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

Any time in pregnancy
- Mean
- % taking 4+

1st Trimester
- Mean
- % taking 4+

Mitchell A. et al AJOG 2011
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

Mazar-Amirshahi M. et al. AJOG 2014
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)

- 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 (OPTIMOM):**
  - 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)

Beigi et al AJOG Supplement JUNE 2011
Glyburide Placental Transport

Glyburide efflux by placental ABC transporters

Metabolism of Glyburide by Hepatic and Placental Microsomes

Zharkova et al., Biochem Pharmacol 2007;73:2012-9; 2009; 78:1483-1496
OPRU Studies on Lactation

**Pharmacokinetics of metoprolol during pregnancy and lactation.**

**Tacrolimus placental transfer at delivery and neonatal exposure through breast milk.**

**Duration of cisplatin excretion in breast milk.**
Hays KE, Ryu RJ, Swisher EM, Reed E, McManus T, Rybeck B, Petros WP, Hebert MF.

**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.

**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.

**Pharmacokinetics of metformin during pregnancy.**

**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.
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 and simulation
Lactation-Related Research Activities Funded by NICHD

Number of Grants

Breastfeeding: 120
Breast Milk: 60
Lactation: 80
Drugs/Meds & Breastfeeding: 10
Drugs/Meds & Breast Milk: 5
Drugs/Meds & Lactation: 3

Number of Grants

- Breastfeeding
- Breast Milk
- Lactation
- Drugs/Meds & Breastfeeding
- Drugs/Meds & Breast Milk
- Drugs/Meds & Lactation
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, PharmD's and others with research focus on pharmacology in pregnancy and lactation
Acknowledgement

- Steve Caritis, MD, Magee Women's Hospital, University of Pittsburgh