Course and Treatment of Psychiatric Disorder During Pregnancy: Lessons Learned over Two Decades

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Disclosures

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12-Month Disclosure

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Honoraria: None
Royalty/patent, other income: None
Are pregnant women protected against relapse or new onset of major depression?

Yonkers et al. *Epidemiology* 2011
Roca et al. *J Affective Disorders* 2013
Time to Relapse in Patients Who Maintained or Discontinued Antidepressant

Relapse of Bipolar Disorder During Pregnancy

For Further Information:

www.womensmentalhealth.org
Identification and Treatment of Antenatal Depression

• Routine screening for antenatal depression has been uncommon but is changing

• Identified antenatal depression is typically untreated or incompletely treated

• Prevalence of SSRI use during pregnancy is 3-7%

SSRI = selective serotonin reuptake inhibitor

Psychotropic Drug Use in Pregnancy

- Medications used when risk to mother and fetus from disorder outweighs risks of pharmacotherapy
- Optimum risk/benefit decision for psychiatrically ill pregnant women
- Patients with similar illness histories make different decisions regarding treatment during pregnancy
- No decision is risk-free
- Collaborative, patient-centered approach required

Henshaw Fam Plann Perspect. 1998
• Focus of concern regarding known and unknown risks of fetal exposure to psychiatric medications is increasingly balanced by data supporting risk of exposure to disorder, stress and HPA-axis dysregulation on fetoplacental unit

• Enhanced appreciation for impact of disorder and chronic stress on long term behavioral outcomes
Relative Impact of AD Exposure vs. Depression in Obstetrical and Neonatal Outcome

• Some data support increased rates of obstetrical complications and poor neonatal outcome in depressed or anxious pregnant women
  – Increased risk of preterm birth
  – Lower birth weight (LBW)
  – Small for gestational age (SGA)

• Depression and anxiety often comorbid

• Increased effort to distinguish impact of illness from medication exposure on obstetrical and neonatal outcome

Wisner Am J Psychiatry 2009
Warburton et al 2010
Maternal Depression in Pregnancy: Obstetric Outcome

Preterm=<37 weeks estimated gestational age; LBW=low birth weight (<2.5 kg); SGA=small for gestational age (<10th percentile); CES-D=Center for Epidemiologic Studies-Depression; BDI=Beck Depression Inventory.

A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction

Table 2

Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Qdf Within</td>
</tr>
<tr>
<td>PTB</td>
<td>20</td>
<td>1.13 (1.06–1.21)</td>
<td>&lt;.001</td>
<td>49.019</td>
</tr>
<tr>
<td>LBW</td>
<td>11</td>
<td>1.18 (1.07–1.30)</td>
<td>.001</td>
<td>33.810</td>
</tr>
<tr>
<td>IUGR</td>
<td>12</td>
<td>1.03 (0.99–1.08)</td>
<td>.14</td>
<td>22.411</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.

*Pooled effect size was estimated using the random-effects model.
Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD
The Problem of Confounding

- Analyses of outcomes typically do not control for depression (or its severity)
- Recent efforts to control for depression in analyses of malformation risk attenuate risks for drug exposure

Palmsten and Hernandez-Diaz *Epidemiology* 2012.  
Huybrechts et al. *NEJM* 2014.
Untreated Psychiatric Disorders During Pregnancy: Effects on Fetal Brain and HPA-Axis

• Newborns of women with depression at 26 weeks gestation demonstrate altered microstructure in right amygdala compared to those born to women without depression during pregnancy

• Dysregulation of HPA-axis during pregnancy may increase risk of onset of depression in older children

Pearson et al. JAMA Psychiatry 2013
Van den Bergh Neuropsychopharmacology 2008
Figure 1. The top and bottom rows, respectively, show the brain using the color map of diffusion tensor imaging and T2-weighted magnetic resonance imaging from one infant of our sample. The axial, coronal, and sagittal slices are respectively illustrated from left to right. The red contour indicates the amygdala on diffusion tensor imaging and T2-weighted magnetic resonance imaging.

What is the Safest Antidepressant for Women of Childbearing Age?
• All pregnancies have an underlying risk for major fetal malformations or pregnancy loss regardless of fetal exposure to medications or maternal illness

• There are more safety and efficacy data on the use of SSRIs during pregnancy than any other drug class
• **Category A:**
  – Well controlled studies in human pregnancy show no increased risk to the fetus

• **Category B:**
  – Animal studies show no increased risk to the fetus OR
  – Animal studies show an increased risk to the fetus but well controlled human studies do not.

• **Category C:**
  – Animal studies show an increased risk to the fetus and there are no well controlled studies in human pregnancy OR
  – There aren’t any animal studies or well controlled human studies.
FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products

For Immediate Release

December 3, 2014

The U.S. Food and Drug Administration published a [final rule](http://womensmentalhealth.org/posts/fda-finalizes-guidelines-pregnancy-lactation-labeling-information/) today that sets standards for how information about using medicines during pregnancy and breastfeeding is presented in the labeling of prescription drugs and biological products.

http://womensmentalhealth.org/posts/fda-finalizes-guidelines-pregnancy-lactation-labeling-information/
SSRI Use During Pregnancy

• Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
  – Consistent conclusions that the *absolute* risk of SSRI exposure in pregnancy is small\(^1-3\)
  – Consistent pattern of malformations with SSRI exposure is lacking
  – Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs\(^4-9\)

**Reproductive safety data on SSRIs exceed what is known about most other medicines used in pregnancy**

• Do more data help?
• Extensive data on risks of psychotropic drug use during pregnancy can complicate interpretation of clinical implications/relevance (varying methodologies, disparate data sources)
• Selectivity of studies described or highlighted in reviews and media (convention and social) complicate clinical decision making
First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects


Use of Selective Serotonin-Reuptake Inhibitors in Pregnancy and the Risk of Birth Defects

Sura Alwan, M.Sc., Jennita Reefhuis, Ph.D., Sonja A. Rasmussen, M.D., M.S., Richard S. Olney, M.D., M.P.H., and Jan M. Friedman, M.D., Ph.D., for the National Birth Defects Prevention Study
Most recent studies/analyses demonstrate either modest increase in relative risk or absence of risk.
Recent analysis of 949,504 pregnant women enrolled in Medicaid

- 3 months prior to pregnancy to 1 month following pregnancy

6.8% use of SSRIs during first trimester

Risk for cardiac defects attenuated with increasing levels of adjustment for confounding
Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D., Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D., Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A., Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

• No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs
Cardiovascular Malformation and Fetal SSRI Exposure

Huybrechts et al. NEJM 2014.

<table>
<thead>
<tr>
<th>Exposure Group According to Outcome</th>
<th>Unadjusted Analysis</th>
<th>Depression-Restricted Analysis</th>
<th>Depression-Restricted Analysis with Propensity-Score Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Right ventricular outflow tract obstruction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antidepressant</td>
<td>1.11 (0.89–1.38)</td>
<td>1.02 (0.78–1.34)</td>
<td>0.92 (0.67–1.25)</td>
</tr>
<tr>
<td>SSRI</td>
<td>1.12 (0.87–1.45)</td>
<td>1.06 (0.79–1.42)</td>
<td>0.99 (0.70–1.43)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.22 (0.74–2.00)</td>
<td>1.09 (0.62–1.90)</td>
<td>1.07 (0.59–1.93)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.03 (0.64–1.66)</td>
<td>1.13 (0.69–1.84)</td>
<td>1.22 (0.67–1.88)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.23 (0.75–2.01)</td>
<td>1.02 (0.57–1.81)</td>
<td>0.93 (0.50–1.72)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>1.14 (0.57–2.28)</td>
<td>1.10 (0.46–2.68)</td>
<td>0.94 (0.37–2.36)</td>
</tr>
<tr>
<td>SNRI</td>
<td>1.47 (0.83–2.60)</td>
<td>1.47 (0.82–2.62)</td>
<td>1.06 (0.55–2.05)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.05 (0.58–1.91)</td>
<td>1.10 (0.58–2.06)</td>
<td>1.09 (0.56–2.10)</td>
</tr>
<tr>
<td>Other</td>
<td>0.96 (0.48–1.93)</td>
<td>0.61 (0.25–1.47)</td>
<td>0.61 (0.24–1.52)</td>
</tr>
<tr>
<td><strong>Ventricular septal defect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antidepressant</td>
<td>1.23 (1.09–1.38)</td>
<td>1.02 (0.88–1.19)</td>
<td>0.95 (0.79–1.14)</td>
</tr>
<tr>
<td>SSRI</td>
<td>1.20 (1.04–1.39)</td>
<td>1.01 (0.85–1.21)</td>
<td>0.98 (0.81–1.26)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.09 (0.81–1.47)</td>
<td>0.77 (0.53–1.22)</td>
<td>0.73 (0.49–1.09)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.24 (0.96–1.59)</td>
<td>1.09 (0.82–1.45)</td>
<td>1.04 (0.76–1.41)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.20 (0.90–1.59)</td>
<td>1.14 (0.83–1.56)</td>
<td>1.12 (0.80–1.57)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>1.11 (0.74–1.66)</td>
<td>1.08 (0.65–1.58)</td>
<td>0.86 (0.50–1.47)</td>
</tr>
<tr>
<td>SNRI</td>
<td>1.56 (1.14–2.14)</td>
<td>1.36 (0.97–1.92)</td>
<td>1.24 (0.85–1.82)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.22 (0.89–1.67)</td>
<td>0.93 (0.63–1.38)</td>
<td>0.88 (0.58–1.34)</td>
</tr>
<tr>
<td>Other</td>
<td>1.21 (0.85–1.73)</td>
<td>1.04 (0.70–1.53)</td>
<td>0.99 (0.64–1.53)</td>
</tr>
<tr>
<td><strong>Other cardiac defect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antidepressant</td>
<td>1.35 (1.21–1.52)</td>
<td>1.27 (1.10–1.47)</td>
<td>1.15 (0.97–1.36)</td>
</tr>
<tr>
<td>SSRI</td>
<td>1.34 (1.17–1.54)</td>
<td>1.25 (1.07–1.47)</td>
<td>1.19 (0.99–1.43)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.18 (0.89–1.57)</td>
<td>1.11 (0.81–1.53)</td>
<td>1.10 (0.78–1.55)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.39 (1.10–1.76)</td>
<td>1.25 (0.96–1.64)</td>
<td>1.19 (0.89–1.59)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.37 (1.05–1.79)</td>
<td>1.26 (0.98–1.71)</td>
<td>1.23 (0.89–1.70)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>0.83 (0.52–1.32)</td>
<td>0.95 (0.55–1.65)</td>
<td>0.79 (0.45–1.46)</td>
</tr>
<tr>
<td>SNRI</td>
<td>1.51 (1.20–2.08)</td>
<td>1.50 (1.08–2.09)</td>
<td>1.31 (0.90–1.90)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.52 (1.14–2.02)</td>
<td>1.34 (0.97–1.87)</td>
<td>1.16 (0.81–1.67)</td>
</tr>
<tr>
<td>Other</td>
<td>1.79 (1.34–2.40)</td>
<td>1.61 (1.17–2.22)</td>
<td>1.65 (1.15–2.37)</td>
</tr>
</tbody>
</table>
Non-SSRIs During Pregnancy

- More limited reproductive safety data available for SNRI’s compared to SSRIs, i.e. venlafaxine, duloxetine (new registry in 2009, limited data)

- Data on bupropion includes growing number of exposures supporting absence of increased risk for malformation, overall and cardiac (Alwan et al. 2010)

- Should bupropion be used more frequently during pregnancy?

http://www.gsk.com/media/paroxetine/ingenix_study.pdf
Non-SSRIs During Pregnancy

• Bupropion
  • Prospective studies have not demonstrated overall increased risk of malformations, compared to control groups exposed to other ADs or non-exposed controls
  • Retrospective case control study from birth defect registry suggested small but increased risk of cardiovascular left outflow defects
    • Absolute risk was approximately 2 out of 1000 pregnancies
  • Recent case control study: increased risk for VSD, no risk for other cardiac malformations

Other Non-SSRI Antidepressants:

- **SNRIs:**
  - Limited reproductive safety data available for SNRIs, i.e. venlafaxine, duloxetine

- **Mirtazapine:**
  - Small prospective study does not suggest increased rate of malformations

“Poor Neonatal Adaptation” and SSRI Use During Pregnancy

• Consistent data: Late trimester exposure to SSRIs is associated with *transient* irritability, agitation, jitteriness, and tachypnea (25-30%)

• Overall studies do not adequately control for maternal mental health condition, adequate blinding of exposure in neonatal assessments

• Clinical implication: Should women be treated with antidepressants late in pregnancy and during labor and delivery (Warburton et al. 2010)

• Are any subgroups of newborns vulnerable to enduring symptoms beyond the first days of life?

Chambers, *BMJ*, 2009
Risk for PPHN Associated with Late Trimester Exposure to Antidepressant
Antidepressants During Pregnancy: Later Pregnancy Considerations

• Risk of persistent pulmonary hypertension of newborn (PPHN) with SSRIs?

• INCONSISTENT FINDINGS
  – Initial report showed SSRIs increased risk by 6-fold (Chambers 2006; approximately 1%)
  – Lower risk (0.15%) seen by Källén and Olausson, 2008 No association seen by others (Andrade et al, 2009; Wichman et al, 2007; Wilson et al, 2010)
  – Other factors may play a role: race, high BMI, delivery by C-section
  – If there is an association, risk extremely low
  – Revised FDA communication (2012) noting earlier overestimation of risk (http://www.fda.gov/drugs/drugsafety/ucm283375.htm)
Antidepressant Use Late in Pregnancy and Risk of PPHN

• Large Medicaid Database – 3.8 million pregnancies
  – 128,950 women (3.4%) filled at least 1 prescription for antidepressants last 90 days of pregnancy; 2.7% used an SSRI and 0.7% used a non-SSRI
  – Overall, 7630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95%CI, 20.4-21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95%CI, 28.3-35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95%CI, 23.3-36.4 per 10,000 births)

• Absolute Risks:
  – With SSRI: 31.5/10,000 = 0.3%
  – No antidepressant: 20.8/10,000 = 0.2%

• Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment

Huybrechts et al., JAMA 2015
• Data to support recommendations to lower AD proximate to delivery are sparse; discontinuation of AD during peripartum period may increase risk for puerperal illness

Are SSRIs associated with an increased risk of autism or other child psychopathology?

Studies have been **inconsistent** – some show low risk, some show no risk

- **Croen et al., 2011**: Case-control study. N= 298 children with and randomly selected control children
  - Prenatal exposure to SSRI was reported for **20 case children** (6.7%) and 50 controls (3.3%)
  - 2-fold increased risk of ASD associated SSRI in year before delivery; strongest effect in first trimester (adjusted OR, 3.8)
  - 4429 cases of autism spectrum disorder; 43,277 matched controls in the full sample (1679 cases of autism spectrum disorder and 16,845 controls with data on maternal antidepressant use nested within cohort (n=589,114)
  - A history of maternal (adjusted odds ratio 1.49, 95% CI 1.08 to 2.08) but not paternal depression was associated with increased risk of ASD
  - Subsample with available data on meds, association confined to women reporting antidepressant use during pregnancy (OR 3.34, 1.50 to 7.47, P=0.003, SSRI or non SSRI)
  - All associations were higher in cases of autism without intellectual disability
  - If causal, SSRI use during pregnancy explained 0.6% of the cases of autism spectrum disorder.

**No association:**

- **Hviid et al., 2013**: Danish population registry study: linked information on maternal use of SSRIs before and during pregnancy, autism spectrum disorders, confounders
  - 3892 cases of autism spectrum disorder, N= 52 cases of women with SSRI use
- **Clements et al., 2014**: N=1377 w ASD matched controls, AD exposure not associated with ASD after controlling for maternal depression- **No risk**
- **Malm et al., 2016**: Finnish population national register cohort study looked at SSRI exposed, exposed to illness but not SSRI, exposed to SSRIs only before pregnancy, and unexposed
  - No association with autism but association with ADHD was noted
### Table 2A. ASD risk associated with maternal antidepressant exposure during pregnancy

<table>
<thead>
<tr>
<th>Antidepressant exposure</th>
<th>ASD</th>
<th>Controls</th>
<th>ASD vs ASD-matched controls&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1377</td>
<td>4022</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Time period</strong></td>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Prepregnancy</td>
<td>6.6%</td>
<td>3.5%</td>
<td>1.98 (1.50–2.59)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.91 (1.41–2.58)&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.62 (1.17–2.23)&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preconception (conception - 30 days)</td>
<td>1.7%</td>
<td>1.0%</td>
<td>1.72 (1.02–2.84)&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.89 (1.07–3.30)&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.47 (0.81–2.61)</td>
</tr>
<tr>
<td>1st trimester</td>
<td>2.3%</td>
<td>1.3%</td>
<td>1.76 (1.11–2.74)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.84 (1.11–3.00)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.43 (0.85–2.38)</td>
</tr>
<tr>
<td>2nd trimester</td>
<td>2.0%</td>
<td>1.2%</td>
<td>1.76 (1.08–2.79)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.81 (1.07–3.00)&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.34 (0.77–2.27)</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>1.8%</td>
<td>1.1%</td>
<td>1.60 (0.96–2.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.48 (0.85–2.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.08 (0.61–1.88)</td>
</tr>
<tr>
<td>Pregnancy (preconception - delivery)</td>
<td>2.9%</td>
<td>2.0%</td>
<td>1.49 (1.01–2.18)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.45 (0.94–2.19)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1.10 (0.70–1.70)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, Autism Spectrum Disorder; CI, confidence interval; OR, odds ratio. <sup>a</sup>Unadjusted and adjusted risk of ASD compared with ASD-matched controls; Significance at P < 0.05 (*), < 0.01 (**), < 0.001 (**). Model 1 is adjusted for gender, race, birth year, insurance type, maternal age and median income tertile. Model 2 is adjusted for variables in model 1 and past history of maternal depression.
What are the Long-term Neurobehavioral Effects of Prenatal Exposure to an Antidepressant?
Results of Neurobehavioral Tests in Infants According to Whether They Were Exposed In Utero to Antidepressants*

<table>
<thead>
<tr>
<th>Tests†</th>
<th>TCAs (N = 80)</th>
<th>Fluoxetine (N = 55)</th>
<th>Controls (N = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley Mental Development Index</td>
<td>118 ± 17</td>
<td>117 ± 17</td>
<td>115 ± 14</td>
</tr>
<tr>
<td>McCarthy General Cognitive Index</td>
<td>117 ± 10</td>
<td>114 ± 16</td>
<td>114 ± 13</td>
</tr>
<tr>
<td>Reynell Verbal Comprehension Scale</td>
<td>1.3 ± 0.8</td>
<td>1.2 ± 1.2</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>Reynell Expressive Language Scale</td>
<td>0.3 ± 0.9</td>
<td>-0.2 ± 1.0</td>
<td>0.1 ± 1.0</td>
</tr>
</tbody>
</table>

*Mean ± SD. †Children were tested between 16 and 86 months of age (mean, 33 ± 14). Bayley and McCarthy scores are typical for this age. Normal range for both tests is 100 ± 1 SD. Lower scores mean lower cognitive function. Mean Reynell score in normal children of this age is 0 ± 1 (range of possible scores, −3 to +3).
Recent review by Suri et al., J Clin Psychiatry 2014:

- 13 prospective studies have assessed neurobehavioral infant outcome after *in utero* antidepressant exposure
- N=721 children with antidepressant exposure and N=380 children without exposure
- The longest follow-up has been 4 to 5 years
- The majority do not suggest major long term adverse effects of prenatal antidepressant exposure on infant/child neurobehavioral development; no significant differences in neurobehavior/development
- Generally encouraging but sample sizes have been small, and there are reports of possible subtle effects on gross motor function and language development, as well as the potential for longer-term consequences following poor neonatal adaptation
- Most studies do not assess for nor quantify the severity of depressive symptoms in mothers across pregnancy
Treatment of Depression During Pregnancy: Lessons Learned

• Treatment decisions are complex (maternal and fetal benefits and risks)

• Absolute quantification of risk associated with fetal exposure to medication or maternal disease is impossible

• No treatment decision is “perfect”
  – Each treatment decision should try to optimize pregnancy outcomes for the mother and her child
  – Consider the risks of untreated disease and the risks of medication treatment

Kallen Obstet Gynecol Int. 2012
Palmsten and Hernandez-Diaz Epidemiology 2012
APA/ACOG Joint Recommendations

- **Psychotherapy: First-line for mild to moderate MDD**
- Lifestyle components: Nutrition, weight management, prenatal care, childbirth education; treatment for substance abuse
- Document all exposures dating back to conception

- **Women trying to conceive who have histories of MDD:**
  - Encourage period of euthymia
  - Sustained remission: may consider tapering and discontinuing
  - More recently depressed or with symptoms: consider remaining on medication, optimizing medication

- **Pregnant women with severe MDD:** Medication is first-line

- **Pregnant women on antidepressants during pregnancy:** take into account patient preferences, previous course of illness

- Medication selection should be based on known safety information

MDD, major depressive disorder.
Antidepressant Use During Pregnancy: Lessons Learned

• Safest AD to use across pregnancy is the medication that affords euthymia

• Amount of data distinguishing AD compounds is very sparse with respect to teratogenic risk

Kallen *Pharmacoepidemiol Drug Safety*. 2008
• Depression during pregnancy is strongest predictor of postpartum depression
• There are known and unknown risks associated with AD use during pregnancy
• Adverse effects of depression in pregnancy on patient, infant and families
• Nothing trumps maternal euthymia
Treatment of Bipolar Disorder During Pregnancy
Pharmacologic Treatment of Pregnant Women with Bipolar Disorder: Weighing Imperfect Options

- Commonly employed antimanic agents are either known teratogens or have sparse available reproductive safety data
- Risks of untreated psychiatric illness
- Risk of discontinuing maintenance psychotropic medications

Suppes T, et al. *Arch Gen Psychiatry*. 1991
Faedda GL, et al. *Arch Gen Psychiatry*. 1993
Typical or “first generation” antipsychotics

- Significant experience available with older “typical” antipsychotics
- Meta-analysis – small but higher risk of congenital malformations after first trimester exposure to low potency agents compared to the general population
  - High potency are preferred: i.e., haloperidol, perphenazine, trifluoperazine, thiothixine

FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns

**Safety Announcement**

http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm
Atypical Antipsychotics in Pregnancy

- **Newer antipsychotics:**
  - Abilify (aripiprazole)
  - Seroquel (quetiapine)
  - Clozaril (clozapine)
  - Zyprexa (olanzapine)
  - Geodon (ziprasidone)
  - Saphris (asenapine)
  - Invega (paliperidone)
  - Fanapt (iloperidone)
  - Risperdal (risperidone)
  - Latuda (lurasidone)

- **Risk of teratogenicity remains unknown**
- **Sparse data for best known atypicals in pregnancy**
- **No human data for newest agents**
- **Studies thus far complicated by:**
  - High rates of polypharmacy
  - Heterogeneous diagnosis
  - Lifestyle factors of known risk to pregnancy among cases compared to healthy non-exposed control groups
- **No signal of teratogenicity is evident based on limited studies**

Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD1; Sonia Hernández-Díaz, MD, DrPH2; Elisabetta Patorno, MD, DrPH1; Rishi J. Desai, PhD1; Helen Mogun, MS1; Sara Z. Dejene, BS1; Jacqueline M. Cohen, PhD2; Alice Panchaud, PhD2; Lee Cohen, MD3; Brian T. Bateman, MD, MSc1,4

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1Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts
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3Center for Women’s Mental Health, Massachusetts General Hospital, Boston
4Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston

A **NEW** Research Study at the Massachusetts General Hospital Center for Women’s Mental Health

To determine the safety of atypical antipsychotics in pregnancy for women and their babies

Participation will involve 3 brief phone interviews over approximately 8 months

**Call Toll-Free:** 1-866-961-2388
Prospective study

As of May 20th, 2016:

- 704 enrolled
- 312 1\textsuperscript{st} trimester exposures enrolled w/ evaluable data at time of analysis
- Risk ratio = 2.27 (0.26, 20.15)

Preliminary conclusions: \textit{atypical antipsychotics are not major teratogens but more data are needed to narrow the confidence interval}

Presented at ASCP, Cohen et al., 2016
Primary aim: Prospectively evaluate rates of major malformations among infants exposed to atypical antipsychotics in utero relative to unexposed infants.

Secondary aim: Evaluate obstetrical outcomes associated with use of atypical antipsychotics in utero relative to unexposed infants.

Secondary aim: Evaluate neonatal outcomes of infants with prenatal exposure to atypical antipsychotics relative to unexposed infants.

Secondary aim: Evaluate maternal health outcomes of mother’s exposed to atypical antipsychotics during pregnancy compared to unexposed mothers.
Lithium: A Known Teratogen

• 1970s Lithium Baby Registry—risk for specific cardiovascular malformation high; Ebstein’s anomaly
• Revised risk based on meta-analysis: 1/1000 to 1/2000 (0.05%)
• Relative risk for Ebstein’s anomaly is 10 to 20 times the rate in general population (1/20,000)
• Absolute risk vs. relative risk: **Absolute risk is low or flat after adjusting for anomalies which resolved spontaneously**
• Limited data regarding long-term neurodevelopmental outcomes
• Clearance is increased in late pregnancy

Cohen et al. *JAMA* 1994
Diav-Citrin et al. *American Journal Psychiatry* 2014
Lithium Use During Pregnancy: Relative Risks and Clinical Dilemmas

Ebstein’s Anomaly

Relapse Following Discontinuation of Lithium in Bipolar Patients*

Proportion Remaining in Remission

Proportion in Remission

Summary of Findings Across Pregnancy AED Registries

• Valproic acid (VPA) is associated with the highest risk for all major malformations
  – Risk estimates around 10% and higher\(^1\)
  – Risk appears to be dose-dependent (>1000 mg/d); may be with LTG\(^2,3\)
  – Folic acid supplementation may not be protective against VPA-associated neural tube defects

• Risk is highest with anticonvulsant polytherapy\(^4,5\)
  – Specifically with VPA

• Carbamazepine (CBZ) and LTG are associated with lower risk than VPA

Lamotrigine (LTG) Monotherapy Exposure: Increased Risk for Oral Clefts

- Overall risk for major malformations with LTG approximately 2.7% across several studies\(^1,2\)

- North American Antiepileptic Pregnancy Registry showed an increased incidence of a specific malformation
  - Oral clefts: 8.9/1000 vs. baseline 0.37/1000\(^3\)

- Finding not corroborated in other registries; further data needed

- Absolute risk remains small

• 2008:
  – N=792 with lamotrigine monotherapy; limited to those with medical records
  – 16/684 (2.3%) – major malformations
  – 5/684 (7.3/1000, or 0.73%) - oral clefts – 10-fold increase from external reference (0.7/1000)
  – From other registries: 4/1623 (2.5/1000)

Holmes et al., Neurology 2008
• 2012:
  – N=1562 with lamotrigine monotherapy
  – 31/1562 (2.0%) – major malformations
  – 7/1562 (0.45%; CI 0.20-0.88) - oral clefts
  – External reference - 0.11%

Holmes et al., Neurology 2008
Neurobehavioral Teratogenicity and Anticonvulsants: Is there a Differential Risk?

• Data from several studies suggest VPA exposure is associated with increased risk for adverse cognitive and neurodevelopmental effects compared with other anticonvulsants.

• Neurobehavioral risk with LTG unknown.

Cognitive Function in 3 year olds Following Fetal Exposure to AED’s

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>No. of Children</th>
<th>Mean IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>28</td>
<td>98</td>
</tr>
<tr>
<td>Valproate</td>
<td>22</td>
<td>87</td>
</tr>
<tr>
<td>Low dose</td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>Valproate</td>
<td>39</td>
<td>97</td>
</tr>
</tbody>
</table>

Mean IQ at Age 3 Yr (95% CI)

Child IQ at 6 years, by exposure to maternal antiepileptic drug use and periconceptional folate

Mean (95% CIs) are shown for folate (solid lines) and no folate (dashed lines).

• Teratogenic risk and neurobehavioral toxicity of valproate make its use in reproductive age women contraindicated

• Risk of PCOS associated with valproate use in reproductive age women in combination with neural tube defect risk and behavioral teratogenicity support this conclusion
• Lithium and lamotrigine have well characterized reproductive safety profiles, low absolute risks

• Lithium may be the best characterized and reasonable alternative for women who require an anti-manic agent but its use is declining

• Lamotrigine appears reasonable for the prevention of depressive episodes

• Atypical antipsychotics have growing body of data and do not at this time appear to be major teratogens
  • More human pregnancy data available for older medications in the class
  • May be reasonable to continue during pregnancy, particularly if patient has had good response, psychotic symptoms, is a lithium non-responder, or atypical was critical in affording euthymia
• Polytherapy of bipolar disorder during pregnancy is the rule
• Frequency of use of atypical antipsychotics demands better data to inform use of these agents during pregnancy
• Absolute small risk may be acceptable versus risk of bipolar relapse during pregnancy and implications for puerperal relapse of the illness
Postpartum Prophylaxis in Bipolar Women

Significant difference between groups (Peto-Peto-Wilcoxon $\chi^2 = 6.966$, df = 1, $p<0.01$)

Benzodiazepines

- Methodological issues have confounded reports: dose, duration, class of BZD, other drug exposures, recall bias
- Risk of oral clefts following first trimester exposure (0-0.6%)
- Review of 12 studies (2001-2011): Most studies show no increase in malformations, no consistent pattern of defects

ECT During Pregnancy

• Treatment of choice when expeditious management is imperative
• Use in delusional depression, mania
• External fetal monitoring, ultrasonography
• Comprehensive treatment team
VA Reproductive Mental Health Initiative: Partnership with MGH

- Enhance Reproductive Mental Health care delivery in VA

- Collaboration between mental health, reproductive health, pharmacy benefits management, primary care, and MGH

- Preconception counseling and safe prescribing are key components

- Develop curriculum for providers addressing reproductive mental health across the lifecycle
Dear Dr. Cohen:
I am just back from a tour in Iraq and am finally settled back in my home with my husband and 3 year old daughter. I am being treated for PTSD and anxiety with venlafaxine and a little bit of Seroquel at night to help me sleep. We would like to grow our family but I am worried about what happens to my PTSD symptoms during pregnancy and what do I do about the medicines. My doctor told me to ask you.
Treatment Guidelines for Psychotropic Drug Use in Pregnancy

LEE S. COHEN, M.D.
VICKI L. HELLER, M.D.
JERROLD F. ROSENBAUM, M.D.

Despite the apparent risks of psychotropic drug exposure in pregnancy, many pregnant women receive psychotropics. The major concerns associated with the use of antipsychotics, antidepressants, benzodiazepines, and lithium carbonate in pregnancy are reviewed, with clinical approaches for assessing the relative risks and benefits of treatment of psychiatrically ill pregnant patients and for choosing and instituting therapy with these agents.
For Further Information:

www.womensmentalhealth.org
References

References (Cont.)

• http://womensmentalhealth.org/posts/neonatal-symptoms-after-in-utero-exposure-to-ssris/


References (Cont.)

- Johnson KC, LaPrairie JL, Brennan PA, Stowe ZN, Newport DJ. Prenatal Antipsychotic Exposure and Neuromotor Performance During Infancy. Arch Gen Psychiatry 2012;Published online April 2, 2012.
References (Cont.)


References (Cont.)


• www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08);


