State of research on medications used during pregnancy and lactation

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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.

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

Data are %. N=1,106,757 for each column.
US Births (2015) and fetal medication exposure

SSRI 6%  
N=238,710  
PMID 27178125

AED 2.2%  
N=87,527  
PMID 23865818

Asthma 7%  
N=278,495  
PMID 23108737

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

**Diffusion**

- Blood flow
- Protein Binding
- Molecular weight
- Lipid Solubility

**Active transport**

- Fetal
- Placental
- Maternal

**Active Counter-transport**

- Brain
- Kidney
- Liver
Maternal-fetal drug transfer

1. Embryogenesis/organogenesis
2. Fetal maturation
3. 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
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
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
Amoxicillin pharmacokinetics in pregnant women: modelling and simulations of dosing strategies for anthrax
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, 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
Gestational Diabetes Mellitus

Low Blood Glucose
Neonatal

Insulin - induced growth
Fetal

PLACENTA

Glucose
Maternal

Insulin
Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice.
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>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo group* (n = 10)</th>
<th>Pravastatin group* (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severe features</td>
<td>3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Postpartum preeclampsia</td>
<td>1 (10)^a</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Gestational age at delivery, wks</td>
<td>36.7 ± 2.1</td>
<td>37.7 ± 0.9</td>
</tr>
<tr>
<td>Indicated preterm delivery less than 37 wks</td>
<td>5 (50)^a</td>
<td>1 (10)^a</td>
</tr>
<tr>
<td>Indicated preterm delivery less than 34 wks</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Length of hospital stay, d^4</td>
<td>4 [3–7]; range, 2–43</td>
<td>3 [3–4]; range, 1–6</td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight, g</td>
<td>2877 ± 630</td>
<td>3018 ± 260</td>
</tr>
<tr>
<td>Highest level of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-baby/routine</td>
<td>5 (50)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Intermediate (level 2)</td>
<td>2 (20)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>NICU</td>
<td>3 (30)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>NICU length of stay ≥ 48 h</td>
<td>3 (30)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>2 (20)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

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

NICU, neonatal intensive care unit.

* None of the comparisons between the 2 groups is statistically significant (P > 0.05).^a This subject developed preeclampsia and was delivered at 35^9/7 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. Three patients were delivered at 33^9/7, 34^9/7, and 35^9/7 for preeclampsia with severe features; patient was delivered at 36^9/7 for worsening gestational hypertension and history of classical cesarean delivery, and 1 patient was delivered at 35^9/7 for placenta previa. One patient was delivered at 35^9/7 weeks for worsening chronic hypertension. ^d Length of hospital stay was for the hospitalization resulting in delivery.

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.
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.

Corticosteroids 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
Thickening with neurologic or myocardioc 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.
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


Table 1  Birth prevalence of congenital malformations.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>OR (CI)</th>
<th>Term</th>
<th>Preterm</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with CM</td>
<td>29.3%</td>
<td>25.0%</td>
<td>28.9%</td>
<td>0.9 (CI, 0.9—1.0)</td>
<td>20.1%</td>
<td>19.4%</td>
<td>1.4 (CI, 1.3—1.5)*</td>
</tr>
<tr>
<td>Syndromic CM</td>
<td>11.7%</td>
<td>10.0%</td>
<td>13.4%</td>
<td>1.0 (CI, 0.8—1.1)</td>
<td>9.0%</td>
<td>9.7%</td>
<td>0.9 (CI, 0.8—1.1)</td>
</tr>
<tr>
<td>Isolated NSCM</td>
<td>25.6%</td>
<td>12.9%</td>
<td>26.9%</td>
<td>1.3 (CI, 1.2—1.5)*</td>
<td>17.5%</td>
<td>22.8%</td>
<td>1.5 (CI, 1.4—1.6)*</td>
</tr>
<tr>
<td>Multiple NSCM</td>
<td>25.3%</td>
<td>10.2%</td>
<td>24.9%</td>
<td>1.1 (CI, 0.9—1.3)</td>
<td>15.4%</td>
<td>2.0%</td>
<td>2.1 (CI, 2.0—2.3)*</td>
</tr>
<tr>
<td>Total Cohort</td>
<td>1014.261</td>
<td>517.273</td>
<td>496.988</td>
<td></td>
<td>770.838</td>
<td>243.423</td>
<td></td>
</tr>
</tbody>
</table>

CI = 95% confidence interval; CM = congenital malformation diagnosis (ICD9 codes 740.0—759.9); Isolated NSCM = isolated nonsyndromic 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

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


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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Basic</th>
<th>PK/PD</th>
<th>Pop/DB</th>
<th>RCT</th>
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</thead>
<tbody>
<tr>
<td><strong>Mental Health</strong></td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Bipolar</td>
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<td>0</td>
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</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schizophrenia</td>
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<tr>
<td><strong>Pain</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Labor Pain</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache/migraine</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td><strong>Preterm labor</strong></td>
<td></td>
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<tr>
<td>Preterm labor</td>
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<td>1</td>
<td>0</td>
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<tr>
<td><strong>Substance Abuse</strong></td>
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<tr>
<td>Alcohol</td>
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<td>Meth/amph</td>
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<td>Opioids</td>
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<td>Tobacco</td>
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<tr>
<td><strong>Infections</strong></td>
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<td>CMV</td>
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<td>Influenza</td>
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<td>Pertussis</td>
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<td>Rubella</td>
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<td>0</td>
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<tr>
<td>Tetanus</td>
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<td>Zika</td>
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<tr>
<td><strong>Vaccines</strong></td>
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<td>CMV</td>
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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

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 + Cardiovascular

Maternal

Opioids

PLACENTA
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.

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
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)

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ALS, amyotrophic lateral sclerosis

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
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
Questions?