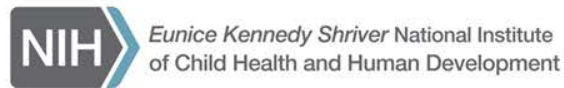


Research on Drugs in Pregnancy and Lactation at NIH

FDA Public Workshop: Evaluation of the Safety of Drugs and
Biological Products used during Lactation

April 27-28, 2016

Zhaoxia Ren, MD, PhD





Disclosure

No conflict of interest in relation to this program/presentation



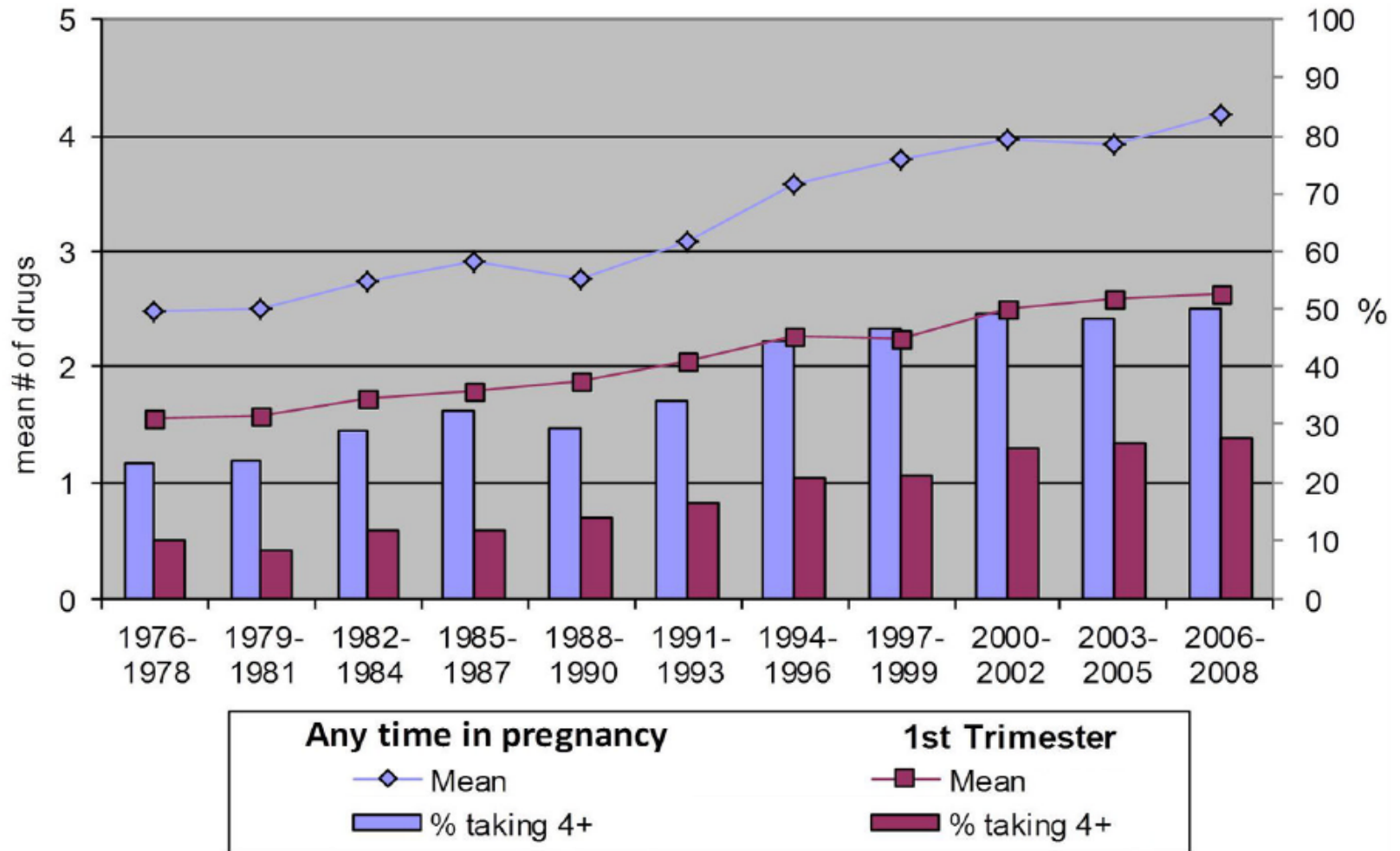
Background and Introduction

- 90% of women take at least one medication during pregnancy
- 50% of pregnant women take 3- 4 medications during pregnancy
- Few drugs used in pregnancy are FDA-approved
- Pharmacokinetic (PK) data are practically non-existent for drugs used in pregnancy
- Dosing regimens of most drugs in pregnancy are based on PK studies in men and NP women
- Pharmacodynamic (PD) data mostly based on data from men and non-pregnant women like PK data





Medications Use During Pregnancy



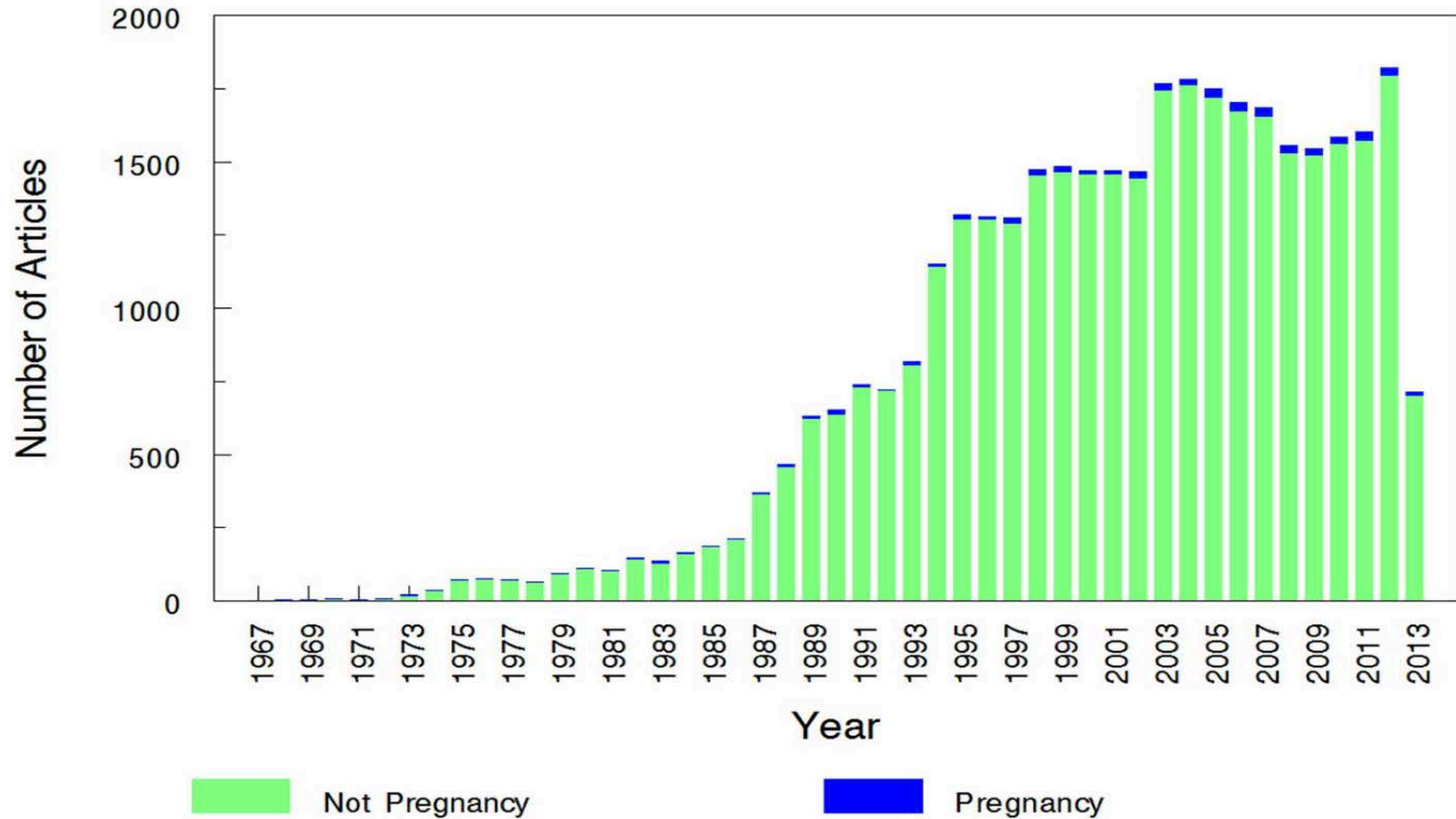


Medications approved 2003-2012

- Pregnancy data:
 - 92.9% based on animal studies
 - 5.2% based on human pregnancy data
- Breast feeding:
 - 47.9% - no data
 - 42.7% - animal data
 - 4.7% - human data



Proportion of PK trials in pregnancy





Obstacles

Problems Intrinsic to Pregnancy

- Liability discourages Pharma involvement
- Market is relatively small
- Revenue benefit is small
- Studies require long term fetal evaluation
- Off- label use of most drugs

Obstetric-Fetal Pharmacology Research Units Network/Centers (OPRU/OPRC)

- OPRU was established in 2004 under a cooperative agreement mechanism.
- Changed to specialized centers in 2015
- Mission: improve the safety and effective use of therapeutic drugs in women during pregnancy and postpartum.
- Goal: promote and facilitate cooperative research to enhance the understanding of obstetric pharmacokinetics and pharmacodynamics.

OPRU/OPRC

- **Objectives and Scope**
 - Provide critical research infrastructure for PK and PD studies of the drugs used in pregnant women
 - Take a multidisciplinary approach through the collaboration of clinical and basic science researchers across the network
 - Perform basic, translational and clinical studies (phase I/II trials) to characterize and evaluate the impact of physiological, cellular, and molecular changes during pregnancy on drug disposition



Research Activities Of OPRU 2004-2009

- **Glyburide in Gestational Diabetes**
 - PK, PD in gestational diabetics and type 2 diabetics, and drug effects during and after pregnancy
 - Placental transport and metabolism of the drug in human and non-human pregnancies with gestational diabetes
- **17-alpha hydroxyprogesterone caproate to prevent preterm labor**
 - Basic science - non-human primate model of PK, mechanisms of action
 - PK model of drug disposition in pregnant women
- **Opportunistic Studies**
 - Drugs being used for medications of diseases/conditions as part of routine clinical care during pregnancy
 - PK in trimester 1,2,3, postpartum and in breast milk
 - Prioritize list: drugs for depression, epileptic seizures, asthma, allergy, nausea and vomiting, flu, hypertension, chemotherapy, and immunosuppressants for organ transplants



Research Activities 2010-2014

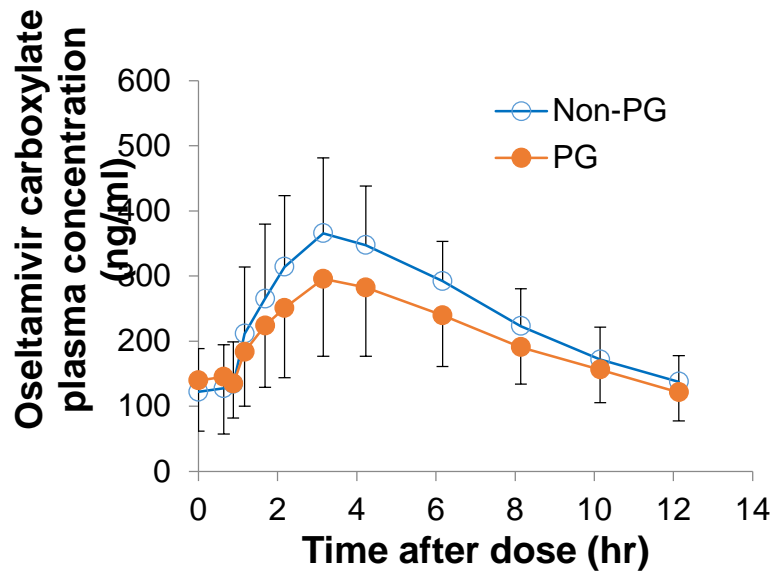
- Glyburide and Metformin for Gestational Diabetes Mellitus (GDM)
 - Prospective, randomized phase I/II trial
 - PK and PD effects for oral anti-diabetic drugs (glyburide and metformin) and the effects of monotherapy as well as combination therapy in the management of GDM
- Pravastatin for the Prevention of Preeclampsia in High-Risk Women
 - Dose finding and escalating randomized, double-blind, placebo-controlled phase I trial (low dose)
 - Published the result: Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Costantine MM. et al [Am J Obstet Gynecol.](#) 2015 Dec 23. pii: S0002-9378(15)02586-7
- Determining the Pharmacodynamic Impact of Vaginal and IM Progestins
 - Exploratory study to identify biomarkers of response and non-response to the progestins
 - Mechanisms of the drug action

Current ongoing Research Activities

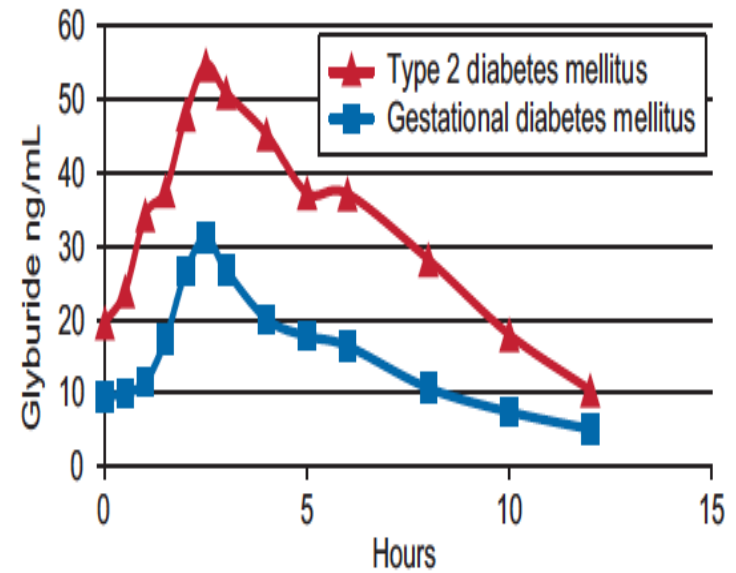
- Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Phase I Pilot Study:
 - Higher dose
 - Active enrolling
- Impact of Pregnancy on Buprenorphine Pharmacokinetics and Pharmacodynamics:
 - To determine the impact of pregnancy on the pharmacokinetics of buprenorphine (BUP) and its metabolites after sublingual administration.
 - To evaluate potential infant exposure to BUP and metabolites through breast milk.
- Optimizing Medication Management for Mothers with Depression (OPTI-MOM):
 - Pharmacokinetics of SSRIs during pregnancy;
 - CYP450 activity and genotyping to predict drug plasma concentrations across pregnancy, and the impact on SSRI efficacy
 - Postpartum (plasma and urine drug screen)

Pharmacokinetic differences between pregnant and non-pregnant subjects

oseltamivir (Tamiflu)

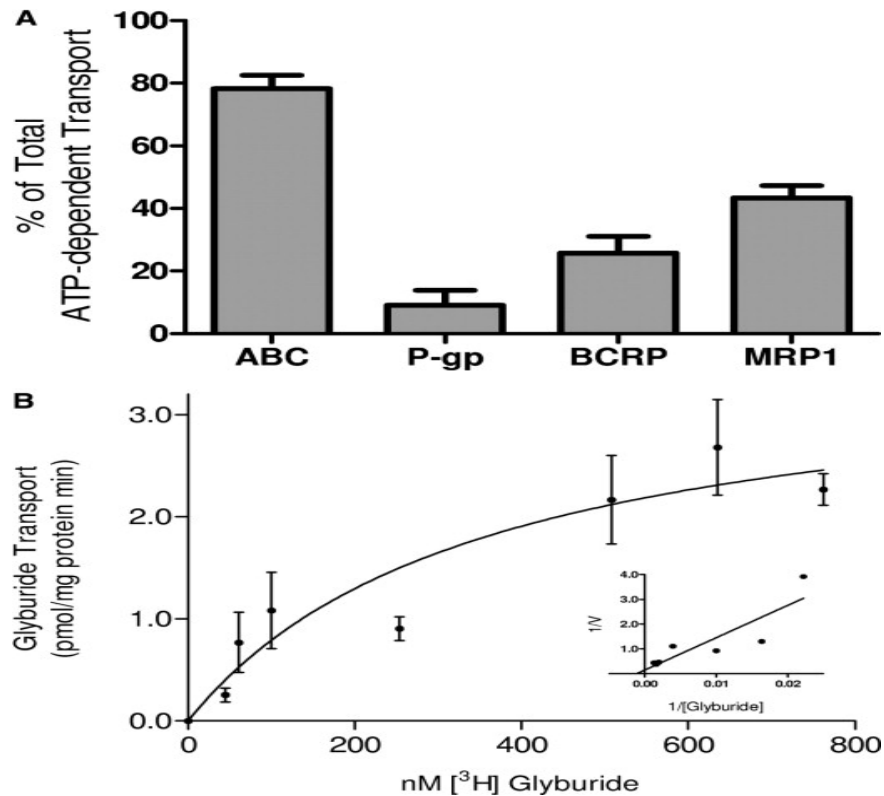


Glibenclamide (Glyburide)





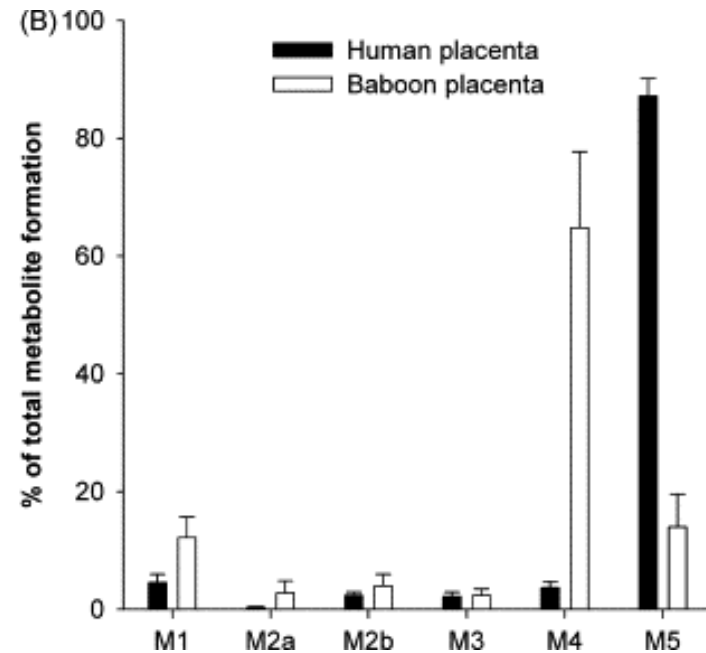
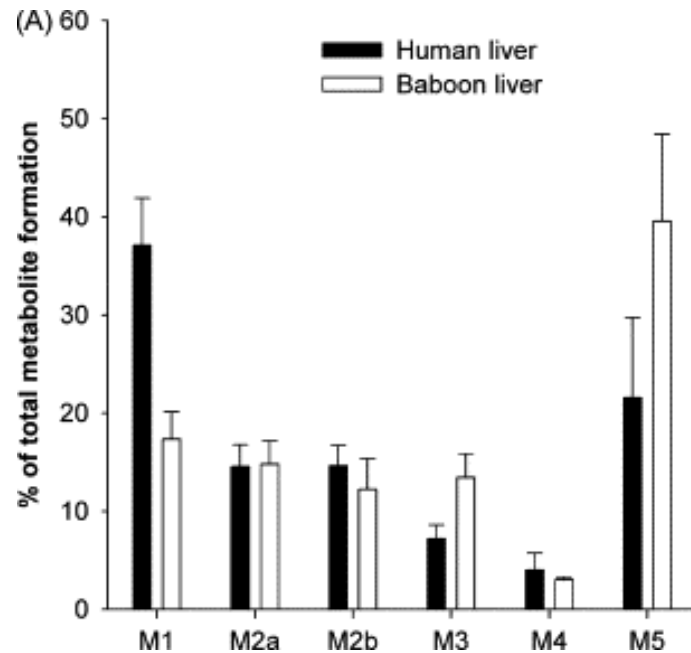
Glyburide Placental Transport



Glyburide efflux by placental ABC transporters



Metabolism of Glyburide by Hepatic and Placental Microsomes





OPRU Studies on Lactation

[Pharmacokinetics of metoprolol during pregnancy and lactation.](#)

Ryu RJ, Eyal S, Easterling TR, Caritis SN, Venkataraman R, Hankins G, Rytting E, Thummel K, Kelly EJ, Risler L, Phillips B, Honaker MT, Shen DD, Hebert MF.
J Clin Pharmacol. 2016 May;56(5):581-9.

[Tacrolimus placental transfer at delivery and neonatal exposure through **breast milk**.](#)

Zheng S, Easterling TR, Hays K, Umans JG, Miodovnik M, Clark S, Calamia JC, Thummel KE, Shen DD, Davis CL, Hebert MF.
Br J Clin Pharmacol. 2013 Dec;76(6):988-96.

[Duration of cisplatin excretion in **breast milk**.](#)

Hays KE, Ryu RJ, Swisher EM, Reed E, McManus T, Rybeck B, Petros WP, Hebert MF.
J Hum Lact. 2013 Nov;29(4):469-72.

[Interpreting tacrolimus concentrations during pregnancy and postpartum.](#)

Hebert MF, Zheng S, Hays K, Shen DD, Davis CL, Umans JG, Miodovnik M, Thummel KE, Easterling TR.
Transplantation. 2013 Apr 15;95(7):908-15.

[Atenolol pharmacokinetics and excretion in **breast milk** during the first 6 to 8 months postpartum.](#)

Eyal S, Kim JD, Anderson GD, Buchanan ML, Brateng DA, Carr D, Woodrum DE, Easterling TR, Hebert MF.
J Clin Pharmacol. 2010 Nov;50(11):1301-9.

[Pharmacokinetics of metformin during pregnancy.](#)

Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GD, Clark SM, Risler L, Wang J, Kelly EJ, Shen DD, Hebert MF.
Drug Metab Dispos. 2010 May;38(5):833-40.

[Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum.](#)

Hebert MF, Carr DB, Anderson GD, Blough D, Green GE, Brateng DA, Kantor E, Benedetti TJ, Easterling TR.
J Clin Pharmacol. 2005 Jan;45(1):25-33.



Difficulties of doing these studies

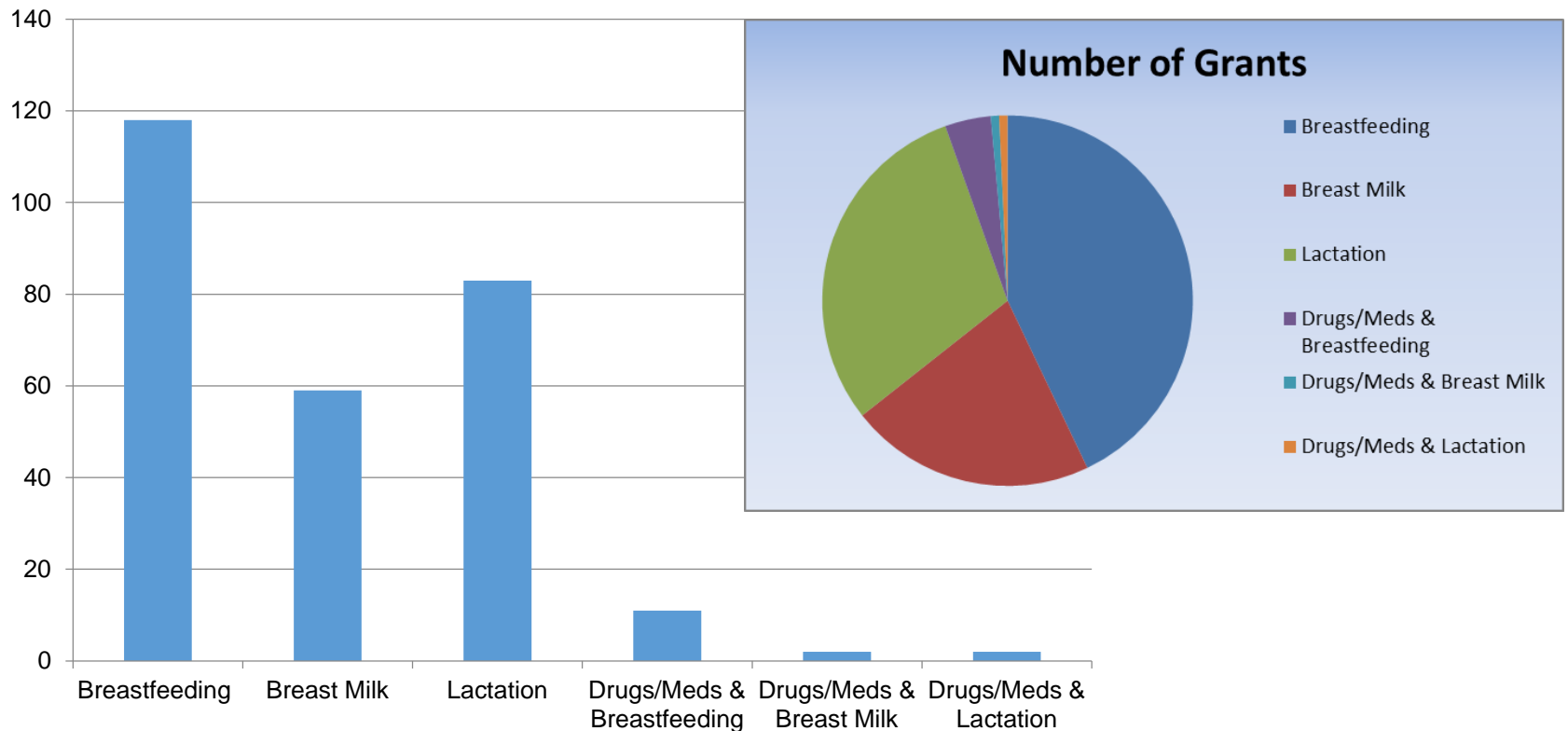
- Collection of breast milk and blood samples (mother and baby)
- Resources to accommodate nursing mother and baby
- Follow up with breastfeeding mothers
- Need for assays that measure drugs in breast milk
- Need for modeling and simulation





Lactation-Related Research Activities Funded by NICHD

Number of Grants





Drugs/Meds & Breastfeeding

- Safer Weaning Practices for HIV-infected women
- The Role of Human Milk in Infant Nutrition and Health
- ART and risk of preterm delivery in a rural high HIV prevalence area
- Pregnancy Outcomes and Infant Survival in the Era of Universal HAART in Africa
- Genetic Variations and HIV Transmission in India
- Developmental and Growth Outcomes for ARV Exposed HIV Uninfected African Children
- Resistance in HIV-infected infants after extended ARV prophylaxis
- Strategies to optimize ART services for maternal & child health
- Early determinants of childhood obesity: Etiology, disparities, policy
- Financial Incentives for Smoking Cessation Among Disadvantaged Pregnant Women



Drugs/Meds & Breast Milk / Lactation

- Maternal, Clinician & Hospital Factors in Breastmilk for Premature Infants
- Differences in Breastmilk Composition and Infant Growth between Healthy and Overweight
- Optimization of Drug Dosing in Pregnant Women through Research and Education (OPRU T32)
- The Perinatal Pharmacology of the Nuclear Receptor (basic science in developmental pharmacology)



Conclusion

- Most drugs have not been tested in nursing mother and their effect on infant is unknown
- Gaps in knowledge in drugs used during lactation
- What is needed?
 - Promote research in this area
 - Training MDs, PhDs, PharmDs and others with research focus on pharmacology in pregnancy and lactation



Acknowledgement

- Steve Caritis, MD, Magee Womens Hospital, University of Pittsburgh