State of research on medications used during pregnancy and lactation

August 21, 2017

Anne Zajicek, MD, PharmD

Deputy Director, Office of Clinical Research

NIH Office of the Director

Disclosure

- I have nothing to disclose.
- My presentation reflects my views only, not those of the NIH or the federal government.

Topics

- Medical conditions in pregnancy
- Medications used during pregnancy and breast-feeding
- Impact
- Maternal-fetal and maternal-infant drug transfer
- Physiologic changes in pregnancy
- Current state of knowledge for existing medications
- Drug development for new medications in pregnancy
- Where we need to be
  - Mechanistic approach to disease understanding and pre-clinical toxicology
  - New drug development with novel drug targets
  - Reliable, valid, feasible short and long term outcome measures
  - methods to determine dosing, safety, efficacy

Frequent medical conditions in pregnancy and lactation

Conditions caused by/co-existing in Pregnancy

- Pregnancy-induced hypertension
- Pre-eclampsia
- Preterm labor
- Gestational Diabetes Mellitus
- Depression
- Infections
- Pain
- Nausea and vomiting of pregnancy

Pre-Existing medical Conditions

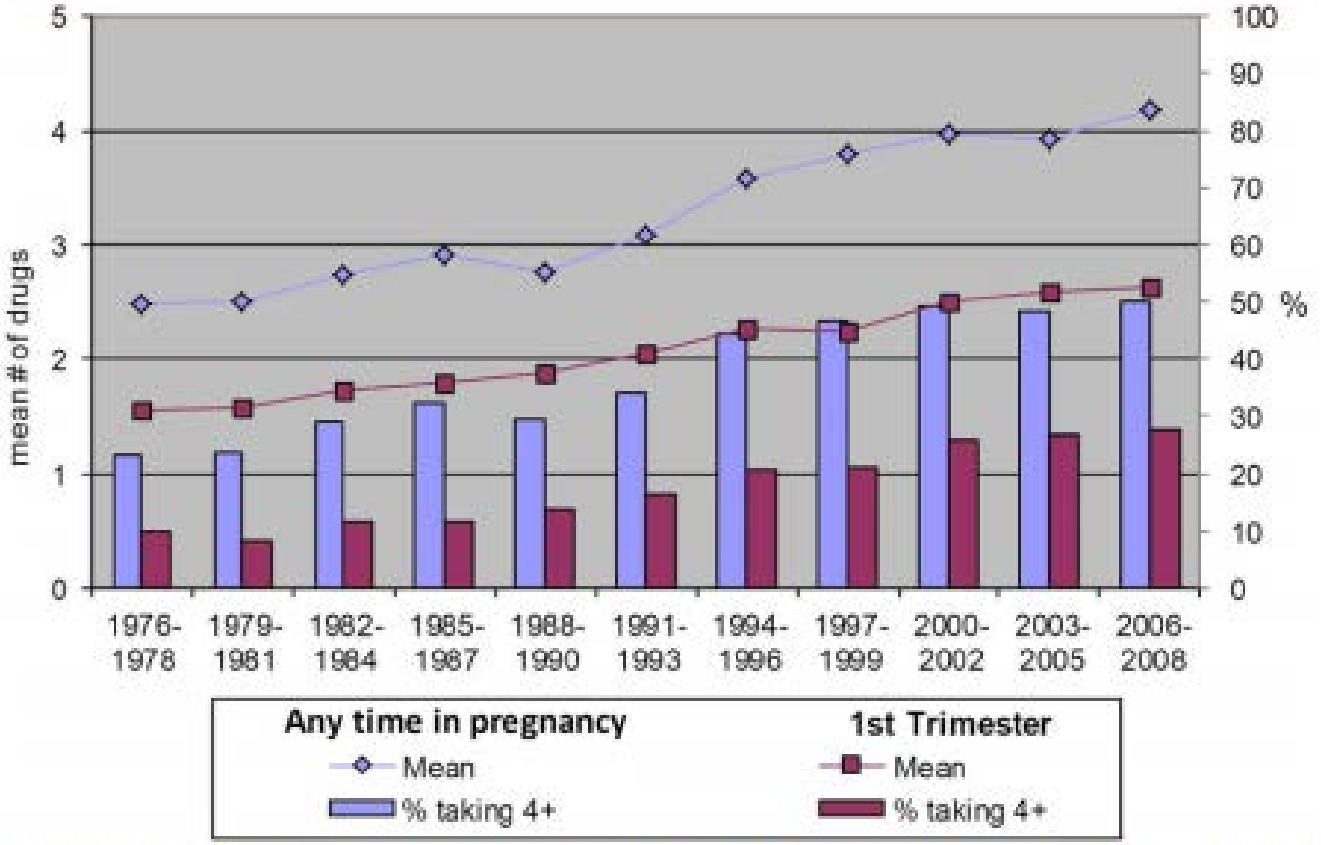
- Hypertension
- Diabetes mellitus
- depression
- Seizure disorder
- Cancer
- Endocrine disorders
- Substance abuse
- Autoimmune disorders

Summary

- Widespread medication use in pregnancy
- Extremely limited data on dosing, safety, efficacy of medications used during pregnancy and breastfeeding
- Many medications used off-label for pregnancy-related conditions do not have a non-pregnant correlate
- Sparse basic science in pregnancy-related conditions

FIGURE 1

BDS: secular patterns of use of any medication at any time during pregnancy and restricted to the first trimester



BDS, 1976-2008, Boston and Philadelphia centers. Secular patterns of use of any medication at any time during pregnancy and restricted to the first trimester. Average number of medications and proportion of women taking 4 or more medications (n = 25,313) is shown.

BDS, Birth Defects Study.

Mitchell. Overall medication use in pregnant women. Am J Obstet Gynecol 2011.

The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the U.S. Medicaid Program

Palmsten, Kristin ScD; Hernández-Díaz, Sonia MD, DrPH; Chambers, Christina D. PhD, MPH; Mogun, Helen MS; Lai, Sophia PharmD; Gilmer, Todd P. PhD; Huybrechts, Krista F. MS, PhD

Obstetrics & Gynecology: September 2015 - Volume 126 - Issue 3 - p 465–473
doi: 10.1097/AOG.0000000000000982

Table 1. The 20 Most Commonly Dispensed Prescription Medications During Pregnancy, Overall Prevalence, Stratified by Pregnancy Period

Medication	During Pregnancy	3 Mo Prepregnancy	1st Trimester	2nd Trimester	3rd Trimester
Nitrofurantoin	21.6	1.4	7.0	9.1	9.8
Metronidazole	19.4	4.5	5.8	9.1	7.7
Amoxicillin	18.0	5.7	7.1	7.2	6.6
Azithromycin	16.9	4.5	6.0	7.1	6.6
Promethazine	13.5	2.0	8.4	4.9	3.4
Cephalexin	12.7	3.1	4.2	4.7	5.6
Codeine and acetaminophen	10.7	3.9	3.4	4.5	4.7
Terconazole	10.2	0.9	2.2	4.3	5.5
Hydrocodone and acetaminophen	9.6	7.7	5.0	3.7	3.5
Albuterol	8.1	3.8	3.8	4.1	3.8
Acetaminophen	5.5	1.2	2.2	2.4	2.0
Metoclopramide	4.8	0.3	2.9	1.6	1.0
Ibuprofen	4.8	8.3	3.5	1.1	0.6
Penicillin V	4.5	2.5	1.9	1.6	1.4
Clindamycin	4.4	1.4	2.0	1.6	1.3
Miconazole	4.4	0.4	1.1	1.7	2.0
Fluconazole	4.0	2.5	1.5	1.3	1.8
Sulfamethoxazole and trimethoprim	4.0	3.4	1.9	1.3	1.0
Amoxicillin and clavulanate	3.8	1.8	1.4	1.3	1.4
Ampicillin	3.8	0.3	1.0	1.3	1.7

Data are %.
N=1,106,757 for each column.

PMID: 23108737

US Births (2015) and fetal medication exposure

3,978,497

https://wonder.cdc.gov/wonder/help/natality.html

SSRI 6%
N=238,710
PMID 27178125

AED 2.2%
N=87,527
PMID 23865818

Asthma 7%
N=278,495
PMID 23108737

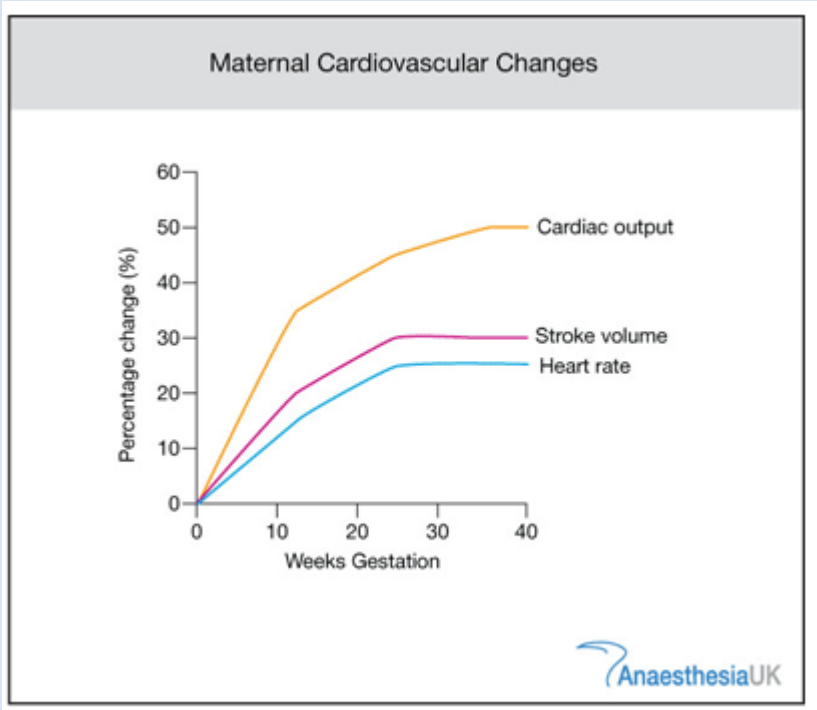
Drugs with pregnancy indications

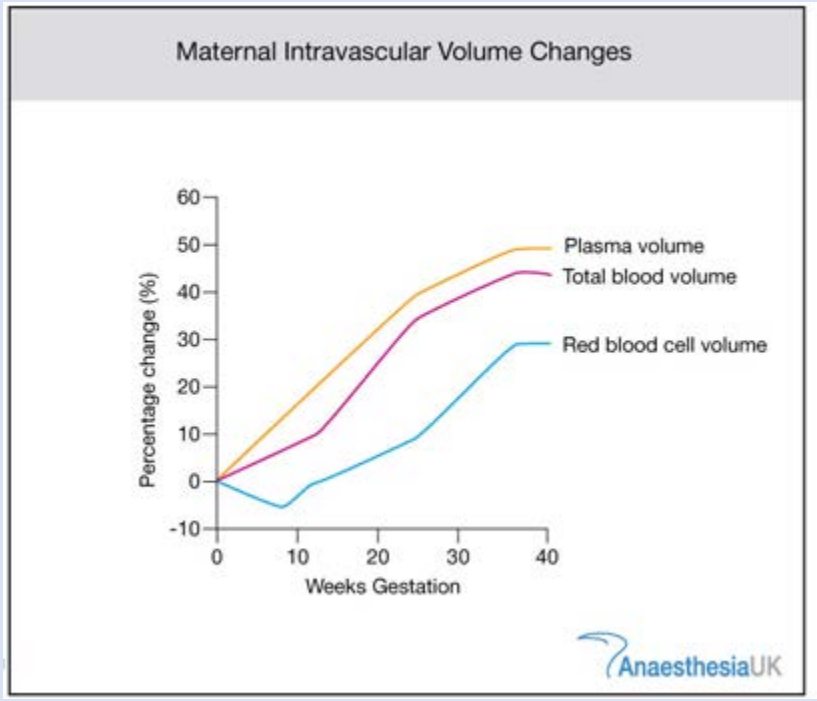
- Pre-term labor: 17-alpha-hydroxyprogesterone caproate
- Nausea and vomiting of pregnancy: Doxylamine + vitamin B6

Questions to consider

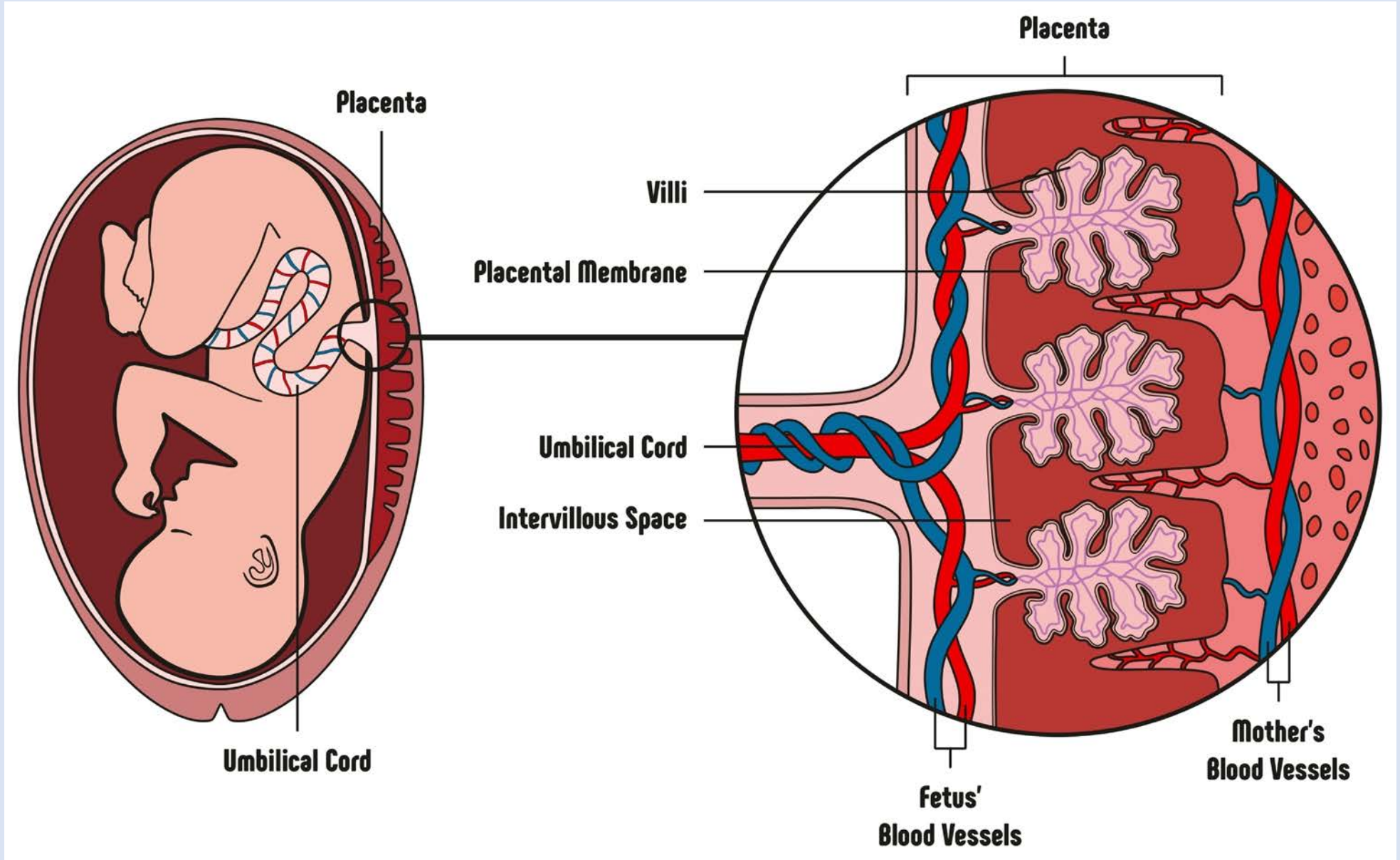
- What is the clinical problem?
- Is there sufficient basic science research investigating the disease mechanism?
- Has the basic research provided any drug targets?
- Is there a condition during pregnancy mechanistically similar to a condition occurring outside of pregnancy?
  - Is pre-eclampsia similar to hypertension?
  - Is gestational diabetes mellitus similar to type 2 diabetes mellitus?
  - Is preterm labor similar to an asthma attack?
- Is a pregnant woman the same as a non-pregnant woman, in terms of drug concentration time course and drug effect?

Examples of physiologic changes in pregnancy

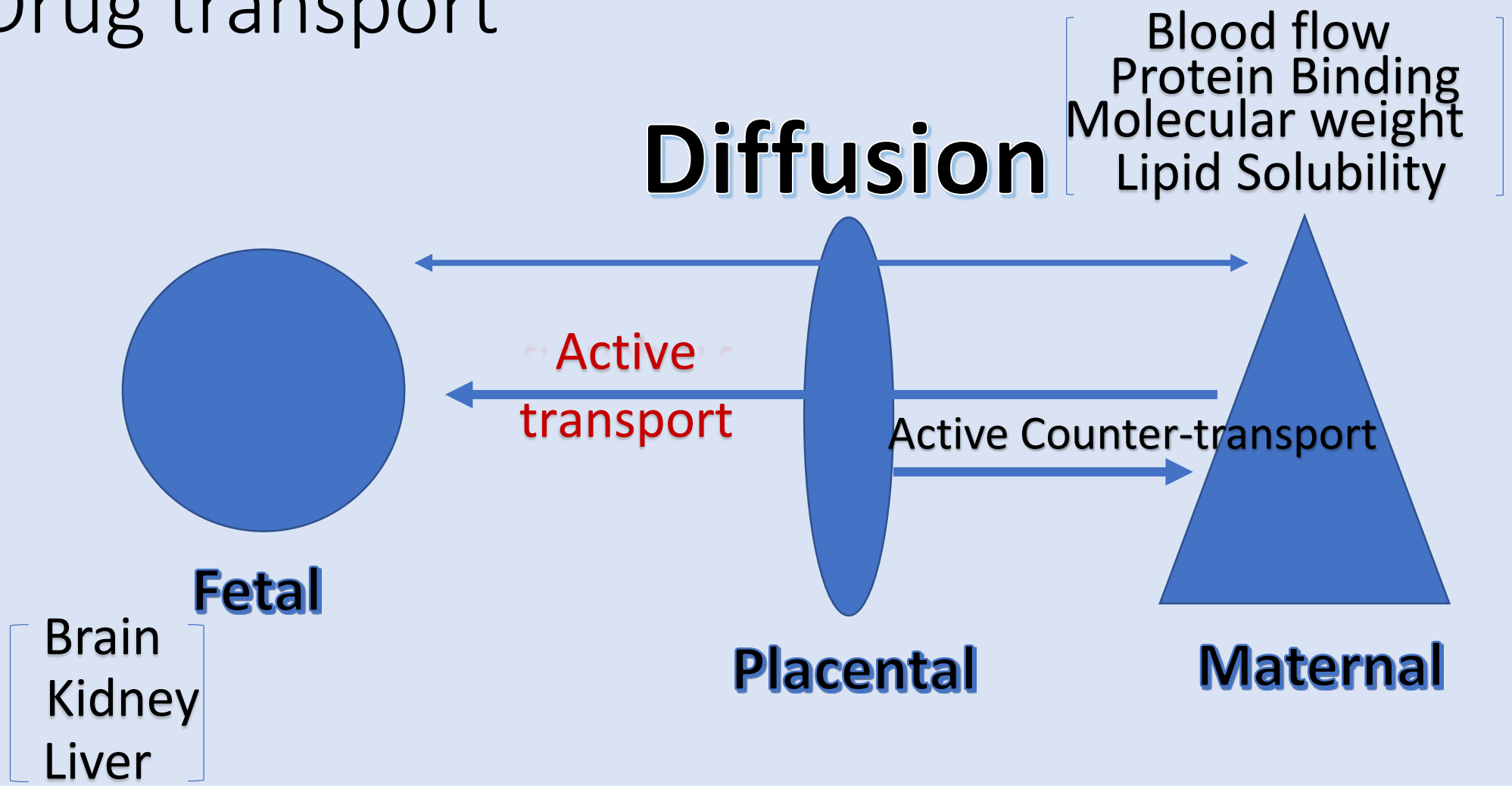




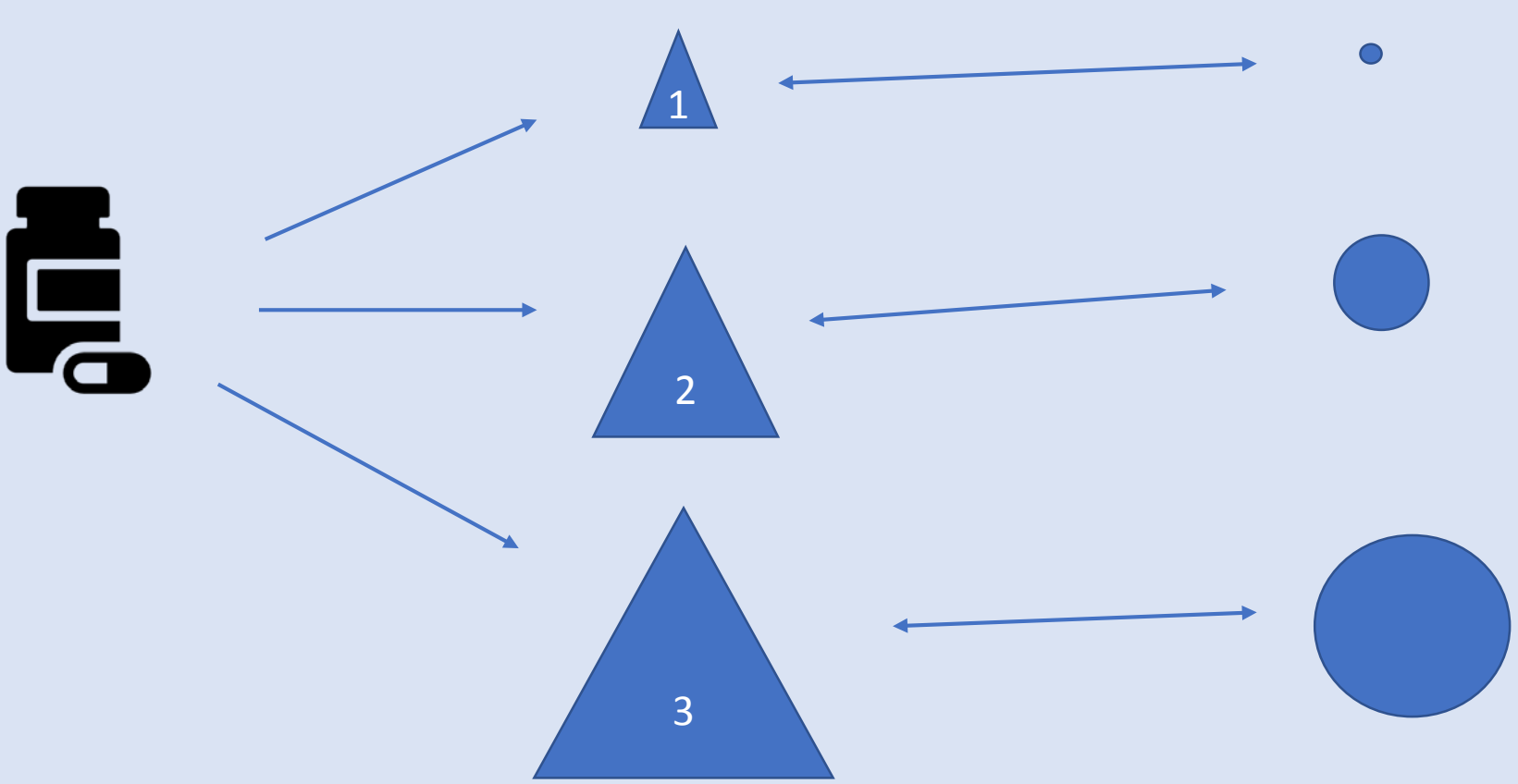
http://www.frca.co.uk/article.aspx?articleid=100601


Placenta
Placenta
Villi
Placental Membrane
Umbilical Cord
Intervillous Space
Umbilical Cord
Fetus'
Blood Vessels
Mother's
Blood Vessels

Drug transport



Maternal-fetal drug transfer



Embryogenesis/ organogenesis

Fetal maturation

Fetal maturation and growth

Embryonic, fetal and infant drug exposure

- What is the exposure?
- What is the risk of the exposure?
- During what embryonic or fetal period is the exposure occurring?
- What are the short- and long-term consequences of this drug exposure?

Maternal outcomes

- If the mother does not treat her medical condition because of concern of infant exposure, what are the short- and long-term consequences for the mother and infant?

NICHD pregnancy and lactation literature analysis: methods

- 12 major diseases/conditions for which pregnant and lactating women often use therapies: Autoimmune, central nervous system, cancer, diabetes, endocrine, hypertension, infection, mental health, pain, preterm labor, substance abuse, vaccines (vaccine-preventable diseases)
- **10 year Time scope**: 2006--July 2017
- Sources:
  - Detailed PubMed searches by NIH Library Informationist for pubs specific to pregnant/lactating women;
  - Pubs from all clinicaltrials.gov entries that included pregnant or lactating women;
  - Pubs from federal grants
- Removed false positives and characterized type of research evidence

NICHD pregnancy and lactation literature analysis 2006-2017: results for pregnancy

- PK/PD publications rare in all topic areas
- National databases and registries have been exploited to look at epilepsy and seizure disorders and their treatment in pregnant women

	Condition	Basic	PK/PD	Pop/DB	RCT
Autoimmune	AA syndrome	9	1	1	3
	Lupus	2	1	2	2
	MS	4	0	1	2
	Rheum. Arthritis	3	0	5	2
Cancer	Breast	28	0	0	2
	Lymphatic	7	1	1	0
	Gynecologic	10	0	1	0
	Lung	11	0	0	0
CNS	Epilepsy	6	7	50	1
	Stroke	1	0	4	0
	Headache/migraine	0	0	5	1
Diabetes	Type I	7	0	2	10
	Type II	18	4	8	8
	Gestational	51	10	18	30
Endocrine	Thyroid	26	1	14	5
	Other endocrine	8	0	6	0

NICHD pregnancy and lactation literature analysis 2006-2017: results for pregnancy

- RCTs rare in almost all areas
  5 Exceptions:
  - Gestational diabetes
  - Hypertension
  - Preterm labor
  - Labor pain medication
  - Opioids and tobacco

	Condition	Basic	PK/PD	Pop/DB	RCT
Hypertension	Hypertension	127	9	18	40
Mental Health	Anxiety	16	0	3	2
	Bipolar	1	0	1	0
	Depression	21	4	21	4
	Schizophrenia	11	0	1	0
Pain	Labor Pain	5	0	7	49
	Headache/migraine	0	0	5	1
Preterm labor	Preterm labor	152	21	35	169
Substance Abuse	Alcohol	26	0	0	0
	Cocaine	6	0	1	0
	Meth/amph	10	3	1	0
	Opioids	22	3	9	25
	Tobacco	22	3	16	27

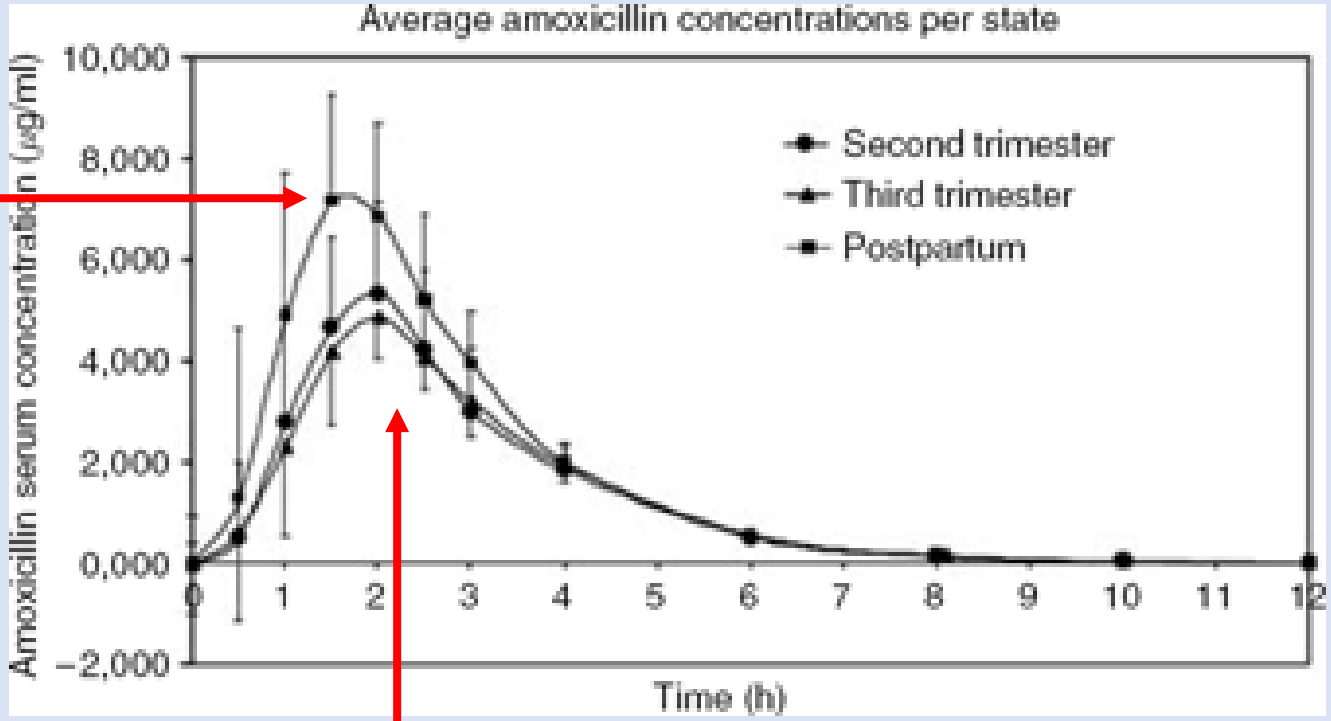
NICHD pregnancy and lactation literature analysis 2006-2017: results for pregnancy

- Few infection or vaccine RCTs included pregnant women
- Researchers have used existing databases to assess use of influenza vaccine in pregnant women

	Condition	Basic	PK/PD	Pop/DB	RCT
Infections	CMV	3	0	4	2
	Group B strep	4	0	2	1
	Hepatitis B	4	1	2	2
	HIV/AIDS	16	7	3	11
	Influenza	12	2	15	2
	Malaria	4	12	1	4
	Parasites	6	1	2	0
	Pertussis	6	1	2	0
	Rubella	2	0	2	0
	Tetanus	0	0	0	0
	Zika	6	0	0	0
Vaccines	Cholera	2	0	3	1
	CMV	4	0	0	0
	Diphtheria	3	0	11	4
	Group B strep	6	0	0	0
	Hepatitis B	4	0	2	1
	HPV	0	0	2	2
	Influenza	17	0	26	7
	Malaria	19	0	0	0
	Pertussis	7	0	16	3
	Rubella	1	0	2	0
	tetanus	6	0	1	1

Amoxicillin pharmacokinetics in pregnant women: modelling and simulations of dosing strategies for anthrax

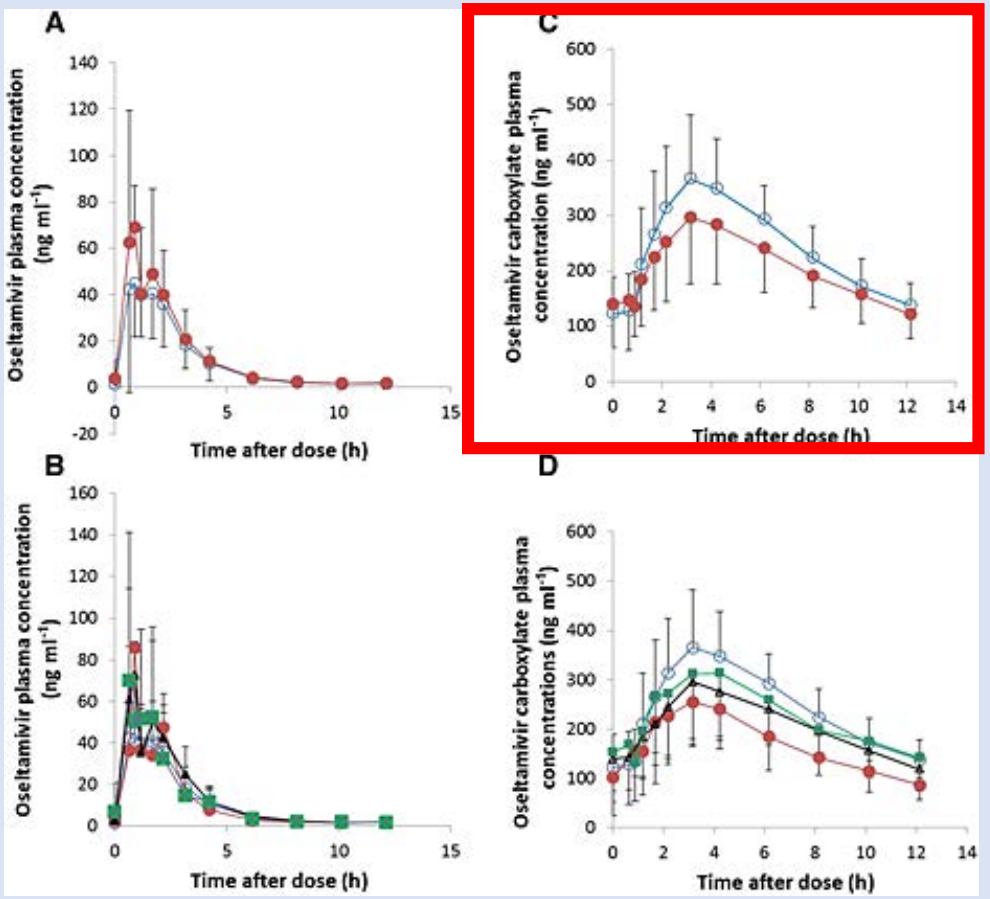
Maximum concentration



Area under the Curve

Clinical Pharmacology & Therapeutics
Volume 81, Issue 4, pages 547-556, 28 FEB 2007 DOI: 10.1038/sj.clpt.6100126
http://onlinelibrary.wiley.com/doi/10.1038/sj.clpt.6100126/full#cpt6100126-fig-0001

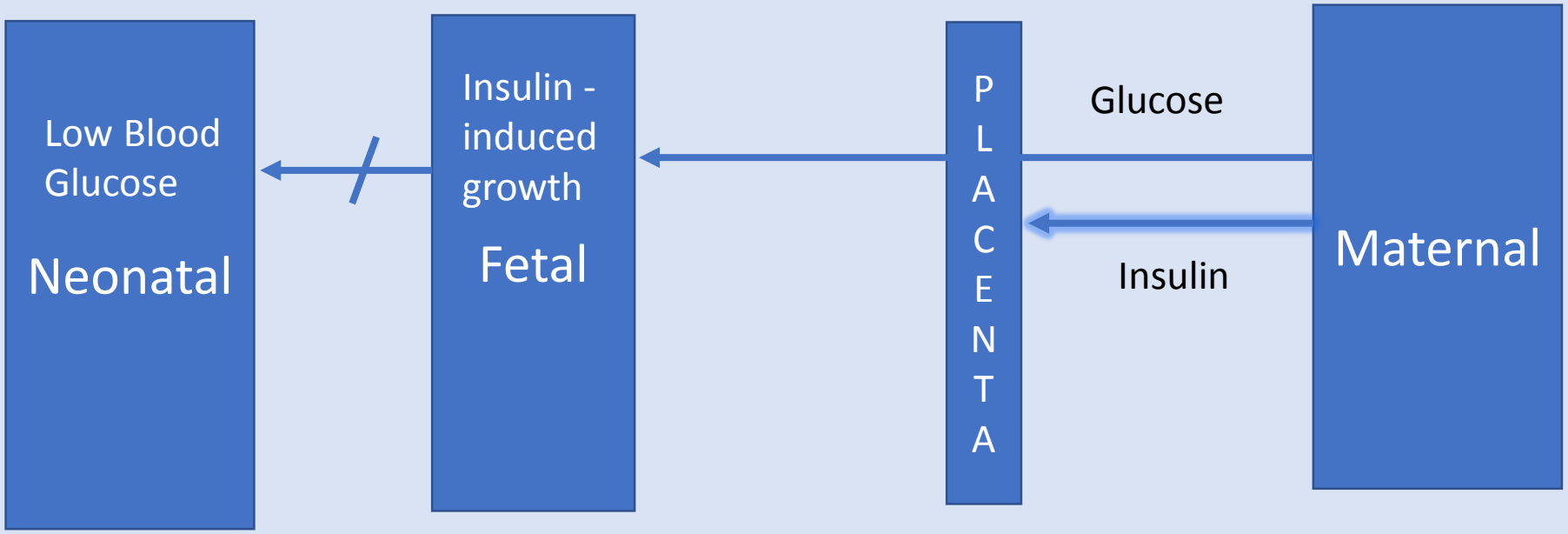
Population pharmacokinetics of oseltamivir (Tamiflu) for influenza in non-pregnant and pregnant women



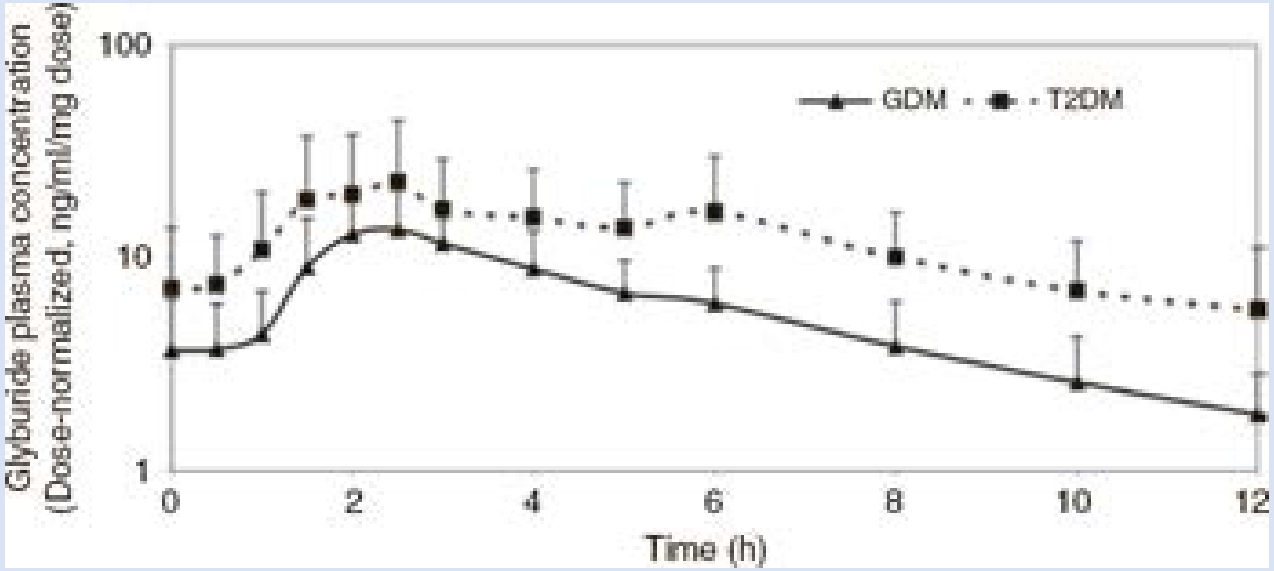
Mean plasma concentration–time profiles of oseltamivir (A and B) and oseltamivir carboxylate (C and D) in non-pregnant and pregnant women. A and C non-pregnant, pregnant. B and D non-pregnant, trimester 1, trimester 2, trimester 3

British Journal of Clinical Pharmacology
Volume 80, Issue 5, pages 1042-1050, 18 AUG 2015 DOI: 10.1111/bcp.12691
http://onlinelibrary.wiley.com/doi/10.1111/bcp.12691/full#bcp12691-fig-0001

Gestational Diabetes Mellitus



Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice.



Clinical Pharmacology & Therapeutics
Volume 85, Issue 6, pages 607-614, 18 MAR 2009 DOI: 10.1038/clpt.2009.5
http://onlinelibrary.wiley.com/doi/10.1038/clpt.2009.5/full#cptclpt20095-fig-0001

Journal of Visualized Experiments
Click Here to Watch this Article on JoVE

J Vis Exp. 2013; (76): 50401.
Published online 2013 Jun 18. doi: 10.3791/50401
PMCID: PMC3729252

Determination of the Transport Rate of Xenobiotics and Nanomaterials Across the Placenta using the *ex vivo* Human Placental Perfusion Model

Stefanie Grafmüller, Pius Manser, Harald F. Krug, Peter Wick, and Ursula von Mandach

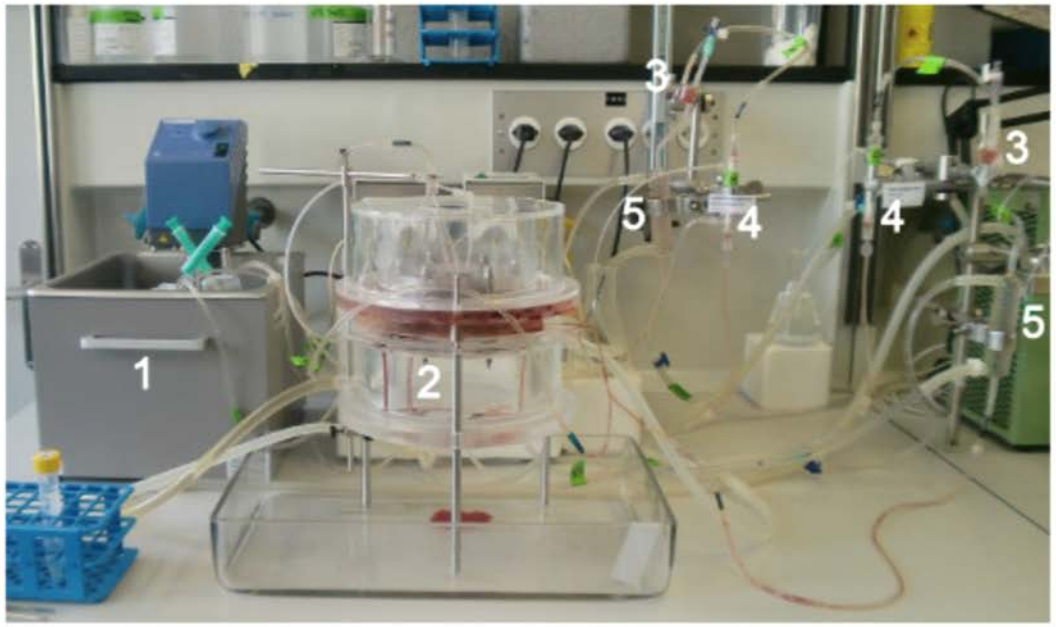


Figure 1. *Ex vivo* human placental perfusion set-up. 1) Water bath with maternal and fetal reservoirs, 2) perfusion chamber, 3) bubble trap, 4) oxygenator columns, and 5) flow heater.

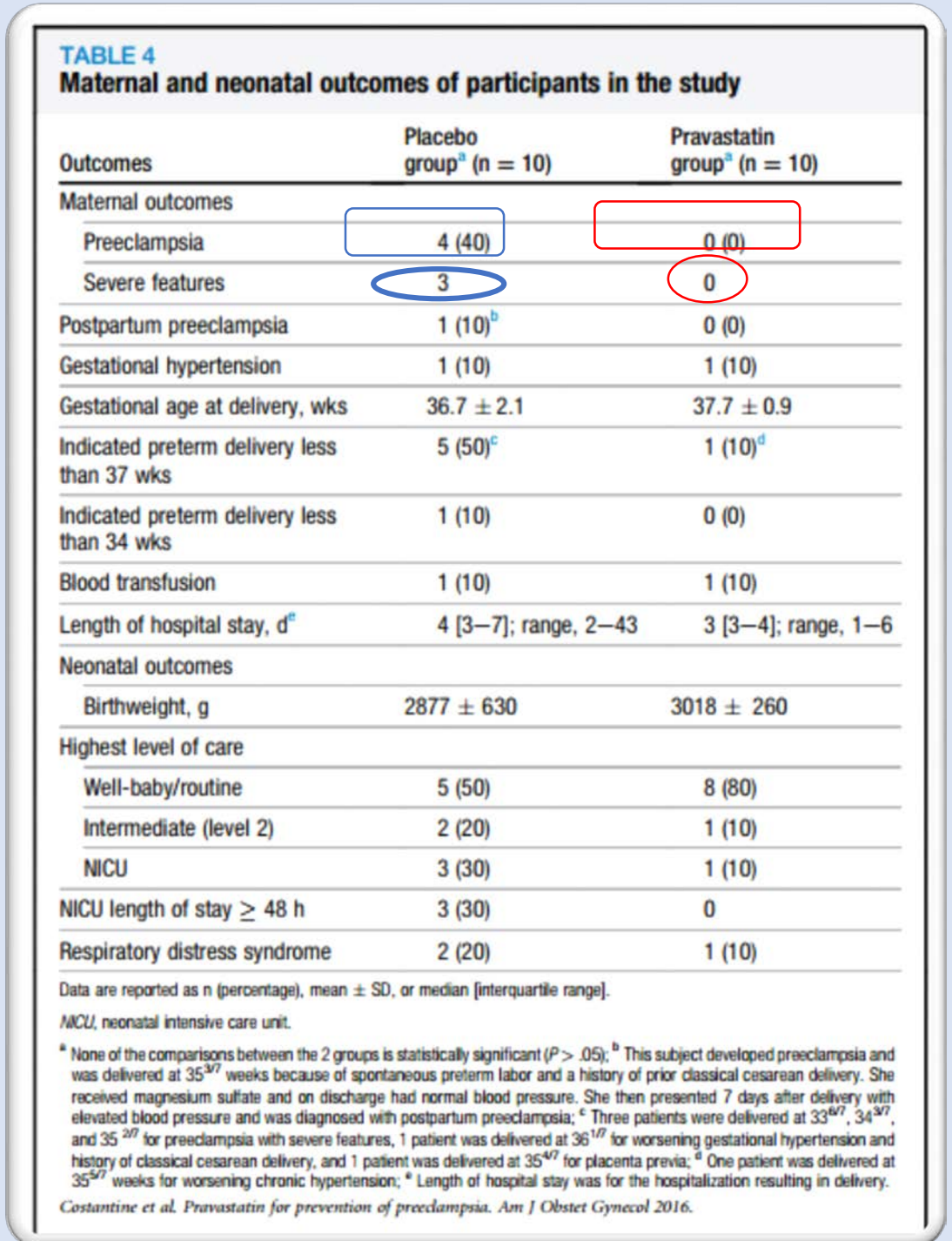


TABLE 4
Maternal and neonatal outcomes of participants in the study

Outcomes	Placebo group[a] (n = 10)	Pravastatin group[a] (n = 10)
Maternal outcomes		
Preeclampsia	4 (40)	0 (0)
Severe features	3	0
Postpartum preeclampsia	1 (10)[b]	0 (0)
Gestational hypertension	1 (10)	1 (10)
Gestational age at delivery, wks	36.7 ± 2.1	37.7 ± 0.9
Indicated preterm delivery less than 37 wks	5 (50)[c]	1 (10)[d]
Indicated preterm delivery less than 34 wks	1 (10)	0 (0)
Blood transfusion	1 (10)	1 (10)
Length of hospital stay, d[e]	4 [3–7]; range, 2–43	3 [3–4]; range, 1–6
Neonatal outcomes		
Birthweight, g	2877 ± 630	3018 ± 260
Highest level of care		
Well-baby/routine	5 (50)	8 (80)
Intermediate (level 2)	2 (20)	1 (10)
NICU	3 (30)	1 (10)
NICU length of stay ≥ 48 h	3 (30)	0
Respiratory distress syndrome	2 (20)	1 (10)

Data are reported as n (percentage), mean ± SD, or median [interquartile range].

NICU, neonatal intensive care unit.

[a] None of the comparisons between the 2 groups is statistically significant ($P > .05$); [b] This subject developed preeclampsia and was delivered at $35^{3/7}$ weeks because of spontaneous preterm labor and a history of prior classical cesarean delivery. She received magnesium sulfate and on discharge had normal blood pressure. She then presented 7 days after delivery with elevated blood pressure and was diagnosed with postpartum preeclampsia; [c] Three patients were delivered at $33^{6/7}$, $34^{3/7}$, and $35^{2/7}$ for preeclampsia with severe features, 1 patient was delivered at $36^{1/7}$ for worsening gestational hypertension and history of classical cesarean delivery, and 1 patient was delivered at $35^{4/7}$ for placenta previa; [d] One patient was delivered at $35^{5/7}$ weeks for worsening chronic hypertension; [e] Length of hospital stay was for the hospitalization resulting in delivery.

Costantine et al. Pravastatin for prevention of preeclampsia. Am J Obstet Gynecol 2016.

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

Costantine MM, Cleary K, Hebert MF, et al. Am J Obstet Gynecol 2016;214:720.e1-17.

ACOG COMMITTEE OPINION

Number 713 • August 2017 (Replaces Committee Opinion No. 677, October 2016)

Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee members Yasser Y. El-Sayed, MD, Ann E.B. Borders, MD, MSc, MPH, and the Society for Maternal–Fetal Medicine's liaison member Cynthia Gyamfi-Bannerman, MD, MSc.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to reflect a limited focused change to clarify that, among specific populations, antenatal corticosteroids should be administered when a woman is at risk of preterm delivery within 7 days.

Antenatal Corticosteroid Therapy for Fetal Maturation

- A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co713.pdf?dmc=1&ts=20170814T1635107812

Betamethasone Acetate/Sodium Label

INDICATIONS AND USAGE

When oral therapy is not feasible, the **intramuscular use** of CELESTONE® SOLUSPAN® Injectable Suspension is indicated as follows:

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders

Congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Hydrocortisone or cortisone is the drug of choice in primary or secondary adrenocortical insufficiency. Synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance.

Gastrointestinal Diseases

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous

Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases

For palliative management of leukemias and lymphomas.

Nervous System

Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e63c73d-30b2-4f47-a817-0313a08281c1

Drug-induced birth defects

Problem with pre-clinical models

Need for mechanistic approach, not database studies, to determine safety

Congenital malformations in the newborn population: a populations study and analysis of the effect of sex and prematurity

Egbe A et al. Pediatrics and Neonatology 2015; 56:25-30.

Table 1 Birth prevalence of congenital malformations.

	No. of cases (incidence per 1000 births)						
	Total	Male	Female	OR (CI)	Term	Preterm	OR (CI)
Patients with CM	29,312 (28.9)	15,507 (29.9)	13,805 (27.7)	0.9 (CI, 0.9–1.0)	20,118 (26.1)	9194 (37.4)	1.4 (CI, 1.3–1.5)*
Syndromic CM	1172	522 (1.0)	650 (1.3)	1.0 (CI, 0.8–1.1)	902 (1.3)	270 (0.7)	0.9 (CI, 0.8–1.1)
Isolated NSCM	25,607	12,966 (26.9)	11,641 (23.4)	1.3 (CI, 1.2–1.5)*	17,575 (22.8)	8032 (33.0)	1.5 (CI, 1.4–1.6)*
Multiple NSCM	2533	1019 (2.1)	1514 (2.9)	1.1 (CI, 0.9–1.2)	1541 (2.0)	992 (4.1)	2.1 (CI, 2.0–2.3)*
Total Cohort	1,014,261	517,273	496,988		770,838	243,423	

CI = 95% confidence interval; CM = congenital malformation diagnosis (ICD9 codes 740.0–759.9); Isolated NSCM = isolated non-syndromic congenital malformations [all CM diagnoses, excluding the genetic syndromes (ICD9 codes 740.0–757.9 and 759.0–759.9)]; Multiple NSCM = nonsyndromic congenital malformations involving two or more organ systems; OR = odds ratio; Syndromic CM = all genetic syndromes (ICD9 codes 758.0–758.9).

* Indicates statistical significance.

Drug-induced birth defects

- Thalidomide: for nausea and vomiting of pregnancy
  - Marketed originally in Germany in 1950s
  - Off-target effect: blood vessel/angiogenesis growth inhibitor
  - Toxicity: phocomelia

www.thalidomide.ca

Diethylstilbestrol (DES)

- Indication: for prior pregnancy loss
- Marketed 1940-1975 + in cattle feed through 1970s
- Off-target effect: endocrine disruptor
- Toxicity: Vaginal clear cell carcinoma, urogenital anomalies (boys), continuing into the third generation

ACOG Recommendations: Chronic Hypertension in Pregnancy

TABLE 7-2. Common Oral Antihypertensive Agents in Pregnancy

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses	Well tolerated Potential bronchoconstrictive effects Avoid in patients with asthma and congestive heart failure
Nifedipine	30–120 mg/d orally of a slow-release preparation	Do not use sublingual form
Methyldopa	0.5–3 g/d orally in two to three divided doses	Childhood safety data up to 7 years of age May not be as effective in control of severe hypertension
Thiazide diuretics	Depends on agent	Second-line agent
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers		Associated with fetal anomalies Contraindicated in pregnancy and preconception period

https://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy

Vaccines to protect both mother and fetus

- Available
  - Influenza
  - Rubella
  - Pertussis
  - Hepatitis B
  - Tetanus
- Needed and/or Under Development
  - Zika virus
  - Toxoplasmosis
  - Parvovirus
  - Malaria
  - HIV

Vaccine monitoring systems: a potential model for medications in pregnancy

Nessin M and Sparer O. Seminars Perinatol 2015; 39:524-529

- Inclusive reporting sources and diversity of reporting methodology
- Rapid detection of adverse events
- Data publicly available
- Consistent data quality and comparability
- Access to denominators and control groups
- Connectivity and compatibility with other safety monitoring systems

Impact of medication use during breast feeding

https://www.cdc.gov/breastfeeding/pdf/2013BreastfeedingReportCard.pdf

- 3,978,497 US Births in 2015
  - 79% of mothers begin to breastfeed (n=3,143,013)
  - 49% at 6 months (n=1,949,464)
  - 27% at 12 months (n=1,074,194)

NICHD pregnancy and lactation literature analysis 2006-2017: results for lactation

- For almost all topic areas:
  - Limited basic research
  - no pharmacokinetic/ pharmacodynamic studies
  - Very few rcts
- Large-scale Databases seldom include sufficient information on lactation for research

	Condition	Basic	PK/PD	Pop/DB	RCT
Autoimmune	AA syndrome	0	0	0	0
	Lupus	0	0	0	1
	MS	0	0	1	1
	Rheum. Arthritis	0	0	0	0
Cancer	Breast	0	0	0	0
	Lymphatic	0	0	0	0
	Gynecologic	0	0	0	0
	Lung	0	0	0	0
CNS	Epilepsy	0	1	1	1
	Stroke	0	0	0	0
	Headache/migraine	0	0	0	0
Diabetes	Type I	1	0	0	0
	Type II	3	0	0	2
	Gestational	5	0	0	1
Endocrine	Thyroid	1	0	0	0
	Other endocrine	1	0	0	0
Hypertension	Hypertension	4	1	0	1

NICHD pregnancy and lactation literature analysis 2006-2017: results for lactation

	Condition	Basic	PK/PD	Pop/DB	RCT
Mental Health	Anxiety	1	0	0	0
	Bipolar	0	1	0	0
	Depression	2	1	0	0
	Schizophrenia	0	0	0	0
Pain	Labor Pain	0	1	0	0
	Headache/migraine	0	0	0	0
Preterm labor	Preterm labor	4	0	1	0
Substance Abuse	Alcohol	4	0	0	0
	Cocaine	0	0	0	0
	Meth/amph	0	0	0	0
	Opioids	2	1	1	0
	Tobacco	1	0	1	0

	Condition	Basic	PK/PD	Pop/DB	RCT
Infections	CMV	0	0	0	0
	Group B strep	0	0	1	1
	Hepatitis B	2	0	0	0
	HIV/AIDS	0	0	0	3
	Influenza	1	0	0	0
	Malaria	0	0	0	0
	Parasites	0	0	0	0
	Pertussis	0	0	0	0
	Rubella	0	0	1	0
	Tetanus	0	0	0	0
	Zika	0	0	0	0
Vaccines	Cholera	0	0	0	0
	CMV	0	0	0	0
	Diphtheria	0	0	0	0
	Group B strep	0	0	0	0
	Hepatitis B	1	0	0	0
	HPV	0	0	0	0
	Influenza	0	0	1	0
	Malaria	0	0	0	0
	Pertussis	0	0	0	0
	Rubella	0	0	0	0
	tetanus	0	0	0	0

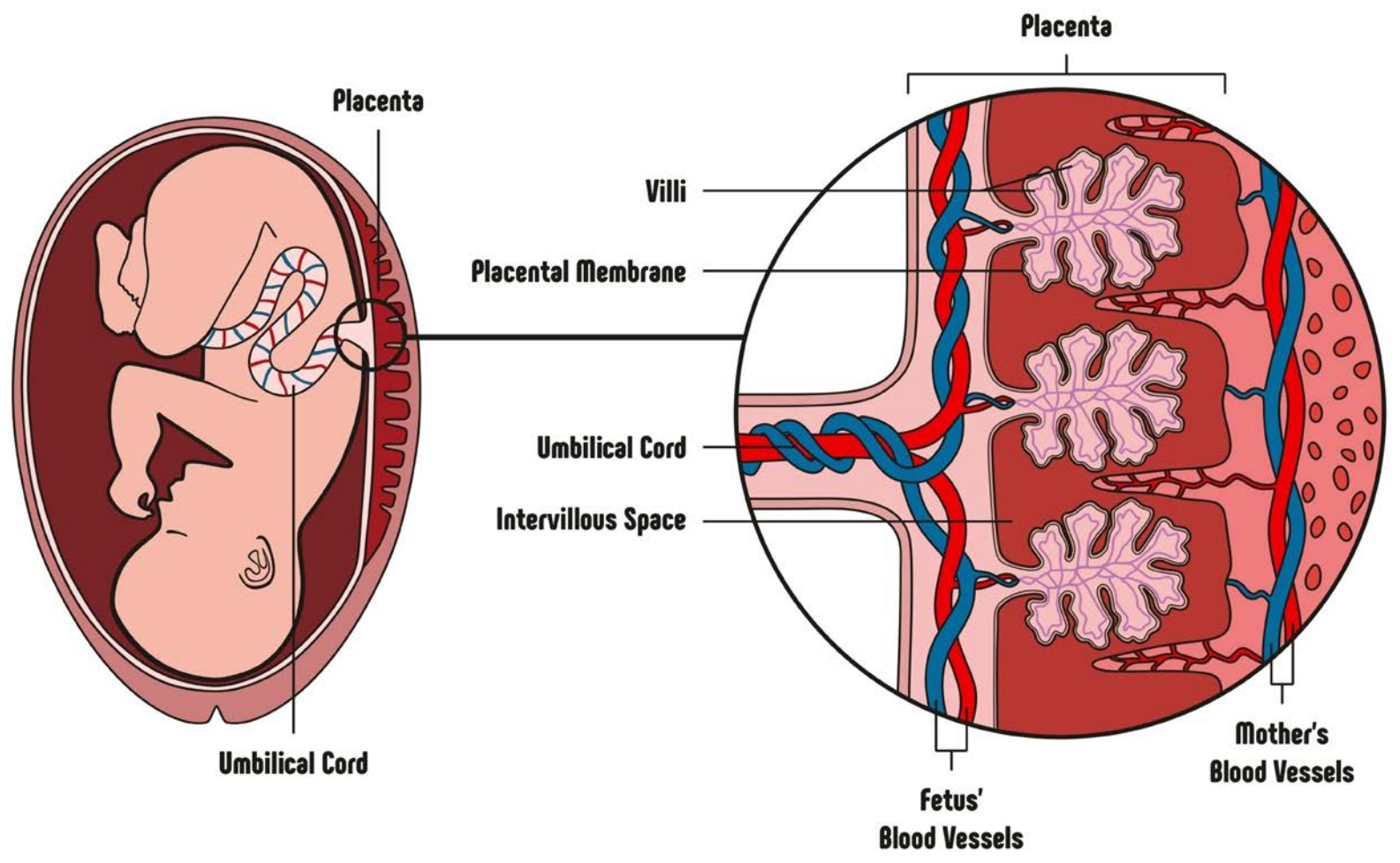
Questions about medications in lactation

- What is the infant exposure? What are the short- and long-term consequences of this drug exposure?
- If the mother does not breastfeed because of concern of infant exposure, what are the short- and long-term consequences?
- If the mother continues to breastfeed but does not take medication for her medical condition, what are the short- and long-term outcomes for the mother and infant?

Pharmacogenomics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study

Madadi P et al. CPT 2008 Aug **DOI:** 10.1038/clpt.2008.157

A large number of women receive codeine for obstetric pain while breastfeeding. Following a case of fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultrarapid metabolizer (UM), we examined characteristics of mothers and infants with or without signs of central nervous system (CNS) depression following codeine exposure while breastfeeding in a case–control study. Mothers of symptomatic infants ($n = 17$) consumed a mean 59% higher codeine dose than mothers of asymptomatic infants ($n = 55$) (1.62 (0.79) mg/kg/day vs. 1.02 (0.54) mg/kg/day; $P = 0.004$). There was 71% concordance between maternal and neonatal CNS depression. Two mothers whose infants exhibited severe neonatal toxicity were CYP2D6 UMs and of the *UGT2B7*2/*2* genotype. There may be a dose–response relationship between maternal codeine use and neonatal toxicity, and strong concordance between maternal-infant CNS depressive symptoms. Breastfed infants of mothers who are CYP2D6 UMs combined with the *UGT2B7*2/*2* are at increased risk of potentially life-threatening CNS depression.



Neonatal Opioid Withdrawal Syndrome (NOWS)

- **Opioids**
- Nicotine
- Alcohol
- Cannabis
- Cocaine
- Benzodiazepines
  [alprazolam (Xanax), diazepam (Valium), lorazepam (Ativan)]

Opioids

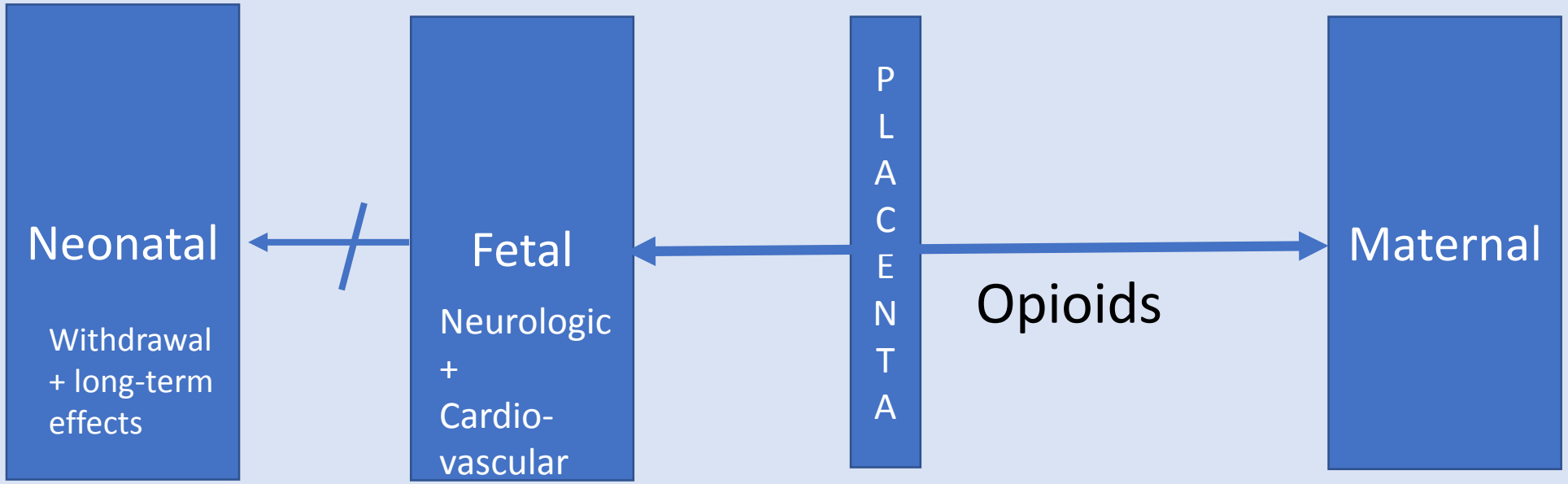
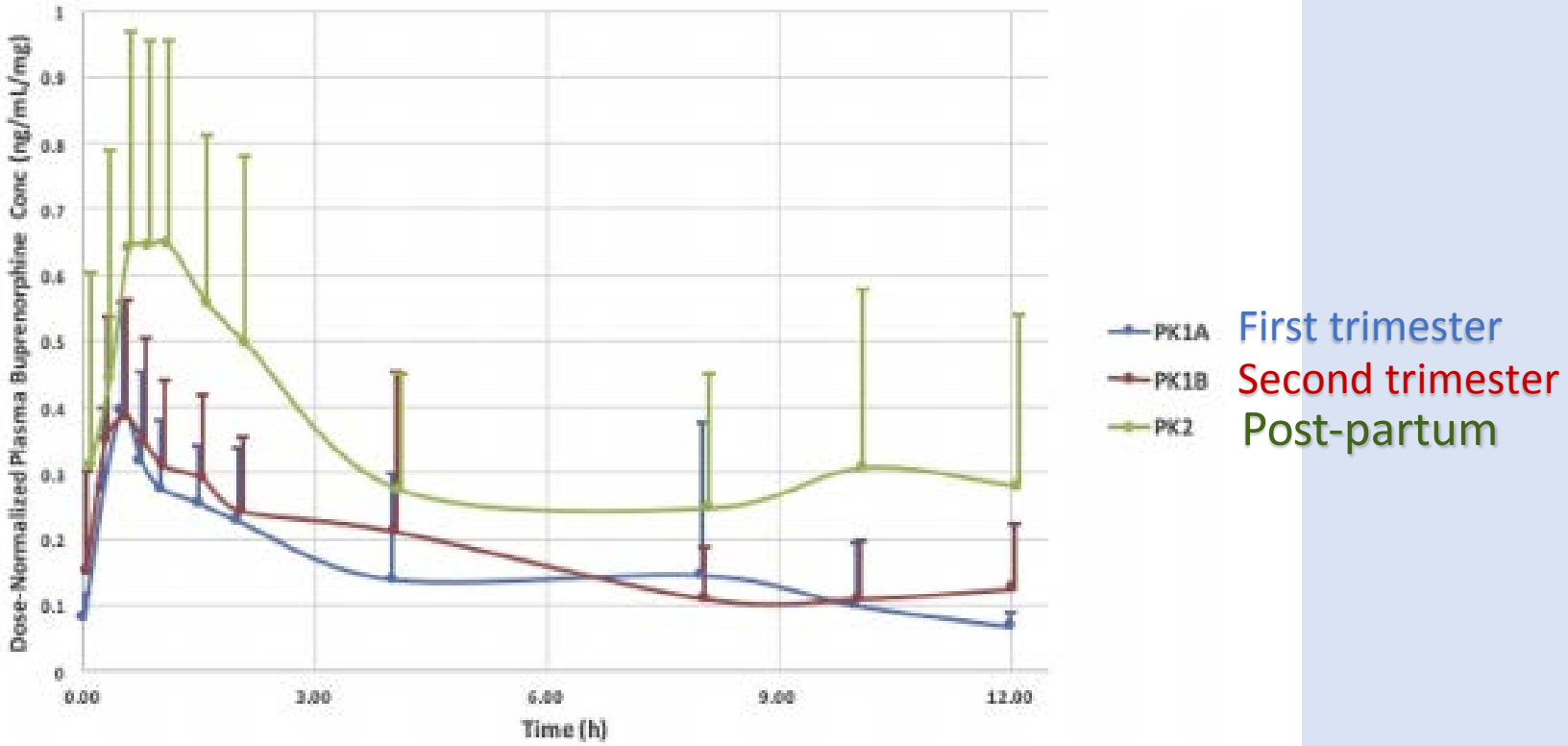

Neonatal
Withdrawal
+ long-term
effects
Fetal
Neurologic
+
Cardio-
vascular
PLACENTA
Opioids
Maternal

FIGURE 1

Dose-normalized buprenorphine plasma concentrations during pregnancy and postpartum



The mean dose-normalized buprenorphine plasma concentration-time curves (±SD) during the 12 hour pharmacokinetic study visits: PK-1a (n = 7), PK-1b (n = 11), and PK-2 (n = 10). The X axis is the time in hours; the Y axis is the mean dose-normalized buprenorphine plasma concentrations in nanograms per milliliter per milligram of buprenorphine.

Bastian et al. Pregnancy decreases exposure to SL BUP. Am J Obstet Gynecol 2017.

Application to opioid epidemic and neonates going through withdrawal

Develop novel drug targets for pain

+

Understand drug transport across blood-brain barrier and placenta

→

Develop a drug for pain which does not cross the placenta

Summary

Drug safety: data from pre-clinical toxicology vs human exposures

- Current pre-clinical toxicology is descriptive, not mechanistic
- Pre-clinical testing showing drug safety does not necessarily correlate to clinical/human experience

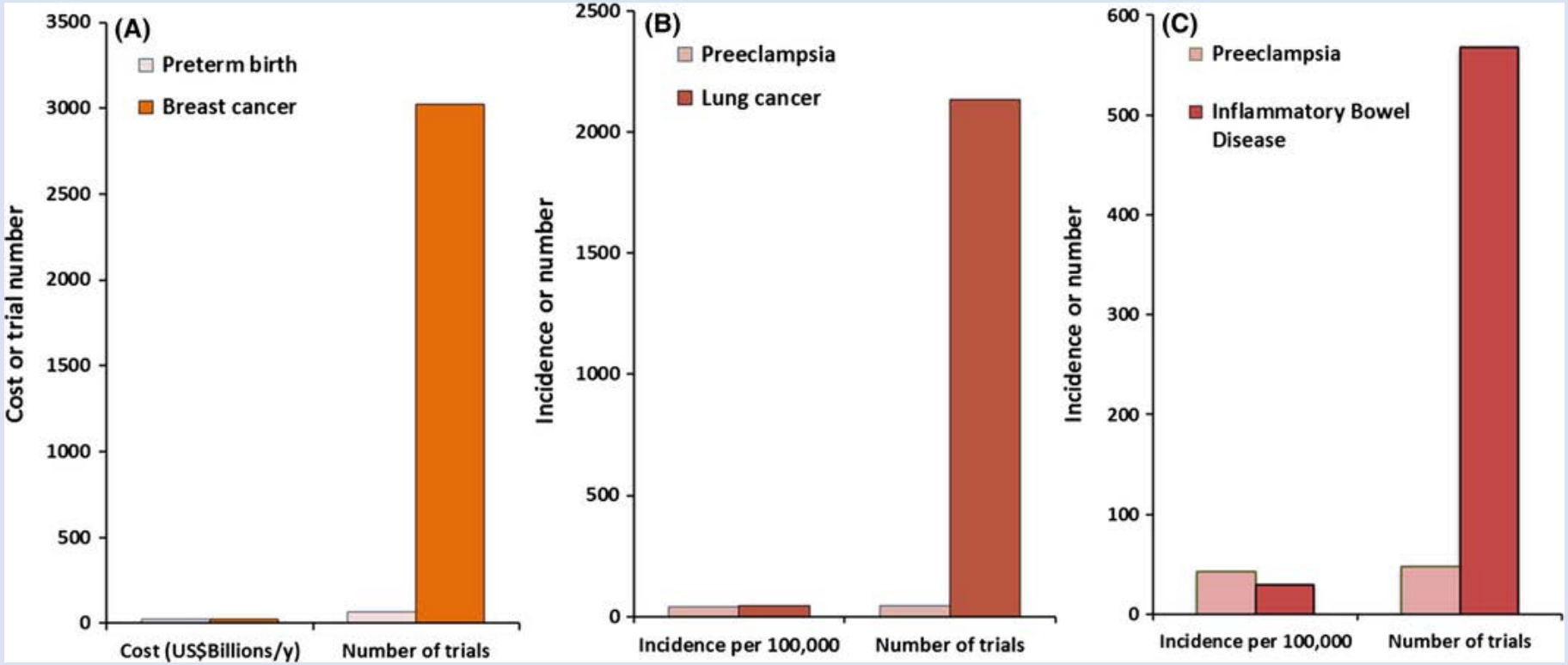
Table 2. Comparison of the Obstetric Drug Pipeline with that of a Mainstream Area (Cardiovascular) and that of a Neglected Disease (Amyotrophic Lateral Sclerosis)

Indication	Obstetric	Cardiovascular	ALS
Pre-clinical	3	303	16
Phase I	5	104	7
Phase II	5	163	7
Phase III	3	73	4
Pre-registration	1	17	0
Total	**17**	**660**	**34**

ALS, amyotrophic lateral sclerosis

Fisk NM, Atun R (2008) Market Failure and the Poverty of New Drugs in Maternal Health. PLOS Medicine 5(1): e22. https://doi.org/10.1371/journal.pmed.0050022
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050022

The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy



BJOG: An International Journal of Obstetrics & Gynaecology
Volume 124, Issue 1, pages 132-140, 14 JUN 2016 DOI: 10.1111/1471-0528.14151
http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.14151/full#bjo14151-fig-0002

Summary Points: **Research Needs**

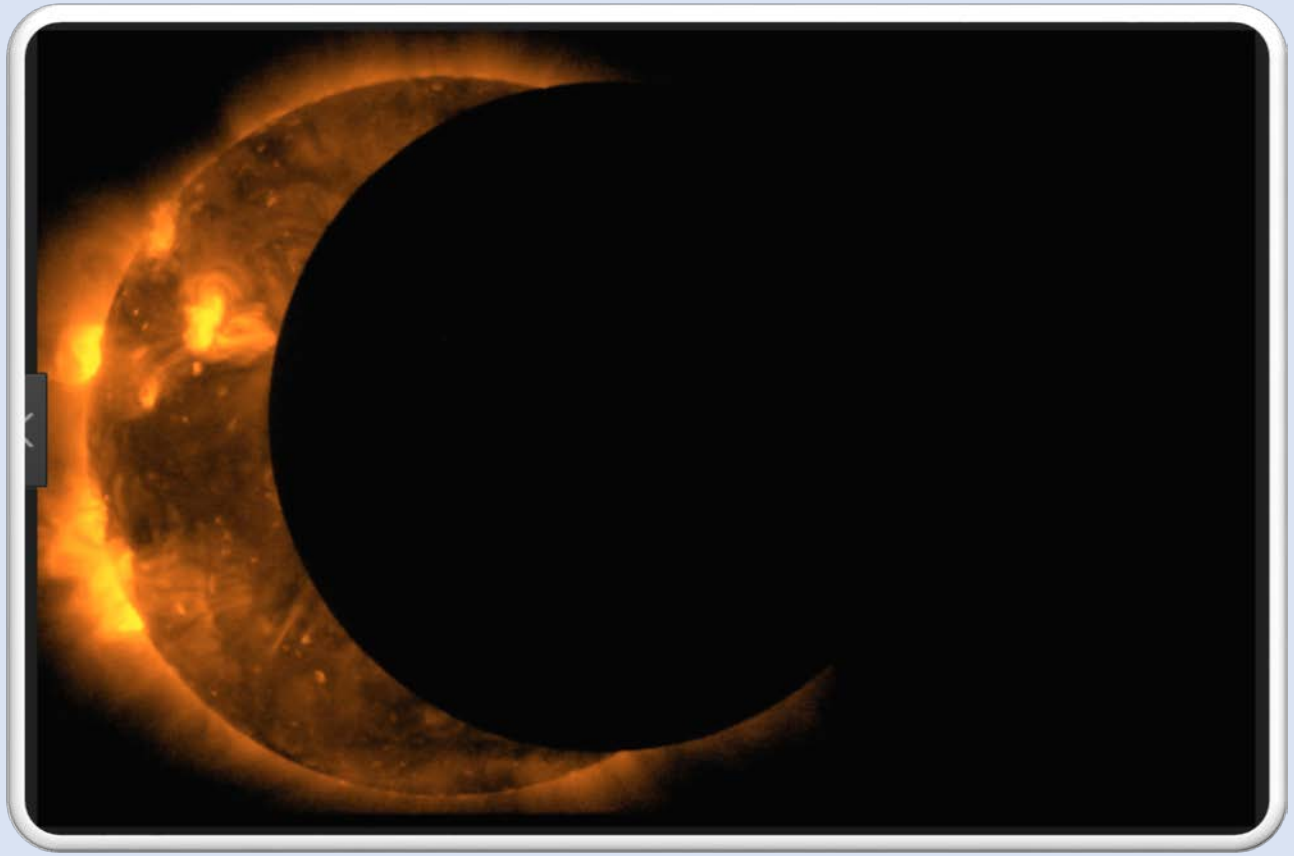
- Lack of **basic science** on **disease mechanisms** in pregnancy
- Need for basic science on **placental** and breast milk **drug transport**
- Lack of **mechanistic approach to pre-clinical toxicology** and off-target effects of drugs
- Lack of **development of novel drug targets** applicable to pregnancy and lactation, including development of placental drug transport inhibitors

Summary Points

- Need for meaningful, feasible validated, accepted, short-term and long-term **clinical trial outcome measures**
- Need for improved **feasibility of clinical trial designs** in pregnancy and lactation
- **Improved tracking** of research in pregnancy and lactation

Thank you

- Sarah Glavin
- Elizabeth Wehr
- Barbara Brandys
- Lisa Kaeser



https://www.nasa.gov/feature/wallops/2017/march-7-1970-nasa-lights-the-sky-for-solar-eclipse

Questions?