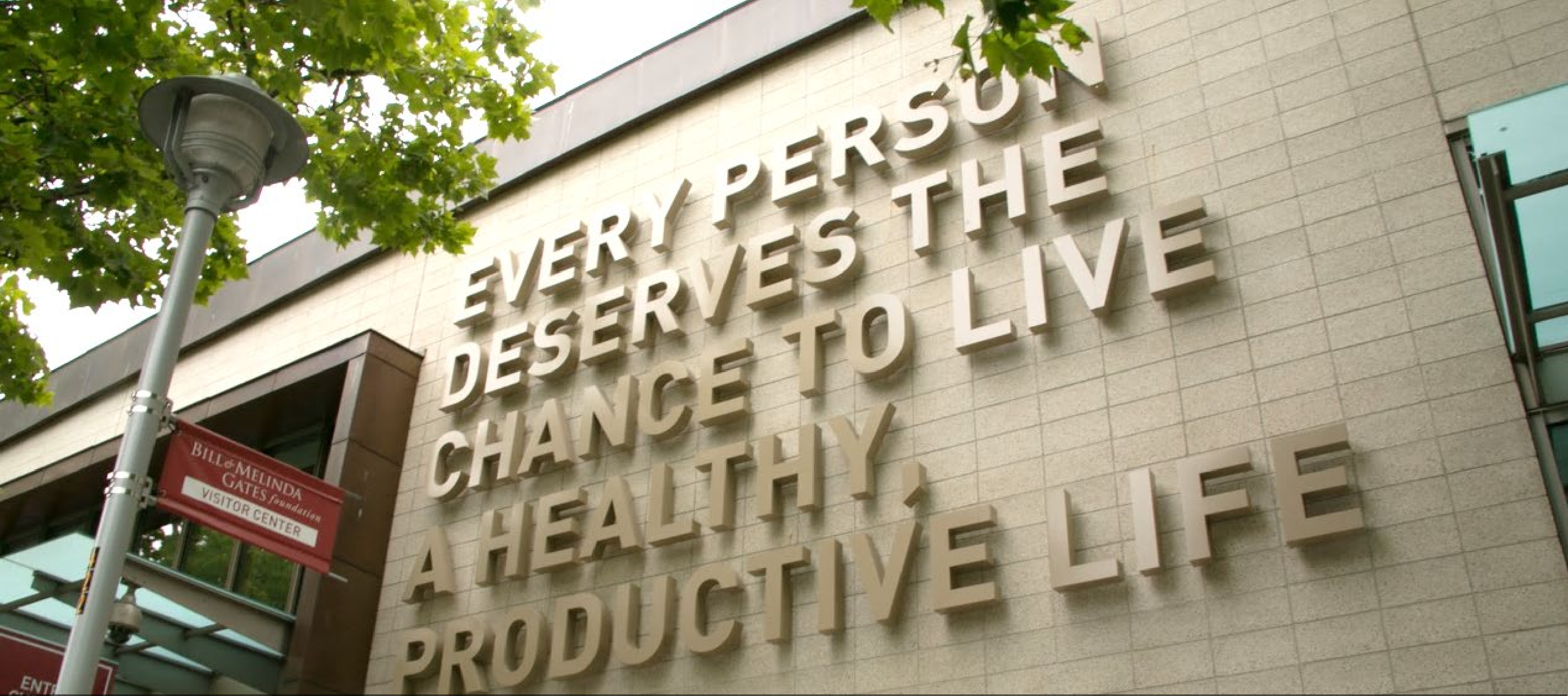
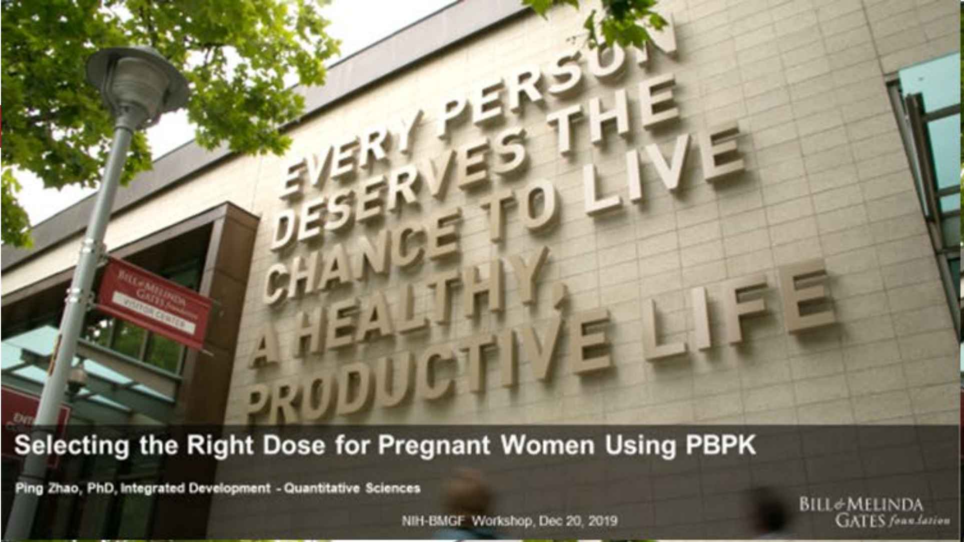


Selecting the Right Dose for Pregnant Women Using PBPK

Ping Zhao, PhD, Integrated Development - Quantitative Sciences

FDA CERSI Fetal Pharmacology and Therapeutics Workshop, Oct, 2021

BILL & MELINDA GATES foundation


EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
Selecting the Right Dose for Pregnant Women Using PBPK
Ping Zhao, PhD, Integrated Development - Quantitative Sciences
NIH-BMGF Workshop, Dec 20, 2019
BILL & MELINDA GATES foundation


EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
Selecting the Right Dose for Pregnant Women Using PBPK
Ping Zhao, PhD, Integrated Development - Quantitative Sciences
MHRA PK Workshop, Jan 24, 2020
BILL & MELINDA GATES foundation


EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
Selecting the Right Dose for Pregnant Women Using PBPK
Ping Zhao, PhD, Integrated Development - Quantitative Sciences
NIH-NICHD Webinar, June 18, 2020
BILL & MELINDA GATES foundation


EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
Selecting the Right Dose for Pregnant Women Using PBPK
Ping Zhao, PhD, Integrated Development - Quantitative Sciences
FDA CERSI Fetal Pharmacology and Therapeutics Workshop, Oct, 2021
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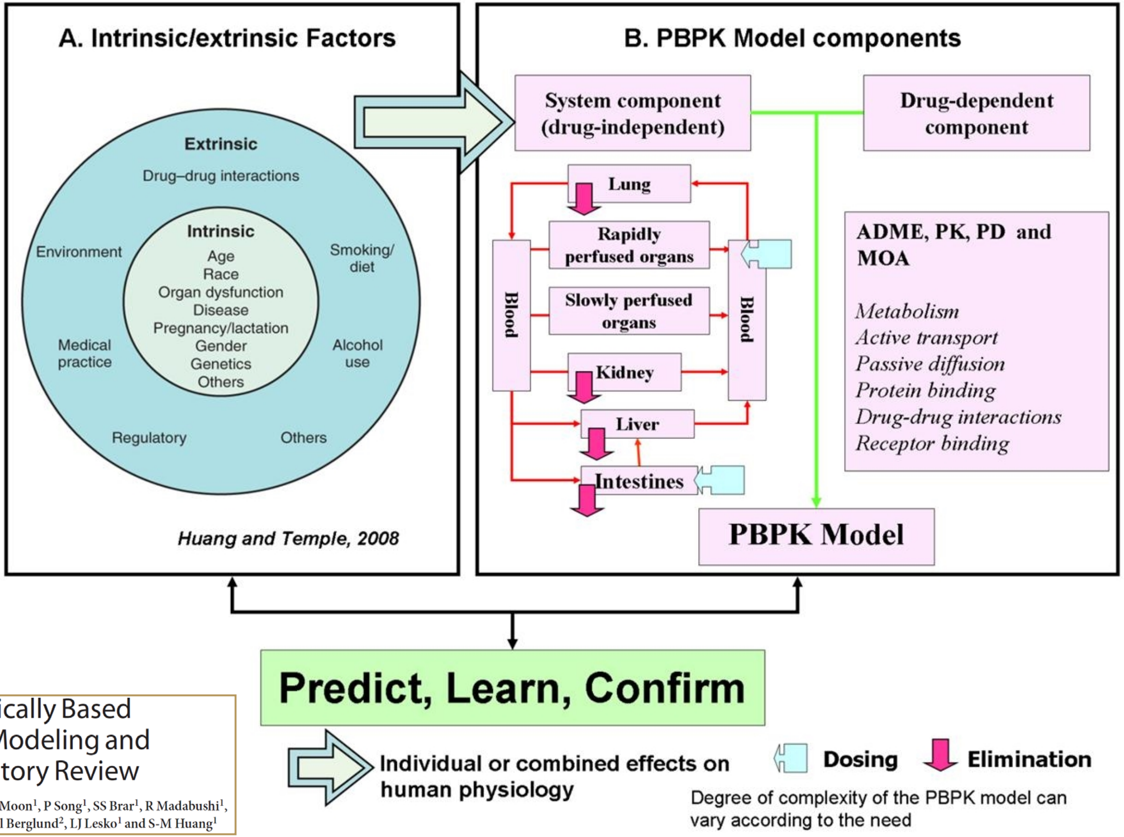
Physiologically-based Pharmacokinetic (PBPK) Modeling



Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

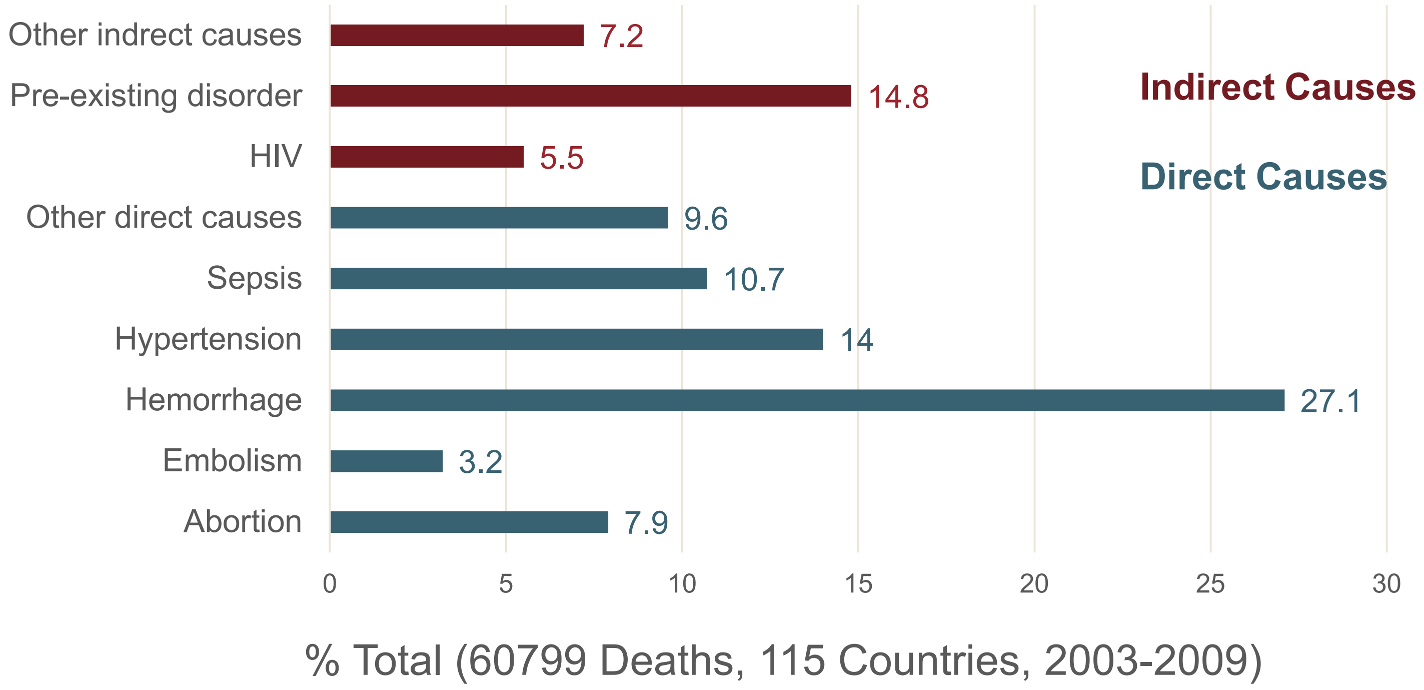
P Zhao[1], L Zhang[1], JA Grillo[1], Q Liu[1], JM Bullock[1], YJ Moon[1], P Song[1], SS Brar[1], R Madabushi[1], TC Wu[1], BP Booth[1], NA Rahman[1], KS Reynolds[1], E Gil Berglund[2], LJ Lesko[1] and S-M Huang[1]

Clin Pharmacol Ther, 2011

Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?

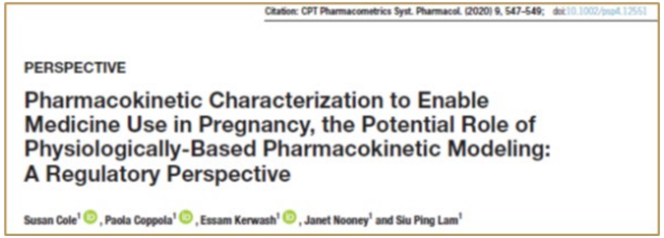
Causes of Maternal Mortality Worldwide



➢ **Medicine intervention targeting some of these causes may reduce maternal mortality globally**

Say et al, Lancet, 2014

The Problem


Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 547–549; doi:10.1002/psp4.12551

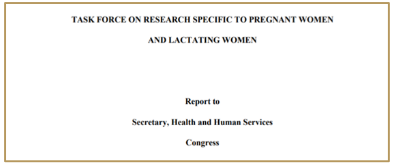
PERSPECTIVE

Pharmacokinetic Characterization to Enable Medicine Use in Pregnancy, the Potential Role of Physiologically-Based Pharmacokinetic Modeling: A Regulatory Perspective

Susan Cole[1], Paola Coppola[1], Essam Kerwash[1], Janet Nooney[1] and Siu Ping Lam[1]

- in 2011 >80% of women in Europe, the Americas, and Australia "used at least one medicinal product during pregnancy"

- UK: Only five prescription medicines specifically licensed "for non-obstetric use in pregnancy"
- USA: Only 22% labels include "human data about pregnancy"



TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN

Report to

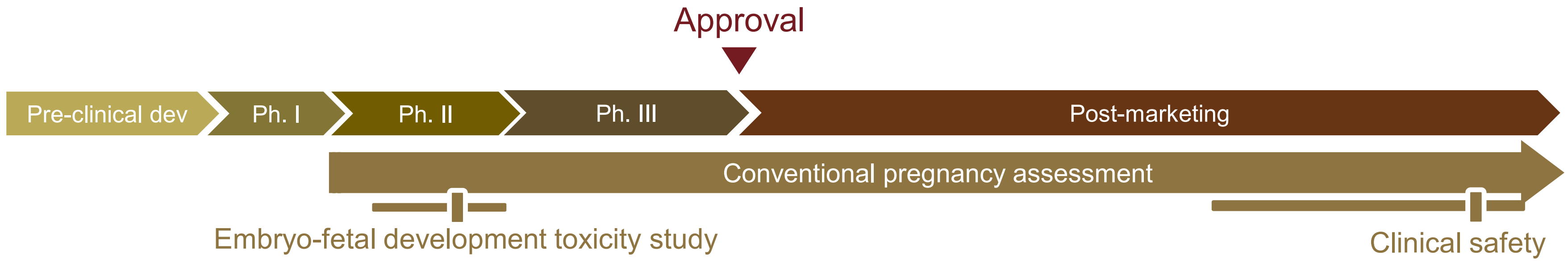
Secretary, Health and Human Services

Congress

2018: https://www.nichd.nih.gov/sites/default/files/2018 09/PRGLAC_Report.pdf

➢ **Wide use of medicines during pregnancy yet clear dosing instructions are lacking**

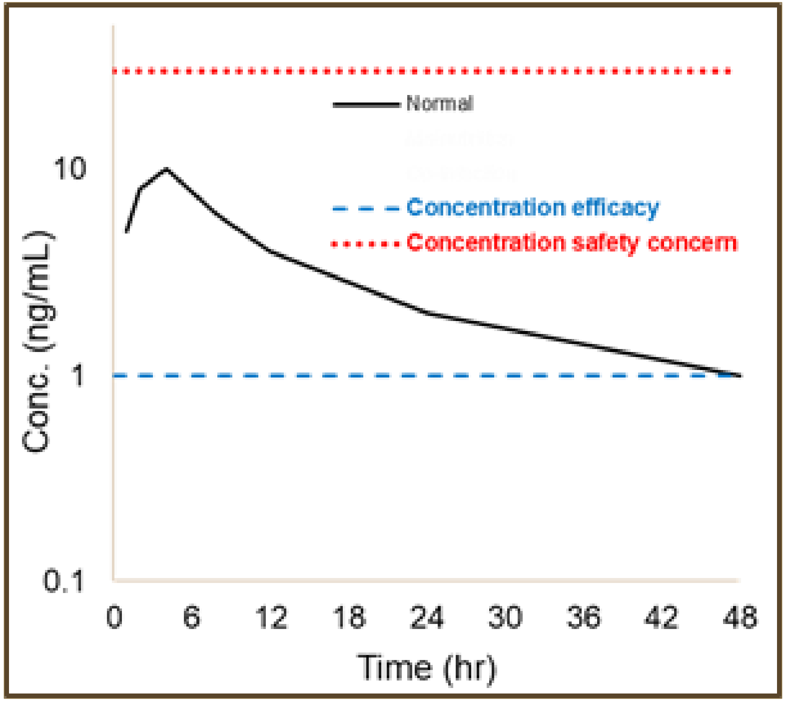
The Problem



- Exclusion of pregnant women from trials
- Difficulty of studying pharmacology in pregnant women
- Limited ability to generalize clinical data in pregnant women

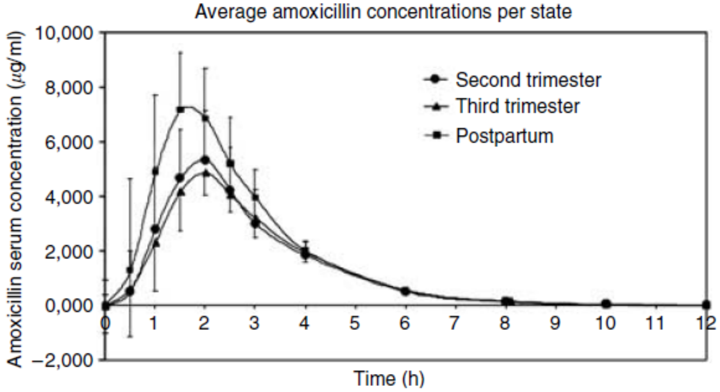
➢ **Off-label drug use during pregnancy is common**

Dose Selection: An Exposure-based Exercise



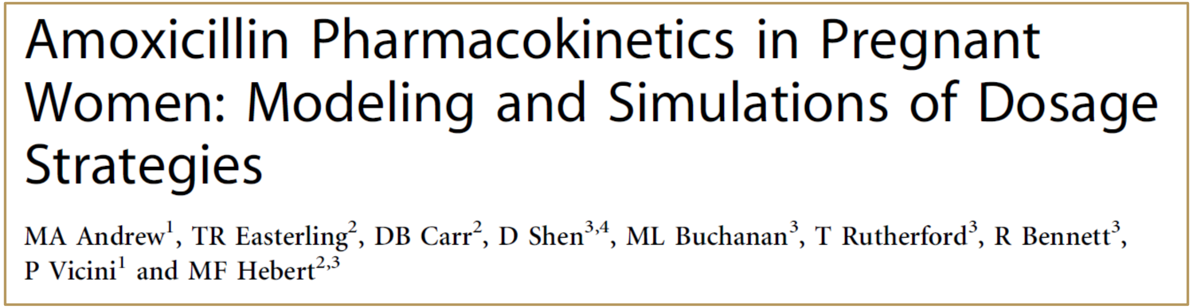
➢ **Characterizing PK is critical for dose selection**

Dose Selection: An Exposure-based Exercise



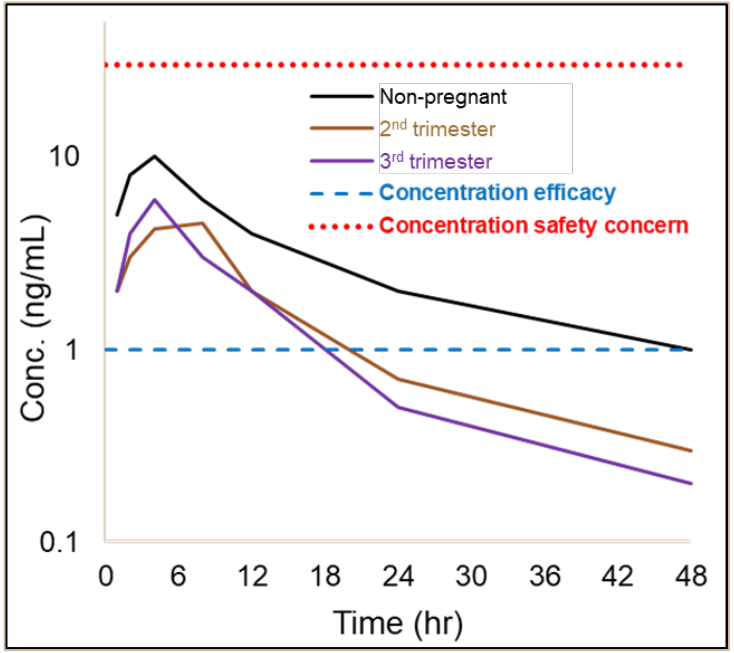
Amoxicillin in pregnant women

- ↓ Drug concentration


Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulations of Dosage Strategies

MA Andrew[1], TR Easterling[2], DB Carr[2], D Shen[3,4], ML Buchanan[3], T Rutherford[3], R Bennett[3], P Vicini[1] and MF Hebert[2,3]

Dose Selection in Pregnant Women



1st trimester?

Co-medication?

Infection?

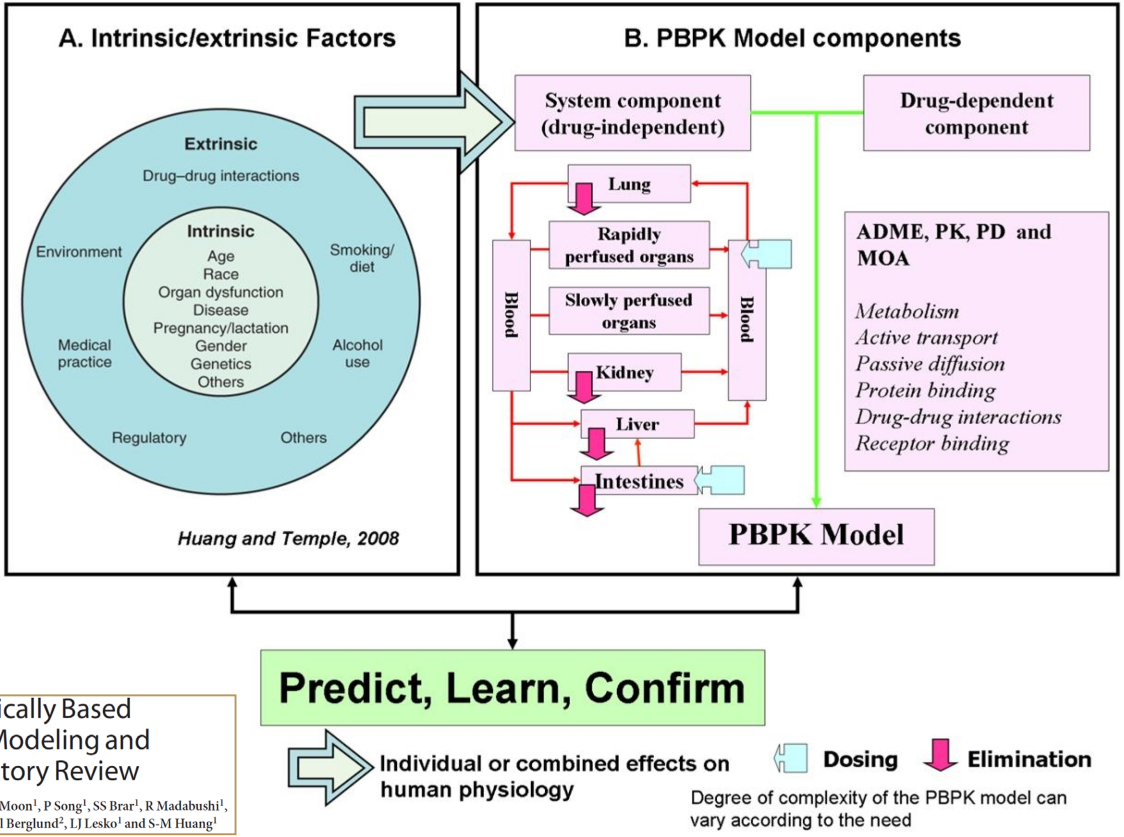
Malnourishment?

Fetus exposure?

…

➢ **Not suitable to address every question through the conduct of clinical PK studies**

Physiologically-based Pharmacokinetic (PBPK) Modeling



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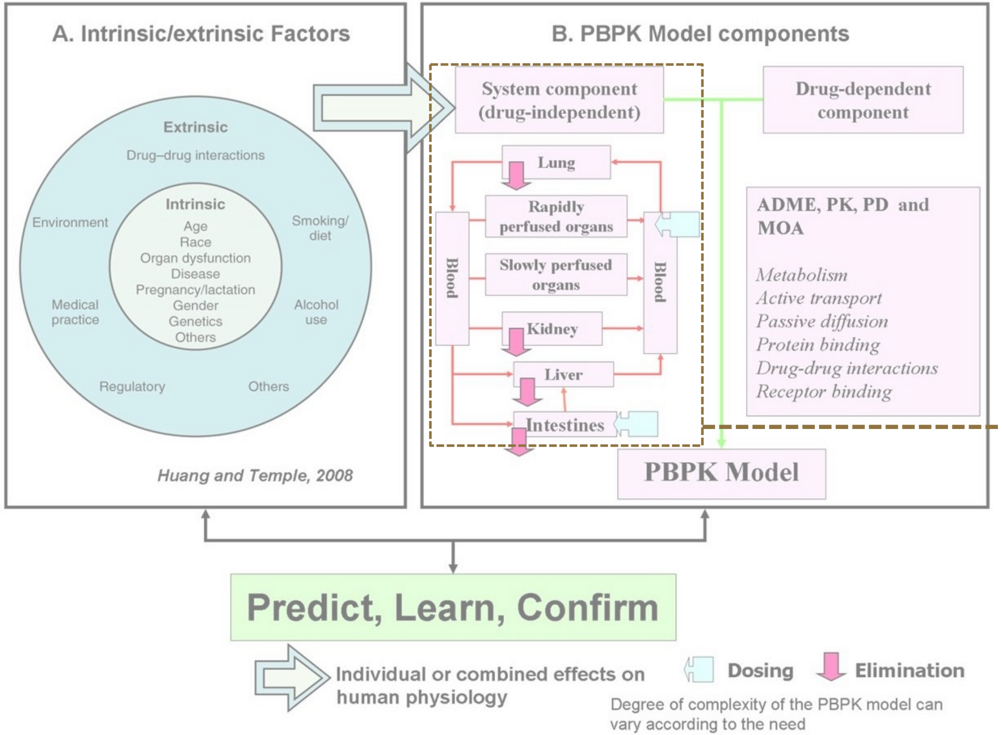
Clin Pharmacol Ther, 2011

Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?

Virtual Studies in Virtual Pregnant Women

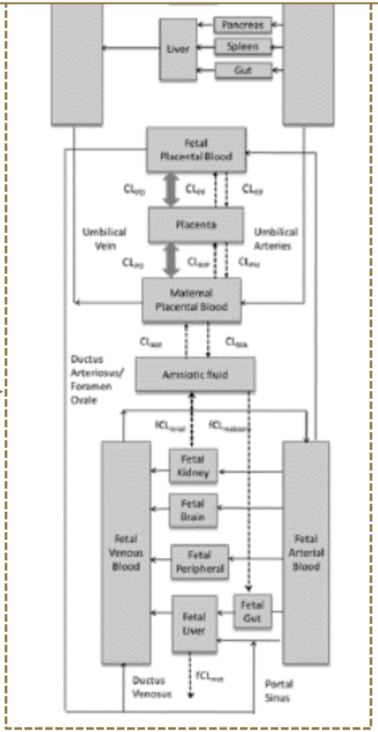


1521-009X/45/8/939–946$25.00
DRUG METABOLISM AND DISPOSITION
https://doi.org/10.1124/dmd.116.073957
Drug Metab Dispos 45:939–946, August 2017

Development of a Novel Maternal-Fetal Physiologically Based Pharmacokinetic Model II: Verification of the Model for Passive Placental Permeability Drugs

Zufei Zhang and Jashvant D. Unadkat

Replacing physiology



➢ **Virtual pregnant women/fetuses enable customized drug dosing in pregnant women**

Known Changes during Pregnancy

Parameter	$T_1{}^a$	$T_2{}^a$	$T_3{}^a$
Total body weight (kg)	↑ 6%	↑ 16%	↑ 23%
Total fat mass (kg)	↑ 11%	↑ 16%	↑ 32%
Total body water (L)	↑ 11%	↑ 27%	↑ 41%
Cardiac output (L)	↑ 18%	↑ 28%	↑ 33%
Plasma volume (L)	↑ 7%	↑ 42%	↑ 50%
Red blood cell volume (L)	↑ 4%	↑ 20%	↑ 28%
Hematocrit (%)	↓ 3%	↓ 8%	↓ 14%
Albumin (g/L)	↓ 5%	↓ 16%	↓ 31%
α1-AGP (g/L)	↓ 1%	↓ 22%	↓ 19%
Glomerular filtration rate (mL/min)[b]	↑ 19%	↑ 37%	↑ 40%
Effective renal plasma flow (L/h)	↑ 38%	↑ 48%	↑ 31%
Creatinine clearance (mL/min)	↑ 28%	↑ 58%	↑ 26%
Uterine blood flow (L/h)	↑ 923%	↑ 1,567%	↑ 2,771%
Hepatic blood flow (L/h)[c]	↔	↔	↔

Pharmacometrics in Pregnancy: An Unmet Need

Alice Ban Ke,[1] Amin Rostami-Hodjegan,[2,3] Ping Zhao,[4] and Jashvant D. Unadkat[5]

**T1, T2, T3: first, second and third trimesters*

Ann Rev Pharmacol Toxicol, 2013

Known Changes during Pregnancy

Drug/probe	Indication	Effect on CL/F (%)[a] T1	T2	T3	Metabolizing-enzyme activity changes	Reference
Caffeine*	CNS stimulant	↓ 33	↓ 48	↓ 65	↓ CYP1A2	48
Theophylline	Asthma	↔	↔	↓ 34		49
Nicotine	Smoking cessation	NA	↑ 54	↑ 54	↑ CYP2A6	50
Phenytoin*,[b]	Epilepsy	↑ 43	↑ 51	↑ 61	↑ CYP2C9	51
Proguanil	Malaria	NA	↓ 60	↓ 60	↓ CYP2C19	52
Metoprolol*	Hypertension	NA	NA	↑ 459	↑ CYP2D6	53
Dextromethorphan[b]	Cough	↑ 26	↑ 35	↑ 48		48
Midazolam*	Sedation	NA	NA	↑ 99	↑ CYP3A4	14
Indinavir	HIV infection	NA	NA	↑ 277		8
Glyburide	Diabetes	NA	NA	↑ 106		9
Methadone	Addiction	NA	↑ 101	↑ 65	↑ CYP2B6	54
Labetalol	Hypertension	NA	↑ 30	↑ 30	↑ UGT1A1	55
Lamotrigine	Epilepsy	↑ 200	↑ 200	↑ 300	↑ UGT1A4	19
Zidovudine[c]	HIV infection	NA	NA	↔	↔ UGT2B7	56
Amoxicillin	Bacterial infection	NA	↑ 23	↑ 20	↑ Renal CL	22
Metformin*	Diabetes	↑ 22	↑ 28	↑ 11		20
Digoxin*	Cardiac diseases	NA	NA	↑ 19		14

Pharmacometrics in Pregnancy: An Unmet Need

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T1, T2, T3: first, second and third trimesters

Ann Rev Pharmacol Toxicol, 2013

Predict-Learn-Confirm: Enzymes

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e3; doi:10.1038/psp.2012.2

www.nature.com/psp

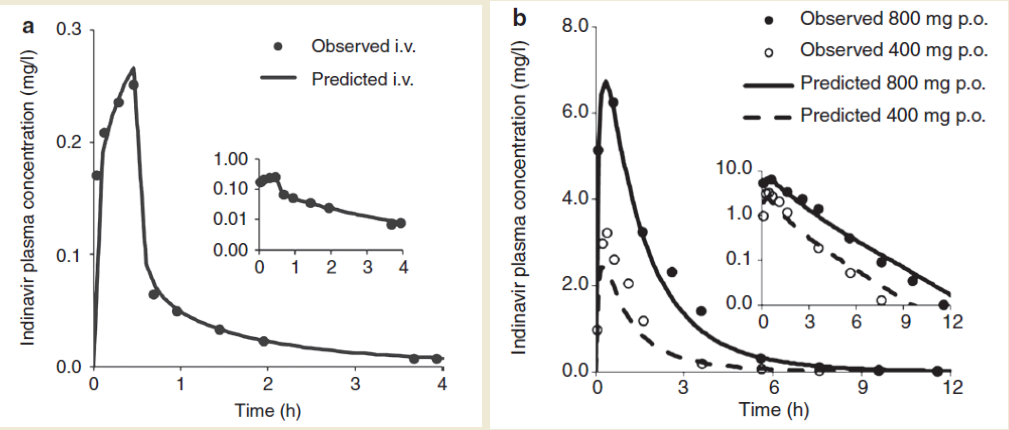
ORIGINAL ARTICLE

A PBPK Model to Predict Disposition of CYP3A-Metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction

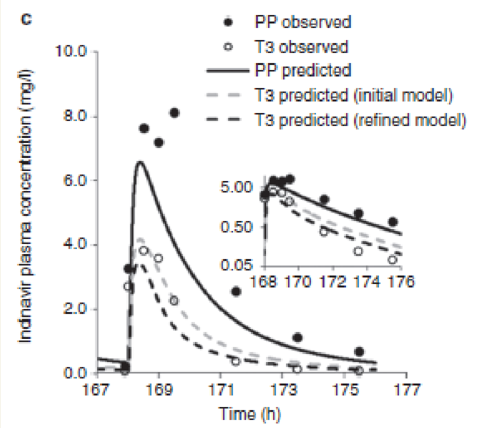
AB Ke[1,2], SC Nallani[2], P Zhao[2], A Rostami-Hodjegan[3,4] and JD Unadkat[1]

Liver CYP3A: 99% ↑ in T3
Learn: midazolam
Confirm: nifedipine and indinavir
Learn/confirm: induction only in liver, not gut

Model describing data in non-pregnant subjects



Model describing data in pregnant women

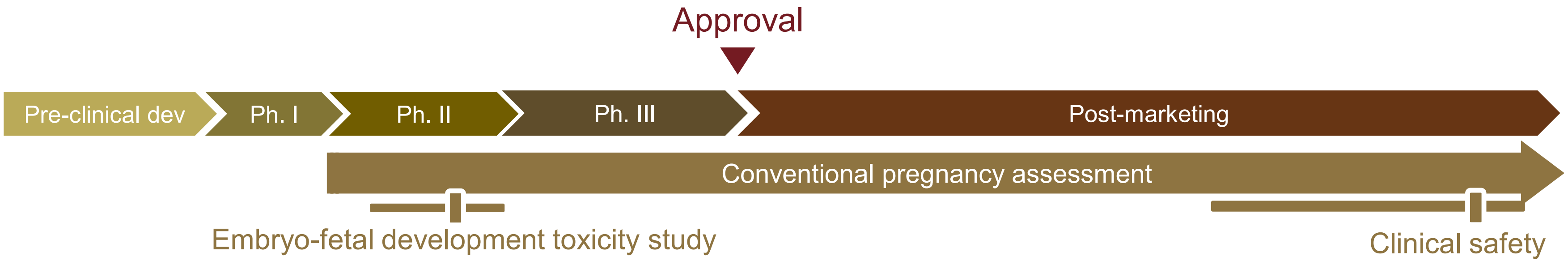


**PP: postpartum; T3: third trimesters*

Selecting the Right Dose for Pregnant Women Using PBPK

- Why?
- How?
- When?

Value Proposition of PBPK Predictions



- *Design of pregnancy studies (e.g., PK)?*
- *Off label use in pregnant women?*
- *Dose recommendation in the labels or description of untested PK scenarios in the label?*

➢ **Intended uses are dependent on level of confidence of the model**

Verifying Enzyme Changes during Pregnancy

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e3; doi:10.1038/psp.2012.2

www.nature.com/psp

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Learn: midazolam
Confirm: nifedipine and indinavir
Learn/confirm: induction only in liver, not gut

1521-009X/41/4/801–813$25.00
Drug Metabolism and Disposition

http://dx.doi.org/10.1124/dmd.112.050161
Drug Metab Dispos 41:801–813, April 2013

A Physiologically Based Pharmacokinetic Model to Predict Disposition of CYP2D6 and CYP1A2 Metabolized Drugs in Pregnant Women

Alice Ban Ke, Srikanth C. Nallani, Ping Zhao, Amin Rostami-Hodjegan, Nina Isoherranen, and Jashvant D. Unadkat

CYP1A2: 65% ↓ in T3; CYP2D6: 100-200% ↑ in T3
Learn: caffeine, metoprolol
Confirm: theophylline, paroxetine, dextromethorphan, clonidine

BJCP British Journal of Clinical Pharmacology
DOI:10.1111/bcp.12207

Expansion of a PBPK model to predict disposition in pregnant women of drugs cleared via multiple CYP enzymes, including CYP2B6, CYP2C9 and CYP2C19

Alice Ban Ke,[1,2] Srikanth C. Nallani,[2] Ping Zhao,[2] Amin Rostami-Hodjegan[3,4] & Jashvant D. Unadkat[1]

Correspondence
Dr Jashvant D. Unadkat, Department of Pharmaceutics, University of Washington, Box 357610, Seattle, WA 98195, USA.
Tel.: +1 206 543 9434
Fax: +1 206 543 3204
E-mail: jash@u.washington.edu

Keywords
CYP2B6, CYP2C19, CYP2C9, PBPK, pharmacokinetics, pregnancy

Received
19 January 2013
Accepted
20 June 2013
Accepted Article Published Online
9 July 2013

CYP2C19, 62-68% ↓ inT2-T3; CYP2C9: 50-60% ↑ in T2-T3

Learn: in vitro by estradiol, proguanil, phenytoin

Predict: Glyburide (CYP3A, 2C9, 2C19) and methadone (CYP3A, 2B6, 2C19) in T2 and T3

➢ **Fourteen (14) CYP substrates in virtual pregnant population**

**T2, T3: first, second and third trimesters*

Verifying Transporter Changes during Pregnancy

Oseltamivir carboxylate drug model

Hsu et al, Clin Pharmacokinet, 2014

+

Pregnancy model

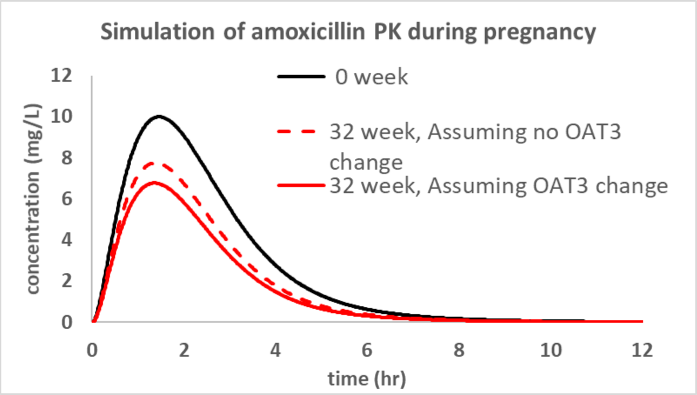
OAT 1/3: 100%↑ in T3

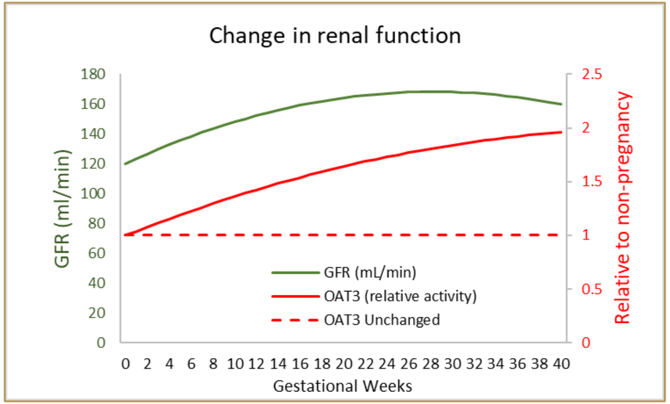
Learn: oseltamivir carboxylate

Confirm: ciprofloxacin

Hsu et al, 2016

Grimstein et al, 2016





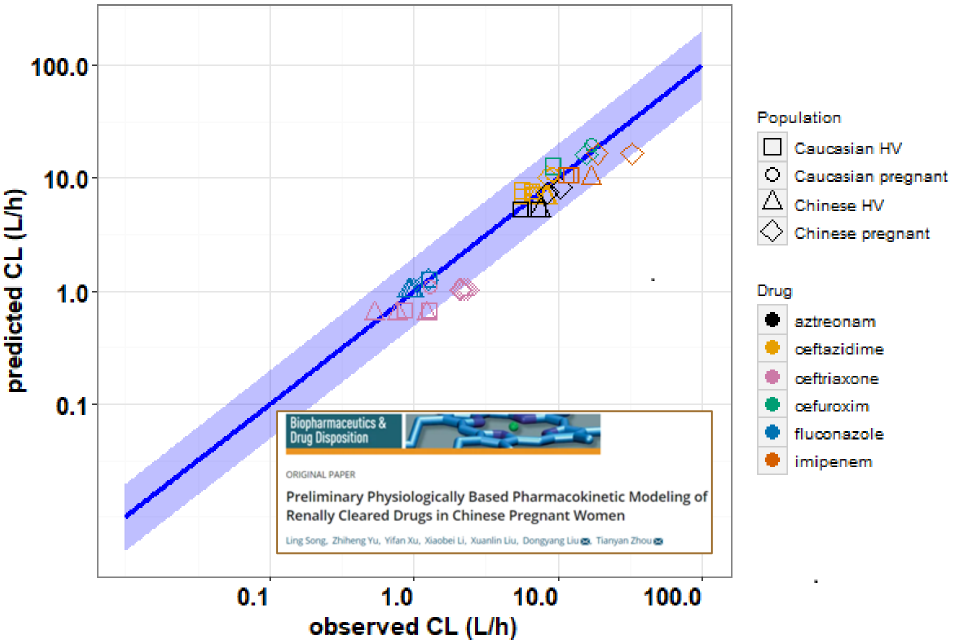
➢ **Three (3) renally cleared, transporter substrates in virtual pregnant population**

GFR: Glomerular filtration rate; OAT3: organic anion transporter 3. Amoxicillin model: Acknowledging X Xiang (Fudan Univ) and K Abduljalil (Certara)

Virtual Chinese Pregnancy Population (Peking Univ 3rd Hospital)

→ All independent predictions in pregnant and non-pregnant subjects

→ Future direction: renal transporter changes



➢ **Six (6) renally cleared drugs in virtual Caucasians <u>and</u> Chinese Pregnant Populations**

https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2019/06/OPP1204780

Verifying Fetal Model

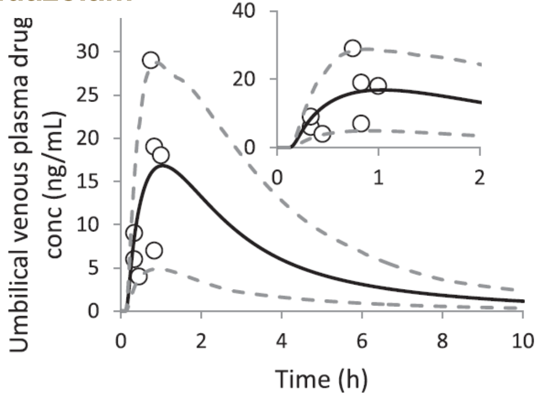
1521-009X/45/8/939–946$25.00
Drug Metabolism and Disposition

https://doi.org/10.1124/dmd.116.073957
Drug Metab Dispos 45:939–946, August 2017

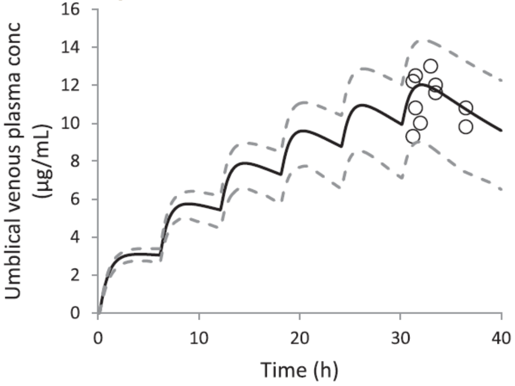
Development of a Novel Maternal-Fetal Physiologically Based Pharmacokinetic Model II: Verification of the Model for Passive Placental Permeability Drugs [S]

Zufei Zhang and Jashvant D. Unadkat

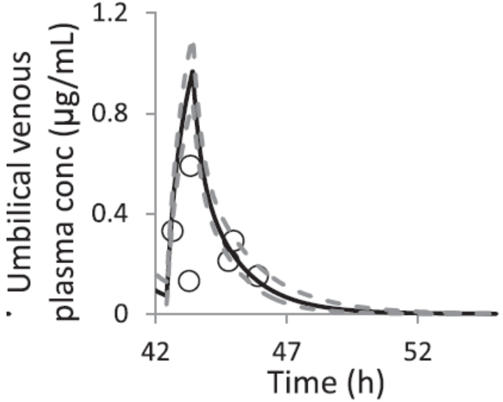
Midazolam



Theophylline



Zidovudine



➢ **Three (3) passive diffusion drugs in virtual Maternal-fetal (m-f) PBPK models**

Expanding Maternal-Fetal Model (Univ Wash)

- ❑ Determine placenta transporter abundance
- ❑ Update m-f model
- ❑ Verify and apply m-f model

1521-009X/48/9/735–741$35.00
DRUG METABOLISM AND DISPOSITION
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https://doi.org/10.1124/dmd.120.000067
Drug Metab Dispos 48:735–741, September 2020

Gestational Age–Dependent Abundance of Human Placental Transporters as Determined by Quantitative Targeted Proteomics

Olena Anoshchenko, Bhagwat Prasad, Naveen K. Neradugomma, Joanne Wang, Qingcheng Mao, and Jashvant D. Unadkat

Department of Pharmaceutics, University of Washington, Seattle, Washington

Received April 7, 2020; accepted June 11, 2020

Received: 11 May 2021 | Revised: 31 May 2021 | Accepted: 7 June 2021
DOI: 10.1002/psp4.12674

ARTICLE

Estimating fetal exposure to the P-gp substrates, corticosteroids, by PBPK modeling to inform prevention of neonatal respiratory distress syndrome

Olena Anoshchenko[1] | Mark A. Milad[2] | Jashvant D. Unadkat[1]

1521-009X/49/10/919–928$35.00
DRUG METABOLISM AND DISPOSITION
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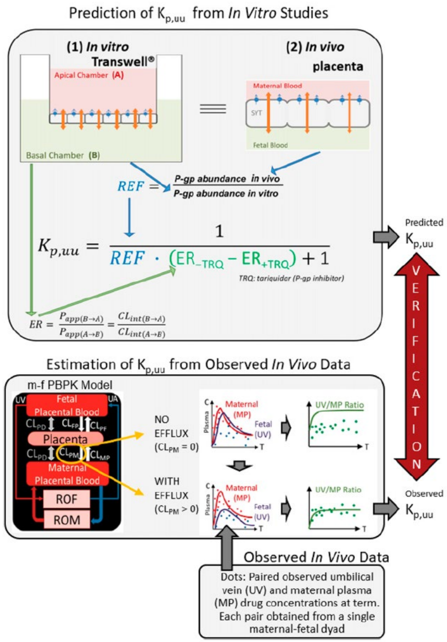
https://doi.org/10.1124/dmd.121.000538
Drug Metab Dispos 49:919–928, October 2021

Successful Prediction of Human Fetal Exposure to P-Glycoprotein Substrate Drugs Using the Proteomics-Informed Relative Expression Factor Approach and PBPK Modeling and Simulation

Olena Anoshchenko, Flavia Storelli, and Jashvant D. Unadkat

Department of Pharmaceutics, University of Washington, Seattle, Washington

Received May 10, 2021; accepted July 20, 2021

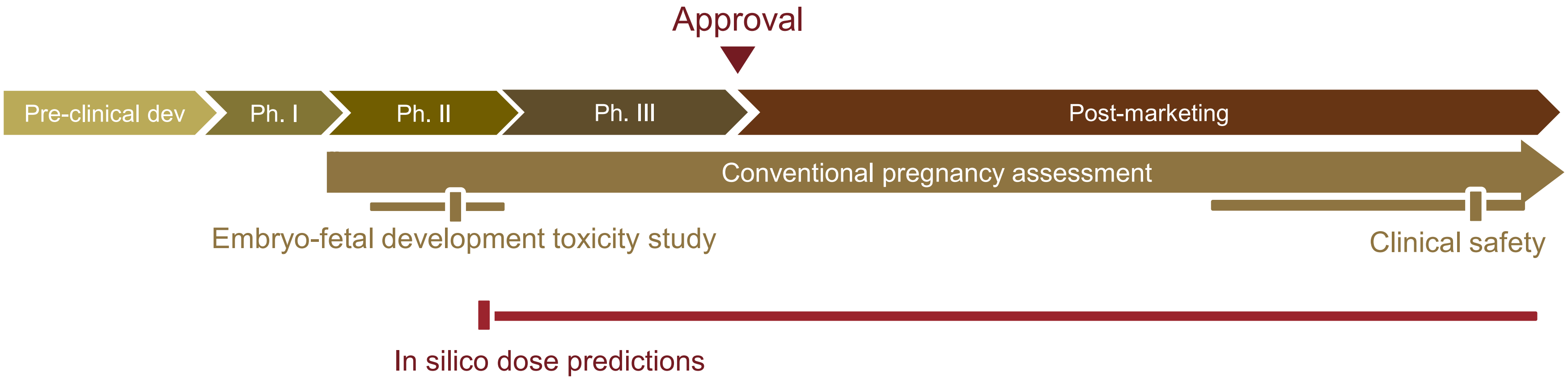


➢ **Four (4) P-gp substrates in virtual m-f PBPK models**

International PBPK Collaborations

Projects	Collaborators
M-f PBPK	University of Washington
Chinese Pregnancy Population	Peking University 3rd Hospital
Model Informed Drug Use during Pregnancy	Radboud University
Repository and Training	UK Medical and Health products Regulatory Agency (MHRA)

The vision



- **Optimized clinical study design**
- **Informed off label use**
- **Quality digital evidence**

Thank you

Workshop objectives

1. Review general regulatory and ethical considerations for fetal pharmacology and therapeutics
2. Describe methods to assess clinical and nonclinical safety and efficacy assessments to support clinical trials of drugs in pregnancy and the fetus
3. Highlight advances and existing knowledge in fetal therapeutics
4. Discuss key aspects of maternal-fetal modeling and simulation