utmb Health
Obstetrics & Gynecology

OPRC
OBSTETRIC-FETAL PHARMACOLOGY
RESEARCH CENTERS

Clinical Pharmacology during Pregnancy:

Efforts of the MFMU and OPRU to expand understanding

Maged Costantine, MD
Associate Professor
Dept. OB/GYN
UTMB-Galveston

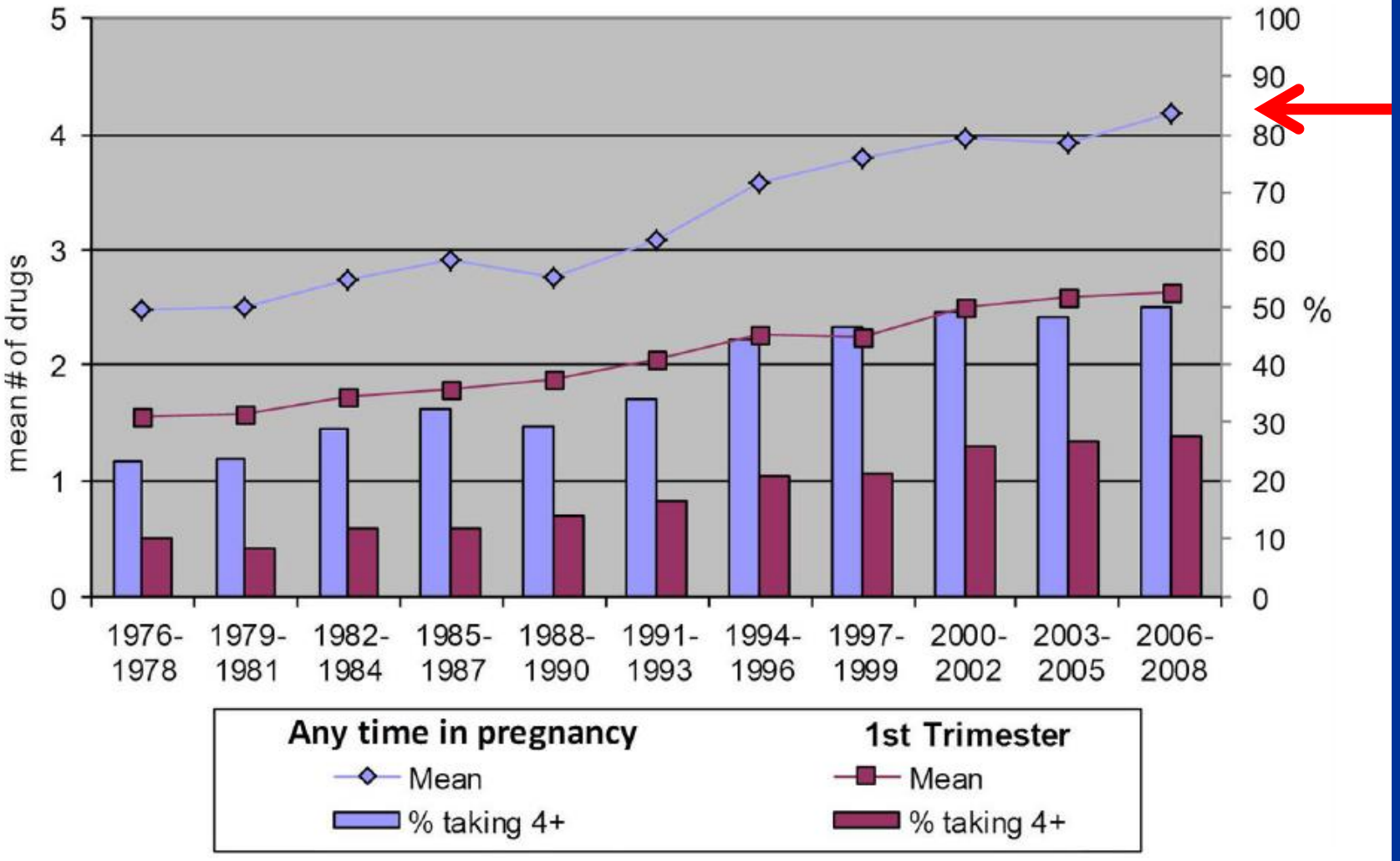
- No conflicts of interest

- Support
  - 2 U54 HD047891
  - 1 R01 HD083003

Objectives

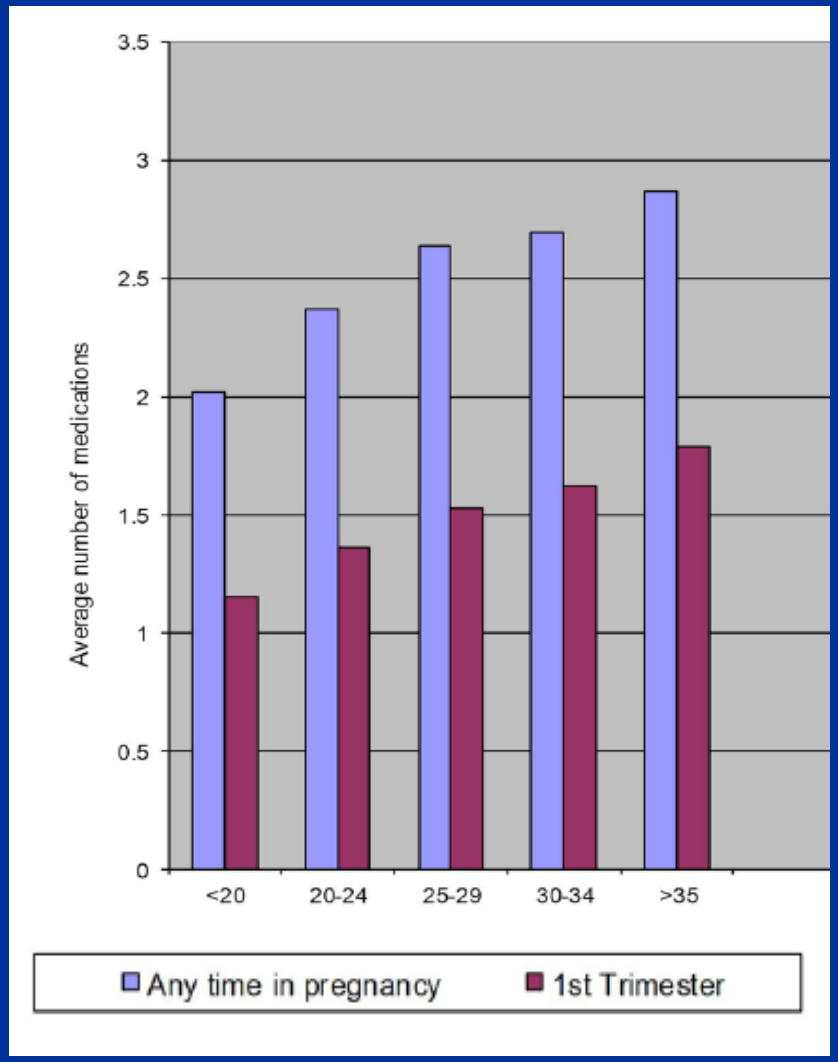
- Issues associated with medications use in pregnancy
- Pregnancy special considerations
- Experience from NICHD MFMU/OPRC networks

Medications Use During Pregnancy



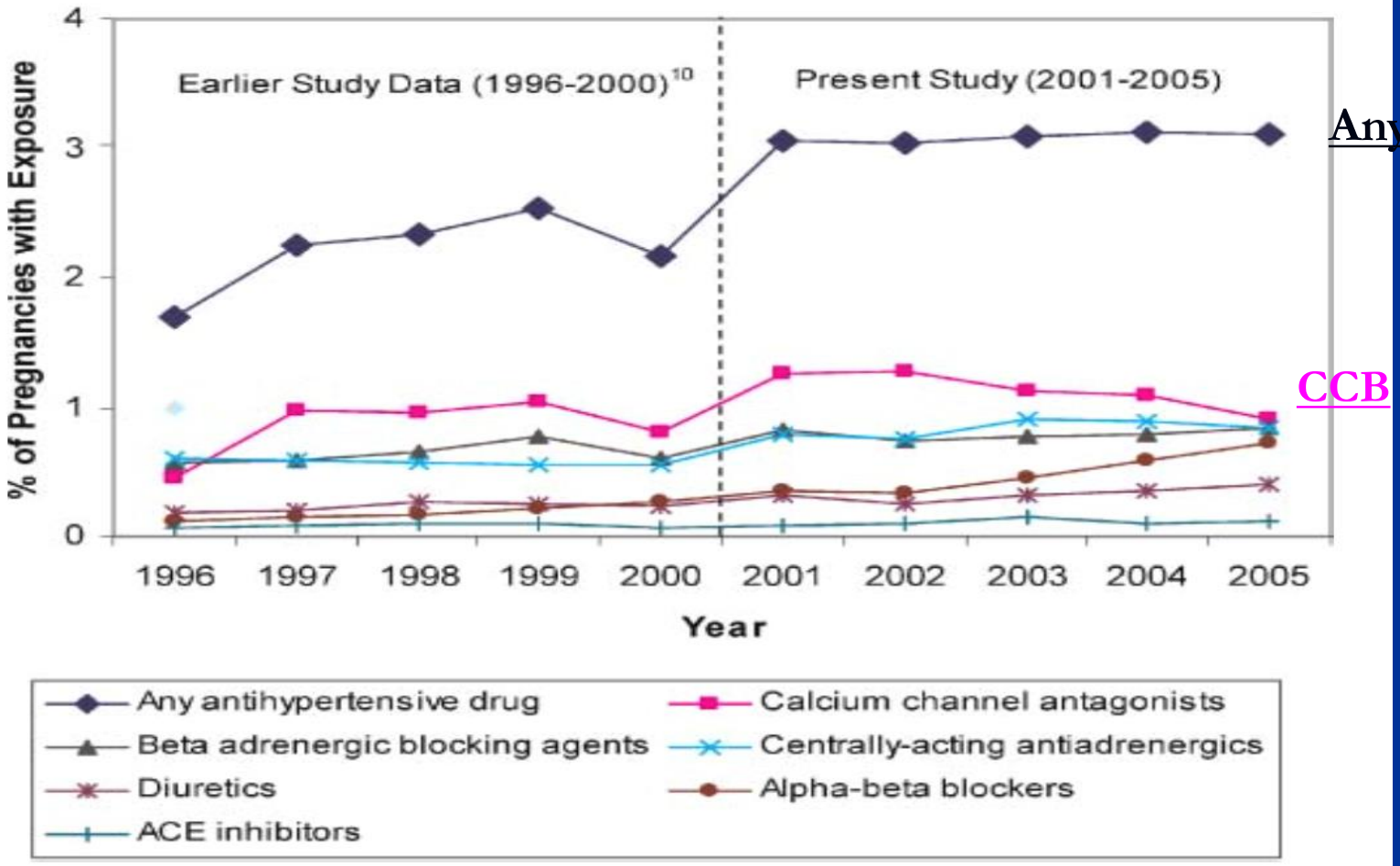
Mitchell A. et al AJOG 2011

Medications use during pregnancy: Maternal Age



Mitchell A. et al AJOG 2011

Exposure to Antihyepertensive Medications in Pregnancy

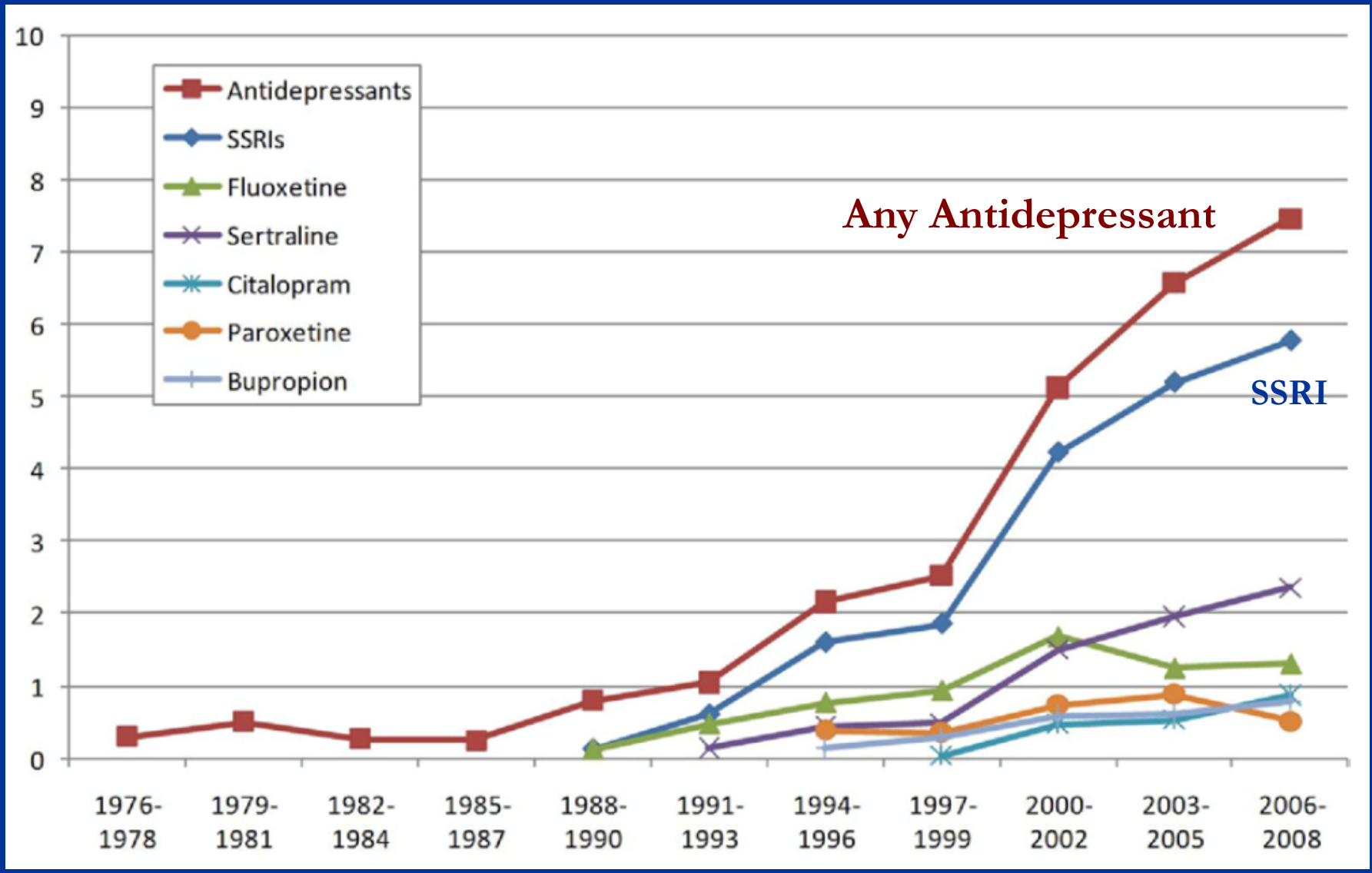


Any anti-HTN

CCB

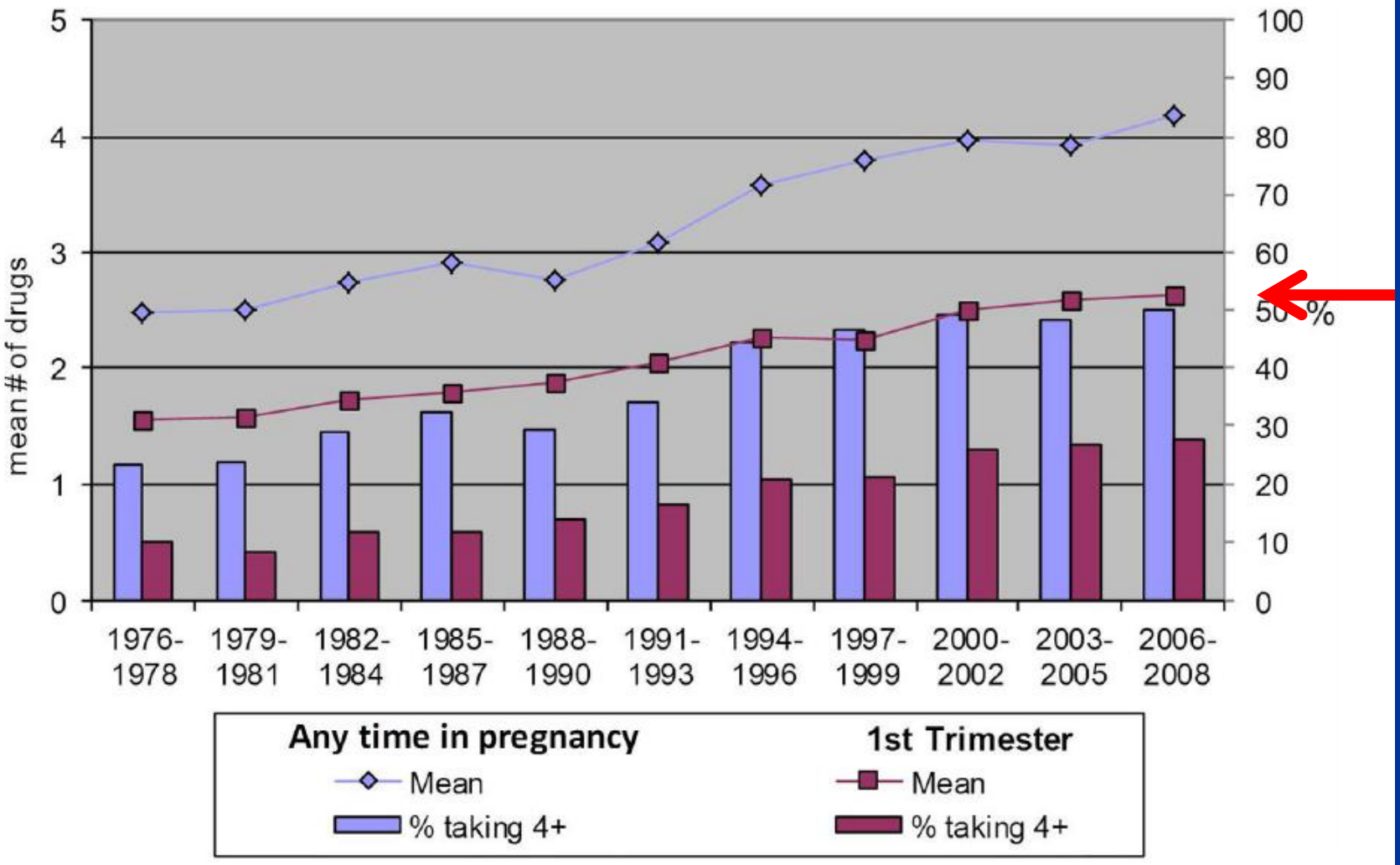
Andrade S. et al Pharmacoepidem Drug Saf 2008

Antidepressants use during pregnancy



Mitchell A. et al AJOG 2011

Medications use during pregnancy



Mitchell A. et al AJOG 2011

First Trimester

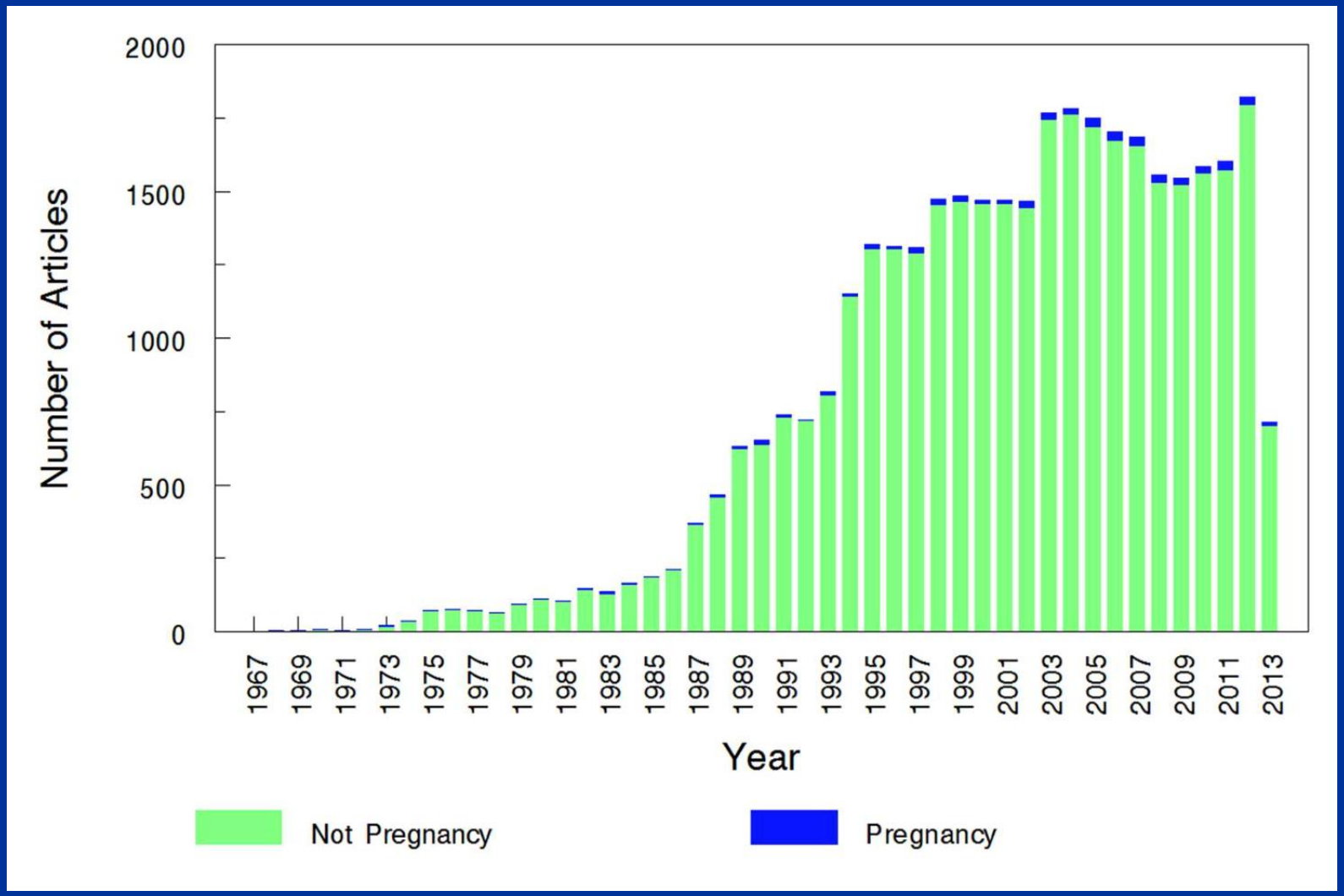
- Critical period for organogenesis
- Many women unaware of their pregnancy

Teratogenicity, while important, is not the only safety concern

Other Concerns in Pregnancy:
Dosing

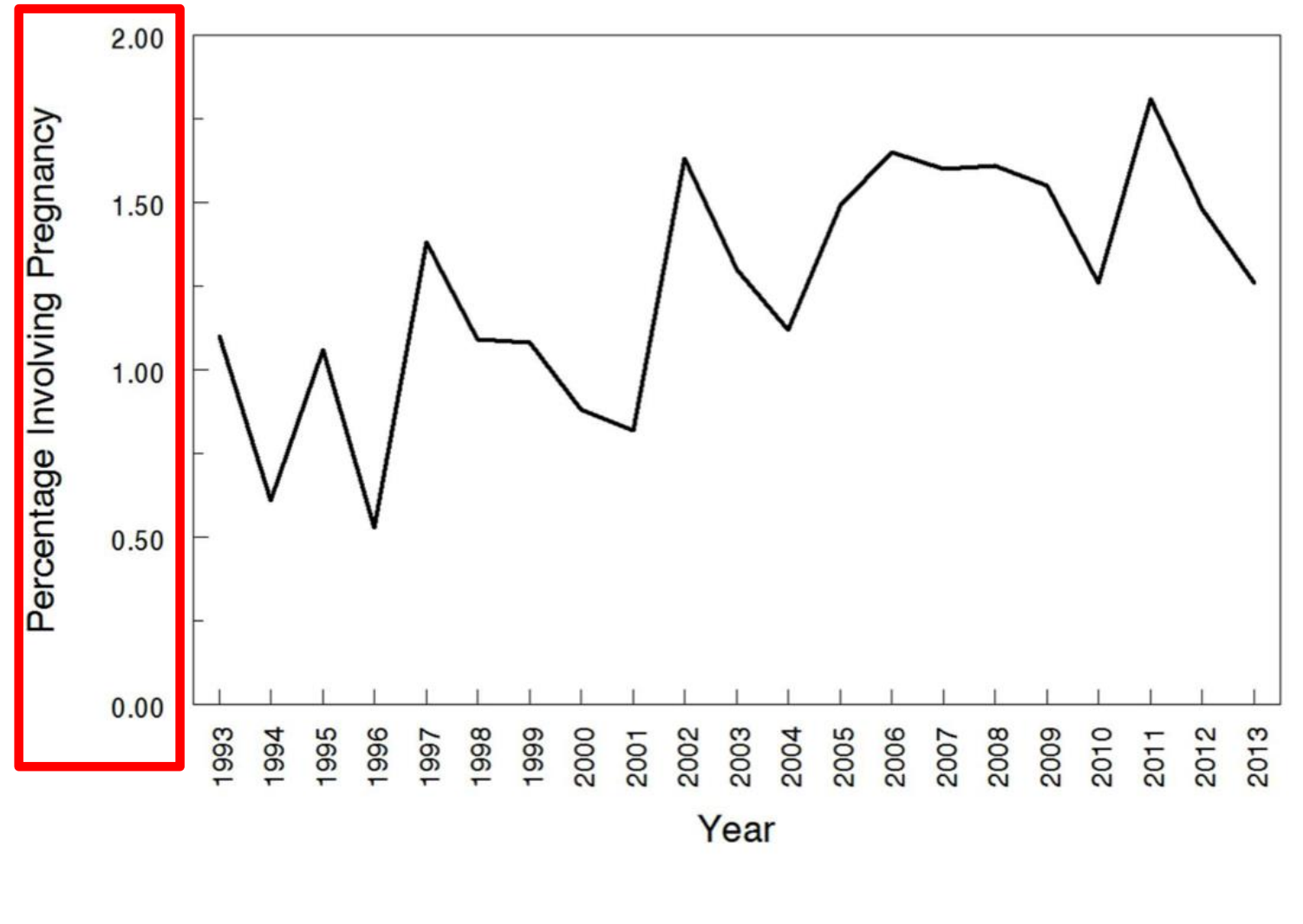
- Lack of data on dosage
- Vast majority of efficacy/safety studies done without knowledge of PK/PD

Proportions of PK trials in pregnancy



McComack & Best. Frontiers 2014

Proportions of PK trials in pregnancy



McComack & Best. Frontiers 2014

Exclusion of Pregnant Women:
Protocols reviewed by an IRB over 1 year

	Exclude pregnant women	Require Pregnancy Testing	Require Contraception
All Protocols (n=71)	53 (75%)	40 (56%)	42 (59%)
All drug studies (n=52)	48 (92%)	37 (71%)	41 (79%)
IND drug studies (n=38)	35 (92%)	31 (82%)	34 (89%)
Non-IND drug studies (n=14)	13 (93%)	6 (43%)	7 (50%)

Schonfeld T, et.al. IRB 2013

Concerns for medications use in pregnancy

- Lack of data on dosage
  - Physicians extrapolate drug dosage regimens from non-pregnant subjects or men
- Can lead to under or overdosing
  - Efficacy and toxicity might be affected

Pregnancy changes

- Pharmacokinetics

"What the body does to the drug"

- **ADME**
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination

- Pharmacodynamics

"What the drug does to the body"

- Clinical relevance
  - Efficacy
  - Safety

Drug disposition during pregnancy: physiologic changes

- Absorption:
  - Delayed gastric emptying and decreases GI motility
- Elimination
  - Increased GFR

Parry et al 1970, Gryboski and Spiro 1976, Pacheco et al. 2013, Hill and Pickinpaugh, 2008

Analysis of Weight Gain During Pregnancy

	Cumulative Increase in Weight (g) Up to:			
Tissues and Fluids	10 weeks	20 weeks	30 weeks	40 weeks (Total)
Fetus	5	300	1500	3400
Placenta	20	170	30	650
Amniotic fluid	30	350	750	800
Uterus	140	320	600	970
Breasts	45	180	360	405
Blood	100	600	1300	1450
Extravascular fluid	0	30	80	1480
Maternal stores (fat)	310	2050	3480	3345
Total	650	4000	8500	12,500

Chapter 8: Williams Obstetrics, 5th edition

Implications

- ↑ water --> larger volume of distribution of water soluble drugs
- ↑ fat --> larger volume of distribution for lipid soluble drugs

- ↓ maximal serum concentrations
  - Less effective
  - Higher dose to obtain therapeutic levels

Anger and Piquette-Miller, 2008
Dawes and Chowienczyk, 2001

Changes in Metabolizing Enzymes Activity & Apparent oral clearance

Drug/probe	Indication	Effect on CL/F (%)[a]			Metabolizing-enzyme activity changes
		T_1	T_2	T_3	
Caffeine*	CNS stimulant	↓ 33	↓ 48	↓ 65	↓ CYP1A2
Theophylline	Asthma	↔	↔	↓ 34	
Nicotine	Smoking cessation	NA	↑ 54	↑ 54	↑ CYP2A6
Phenytoin*,[b]	Epilepsy	↑ 43	↑ 51	↑ 61	↑ CYP2C9
Proguanil	Malaria	NA	↓ 60	↓ 60	↓ CYP2C19
Metoprolol*	Hypertension	NA	NA	↑ 459	↑ CYP2D6
Dextromethorphan[b]	Cough	↑ 26	↑ 35	↑ 48	
Midazolam*	Sedation	NA	NA	↑ 99	↑ CYP3A4
Indinavir	HIV infection	NA	NA	↑ 277	
Glyburide	Diabetes	NA	NA	↑ 106	
Methadone	Addiction	NA	↑ 101	↑ 65	↑ CYP2B6
Labetalol	Hypertension	NA	↑ 30	↑ 30	↑ UGT1A1
Lamotrigine	Epilepsy	↑ 200	↑ 200	↑ 300	↑ UGT1A4
Zidovudine[c]	HIV infection	NA	NA	↔	↔ UGT2B7
Amoxicillin	Bacterial infection	NA	↑ 23	↑ 20	↑ Renal CL
Metformin*	Diabetes	↑ 22	↑ 28	↑ 11	
Digoxin*	Cardiac diseases	NA	NA	↑ 19	

Ke AB et al. Annu Rev Pharmacol toxicol 2014

Need Drug Research in Pregnancy and Lactation

Preeclampsia

- 5-7 %
- 1/5 of all maternal death in the US
- 50,000/yr maternal death from eclampsia in the world

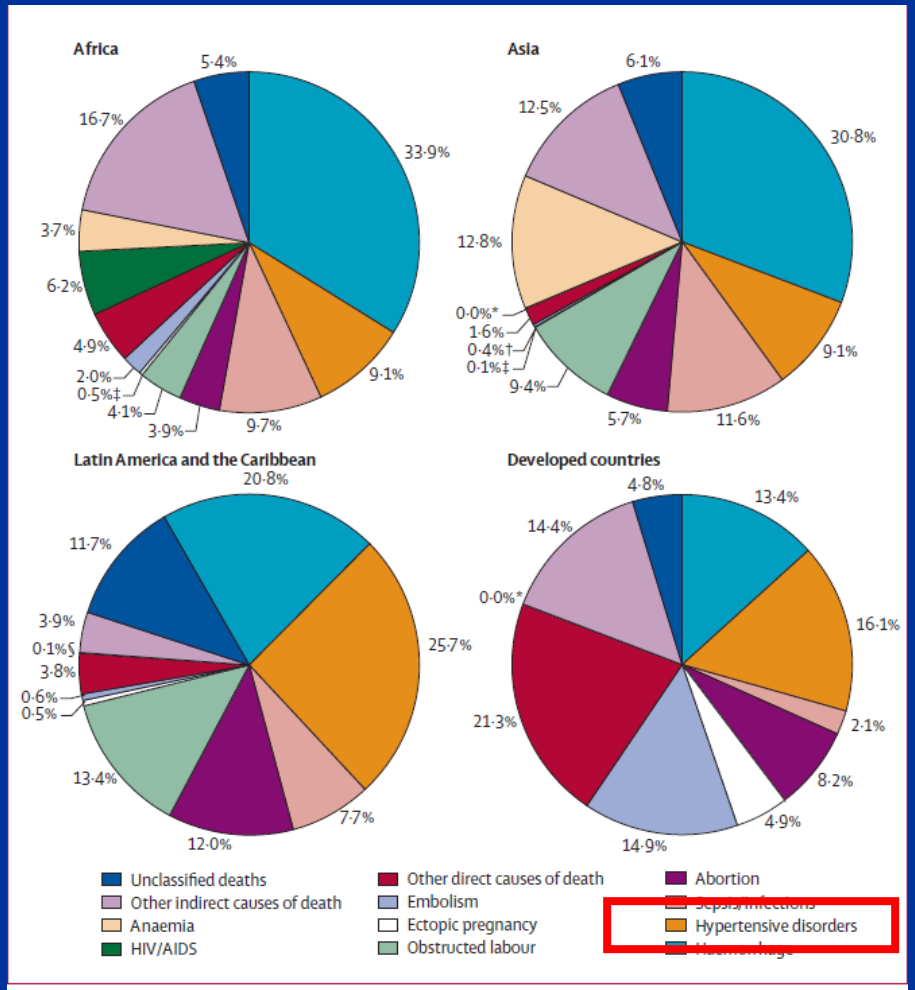


Figure 3: Geographical variation in distribution of causes of maternal deaths
*Represents HIV/AIDS. †Represents embolism. ‡Represents ectopic pregnancy. §Represents anaemia.

Complications in severe preeclampsia

Maternal

- Eclampsia
- CVA
- Uncontrolled hypertension
- Kidney injury
- Pulmonary edema
- Liver injury
- Death

Fetal/neonatal

- Stillbirth
- Abruption
- Growth restriction
- Premature delivery
- Long term adverse outcomes

Preeclampsia: a Cardiovascular Disease

- Overlapping pathophysiology & common risk factors
  - DM, HTN, Obesity, Dyslipidemia
- Common mechanisms
  - Inflammation
  - Endothelial dysfunction
- American Heart Association - 2011

Brends et al. Hypertension 2008
Hansson et al. NEJM 2005
Redman et al. Science 2005

Prevention

- Preeclampsia prevention
  - Ca, Vit C & E, fish oil
  - Low dose aspirin

- Cardiovascular disease prevention
  - HMG-CoA reductase inhibitors (statins)

Barton et al Obstet Gynecol 2008

Askie et al Lancet 2007

Brugts et al BMJ 2009

Mills et al J Am Coll Cardiol 2008

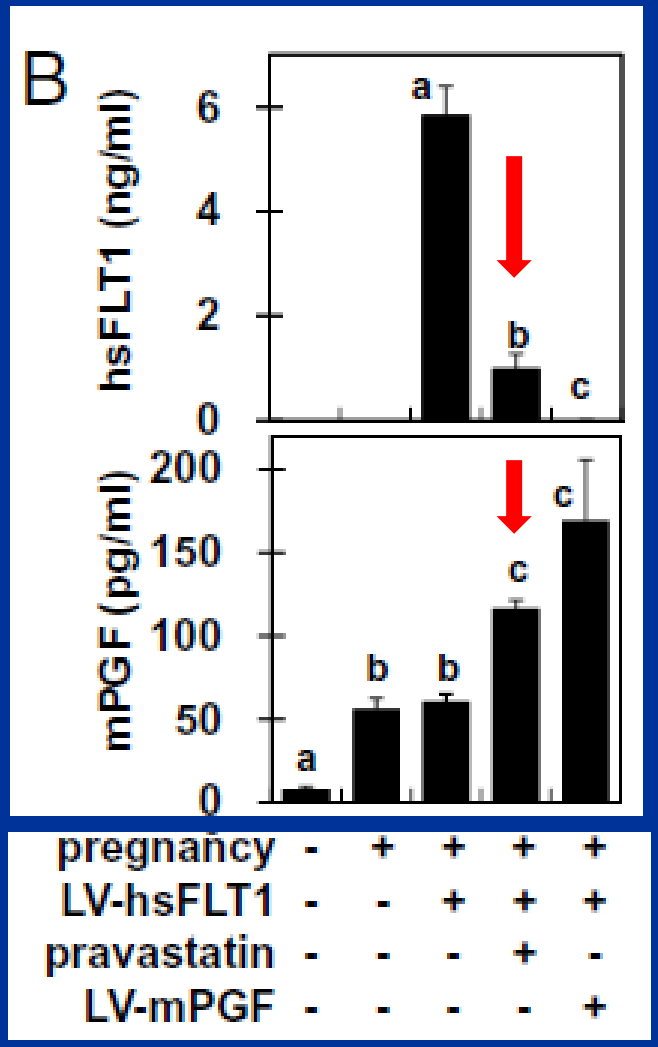
Statins for Preeclampsia Prevention

Murine Preeclampsia Model sFlt-1 expression

- High BP
- Altered vascular profile
- Proteinuria
- Glomerular endotheliosis
- Placental hypoxia
- IUGR

Kumasawa et al. PNAS 2011
Maynard et al., JCI 2003
Lu et al., Am J Obstet Gynecol 2007

Pravastatin in Animal Models of Preeclampsia



- ↓ sFlt-1 & ↑ PlGF
- ↓ BP
- ↑ eNOS
- Improves vascular reactivity
- ↓ Proteinuria
- ↓ Oxidative stress
- Restores fetal growth

- No ↑ pup resorption
- No pup deformation

Kumasawa et al. PNAS 2010
Costantine et al., Obs Gyn 2010
Ahmed et al., PLoS ONE 2010
Singh et al, HTN 2011
Fox et al., AJOG 2011
Bauer et al, HTN 2013

Can We Use Statins in Pregnancy?

Class X

- Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

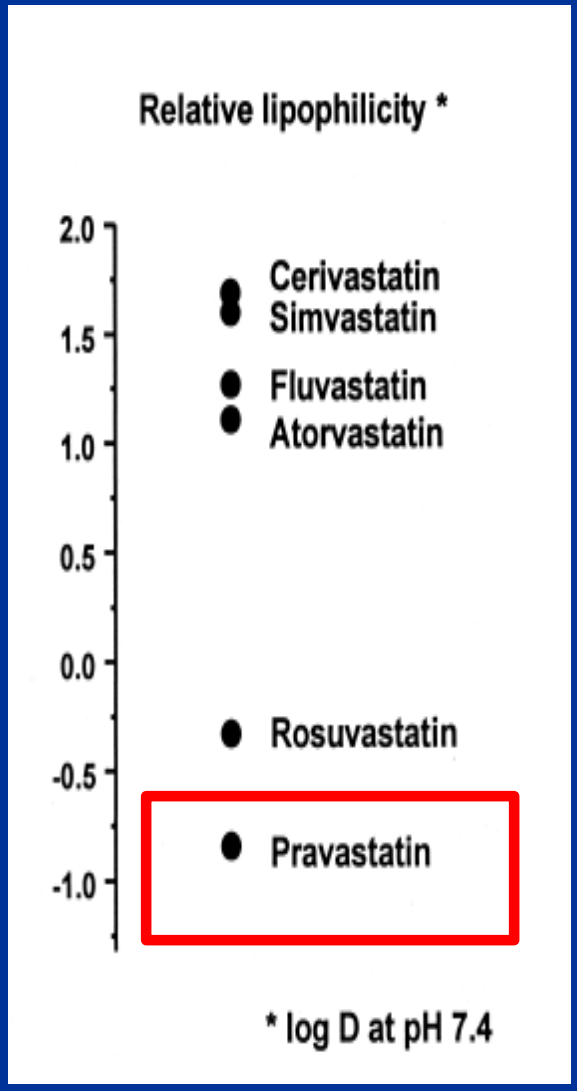
Pravastatin: Pregnancy Experience

- Animal data:
  - Not teratogenic (10-120x human exposure)
  - No effect on placental and pup weights

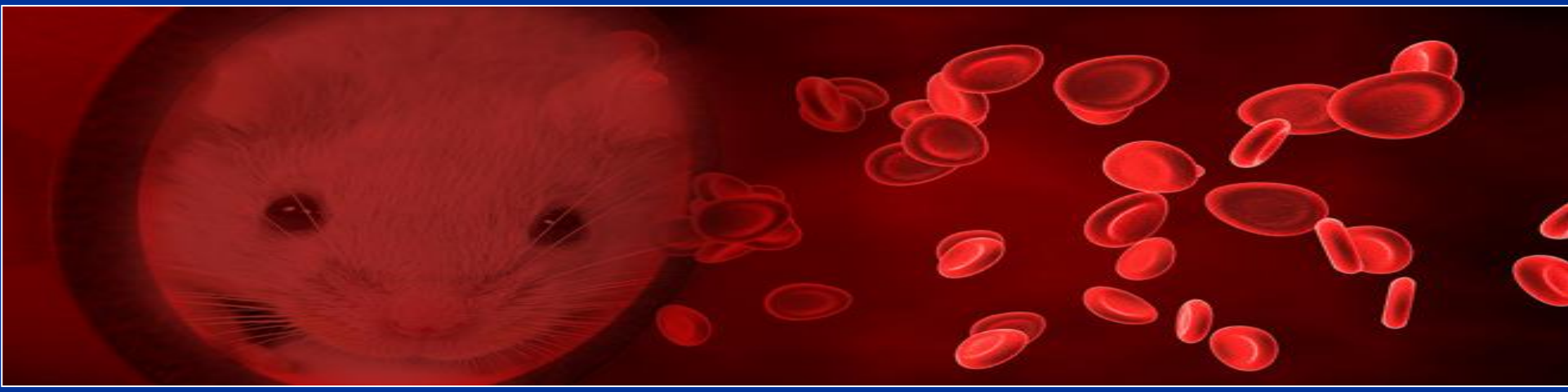
- Human Cohorts:
  - No increased rate of congenital anomalies, SAB, IUFD.
  - No effect on fetal growth

Bateman et al. BMJ 2015, Eddison et al. Am J Med Genet 2004, Taguchi et al. Reprod Toxicol 2008, Ofori et al. Br J Clin Pharm 2007, Winterfeld et al. Br J Ob Gynecol2013, Kumasawa K et al. PNAS 2011, ArmentI & Brent, personal communications

Relative Lipophilicity of Statins



McTaggart, Am J Cardiol 2001

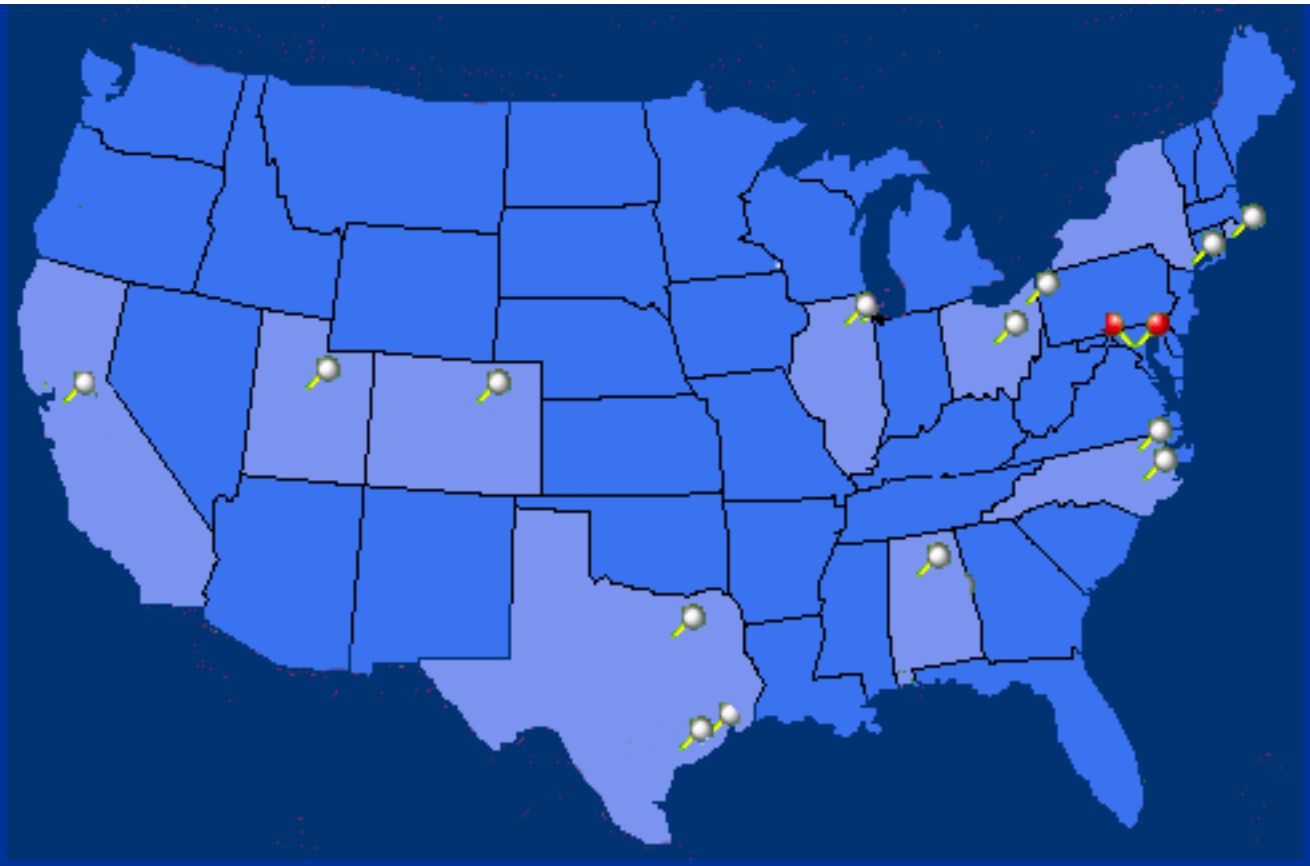


A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

utmb Health

Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Maternal-Fetal Medicine Units Network



UAB - Birmingham
Houston
Brown University
Chapel Hill
UT
UNC
Case Western
University of Colorado
Ohio State University
Northwestern
Stanford University
Duke University
SW - Dallas
UTMB-
Texas

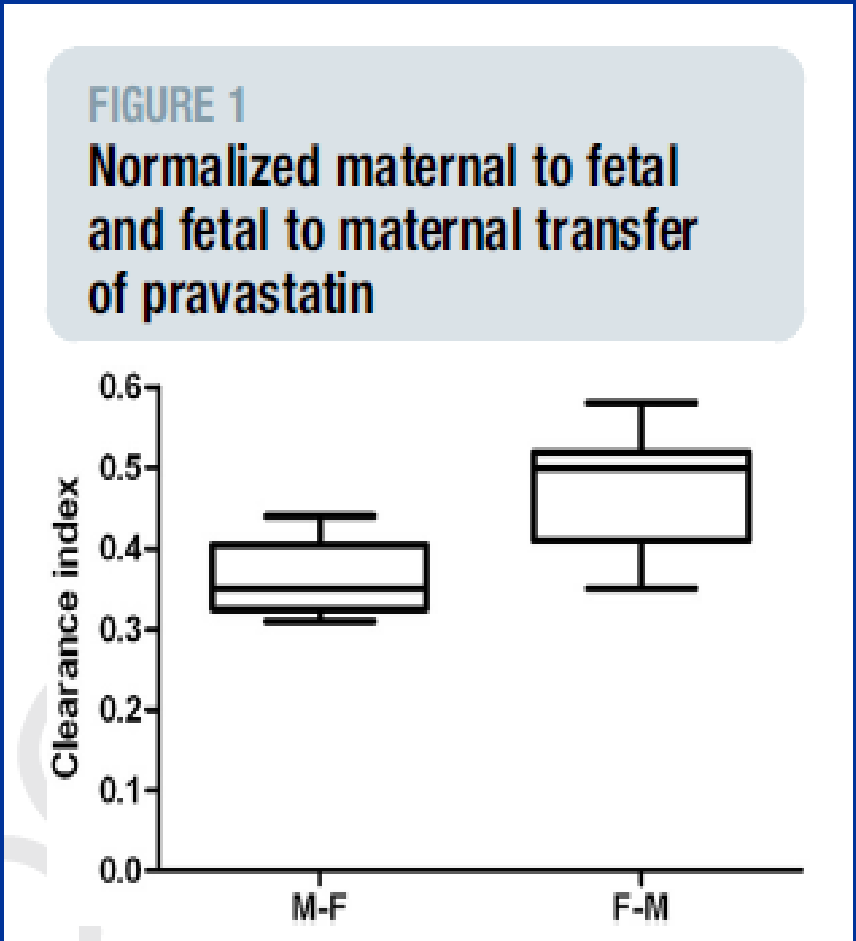
VOTE

9 YES 7 NO

Transplacental transfer and distribution of pravastatin

Tatiana N. Nanovskaya, PhD; Svetlana L. Patrikeeva, MS; Jonathan Paul, PhD; Maged M. Costantine, MD; Gary D. V. Hankins, MD; Mahmoud S. Ahmed, PhD

Placental transfer studies:
Clearance index



Nanovskaya et al, Am J Obstet Gynecol 2013

Placental transfer studies

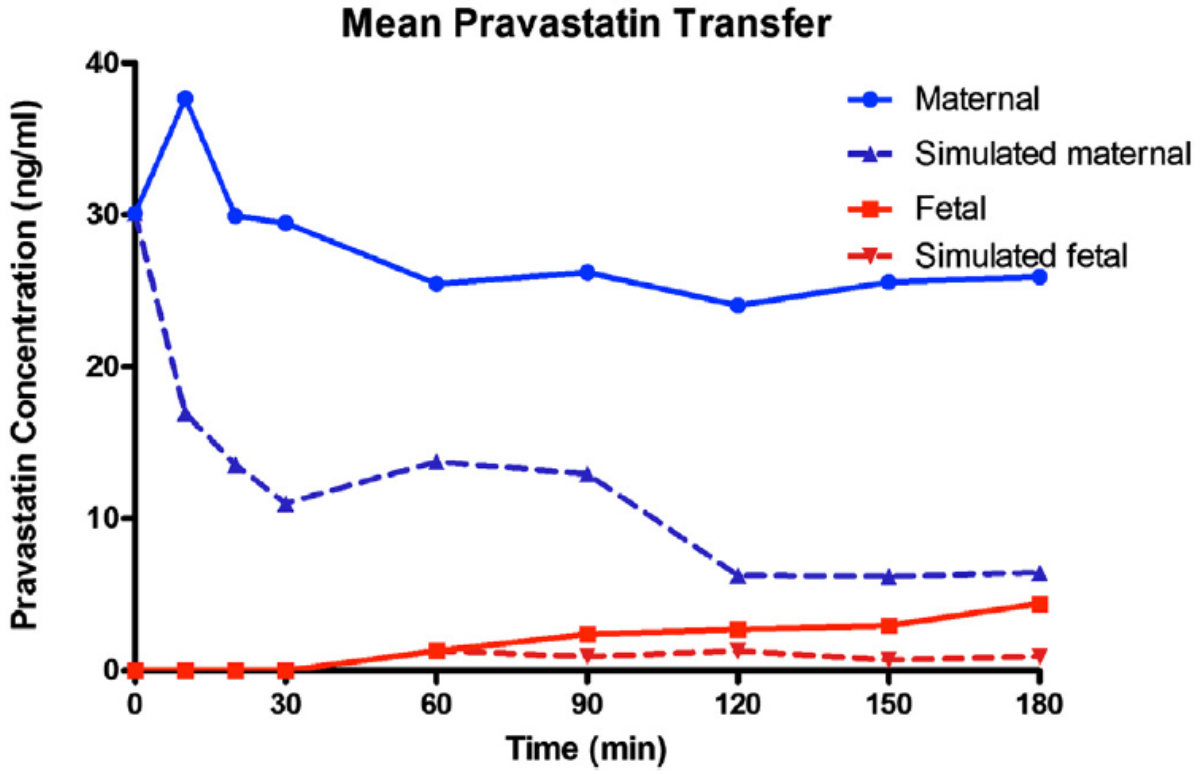
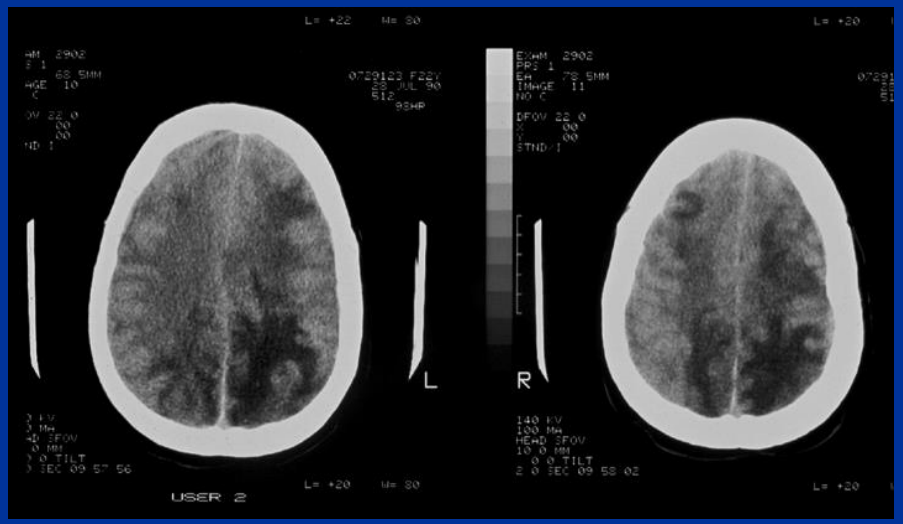


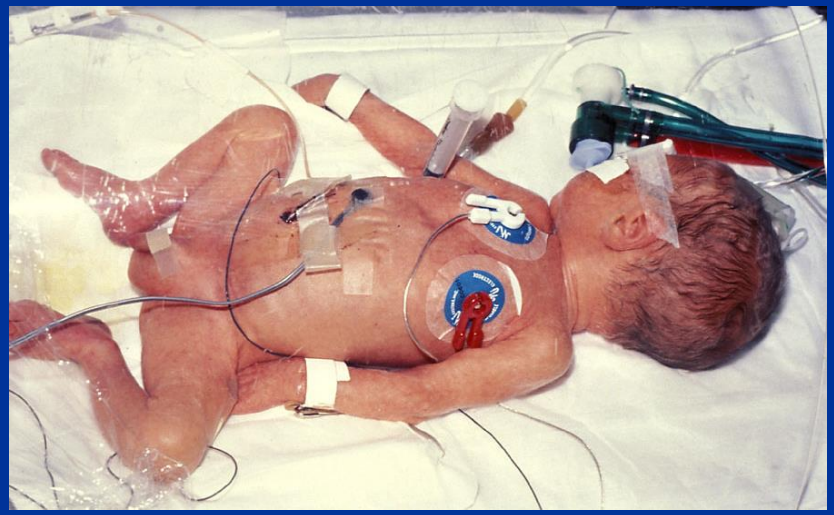
Fig. 1. Mean pravastatin transfer with simulation to correct for protein binding and elimination half life.

Zarek et al, Placenta 2013

Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Pilot Study

Obstetric-Fetal Pharmacology Research Units (OPRU) Network
The National Institute of Child Health and Human Development





Primary Research Questions

- What are the Pharmacoknetic properties and maternal and fetal safety profiles of pravastatin when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia?

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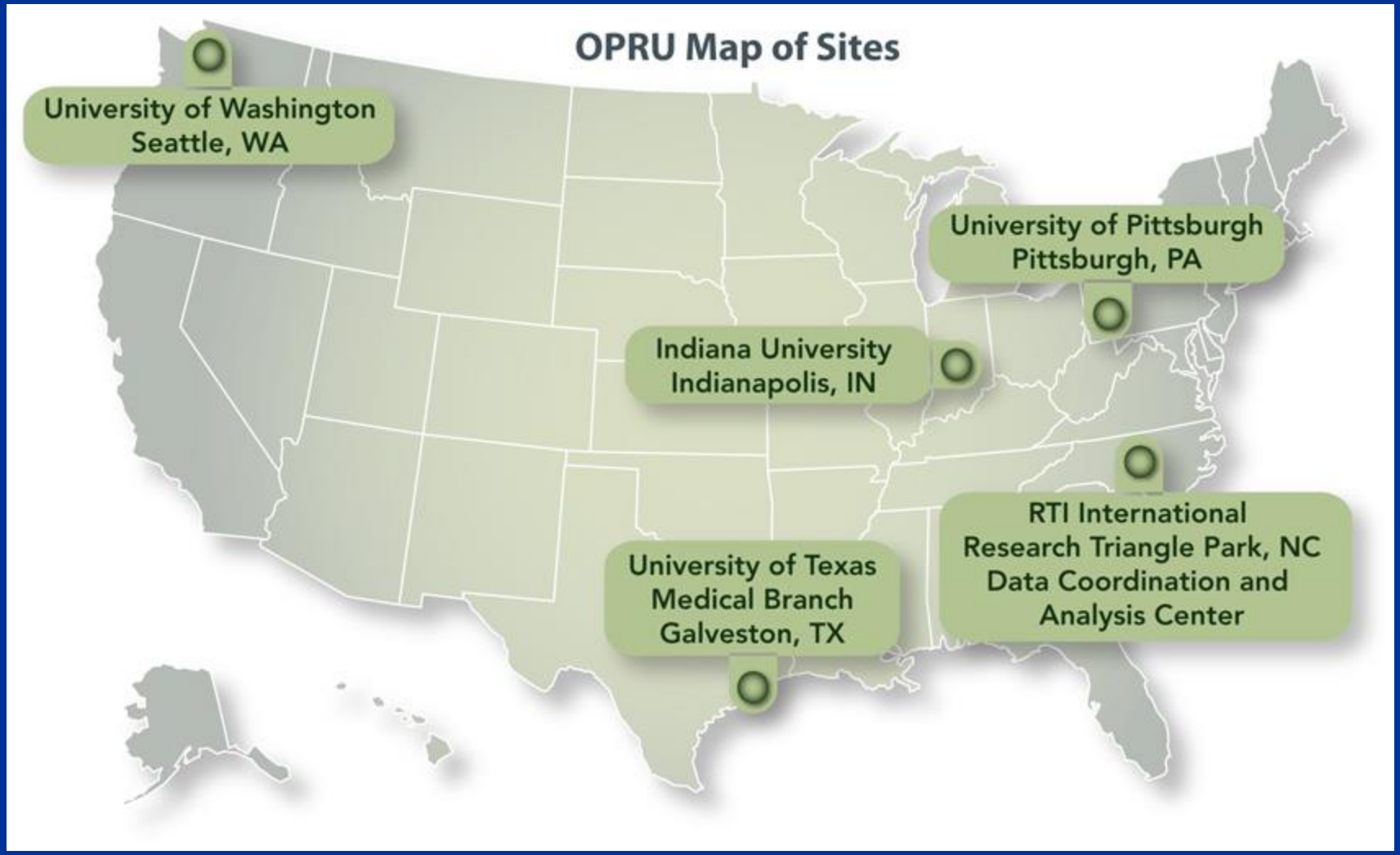
Obstetric-Fetal Pharmacology Research Units Network

ClinicalTrials.gov

NCT01717586

NICHD-OPRU


OPRU Map of Sites
University of Washington
Seattle, WA
University of Pittsburgh
Pittsburgh, PA
Indiana University
Indianapolis, IN
RTI International
Research Triangle Park, NC
Data Coordination and
Analysis Center
University of Texas
Medical Branch
Galveston, TX

OBSTETRICS

Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial

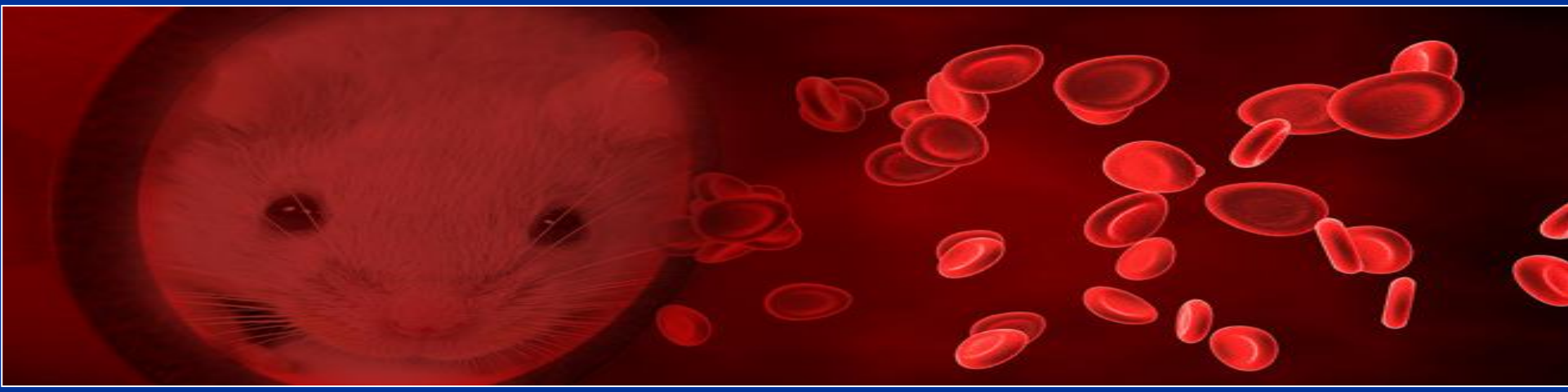
Maged M. Costantine, MD; Kirsten Cleary, MD; Mary F. Hebert, PharmD, FCCP; Mahmoud S. Ahmed, PhD; Linda M. Brown, DrPH; Zhaoxia Ren, MD, PhD; Thomas R. Easterling, MD; David M. Haas, MD, MS; Laura S. Haneline, MD; Steve N. Caritis, MD; Raman Venkataramanan, PhD; Holly West, DHEd; Mary D'Alton, MD; Gary Hankins, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network

ClinicalTrials.gov

NCT01717586

Estimated steady-state pravastatin pharmacokinetics in subjects during the second and third trimesters of pregnancy compared with postpartum

Parameter	18–24 wks gestation (n = 11)	30–34 wks gestation (n = 10)	4–6 mo postpartum (n = 9)
C_{max}, ng/mL	14.9 ± 11.3	11.1 ± 6.2	17.2 ± 11.5
T_{max}, h	1.6 ± 0.6	1.5 ± 0.4	1.6 ± 1.0
Half-life$_{apparent}$, h	2.1 ± 0.9	3.0 ± 1.6	2.4 ± 1.3
CL/F, L/h	396 ± 190	389 ± 215	289 ± 142
CL/F, L/h/kg	4.6 ± 2.4	4.2 ± 2.0	3.2 ± 1.5
$AUC_{(0\text{-}24)}$, ng/h/mL	31 ± 16	32 ± 16	43 ± 20
Amount excreted$_{(0\text{-}24\ h)}$, mg	0.98 ± 0.60	1.04 ± 0.57	0.93 ± 0.60
Percent excreted unchanged	10 ± 6	10 ± 6	9 ± 6
CL_{renal}, L/h	34 ± 16[a]	34 ± 11[a]	23 ± 4
$CL_{secretion}$, mL/min	480 ± 273[a]	471 ± 151[a]	325 ± 65



A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

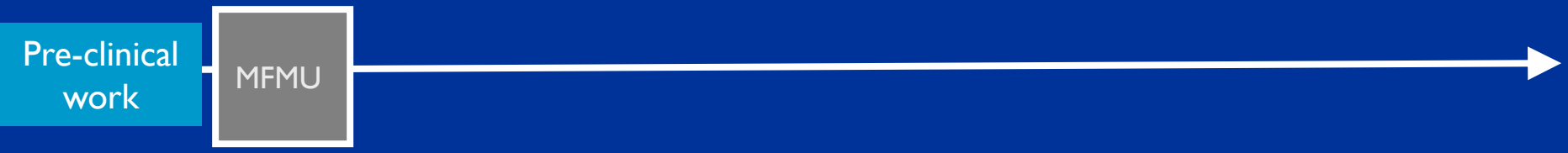
utmb Health

VOTE

15 YES 1 NO

Project Development Timeline

Project Development Timeline



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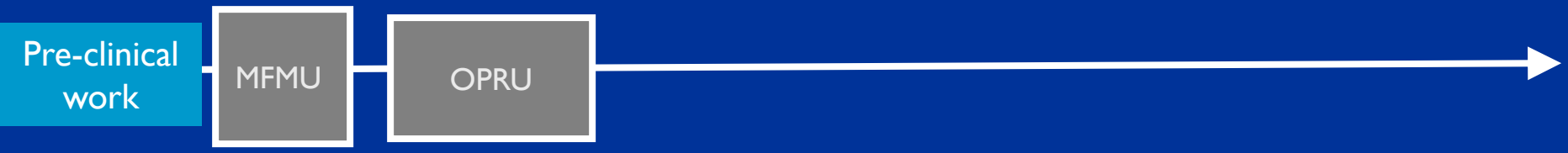

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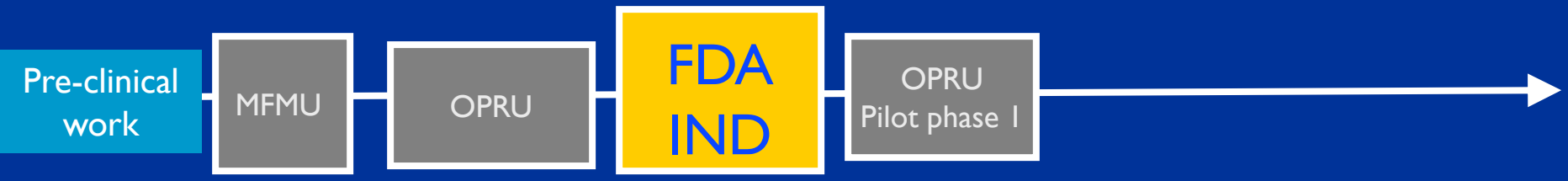

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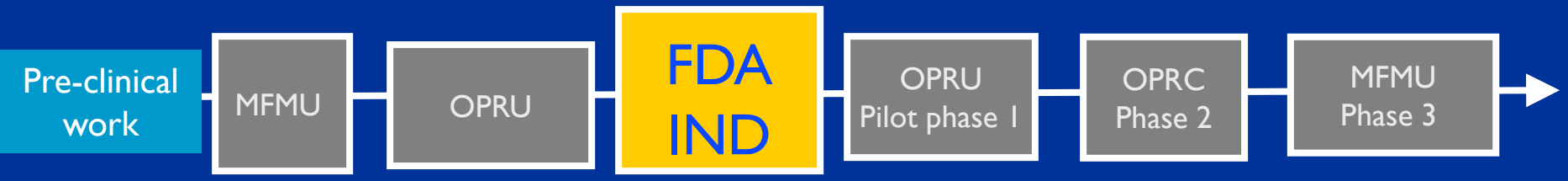

OPRU – Other Studies

- Glyburide and 17 OHP biotransormation
- Diclectin
- Opportunistic study
- Oseltamivir
- Glyburide and Metformin for GDM
- PD impact of vaginal and IM progestin on cervix

NICHD-OPRC
Current Sites

- University of Texas Medical Branch, Galveston, TX
  - Pravastatin to prevent preeclampsia
- Northwestern University, Chicago, IL
  - SSRI
- University of Pittsburg, Pittsburg, PA
  - Bupronorphine

- DM-Stat, Boston, MA

Challenges in conducting medications trials in pregnancy

- Patient enrollment
- Unlikely to consent when healthy
- Physiologic adaptations of pregnancy
- Perceived risk to pregnant women and fetuses/infants
- Pharmaceutical companies interest

Cohen-Wolkowiez M. obstet gynecol 2014

Possible Solutions

- Sampling strategies
- PK/PD modeling and simulation
- Increasing the support of PK trials in pregnancy
  - Private/government-funded organizations
  - Support existing networks charged to perform obstetric-fetal pharmacology studies
  - Incentivize pharmaceutical companies
  - Obstetric pharmacology training programs
- Legislation

Cohen-Wolkowiez M. 2014

UTMB

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Tatiana Nanovskaya, PhD
Shannon Clark, MD
Wayne Snodgrass, MD, PhD
Sherif Abdel-Rahman, PhD
Erik Rytting, PhD

Perinatal Research Division

Holly West, ANP
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Eunice Kennedy Shriver - NICHD
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1 R01 HD083003

Eunice Kennedy Shriver – NICHD

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DM STAT

Kim Dukes, PhD
Julie Peterson

University of Pittsburg

Steve Caritis, MD
Raman Venkataramanan, PhD

Northwestern University

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Catherine Stika, MD
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Thomas Easterling, MD
Mary Hebert, PhD

Columbia University
Kirsten Cleary, MD
Mary D'Alton, MD

RTI
Linda Brown, PhD
Katrina Burson, RN

Eunice Kennedy Shriver – NICHD U10HD047891, U10HD063094, U10HD047892, U10HD047905, and U10HD057753

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Thank You

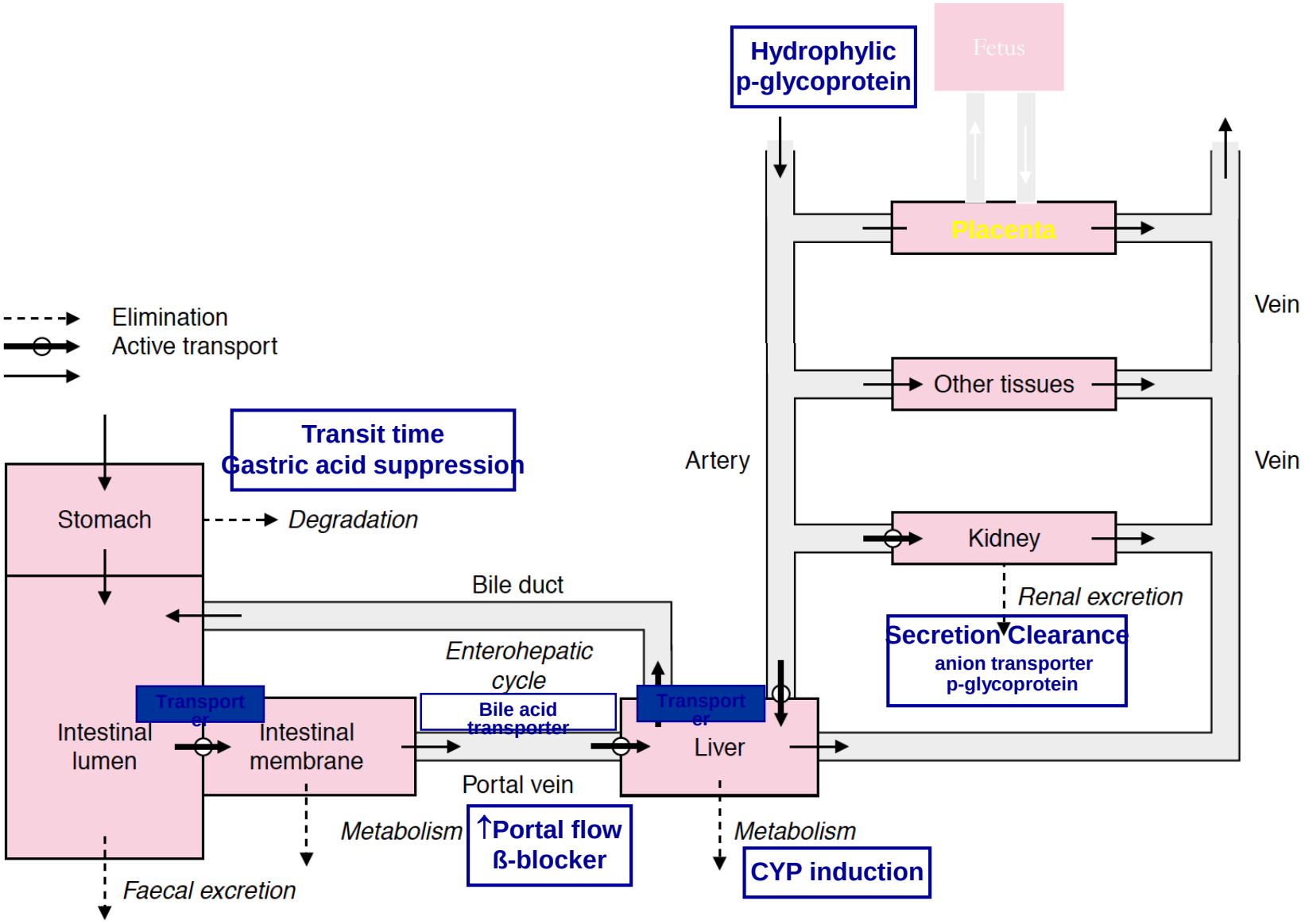


Fig. 3. Simplified view of the pharmacokinetics of pravastatin in humans.

Modified from Hatanaka T. Clin Pharmacokinet 2000

T Easterling, MD

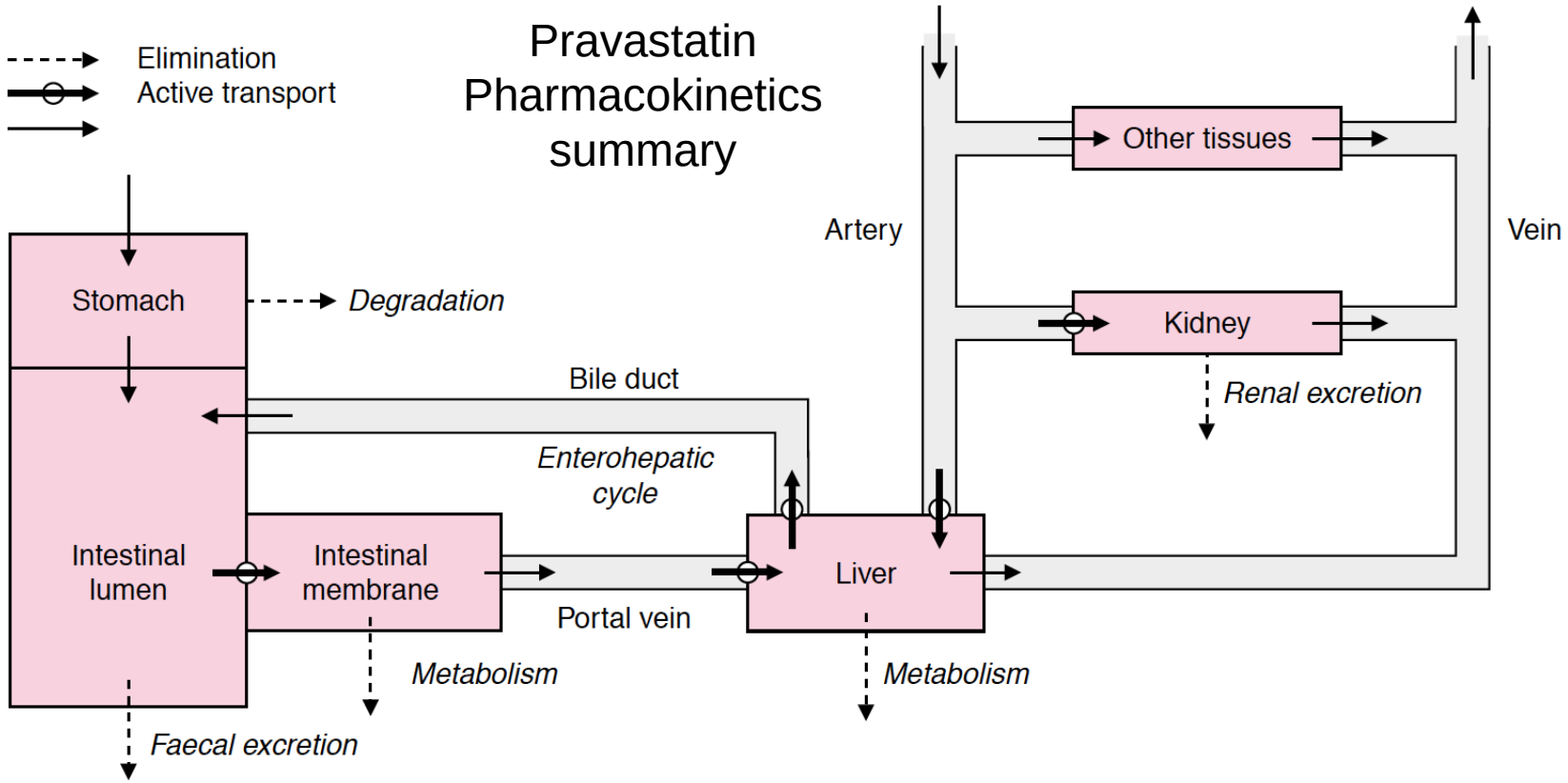


Fig. 3. Simplified view of the pharmacokinetics of pravastatin in humans. *Hatanaka T. Clin Pharmacokinet 2000*

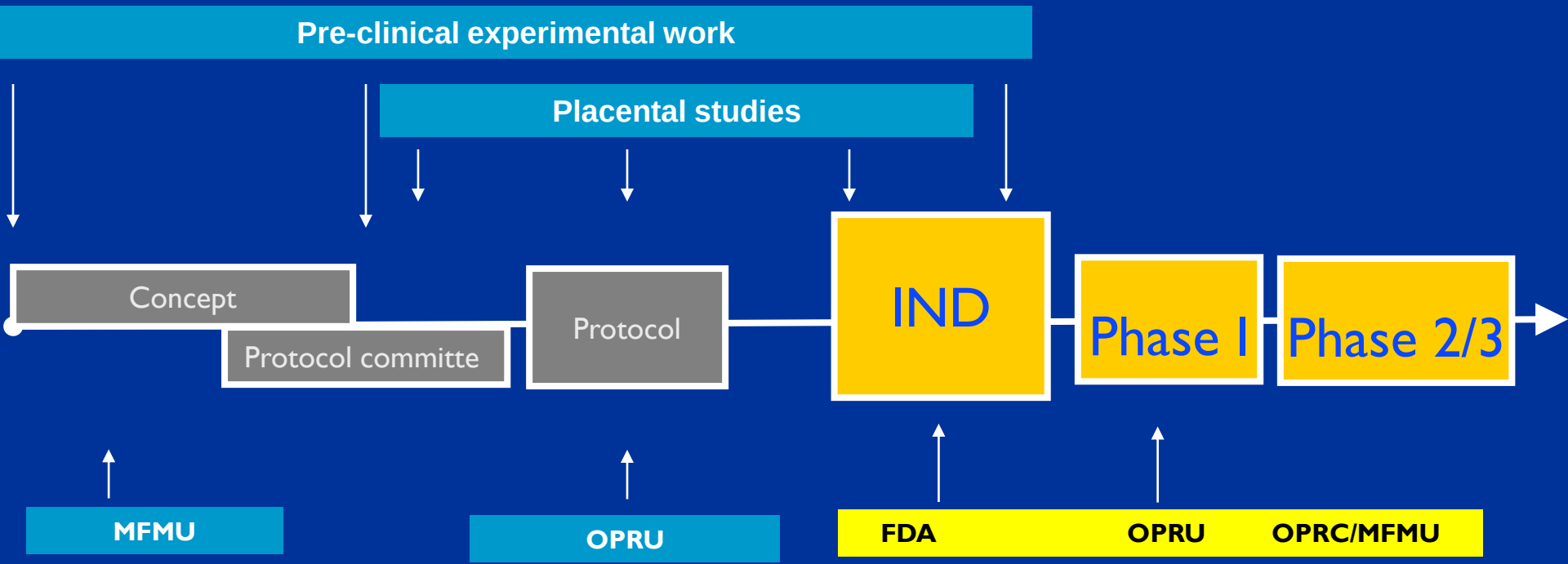
MW 446
β-hydroxy acid
Hydrophilic
Protein binding (43-54%)
High extraction ratio
Hepatoselective
Organic anion transporter
Biliary secretion (23% fecal)
Renal tubular secretion (47%)

portal flow (↓10% AUC - ß blocker)
CYP metabolism, minor - oxidized metabolites
- 1000-fold < other statins

P-glycoprotein
- CNS - substrate (undetectable in brain)

Grapefruit juice - no interaction
Cyclosporin
- heart transplant 20-fold increase in AUC
- renal transplant - several-fold higher

Project Development Timeline - Pravastatin



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