MOOD DISORDERS DURING PREGNANCY AND THE POSTPARTUM
Learning Objectives

• Implement evidence-based strategies to manage mood disorders during pregnancy

• Improve diagnosis and treatment of mood disorders during the postpartum period
When do disorders start?

• “Mental illnesses are the chronic diseases of the young.”

• Half of all diagnoses present by age 14

• 3/4 by age 24

– Kessler et al., 2005; Insel and Fenton, 2005
Treating Women of Childbearing Potential

• 49% of pregnancies in US are unintended\textsuperscript{1}
• 80% of teen pregnancies are unintended\textsuperscript{1}
• 82% of US women have had a child by age 40\textsuperscript{2}

CDC Recommendations for Women of Reproductive Age

- Take folic acid
- Maintain healthy diet and weight
- Regular physical activity
- Quit/abstain from tobacco use, alcohol, and drugs
- Communicate with healthcare providers about screening and management of chronic diseases
- Use effective contraception correctly if one is sexually active and wishing to delay/avoid pregnancy

Context for Assessing Risk

• Rate of major malformations: 3-4%
• Rate of premature delivery: 11-12%
• Rate of gestational diabetes: 2-7%
• Untreated psychiatric disorders carry risks for woman and baby
• Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
• Obesity increases obstetrical risks

Risks of Untreated Antenatal Depression

Possible complications:

• May negatively affect maternal weight gain
• May increase the risk of low birth weight, prematurity, and small for gestational age
• Neonatal behavioral differences, such as irritability and decreased activity
• May lead to less compliance with prenatal care

Risks of Untreated Anxiety During Pregnancy

Potential Physiological Risks:

• Fetal exposure to increased cortisol; higher anxiety symptom burden associated with higher maternal plasma and amniotic fluid cortisol levels, catecholamines

• May result in maternal vasoconstriction and limit oxygen and nutrient delivery to fetus

• Impact on long-term CNS development
  – longitudinal cohort study, investigators demonstrated that children exposed in utero to perinatal anxiety are at increased risk for attentional problems

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling
The Pregnancy and Lactation Labeling Rule (PLLR) or “Final Rule”

- **Subsections**
  - Pregnancy
  - Lactation
  - Females and males of reproductive potential

- **Pregnancy Exposure Registry**
  - Scientifically acceptable registry and contact info

- **Risk Summary**
  - Human, animal, pharmacologic data
  - Adverse developmental outcomes
  - Background risks from the US population (i.e., CDC data)

- **Context**
  - Includes information about background rates of adverse events
  - Risks to be quantitatively compared to the risk for the same outcome in infants born to women not exposed to the drug, but who have the disease or condition for which the drug is indicated (i.e., appropriate controls)

US Food and Drug Administration.
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
• 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.
For more information and our blog:

www.womensmentalhealth.org
SSRI Use During Pregnancy

• Prevalence of SSRI use during pregnancy is 3% to 7%
• 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
  • Recent case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs
• Reproductive safety data on SSRI exceed what is known about most other medicines used in pregnancy

SSRI, selective serotonin reuptake inhibitor.
RESULTS:
Nineteen studies were above quality threshold and make up the primary meta-analyses. Pooled relative risks (RRs) were derived by using random-effects methods. Antidepressant exposure was not associated with congenital malformations (RR = 0.93; 95% CI, 0.85-1.02; P = .113) or major malformations (RR = 1.07; 95% CI, 0.99-1.17; P = .095). However, increased risk for cardiovascular malformations (RR = 1.36; 95% CI, 1.08-1.71; P = .008) and septal heart defects (RR = 1.40; 95% CI, 1.10-1.77; P = .005) were found; the RR for ventral septal defects was similar to septal defects, although not significant (RR = 1.54; 95% CI, 0.71-3.33; P = .274). **Pooled effects were significant for paroxetine and cardiovascular malformations (RR = 1.43; 95% CI, 1.08-1.88; P = .012).** These results are contrasted with those addressing methodological limitations but are typically consistent.
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.

NEJM 370:25  NEJM.org  June 19, 2014

- No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs
Risk of Cardiovascular Malformation Following SSRI Exposure

- 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
# 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><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>SSRIs</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>1.27 (0.74–2.06)</td>
<td>1.19 (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>1.12 (0.67–1.88)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.23 (0.75–2.01)</td>
<td>1.02 (0.57–1.82)</td>
<td>0.93 (0.50–1.72)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>1.14 (0.57–2.28)</td>
<td>1.19 (0.46–2.68)</td>
<td>0.94 (0.37–2.36)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>1.47 (0.83–2.60)</td>
<td>1.47 (0.82–2.62)</td>
<td>1.06 (0.55–2.03)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.05 (0.58–1.93)</td>
<td>1.20 (0.58–2.66)</td>
<td>1.09 (0.56–2.19)</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>1.00 (0.88–1.19)</td>
<td>0.95 (0.79–1.14)</td>
</tr>
<tr>
<td>SSRIs</td>
<td>1.26 (1.04–1.50)</td>
<td>1.01 (0.85–1.22)</td>
<td>0.98 (0.81–1.20)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.09 (0.81–1.47)</td>
<td>0.77 (0.53–1.12)</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 (0.82–1.55)</td>
<td>1.04 (0.76–1.41)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1.26 (0.90–1.93)</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 (0.65–1.63)</td>
<td>0.86 (0.50–1.47)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>1.56 (1.14–2.14)</td>
<td>1.16 (0.97–1.42)</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 (0.61–1.38)</td>
<td>0.88 (0.58–1.34)</td>
</tr>
<tr>
<td>Other</td>
<td>1.21 (0.83–1.73)</td>
<td>1.04 (0.70–1.50)</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>SSRIs</td>
<td>1.34 (1.17–1.56)</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 (1.20–1.76)</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 (0.93–1.71)</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 (0.45–1.40)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>1.52 (1.26–2.08)</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 (1.24–2.02)</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>
Are SSRIs associated with increased risk of autism?

Studies have been inconsistent; confounding variables

Two new papers in *JAMA* 2017

1) **Canadian Study**: Health administrative data sets factored in large number of potential confounders and compared exposed children with unexposed siblings
   - 35,906 singleton births: After factoring in propensity scores for confounding, **association not significant**; association also not significant when exposed children were compared with unexposed siblings

2) **Swedish Study**: Controlled for pregnancy, maternal and paternal covariates, sibling comparisons, timing of exposure
   - Offspring born to 943,776 mothers
   - First trimester exposure associated with a small increased risk of preterm birth, but no increased risk of small for gestational age, autism spectrum disorder, or ADHD

ADHD: attention-deficit/hyperactivity disorder.
Antidepressants During Pregnancy: Later Pregnancy Considerations

• Risk of persistent pulmonary hypertension of newborn with SSRIs?

• Inconsistent results:
  • One report showed increased risk by 6-fold (approximately 1%)\(^1\)
  • Lower association seen (0.15%)\(^2\)
  • No association seen\(^3,4,5\)

Antidepressant Use Late in Pregnancy and Risk of PPHN

• Large Medicaid Database – 3.8 million pregnancies
  • 128,950 women (3.4%) filled at least one prescription for antidepressants during last 90 days of pregnancy; 2.7% used an SSRI; 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

Antidepressants During Pregnancy: Later Pregnancy Considerations

• Reports of suspected neonatal syndrome: “withdrawal” or “toxicity,” complications after in utero exposure to SSRIs; low birth weight; prematurity

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

• Tapering does not appear to decrease occurrence when confounders assessed

Bupropion and Pregnancy

- Bupropion Pregnancy Registry, prospective birth outcome data
  - 3.6% (24/675) of the cohort experienced a congenital anomaly after first trimester exposure
  - There was no clear pattern of type of birth defects
- Small prospective study N=136 women who used bupropion in the first trimester, there was no evidence of increased rates of malformations compared with two groups of women, those who used other antidepressants or and those who had known nonteratogenic exposures
- Small but increased risk of cardiovascular left outflow defects was reported in a retrospective case-control study from a birth defect registry
  - The absolute risk was approximately 2 out of 1000 pregnancies

Risk of Relapse for Major Depression During Pregnancy

- Prospective study of MDD during pregnancy: N=201; euthymic prior to pregnancy, currently/recently using antidepressants; patients decided to continue/discontinue medication (not randomized)

- 43% relapsed during pregnancy
  - 26% of those who continued medication
  - 68% of those who discontinued medication

- Predictors of relapse
  - Unmarried; younger (<32 years); more recurrent depression, earlier onset of depression

Postpartum Mood Disorders

• Postpartum blues
• Postpartum depression (PPD)
  – *DSM-5*: Peripartum onset specifier
  – Onset within 4 weeks of delivery, debatable
• Postpartum psychosis
• Considerations for bipolar disorder
Postpartum Depression

- Prevalence: 10% to 20%
- Anxiety is common
- Risks of untreated maternal depression
- Risks of medication exposure via breastmilk

Negative Effects of Maternal Depression on the Child

- Insecure attachment
- Behavioral problems
- Cognitive function
- Increased risk of abuse, neglect
- Childhood psychiatric diagnoses & symptoms
- Compliance with preventative measures
- Thoughts of harming infant

Breastfeeding

• …The experience of breastfeeding is special for so many reasons – the joyful bonding with your baby, the cost savings, and the health benefits for both mother and baby…

• …Time to declare an end to the breastfeeding dictatorship that is drowning women in guilt and worry just when they most need support...

Gayle Tzemach Lemmon, Breastfeeding is a Choice, Let’s Treat it that Way
Treatment Recommendations: Perinatal Depression

- Moderate to severe depression
  - Consider role of antidepressants; discuss risks and benefits with mother
- Use lowest effective doses
- Consultation with experts
- Maximize non-medication alternatives
# Trials of Antidepressants for PPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and size</th>
<th>Medication studied, result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appleby et al., 1997</td>
<td>Placebo-controlled, N=87. CBT studied in same trial</td>
<td>Fluoxetine - superior to placebo</td>
</tr>
<tr>
<td>Yonkers et al, 2008</td>
<td>Placebo-controlled, N=70</td>
<td>Paroxetine - not superior to placebo)</td>
</tr>
<tr>
<td>Wisner et al., 2006</td>
<td>RCT, Setraline vs. Nortriptyline, N=109</td>
<td>Sertraline vs. Nortriptyline - no significant difference</td>
</tr>
<tr>
<td>Hantsoo et al., 2013</td>
<td>Placebo-controlled RCT, N=36</td>
<td>Setraline- superior to placebo</td>
</tr>
<tr>
<td>Bloch et al., 2012</td>
<td>N=40, all received brief psychodynamic therapy, RCT to sertraline or placebo</td>
<td>Both groups improved – no significant difference for sertraline vs. placebo</td>
</tr>
<tr>
<td>Sharp et al., 2010</td>
<td>RCT, AD selected by general practitioner or counseling, N=254</td>
<td>Antidepressants- superior to placebo</td>
</tr>
<tr>
<td>Misri et al., 2012</td>
<td>Open trial, N=15</td>
<td>Citalopram – open study</td>
</tr>
<tr>
<td>Misri et al., 2004</td>
<td>N=35, all received parox, half randomized to CBT also</td>
<td>Paroxetine – no control group</td>
</tr>
<tr>
<td>Stowe et al., 1995</td>
<td>Open-label; N=21</td>
<td>Sertraline – open study</td>
</tr>
<tr>
<td>Cohen et al., 1997</td>
<td>Open-label; N=19</td>
<td>Venlafaxine- open study</td>
</tr>
<tr>
<td>Suri et al., 2001</td>
<td>Open-label; N=6</td>
<td>Fluvoxamine - open</td>
</tr>
<tr>
<td>Nonacs et al., 2005</td>
<td>Open-label; N=8</td>
<td>Bupropion- open</td>
</tr>
</tbody>
</table>

CBT: cognitive-behavioral therapy. RCT: randomized controlled trial.

# Breastfeeding and Antidepressants

Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum\(^1,2\)

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Due to long half-life, may be more likely to be found at detectable levels in infant serum, especially at higher doses. Reasonable for use if a woman has had a good previous response to it and reasonable to consider if used during pregnancy</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Consistent reports of low levels of exposure, relatively large amount of study</td>
</tr>
<tr>
<td>Citalopram, escitalopram</td>
<td>Less systematic study of mom-baby pairs compared with sertraline and paroxetine, observed low levels of exposure to infant via breastfeeding</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Consistent reports of low levels of exposure; relatively large amount of study. Use limited by commonly experienced withdrawal symptoms, maybe more sedating than other SSRIs</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Paucity of systematic study; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding. May be advantageous in smokers. Reasonable for use if women have had good previous response. One case report of possible infant seizure</td>
</tr>
<tr>
<td>Venlafaxine, desmethyl-venlafaxine</td>
<td>Higher levels of desmethylvenlafaxine found in breastmilk than venlafaxine. No adverse events reported</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Considered reasonable for breastfeeding if use clinically warranted; few adverse affects in babies and generally low levels of exposure reported</td>
</tr>
<tr>
<td>Mirtazapine, nefazodone, MAOIs, duloxetine</td>
<td>Systematic human lacking in the context of breastfeeding</td>
</tr>
</tbody>
</table>

Brexanolone (SAGE-547)
Allopregnanolone/Neurosteroids

• Allosteric modulator of GABA_A receptors

• Phase 2 trial of SAGE-547 for the treatment of PPD
  • Severe depressive symptoms; Randomized to receive either SAGE-547 (n=10) or placebo (n=11); blinded infusion taking place over 60 hours
  • At 24 hours, participants receiving SAGE-547 experienced a 19.0 point mean reduction in their HAM-D scores (P=.006), compared to 8.4 points in the placebo group;

• Phase 3 trials
  • Two double-blind trials of infusion of SAGE-547 vs placebo for moderate and severe depression; 2 doses; Study 1: N=138, Study 2: N=108. Both doses significantly more efficacious than placebo in reduction of HAM-D scores.

• Main adverse events: headache, dizziness, somnolence

• Not yet approved by US FDA; oral trials underway

HAM-D = Hamilton Rating Scale for Depression.
Meltzer-Brody et al., Lancet 2018; MGH Center for Women’s Mental Health. womensmentalhealth.org/posts/10832/.
Perinatal Depression: Non-medication Treatments

- Psychotherapy\(^1,2,3\)
- Electroconvulsive therapy\(^4\)
- Complementary and Alternative Medicine (CAM treatments) (Integrative Medicine)

---

\(^1\)Spinelli MG. Am J Psychiatry 1997;154(7):1028-30;
\(^2\)Dennis CL. J Clin Psychiatry 2004;65(9):1252-65;
\(^3\)Yonkers KA et al. Obstet Gynecol 2009; 114(3):703-13;
CAM/Integrative Treatments

- Omega-3 fatty acids—add-on
- Exercise—add-on
- Folate—add-on; methylfolate
- SAMe—monotherapy(?) (no specific study)
- St John’s wort—similar to antidepressants but less known
- Acupuncture—monotherapy or add-on
- Bright light therapy—monotherapy or add-on
- Massage—add-on

SAMe, S-adenosylmethionine
Bipolar Disorder in Pregnancy and Postpartum
Pregnancy and Postpartum: Risks of Discontinuing Medication

• Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%

• Women who discontinue medication more likely to experience recurrences (85.5% vs. 37%) and spend more time ill

• Particularly high rate of mood episodes postpartum (70%)

• Recurrence risk greater after rapid discontinuation (<2 weeks) than gradual (2 to 4 weeks)

• Unplanned pregnancy associated with greater risk of recurrence

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum

Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first three months

Postpartum Psychosis
Postpartum Psychosis

• 1 to 2 per 1000 pregnancies
• Rapid, dramatic onset within first 2 weeks
• High risk of harm to self and infant
• Suspect bipolar disorder
  • Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
  • Family and genetic studies, index episode follow-up

Postpartum Psychosis

- Psychiatric emergency

- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be underreported

### Differentiating OCD and Psychosis

<table>
<thead>
<tr>
<th>Postpartum OCD</th>
<th>Postpartum psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thoughts are ego-dystonic</td>
<td>• Thoughts are ego-syntonic</td>
</tr>
<tr>
<td>• Disturbed by thoughts</td>
<td>• Rarely distressed by thoughts</td>
</tr>
<tr>
<td>• Avoid objects or being with their newborn</td>
<td>• Do not have avoidant behaviors</td>
</tr>
<tr>
<td>• Very common disorder</td>
<td>• Not common disorder</td>
</tr>
<tr>
<td>• Low risk of harm to baby</td>
<td>• High risk of harm to baby</td>
</tr>
</tbody>
</table>

OCD: obsessive-compulsive disorder.
Mood Stabilizers in Pregnancy

• Lithium: First-trimester risk of cardiovascular malformations
  • Ebstein's anomaly: 0.1% to 0.2% (risk ratio 10 to 20)
  • Risk ratio for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein's anomaly rises from 1/20,000 to 1/1000

• Lithium
  • Complicated by maternal glomerular filtration rate (GFR) changes during pregnancy. Excreted more rapidly—may need to increase dose
  • After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed

1Yonkers KA et al. Am J Psychiatry 2004;161:608-20;
Valproic Acid

• WORST TERATOGEN KNOWN AMONG PSYCHOTROPICS

• Rate of major malformations: ≥ 10%
  • Neural tube defects, craniofacial, cardiovascular, and others
  • Risk of defects is substantial in very early pregnancy

• Associated with increased risk for adverse cognitive and neurodevelopmental effects
  • Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Carbamazepine (N=73)</th>
<th>Lamotrigine (N=84)</th>
<th>Phenytoin (N=48)</th>
<th>Valproate (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ (95% CI)†</td>
<td>98 (95–102)</td>
<td>101 (98–104)</td>
<td>99 (94–104)</td>
<td>92 (88–97)</td>
</tr>
<tr>
<td>Mean difference in IQ from valproate group (95% CI)‡</td>
<td>6 (0.6–12.0)</td>
<td>9 (3.1–14.6)</td>
<td>7 (0.2–14.0)</td>
<td></td>
</tr>
<tr>
<td>P value§</td>
<td>0.04</td>
<td>0.009</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).

† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant’s gestational age at birth, and maternal preconception use of folate.

‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.

§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.23
Lamotrigine in Pregnancy

- Pregnancy increases lamotrigine clearance by >50%\textsuperscript{1,2}
  - Returns to baseline after delivery
- Association with oral clefting - not seen with larger numbers
  - North American Antiepileptic Drug Pregnancy Registry; 5 of 564; first-trimester exposures rate of 8.9 per 1000, compared with 0.37 in general population\textsuperscript{3}
  - Recent large study of registries did not find any association between oral clefts and lamotrigine\textsuperscript{3}
- First-trimester birth defects more likely with anticonvulsant polypharmacy (International Lamotrigine Pregnancy Registry)
  - 3/168 (1.8%) with monotherapy; 5/50 (10%) lamotrigine + valproate

Atypical Antipsychotics in Pregnancy

• Large administrative Medicaid database
  • Nationwide sample of N=1360 101 pregnant women
  • After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96-1.16) for atypical APs and 0.90 (95% CI, 0.62-1.31) for typical APs. The findings for cardiac malformations were similar
  • For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02-1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.88-1.81) was found for risperidone that was independent of measured confounders

• Pooled odds ratios of prospective studies
  • Antipsychotic exposure associated with slightly increased risk of major malformations, heart defects), preterm delivery, small-for-gestational-age births, decreased birth weight
  • There was no significant difference in the risk of major malformations differences between typical (and atypical) antipsychotic medications

National Pregnancy Registry
for Atypical Antipsychotics

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 three brief phone
interviews over approximately 8 months

Call toll-free: 1-866-961-2388
National Pregnancy Registry for Atypical Antipsychotics

- Now enrollment > 1400 patients
- As of Dec 2014, N=487 enrolled
- N=303 eligible for analyses:
  - Rates of major malformations in the two groups similar:
    - 1.4% (3/214 live births) in exposed group
    - 1.1% (1/89) in the comparison group
  - Odds ratio for major malformations comparing exposed infants with unexposed infants was 1.25 (95% CI=0.13-12.19) – not statistically significant

Mood Stabilizers and Breastfeeding

Lithium

• Toxicity reported in cases with infant serum levels at 0.1 to 0.5 times the maternal level

• Contraindicated at one time by the American Academy of Pediatrics¹

• Revised to classification “Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution”

Mood Stabilizers and Breastfeeding (cont.)

Lithium and Breastfeeding
- N=10 mother-baby pairs
- Mothers stable, lithium monotherapy 600 to 1,200 mg/day
- Babies’ serum levels 0.09 to 0.3 meq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

Recommendations
Consider lithium when:
- Bipolar disorder in mother who is stable
- Lithium monotherapy (or simple regimen)
- Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
- Healthy infant
- Collaborative pediatrician

Perinatal Mood Disorders: Summary

• Women, children, and families are impacted
• Effective, safe, accessible, and acceptable treatments are needed
• Treatment considerations involve risks of medications, risks of the untreated disorder
• Unknowns: Collaborative treatment decisions, patient preferences highly prioritized