IGNORANCE IS NOT BLISS: THE SAFETY OF MEDICATIONS AND OTHER EXPOSURES IN PREGNANT AND BREASTFEEDING WOMEN

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Altman Clinical and Translational Research Institution
DISCLOSURES

I receive research funding from the following industry sponsors: AbbVie; Amgen Inc.; Astra Zeneca; Apotex, Barr Laboratories, Inc.; Bristol-Myers Squibb; Celgene; Gerber Foundation; GlaxoSmithKline; Janssen Pharmaceuticals; Kali Laboratories, Inc.; Pfizer, Inc.; Hoffman La Roche-Genentech; Sandoz Pharmaceuticals; Genzyme Sanofi-Aventis; Regeneron; Seqirus; Takeda Pharmaceutical Company Limited; Teva Pharmaceutical Industries Ltd.; and UCB, USA.
OUTLINE

▪ Birth prevalence of congenital anomalies (birth defects) in the general population

▪ Known causes of birth defects and other abnormal developmental outcomes

▪ How do we identify preventable (environmental) causes of birth defects?

▪ The value of pregnancy registries: strengths and limitations

▪ Examples of pregnancy registry studies conducted by MotherToBaby

▪ Changes to safety information in the product label for medications that may be used in pregnancy
BACKGROUND

- Each year in the US, ~11.7 million women of childbearing age are prescribed a medication labeled by the US FDA as increasing the risk of birth defects if used during pregnancy

- Only half of all pregnancies are planned

- Birth defects are most likely to occur when teratogenic medications are used early in pregnancy, before many women are aware they are pregnant

ADVERSE PREGNANCY OUTCOMES DUE TO EXPOSURES

- Birth defects affect 1 in every 33 babies born in the US each year
  ~120,000 babies a year
- Exposures such as radiation, alcohol, and certain medications are known to increase rates of birth defects
  - However, the causes of most birth defects remain unknown

TERATOGEN

- Any environmental agent (e.g. medication, chemical, infection, medical condition) that interferes with the normal development of the embryo or fetus
  - examples of known teratogens: alcohol, valproic acid, lead, methylmercury, DES, isotretinoin, Zika virus

- Broadly defined, teratogens can cause specific patterns of structural and functional defects, but also:
  - other adverse pregnancy outcomes (e.g., pregnancy loss, fetal and/or postnatal growth deficiency)
  - long-term neurodevelopmental issues
  - other effects, e.g., cancers
EXAMPLES OF RECOGNIZED HUMAN TERATOGENS

- Recreational Substances
  - Alcohol/ethanol
  - Tobacco

- Medications
  - ACE Inhibitors/ARBs
  - Thalidomide
  - Isotretinoin
  - Lithium
  - Methotrexate
  - Mycophenolate mofetil
  - Some anticonvulsants
  - Some anti-cancer agents
  - Warfarin

- Heavy Metals
  - Methylmercury

- Medical Conditions
  - High fever

- Infections
  - Rubella
  - Varicella
  - Zika virus

- High dose ionizing radiation

- Dietary
  - Folic acid deficiency
THALIDOMIDE EXPOSURE

WARFARIN EXPOSURE

Fig. 1 and 2 Abnormal facial features: nasal abnormality, small nose with markedly depressed nasal bridge

Fig. 3 Severe shortening of lower extremities

Fig. 4 Brachydactyly, hypoplasia of all distal phalanges
FETAL ALCOHOL SPECTRUM DISORDERS

A child with Fetal Alcohol Syndrome (FAS; a), an alcohol-affected fetal mouse (b), and a comparably-staged normal fetal mouse (c) are shown. Modified from Sulik et al. 1981.

Del Campo M and Jones KL. https://www.teratology.org/primer/fas.asp
MICROCEPHALY DUE TO THE ZIKA VIRUS

FIGURE 1 Frontal and profile views of five children with congenital Zika syndrome showing varying degrees of craniofacial disproportion and abnormal skull morphology. Significant abnormalities of the cranium are seen in some infants, such as narrow and laterally depressed frontal bone (A–C) and occipital prominence (F and G). In other infants (D, E, I, J), less severe microcephaly and more subtle features were observed. In a third patient, a narrow bifrontal diameter is observed (C) but no occipital prominence is seen (H), and a fourth patient, has a normal frontal region (D) and a subtle occipital prominence (I).

HOW DO WE IDENTIFY HUMAN TERATOGENS?

▪ Typically no RCTs
▪ Animal studies
▪ Pharmacovigilance
▪ Case reports
▪ Observational studies
PREGNANCY REGISTRIES

- The safety of medications in pregnancy is often poorly understood
- FDA released a Guidance to Industry for Establishing Pregnancy Exposure Registries in 2002 and in 2007
- Ultimate goal of pregnancy exposure registries is to provide clinically relevant human data that can be used in a product’s labeling to provide medical care providers with useful information
- Pregnancy exposure registry is a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes
  - Differs from other postmarketing surveillance techniques as pregnant women are enrolled before the outcome of pregnancy is known

Many women need to take medications for health problems, but getting pregnant when a woman is pre-out they are pregnant.

A pregnancy exposure registry is designed to take pregnancy medications also collected on the newborn and have not taken medicine during enrollment in a pregnancy exposure registry. Use the search below to learn more about how you can help.

Pregnant Women | Health Prof.
List of Pregnancy Exposure Registries

Pregnancy exposure registries are studies that collect health information on medical product exposures such as drugs and vaccines during pregnancy. The registries on this page are posted based on a sponsor or investigator's request to list their registry. The registries listed on the webpage may not represent a comprehensive list of pregnancy exposure registries. FDA does not conduct any of these studies. FDA does not endorse any registry and is not responsible for the content of registries listed on this webpage. This webpage is open to the public and intended for informational purposes only.

Search by Medicine or Medical Condition:

(Search results update automatically as you type)

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Medical Condition</th>
<th>Registry</th>
<th>How to contact</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Drugs</td>
<td>Autoimmune Diseases: Crohn's Disease, Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Multiple Sclerosis (MS)</td>
<td>OTIS Autoimmune Diseases Study</td>
<td>MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) Website: <a href="http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/">http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/</a> Phone: 1-877-311-8972</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Multiple Drugs</td>
<td>Asthma</td>
<td>OTIS Pregnancy Outcomes and Asthma Medications in Pregnancy Study</td>
<td>MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) Website: <a href="http://www.pregnancystudies.org/ongoing-pregnancy-studies/asthma-study/asthma-treatments-pregnancy/">http://www.pregnancystudies.org/ongoing-pregnancy-studies/asthma-study/asthma-treatments-pregnancy/</a> Phone: 1-877-311-8972</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
MOTHERTOBABY

- First MotherToBaby service established in 1979; currently 15 sites located throughout the U.S. & Canada (including one here at UCSD)
- Provide individualized, evidence-based information to women, health care providers, and the public about medications and other exposures pregnant women may have had already or are anticipating during pregnancy and lactation
- Services provided at no cost to the patient or health care provider
- MotherToBaby is a service provided by the non-profit Organization of Teratology Information Specialists (OTIS)
200+ fact sheets on variety of exposures. Available in both English & Spanish; free to download. Updated as new info becomes available.
MOTHERTOBABY APP

Free app available for iOS and Android devices
MOTHERTOBABY PREGNANCY STUDIES CONDUCTED BY OTIS RESEARCH CENTER

- Enroll women throughout the U.S. and Canada

- Study model has been utilized effectively for identification, enrollment and follow-up of pregnant women, with and without specific conditions or treatments, and their children through 5 years of age*

- Participants who breastfeed are asked to complete a standard questionnaire at 2 and 6 months postpartum

- Women may also be consented into UC San Diego Human Milk Research Biorepository

*Some studies
Pregnancy Studies

We are actively engaged in research to improve the health of moms and babies. MotherToBaby Pregnancy Studies examine the effects of medications, vaccines, and diseases during pregnancy. Right now there is limited information to help moms-to-be and their health care providers navigate treatment decisions and other complex issues. Our studies aim to fill this critical gap.

MotherToBaby Pregnancy Studies are observational, which means you will not be asked to take any medications or vaccines or change any part of your routine. By sharing information about your pregnancy, you can play a key role in helping us learn more for your benefit and the benefit of future moms and babies.

Browse Our Studies

Volunteer Today
TARGET MEDICATIONS FOR MTB PREGNANCY STUDIES

- **Autoimmune**
  - Adalimumab (completed)
  - Etanercept (completed)
  - Leflunomide (completed)
  - Abatacept
  - Apremilast
  - Certolizumab pegol
  - Guselkumab
  - Sarilumab
  - Teriflunomide
  - Tocilizumab
  - Tofacitinib
  - Ustekinumab
  - Vedolizumab

- **Asthma**
  - Mepolizumab
  - Long acting beta-agonists (completed)

- **Lipid-lowering**
  - Alirocumab
  - Evolocumab

- **Vaccines**
  - Influenza vaccine (completed)
  - Antiviral medications used to treat influenza
  - TDaP vaccine
COHORT INCLUSION/EXCLUSION CRITERIA

All cohorts:
▪ Some enroll prior to 20 weeks’ gestation, some enroll anytime in pregnancy
▪ No prior knowledge of a major birth defect through prenatal diagnosis
▪ No retrospective enrollments in the cohort groups

Exposed and unexposed cohorts:
▪ Exposed to medication of interest for some time in the first trimester (most)
▪ In unexposed comparison group 1 – have underlying disease diagnosis but no treatment with medication of interest anytime in pregnancy
▪ In unexposed comparison group 2 – no exposure to major human teratogens
OUTCOMES COMPARED IN EXPOSED VS. DISEASE-MATCHED PREGNANCIES

- Overall proportion of live born and of all pregnancies excluding LTFU resulting in major birth defects
- Specific pattern of minor malformations*
- Spontaneous abortion
- Preterm delivery/shortened gestational age
- Birth weight, length, head circumference
- Postnatal weight, length, head circumference
- Proportion of infants with serious/opportunistic infections 1 to 5 years of age (serious infections not for all studies. Most studies to 1 year, 3 studies to 5 years)
- Proportion of infants with malignancies up to 1 year*
- Neurodevelopmental outcomes*

*Not an outcome for all studies
MOTHERTOBABY GENERAL STUDY DESIGN

Referral to OTIS Research Center
(Teratogen Information Service, Health Care Providers, Sponsor, Internet, Other)

Screening of Callers by Trained Interviewers

Medication-Exposed Women Cohort I

Disease-Matched Comparison Women Cohort II

Health Comparison Women Cohort III

Outcome Interview
Medical Records Review; Follow-up 1-5 Years of Age, Blinded Dysmorphological Examination*, Neurodevelopmental Testing or Screening*, and/or Antibody Titer Testing*

* Select Studies
# DYSMORPHOLOGY EXAM

<table>
<thead>
<tr>
<th>DAI Photo Guide: Fifteen still photos and 3 videos</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
<td><img src="image13.png" alt="Image" /></td>
</tr>
<tr>
<td>13. FootTopR</td>
</tr>
<tr>
<td>1. FullbodyDorsal newborn only (10-second video)</td>
</tr>
</tbody>
</table>

Still photo of each anomaly identified on child, but not already captured in one of these photos.
POTENTIAL CONFOUNDERS OR EFFECT MODIFIERS

- Age
- Race/ethnicity
- Pre-pregnancy body mass index (BMI)
- Socioeconomic status (SES)
- Prior pregnancy history
- Comorbidities
- Folic acid/vitamin supplement use
- Alcohol and tobacco use
- Other medications/vaccines timing in gestation and dose
- Measures of disease severity/symptoms; years since diagnosis
- Referral source
COHORT STUDY VS EXPOSURE SERIES

- In addition to cohort study, collection of the same breadth/depth of information on exposed pregnancies that do not meet the cohort criteria

- The “exposure series” represents
  - Retrospective reports
  - >20 weeks’ in pregnancy
    - exposures for indications not yet approved
    - pre-conception exposed pregnancies
    - prenatal diagnosis of major malformation prior to enrollment
    - exposure to a disqualifying medication
**The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation**

Carina Götestam Skorpen, 1,2,3 Maria Hoeltzerbein, 4 Angela Tincani, 5
Rebecca Fischer-Betz, 6 Elisabeth Elenfant, 7 Christine Chambers, 7,8 José da Silva, 9
Catherine Nelson-Piercy, 10 Irene Cetin, 11 Nathalie Cosset-Delatourelle, 12,13
Radboud Dohain, 14 Frauke Förger, 15 Munther Khamash, 16
Guillermo Ruiz-Iturzoa, 15 Angella Zink, 16 Jin Wennovsky, 19 Maurizio Cutolo, 20
Nele Caeyers, 17 Claudia Zumbühl, 22 Monika Østensen, 22

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**Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis**

G. Randić, 1 D.I. Johnson, 1 R.I. Jones, 1 J.J. Lopez-Jimenez Jr., 1 E. Sales, 1 N. Mirandola, 1 A.S. Van Vuuren, 2 C.J. Chambers, 1

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**Birth Outcomes in Women Who Have Taken Leflunomide During Pregnancy**

Christina D. Chambers, 1 Diana L. Johnson, 1 Luther K. Robinson, 1 Stephen R. Bradock, 1 Ronghui Xu, 1 Jasmin Lopez-Jimenez, 1 Nicole Mirandola, 1 Elizabeth Sales, 1 Yujuan J. Liu, 1 Shelia Jin, 1 Kenneth Lyons Jones, 1 and the Organization of Teratology Information Specialists

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**Research**

**Outcome following high-dose methotrexate in pregnancies misdiagnosed as ectopic**

Laila Narmouneh, MD, Myka E. Moore-Monger, MS; Tal Schechter, MD; Adrienne Einarson, RN; Diana Johnson, MS; Sharon V. Lavigna, MD; Aida Erbeto, MD; Gulsen Koren, MD; Yaron Feldstein, MD

---

**Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth**

Lalumila N. Bakireva, MD, PhD, MPH*, Michael Schatz, MD, MS; Kenneth Lyons Jones, MD; and Christina D. Chambers, PhD, MPH*; for the Organization of Teratology Information Specialists Collaborative Research Group

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**Theory-based predictors of influenza vaccination among pregnant women**

Jessica R. Giovannetti, 1 Neel E. Brewer, 1 Julie R. Wang, 1 Christina D. Chambers, 1

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ETANERCEPT

- Prospective cohort study
- Initiated in 2005; completed 2014
- Sponsored by Amgen
- Target sample size of 900 pregnant women
  - 300 ETA-exposed in pregnancy
  - 300 disease-matched (RA, psoriasis, ankylosing spondylitis)
  - 300 historical non-diseased comparison women
- Comparison group selected from MotherToBaby CA cohort pregnancies enrolled 1993-2008
- Increased risk of major birth defects overall in ETA-exposed group, but no evidence of a pattern of defects
- No significant differences between ETA-exposed and the disease-matched comparison pregnancies for all other outcomes evaluated through one year of age
<table>
<thead>
<tr>
<th>Condition</th>
<th>ETA Exposed N = 370</th>
<th>Diseased Unexposed N = 164</th>
<th>Non-Diseased Unexposed N = 296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>222</td>
<td>92</td>
<td>--</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>59</td>
<td>47</td>
<td>--</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>42</td>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>Ankylosing Spondylitis</td>
<td>47</td>
<td>18</td>
<td>--</td>
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</table>
# CHARACTERISTICS OF PREGNANT WOMEN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ETA Exposed N = 370</th>
<th>Diseased Unexposed N = 164</th>
<th>Non-Diseased Unexposed N = 296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age - yrs</td>
<td>32.6 (4.9)</td>
<td>33.4 (5.0)</td>
<td>32.4 (5.6)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Hispanic White</td>
<td>292 (78.9)</td>
<td>138 (84.1)</td>
<td>234 (79.1)</td>
</tr>
<tr>
<td>Maternal Education &gt;15 yrs</td>
<td>243 (65.7)</td>
<td>118 (72.0)</td>
<td>169 (57.5)</td>
</tr>
<tr>
<td>Gestational Age at Enrollment - wks</td>
<td>14.3 (8.3)</td>
<td>13.8 (6.7)</td>
<td>14.5 (8.8)</td>
</tr>
<tr>
<td>Primigravid</td>
<td>135 (36.5)</td>
<td>62 (37.8)</td>
<td>97 (32.9)</td>
</tr>
<tr>
<td>Previous Preterm</td>
<td>37 (10.0)</td>
<td>6 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Previous Child with a Birth Defect</td>
<td>20 (5.4)</td>
<td>8 (4.9)</td>
<td></td>
</tr>
<tr>
<td>IVF</td>
<td>27 (7.3)</td>
<td>5 (3.0)</td>
<td></td>
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</table>
### CHARACTERISTICS OF PREGNANT WOMEN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ETA Exposed N = 370</th>
<th>Diseased Unexposed N = 164</th>
<th>Non-Diseased Unexposed N = 296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin Use - Preconception</td>
<td>217 (58.6)</td>
<td>114 (69.5)</td>
<td></td>
</tr>
<tr>
<td>Alcohol - Any</td>
<td>177 (47.8)</td>
<td>80 (48.8)</td>
<td>108 (36.5)</td>
</tr>
<tr>
<td>Tobacco - Any</td>
<td>40 (10.8)</td>
<td>17 (10.4)</td>
<td>25 (8.4)</td>
</tr>
<tr>
<td>Pre-pregnancy BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>92 (24.9)</td>
<td>30 (18.3)</td>
<td>61 (21.4)</td>
</tr>
<tr>
<td>&gt;=30</td>
<td>74 (20.0)</td>
<td>25 (15.2)</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>Prenatal Dx &lt; Enrollment</td>
<td>68 (18.4)</td>
<td>28 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>45 (12.2)</td>
<td>23 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>48 (13.0)</td>
<td>33 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (5.1)</td>
<td>10 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Systemic Corticosteroid Use</td>
<td>163 (44.3)</td>
<td>65 (39.6)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
MEASURES OF DISEASE SEVERITY RHEUMATIC DISEASES

![Bar chart showing measures of disease severity for rheumatic diseases, with Intake 1, Intake 2, Intake 3, 3rd 1, 3rd 2, 3rd 3, ETA, and Unexp categories.]
### OUTCOMES BY EXPOSURE GROUP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ETA Exposed N = 370 n (%)</th>
<th>Diseased Unexposed N = 164 n (%)</th>
<th>Non-Diseased Unexposed N = 296 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>342 (92.4)</td>
<td>144 (87.8)</td>
<td>257 (86.8)</td>
</tr>
<tr>
<td>Twin</td>
<td>14 (4.1)</td>
<td>2 (1.4)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>SAb</td>
<td>14 (3.8)</td>
<td>13 (7.9)</td>
<td>16 (5.4)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Termination</td>
<td>2 (0.9)</td>
<td>1 (0.6)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>11 (3.0)</td>
<td>6 (3.7)</td>
<td>19 (6.4)</td>
</tr>
</tbody>
</table>
# MAJOR STRUCTURAL DEFECTS

<table>
<thead>
<tr>
<th>Major Birth Defects in Live-born Infants</th>
<th>ETA Exposed n/N (%)</th>
<th>Diseased Unexposed n/N (%)</th>
<th>Adj OR (95%CI)</th>
<th>Non-Diseased Unexposed n/N (%)</th>
<th>OR or Adj OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Birth Defects in All Pregnancies</td>
<td>30/319 (9.4%)</td>
<td>5/144 (3.5%)</td>
<td>2.77* [1.04, 7.35]</td>
<td>8/257 (3.1%)</td>
<td>3.58** [1.60, 8.03]</td>
</tr>
<tr>
<td>Major Birth Defects in All Pregnancies</td>
<td>33/335 (9.9%)</td>
<td>7/158 (4.4%)</td>
<td>2.37* [1.02, 5.52]</td>
<td>10/277 (3.6%)</td>
<td>2.91 [1.37, 6.76]</td>
</tr>
</tbody>
</table>

*Adjusted for PS comprised of maternal asthma and maternal height
**Adjusted for maternal age
## MINOR STRUCTURAL DEFECTS

<table>
<thead>
<tr>
<th></th>
<th>ETA Exposed n/N (%)</th>
<th>Diseased Unexposed n/N (%)</th>
<th>OR (95% CI)</th>
<th>Non-Diseased Unexposed n/N (%)</th>
<th>Adj OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants Examined</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with 3+ Minor Defects</td>
<td>66/257 (25.7%)</td>
<td>25/111 (22.5%)</td>
<td>1.19 [0.70, 2.01]</td>
<td>26/176 (14.8%)</td>
<td>2.27* [1.34, 3.84]</td>
</tr>
<tr>
<td><strong>Infants Examined</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with Specific Pattern</td>
<td>6/262** (2.3%)</td>
<td>0/113**</td>
<td></td>
<td>0/181**</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for maternal alcohol use in first trimester

**Includes twins for consideration of a pattern but no co-twin could define a pattern
## SPONTANEOUS ABORTION

<table>
<thead>
<tr>
<th>Number of SAb</th>
<th>ETA Exposed N = 288</th>
<th>Diseased Unexposed N = 137</th>
<th>Adj HR (95%CI)</th>
<th>Non-Diseased Unexposed N = 215</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAb rate (95% CI)</td>
<td>14.7% [7.4,28.3]</td>
<td>28.8% [16.0,48.5]</td>
<td>0.47* [0.20,1.12]</td>
<td>14.9% [8.7,25.0]</td>
<td>0.79 [0.37,1.65]</td>
</tr>
</tbody>
</table>

*Adjusted for PS comprised of referral source and maternal height
## PRETERM BIRTH

<table>
<thead>
<tr>
<th>Number of PTB</th>
<th>ETA Exposed N = 324</th>
<th>Diseased Unexposed N = 142</th>
<th>Adj HR (95%CI)</th>
<th>Non-Diseased Unexposed N = 244</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>14</td>
<td>17</td>
<td>1.60** [0.86, 2.98]</td>
<td>7.1% [4.5, 11.2]</td>
<td>2.02 [1.15, 3.53]</td>
</tr>
</tbody>
</table>

PTB rate (95% CI) - 13.9% [10.5, 18.2] 10.0% [6.1, 16.3] 1.60** [0.86, 2.98] 7.1% [4.5, 11.2] 2.02 [1.15, 3.53]

*Excluding twins

**Adjusted for preeclampsia; unadjusted estimate 1.39 [0.76, 2.54]
SMALL FOR GESTATIONAL AGE INFANTS AT BIRTH

Weight  Length  OFC

- ETA
- Unexp
### INFECTIONS/HOSPITALIZATIONS/MALIGNANCIES IN INFANTS TO ONE YEAR OF AGE

<table>
<thead>
<tr>
<th></th>
<th>ETA Exposed n/N (%)</th>
<th>Diseased Unexposed n/N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections/Hospitalizations</strong></td>
<td>18/342 (5.3%)</td>
<td>6/144 (4.2%)</td>
<td>1.28 [0.47, 4.02]</td>
</tr>
<tr>
<td><strong>Infections/Hospitalizations in 3rd tri ETA Exposed</strong></td>
<td>7/184 (3.8%)</td>
<td>6/144 (4.2%)</td>
<td>0.91 [0.26, 3.36]</td>
</tr>
<tr>
<td><strong>Malignancies</strong></td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>
## DEVELOPMENTAL SCREENING AGES & STAGES ONE YEAR OF AGE

<table>
<thead>
<tr>
<th></th>
<th>ETA Exposed N = 287</th>
<th>Diseased Unexposed N = 117</th>
<th>OR or Adj OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen Positive Overall</td>
<td>81 (28.2%)</td>
<td>32 (27.4%)</td>
<td>1.04 [0.65,1.69]</td>
</tr>
<tr>
<td>Screen Positive in Any 1 or More Domains</td>
<td>67 (23.3%)</td>
<td>29 (24.8%)</td>
<td>0.92 [0.56,1.53]</td>
</tr>
<tr>
<td>Screen Positive in any 2 or More Domains</td>
<td>22 (7.7%)</td>
<td>5 (4.3%)</td>
<td>1.86 [0.56,5.20]*</td>
</tr>
</tbody>
</table>

*Adjusted for PS comprised of primary disease, psoriasis severity score in third trimester; excluding severity score, adjusted OR was 2.11 [0.77,5.83]
VAMPSS
Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

If you are pregnant and have asthma you may feel uneasy about taking medications, but it is very important to keep your symptoms under control. Uncontrolled asthma symptoms can cause a decrease in the amount of oxygen in your blood supply. A developing baby needs a regular supply of oxygen for normal growth and development; if your asthma is uncontrolled during pregnancy, this can harm your baby.

During flu season, it is especially important to get a flu shot because flu is more likely to cause severe illness in women who are pregnant. Pregnant women with flu also have a greater chance for serious problems for their unborn baby, including premature labor and delivery.

Why was VAMPSS developed?
Major congenital malformations (birth defects) occur in 3-5% of all infants, and other complications such as prematurity and low birth weight occur in 10-15% of pregnancies. Although medications and vaccines are uncommon causes of these adverse events, they are among the most preventable. Because pregnant women are excluded from clinical trials, there is a lack of adequate safety information for most medications taken during pregnancy. The VAMPSS surveillance system aims to collect this information in a systematic fashion and help close the knowledge gap.
Risks and safety of pandemic h1n1 influenza vaccine in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants

Christina D. Chambers, Diana Johnson, Ronghui Xu, Yunjun Luo, Carol Louik, Allen A. Mitchell, Michael Schatz, Kenneth L. Jones, the OTIS Collaborative Research Group

Department of Pediatrics, University of California San Diego, La Jolla, CA, United States
Clinical Translational Research Institute, University of California San Diego, La Jolla, CA, United States
Department of Mathematics, University of California San Diego, La Jolla, CA, United States
Stone Epidemiology Center at Boston University, Boston, MA, United States
American Academy of Allergy Asthma and Immunology, Milwaukee, WI, United States
Vaccines and Medications in Pregnancy Surveillance System, United States

Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: Exposure prevalence, preterm delivery, and specific birth defects

Carol Louik, Katherine Ahrens, Stephen Kerr, Junhee Pyo, Christina Chambers, Kenneth L. Jones, Michael Schatz, Allen A. Mitchell
MOMMY’S MILK

We are building the first-ever research database of human breast milk.

Excited about the possibilities? We are too. Learn more.
STUDY DESIGN, RECRUITMENT AND DATA

- **Study Design**
  - 50 mL milk sample up to full pump: local collection or mailed
  - Samples are stored in a -80°C Freezer at UCSD

- **Recruitment Sources**
  - MotherToBaby Pregnancy Studies (US and Canada)
  - Social Media
  - Local newborn nurseries
  - San Diego Blood Bank/San Diego Milk Bank

- **Data**
  - Demographics, maternal and child health, and breastfeeding habits
  - Exposures to recreational drugs, alcohol, tobacco, caffeine, prescription medications, and over-the-counter medications over past 14 days
  - Infant adverse reaction checklist
  - Stress, anxiety, depression, food frequency questionnaires (on-line)
  - Neurobehavioral questionnaires 12-36 months; face-to-face testing for subset
  - Access to medical records
MOMMY'S MILK SAMPLES DASHBOARD

DIRECTIONS: This dashboard shows current bio-specimens available for withdrawal from the Human Milk Biorepository. This dashboard is fully interactive. Please click on any map, table, or pie-chart data point(s) to get specific information for those bio-specimens. For example, select a state (or multiple states) to view specimens available from that specific location, click the 'Reset All' button to undo your selection or choose a new location. To get more information about a map, table, or pie-chart please click on the title to view a brief description.

Note: If using a mobile device, dashboard best viewed in landscape orientation.

BIO SPECIMEN DISTRIBUTION BY STATES

TOTAL ALIQUOTS
18,286

TOTAL MOTHERS
1,137

COLLECTION CRITERIA

PRETERM BIRTH

Specimen Quantity

10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0

Specimen Qty (mL)
**MOMMY’S MILK DEMOGRAPHICS DASHBOARD**

**DIRECTIONS:** This dashboard shows current demographic information for all Mommy’s Milk participants. This dashboard is fully interactive. Please click on **any** map, table, or pie-chart data point(s) to get specific demographic information for participants who fall within the parameters selected. For example, select a state (or multiple states) to view information for that specific location, click the ‘Reset All’ button to undo your selection or choose a new location. To get more information about a map, table, or pie-chart please click on the title to view a brief description.

**Note:** Using a mobile device, dashboard best viewed in landscape orientation.
ONGOING ANALYSES

- >1400 samples banked in the biorepository
- Simultaneous analyses completed for first ~600 samples:
  - Microbiome: 16S
  - Untargeted Metabolomics
  - Human Oligosaccharides
  - Macronutrient Profile
CANNABINOIDS IN BREASTMILK

- 54 human milk samples with known maternal marijuana exposure in previous 14 days were collected from consented volunteers
- Analyzed at Skaggs School of Pharmacy at University of California San Diego
- Measured levels of THC, 11-OH-THC, CBD, and CBN

Bertrand K et al, *Pediatrics*, 2018
CANNABINOIDS IN BREASTMILK

METHODS AND FREQUENCY OF MARIJUANA USE IN BREASTFEEDING WOMEN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=50 mothers, No. (%)</th>
<th>N=4 mothers who gave a repeat sample, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of Marijuana Exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation Only</td>
<td>32 (64)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Other Only</td>
<td>7 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Both</td>
<td>11 (22)</td>
<td>2 (50)</td>
</tr>
<tr>
<td><strong>Frequency of Marijuana Use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 use/day</td>
<td>6 (12)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>1 use/day</td>
<td>23 (46)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>&gt;1 use/day</td>
<td>21 (42)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*a Inhalation Only was defined as a dose unit of joints, puffs, or grams. Other Only was defined as a dose unit of drops, milligrams or servings. Both was defined as a dose unit from both the Inhalation Only and the Other Only groups*
### THC, 11-OH-THC, AND CBD LEVELS DETECTED IN BREAST MILK

<table>
<thead>
<tr>
<th></th>
<th>Min.</th>
<th>1st Qu.</th>
<th>Median</th>
<th>3rd Qu.</th>
<th>Max.</th>
<th>AQL*</th>
<th>BQL*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Δ9-THC (ng/mL)</strong></td>
<td>1.01</td>
<td>2.29</td>
<td>9.47</td>
<td>46.78</td>
<td>323.00</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td><strong>11-OH-THC (ng/mL)</strong></td>
<td>1.33</td>
<td>1.35</td>
<td>2.38</td>
<td>5.45</td>
<td>12.80</td>
<td>5</td>
<td>49</td>
</tr>
<tr>
<td><strong>CBD (ng/mL)</strong></td>
<td>1.32</td>
<td>2.92</td>
<td>4.99</td>
<td>5.97</td>
<td>8.56</td>
<td>5</td>
<td>49</td>
</tr>
</tbody>
</table>

* AQL (above quantification limits) was defined as ≥1ng/ mL and BQL (below quantification limits) was defined as <1 ng/mL

** The concentration of CBN was BQL in all 54 samples

Δ9-THC was detectable in 34 of 54 samples (63%); among these, the median concentration of Δ9-THC was 9.47 ng/mL of breast milk (range: 1.01, 323.00)
CANNABINOIDs IN BREASTMILk

Scatterplot and Fitted Regression Last Use of Marijuana, N=34

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>95% CI</th>
<th>t value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>3.166</td>
<td>0.344</td>
<td>(2.463, 3.869)</td>
<td>9.208</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hours</td>
<td>-0.026</td>
<td>0.008</td>
<td>(-0.043, -0.008)</td>
<td>-3.025</td>
<td>0.005</td>
</tr>
</tbody>
</table>
FDA PREGNANCY AND LACTATION (DRUG) LABELING FINAL RULE
OLD PREGNANCY LABELING SYSTEM - LIMITATIONS

▪ Did not advise prescribers and patients of the potential harm from withholding a needed medication in pregnancy

▪ Thought of as a grading system where risk increase from lowest (Category A) to highest (Category X)

▪ Led to false assumptions that drugs in the same category carried a similar risk or that Category X drugs were known human teratogens
  - most approved drugs were Category C
  - includes drugs with adverse animal data or no animal data
Pregnancy and Lactation Labeling (Drugs) Final Rule

The FDA published the Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling, referred to as the “Pregnancy and Lactation Labeling Rule” (PLLRR or final rule).

The PLLRR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLRR removes pregnancy letter categories – A, B, C, D and X. The PLLRR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLRR labeling requirements.

---

PLR Requirements for Prescribing Information

On January 24, 2006, the U.S. Food and Drug Administration (FDA) issued final regulations governing the content and format of prescribing information (PI) for human drug and biological products. The rule is commonly referred to as the “Physician Labeling Rule” (PLR) because it addresses prescription drug labeling that is used by prescribers and other health care providers.

The goal of the PLR content and format requirements as described at 21 CFR 201.56 and 201.57 is to enhance the safe and effective use of prescription drug products by providing health care providers with clear and concise PI that is easier to access, read, and use. The PLR format also makes PI more accessible for use with electronic prescribing tools and other electronic information resources.

PI submitted with new drug applications (NDAs), biologic license applications (BLAs), and efficacy supplements must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. The Labeling Development Team works with review divisions to ensure PI conforms with the PLR. This page includes links to the Final Rule, regulations, related guidance documents, and additional labeling resources.

On December 3, 2014, the FDA published the Pregnancy and Lactation Labeling Rule (PLLRR). The goal of the PLLRR is to enhance the safe and effective use of prescription drug products in pregnant women, lactating women, and females and males of reproductive potential.

---

NEW PREGNANCY LABELING SYSTEM (PLLR)

▪ Removal of Categories A, B, C, D, X

▪ Prominent listing of contact information for Pregnancy Exposure Registries if one exists for the drug

▪ Narrative presentation of information including 1) risk summary, 2) clinical considerations for use, and 3) supporting data

▪ Must be updated as new information becomes available
NEW PREGNANCY LABELING SYSTEM (PLLR)

- Lactation subsection provides information about using the drug while breastfeeding, including amount of drug in breast milk, effects on milk supply, and potential effects on the breastfed infant

- A subsection on females and males of reproductive potential with information about: 1) pregnancy testing, 2) contraception, and 3) effects on fertility
NEW PREGNANCY LABELING SYSTEM (PLLR)

- Implemented June 30, 2015

- A,B,C,D,X drugs labels must be removed by June 29, 2018

- All drugs marketed after June 30, 2001 must revise label by 2020

- All new drugs marketed after June 30, 2015 must use new label format
Evolving Knowledge of the Teratogenicity of Medications in Human Pregnancy

MARGARET P. ADAM, * JANINE E. POLIFKA, AND J.M. FRIEDMAN

A majority of pregnant women take at least one medication during pregnancy, although the safety of such drugs during pregnancy is not always known. We reviewed the safety during pregnancy of 172 drugs approved by the US Food and Drug Administration (FDA) from 2000 to 2010 using the TEKIS risk rating system. We also reviewed safety information for 468 drugs approved by the FDA from 1980 to 2000 to determine if revisions in risk categories had been made in the last 10 years. The teratogenic risk in human pregnancy was “undetermined” for 168 (97.7%) of drug treatments approved between 2000 and 2010. Furthermore, the amount of data available regarding safety in pregnancy was rated as “none” for 126 (73.3%) of these drugs. For those drugs approved between 1980 and 2000, only 23 (5%) changed a full risk category or more in the past 10 years. Sources of data that led to a revised risk were derived from exposure cohort studies performed through record linkage studies, teratogen information services, large population-based case-control studies, and pregnancy registries. The mean time for a treatment initially classified as having an “undetermined” risk to be assigned a more precise risk was 27 years (95% confidence interval 26–28 years). The lack of information needed to assess the safety of drug treatments during human pregnancy remains a serious public health problem. A more active approach to post-marketing surveillance for teratogenic effects is necessary. © 2011 Wiley-Liss, Inc.
THANK YOU

https://betterbeginnings.org/

https://mothertobaby.org/

https://medschool.ucsd.edu/research/actri/clinical/Pages/CenterforLifeCourseResearch.aspx

chchambers@ucsd.edu