Identification and Treatment of Bipolar Disorder in Pregnancy and Postpartum

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Disclosures

• Dr. Berg
  • No disclosures

• Dr. Jones
  • Principal Investigator –
    • Alpha Genomix Laboratories funded study on pharmacogenomics
    • No conflicts or disclosures related to content of this plenary
Disclosure

• NO medication for bipolar disorder is FDA approved for use in pregnancy
• All medication discussion is off label

Risks               Benefits
Objectives

Introduction
- Epidemiology
  - Identification
  - Study Considerations

Bipolar Disorder
- Pharmacological Treatments
  - Pregnancy
  - Lactation

Review
Recommendations
Resources
References
• Prevalence of psychiatric disorders in reproductive age females
• 2 medical conditions
  — Pregnancy
  — Psychiatric Illness
• 2 patients
  — Mother
  — Fetus
• Family Unit
• Stage of Symptom Presentation
  • Pregnancy
  • Postpartum

• Type of Presentation
  • New illness
  • Exacerbation of pre-existing illness
  • Worsening symptoms of active illness
**Bipolar Disorder - Epidemiology**

### General Population
- 3.9% lifetime prevalence rate
- 102% of people in U.S.
- Type I: M=F
  - Women tend to experience more depression during active phase of illness
- Type II: F>M
  - Depressive episodes 30 times more prevalent

### Pregnancy
- Risk for depression higher than in patients with unipolar depression
- Depression most frequent episode
- 23% mood episode

### Postpartum
- Higher rates of mood episodes when compared to pregnancy
- 52% mood episode
  - Some estimates 50-70% of women relapse
- 40-70% will have recurrent episodes after delivery
Bipolar Disorder - Epidemiology

**Risk**

- Relapse seen in pregnant and nonpregnant women equally up to 40 weeks after discontinuation of lithium.
- Relapse 2.9 times greater in postpartum women 41-50 weeks after discontinuation of lithium.
- Rapid discontinuation more associated with relapse (than gradual)
- Twice as likely to have a relapse/episode, 4 times more quickly, 5 times longer lasting
- Most common episode – depression.

**PMDD**

**Discontinuation of Medication (Viguera, et al)**

- Relapse seen in pregnant and nonpregnant women equally up to 40 weeks after discontinuation of lithium.
- Relapse 2.9 times greater in postpartum women 41-50 weeks after discontinuation of lithium.
- Rapid discontinuation more associated with relapse (than gradual)
- Twice as likely to have a relapse/episode, 4 times more quickly, 5 times longer lasting
- Most common episode – depression.
### Mood Disorder Questionnaire

Please answer each question to the best of your ability.

1. Has there ever been a period of time when you were not your usual self and...

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td></td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td></td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td></td>
</tr>
<tr>
<td>...you got much less sleep than usual and found that you didn’t really miss it?</td>
<td></td>
</tr>
<tr>
<td>...you were more talkative or spoke much faster than usual?</td>
<td></td>
</tr>
<tr>
<td>...thoughts raced through your head or you couldn’t slow your mind down?</td>
<td></td>
</tr>
<tr>
<td>...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td></td>
</tr>
<tr>
<td>...you had more energy than usual?</td>
<td></td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td></td>
</tr>
<tr>
<td>...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td></td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td></td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td></td>
</tr>
<tr>
<td>...spending money got you or your family in trouble?</td>
<td></td>
</tr>
</tbody>
</table>

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

3. How much of a problem did any of these cause you - like being unable to work; having family, money or legal troubles; getting into arguments or fights?

<table>
<thead>
<tr>
<th>No problems</th>
<th>Minor problem</th>
<th>Moderate problem</th>
<th>Serious problem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CIDI-based Bipolar Disorder Screening Scale

Stem Questions

Euphoria Stem Question
1. Some people have periods lasting several days when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still and they sometimes do things that are unusual for them, such as driving too fast or spending too much money.

Have you ever had a period like this lasting several days or longer?

If this question is endorsed, the next question (the irritability stem question) is skipped and the respondent goes directly to the Criterion B screening question.

Irritability Stem Question
2. Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you either started arguments, shouted at people, or hit people?

Criterion B Screening Question
3. People who have episodes like this often have changes in their thinking and behavior at the same time, like being more talkative, needing very little sleep, being very restless, going on buying sprees, and behaving in many ways they would normally think inappropriate.

Did you ever have any of these changes during your episodes of being excited and full of energy or very irritable or grouchy?

Criterion B Symptom Questions

Think of an episode when you had the largest number of changes like these at the same time. During that episode, which of the following changes did you experience?

1. Were you so irritable that you either started arguments, shouted at people, or hit people?
   (This symptom question is asked only if the euphoria stem question (#1 above) is endorsement.
2. Did you become so restless or fidgety that you paced up and down or couldn’t stand still?
3. Did you do anything else that wasn’t usual for you—like talking about things you would normally keep private, or acting in ways that you would usually find embarrassing?
4. Did you try to do things that were impossible to do, like taking on large amounts of work?
5. Did you constantly keep changing your plans or activities?
6. Did you find it hard to keep your mind on what you were doing?
7. Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn’t keep track of them?
8. Did you sleep far less than usual and still not get tired or sleepy?
9. Did you spend so much more money than usual that it caused you to have financial trouble?
Back to Basics:
Don’t Skip the Good Stuff

INTERVIEW  ASSESSMENT  PLAN
Symptoms: “Mood Swings”

Bipolar Disorder

Sustained moods
- Do not shift quickly
- Last days-weeks
- Hypomania: 2 day minimum
- Rapid cycling: 4 manic episodes in one year

Elation & Depression
Mostly occur spontaneously, or trigger could be sleep deprivation

Borderline Personality Disorder

Non-sustained moods
- Rapid shifting or affective lability or dysregulation
- Lasts minutes or hours

Anxiety, Anger, Desperation
Can often find precipitant or stressor, particularly interpersonal
Anxiety

- Racing thoughts
- Distractibility/Concentration
- Sleep Disturbance
- Impulsive Behavior
- Restless Anxiety

Mania

- Severe mood swings
- Rapid cycling
- Elation; grandiosity
- Racing thoughts
- Rapid pressured speech
- Risk-taking behavior;
- Tantrums
- Aggression; rages
- Low need for sleep
- Hypersexual

- Irritability
- Hyperactivity
- Restlessness
- Impulsivity
- Oppositional
- Increased energy

- Continuous (always present)

Medscape
Intrusive Thoughts

Risk of harm to baby

**OCD/anxiety**
- Good insight
- Thoughts are intrusive and scary
- No psychotic symptoms
- Thoughts cause anxiety

**Postpartum Psychosis**
- Poor insight
- Psychotic symptoms
- Delusional beliefs or distorted reality present

Low risk

High risk
Postpartum Psychosis

• “Postpartum Psychosis”
• Clinical Symptoms:
  • Typically start with mood symptoms
    • Insomnia
    • mood fluctuations
    • Irritability
    • Obsessions
    • Possibly some delirium/disorientation
  • Psychotic symptoms like hallucinations, delusions, disorganization tend to present a little later.
  • Also includes severe mood symptoms like mania and depression
Postpartum Psychosis

- Postpartum Psychosis is a psychiatric emergency
  - You should always consider hospitalization
- 1-2/1,000
- Rapid onset
- Within 2 weeks of delivery – but monitor longer
- Highly elevated risk of suicide and infanticide
- Risk factors: first baby
Study Considerations

• Read literature

• Be aware of the impact of potential confounders

• We can always use more!

• Methods-appropriate treatment and control groups comparisons.

• Statistical significance does not always equal clinical significance

• Each treatment plan is individualized.

• We can always use more!
Risks of Untreated Mood Disorders/Schizophrenia

- Poor birth outcomes
  - Preterm birth
  - Low birth-weight
  - Intra Uterine Growth Retardation
  - Small for Gestational Age
  - Fetal Distress
  - Long term neurodevelopmental impairment
  - Placenta Previa (OR 2.04)
  - Antepartum hemorrhages

Jablensky et al, AJP 2005
Risks Untreated Bipolar Disorder

- Insomnia
- Obsessive thoughts
- Psychosis
- Suicide
- Infanticide
- Postpartum psychiatric admissions (Kendall 1987)
Risks of Untreated Illness

• Behavioral risk factors
  • Increased alcohol, tobacco, illicit/non prescribed drug use
  • Decreased compliance with obstetrical care
  • Poor nutrition
  • Difficulty parenting
  • Relationship conflict

Kahn 2016
Discontinuing Medications in Pregnancy

• Viguera et al 2007
  • N=89 pregnant women with BPAD I and II
    • N=62 discontinued mood stabilizer
      • 85.5% relapsed
    • N=27 continued mood stabilizer
      • 37% relapsed
  • 2.3 times greater risk of recurrence with stopping psychiatric medications
# Discontinuing Medications in Pregnancy

Viguera et al. 2007

## Recurrence of Bipolar Disorder in Pregnancy

### Table 2: Morbidity During Pregnancy Versus Treatment Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Subjects (N=89)</th>
<th>Subjects Who Maintained Treatment (N=27)</th>
<th>Subjects Who Discontinued Treatment (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Risk of at least one recurrence</strong>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>63/89</td>
<td>70.8</td>
<td>10/27</td>
</tr>
<tr>
<td>First trimester risk</td>
<td>42/89</td>
<td>47.2</td>
<td>6/27</td>
</tr>
<tr>
<td>Second</td>
<td>15/47</td>
<td>31.9</td>
<td>3/21</td>
</tr>
<tr>
<td>Third</td>
<td>6/32</td>
<td>18.8</td>
<td>1/18</td>
</tr>
<tr>
<td>**Recurrence polarity (all recurrences)**b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>34/89</td>
<td>38.2</td>
<td>5/27</td>
</tr>
<tr>
<td>Mixed state</td>
<td>26/89</td>
<td>29.2</td>
<td>0/27</td>
</tr>
<tr>
<td>Hypomania</td>
<td>15/89</td>
<td>16.8</td>
<td>7/27</td>
</tr>
<tr>
<td>Mania</td>
<td>6/89</td>
<td>6.7</td>
<td>2/27</td>
</tr>
<tr>
<td><strong>Percent of pregnancy weeks ill</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SD</td>
<td>32.8</td>
<td>31.5</td>
<td>8.8</td>
</tr>
<tr>
<td>N %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable subjects (%)d</td>
<td>26/89</td>
<td>29.2</td>
<td>17/27</td>
</tr>
</tbody>
</table>

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* Risk ratio for any recurrence, comparing subjects who discontinued versus maintained mood stabilizing treatment (2.3, 95% CI=1.4–3.8, p<0.001).

* Sixty-three subjects experienced a total of 81 episodes of varying polarity during pregnancy (1.43 versus 0.32 episodes/subject with mood stabilizer treatment discontinued versus continued).

* Absolute difference between the mean percentages of weeks ill, comparing subjects who discontinued versus maintained mood stabilizing treatment (34.5%, 95% CI=22.1–46.9%, p<0.001).

* For the percent of subjects remaining stable throughout pregnancy, comparing subjects who maintained versus discontinued mood stabilizing treatment (rate ratio=4.3, 95% CI=2.2–8.5, p<0.001).
Discontinuing Medications Postpartum

• Wesseloo 2016
  • N=4023 in meta analysis of 37 articles
  • High rate relapse
    • 66% if unmedicated
    • 23% if medicated
Medication Background

- Incidence of major birth defects in US is 2 – 4%
  - 65 – 70% of unknown cause
  - 2 – 4% medication related

- Period of maximum vulnerability for structural and neurochemical abnormalities of CNS is 14 – 35 days post conception
Drowning in Plain Sight

LITHIUM SAVED MY LIFE,” SAID LISA TO HER PSYCHIATRIST. YET WHEN SHE TOLD HIM THAT SHE WAS PREGNANT, HE SAID, “OF COURSE, YOU CAN’T TAKE MEDICINE WHILE YOU’re PREGNANT. MAYBE WE CAN GIVE YOU HALDOL, BUT EVEN THAT WOULDN’T BE SAFE.” IMAGES FLASHED THROUGH LISA’S MIND OF THE CHAOS AND SELF-DESTRUCTION SHE FELT BEFORE SHE STARTED TAKING LITHIUM. YET HERE WAS THE PHYSICIAN SHE HAD KNOWN AND TRUSTED FOR YEARS. SHE TOOK COMFORT IN HIS CERTAINTY THAT STOPPING HER MEDICINE WAS THE RIGHT THING TO DO. IN HER MIND SHE CHALLENGED HERSELF TO BE A GOOD MOTHER AND TO PUT HER OWN NEEDS SECOND. SHE STOPPED HER MEDS—DOCTOR’S ORDERS.

Without lithium, Lisa began to feel a rising agitation that made it impossible to sleep or think. The thought of her manic episode seven years ago terrified her. This is how it had begun—the sleepless nights and frenetic energy that led to desperate efforts to quell the agitation. The drinking helped back then, but what could she do now that she was pregnant? How could she keep going for seven more months until the baby came? Drinking was so tempting but seemed unsafe. In her irrationally rational mind, she imagined a more acceptable solution—driving into a tree.

The image of her bloody, mangled body stunned her into lithium was dangerous in all pregnancies rather than pausing to consider available reproductive safety data about lithium and the specifics about Lisa’s situation.

After Lisa was discharged, I saw her for an initial consultation in the perinatal psychiatry clinic where I work. She told me about this devastating experience in the hospital in which she was turned away without help. “I was desperate, but the doctor in the hospital said my medicine could hurt the baby. I didn’t know what to do.” As she spoke an image passed through my mind. I pictured her drowning—screaming, bobbing up and down in the water, arms flailing. Men and women in white coats were standing on the dock beside her and dispassionately jotting down notes about her gestational age and lethal heart tones. One physician finally noticed that she was panicked and drowning. He conferred with his colleagues, who crossed their arms and furrowed their brows as they considered her dilemma. She screamed at them: “Help me! I’m drowning!” They turned to her and called out: “Hang in there. Just seven more months until you deliver.”

Lisa and I talked about the risks associated with first-trimester use of lithium, including Ebstein’s anomaly, a rare heart defect that is estimated to occur in 1 in 2000
Many health care professionals told Lisa that she had to choose between her own health and her baby's health. She and I reframed the challenge as one of reducing shared risks to herself and her baby—the risks of medication as well as the risks of untreated bipolar disorder. I told her what she instinctively knew all along—that if she relapses with alcohol or hurts herself with either self-neglect or a suicide attempt, her pregnancy and her baby's health will suffer. It's not an either/or; it's a both/and.

Lisa quickly stabilized on lithium and took it throughout the remainder of her pregnancy. She recently gave birth to a healthy baby boy who was lovingly welcomed by his mother. Lisa felt very supported by a community of family and friends that she had retreated from earlier in her pregnancy and then later sought out and embraced. When I saw Lisa tenderly cooing and gazing at her baby at our last appointment, I remembered the image of her drowning while her health care team stood by and watched. Her well-intentioned physicians carefully tried to protect the pregnancy without protecting the mother. If health care professionals let mothers with depression and other forms of mental illness drown, what do we think will happen to their babies?

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: I thank my patient Lisa (not her real name) for giving permission to publish her story.

3. Wienerwitz DF, Nambisan M, Sene T, Alcedo R, Smith CR, Holmes IP. An-
Research Gaps Leave Doctors Guessing About Treatments For Pregnant Women

December 10, 2018 - 3:26 PM ET
Heard on All Things Considered

ALISON KODJAK
Researchers have to take special precautions to do studies on vulnerable populations, including children, the mentally disabled, incarcerated people and pregnant women. So researchers typically exclude these groups to get their studies approved.

But one result is that doctors caring for pregnant women have fewer tools to care for them when they're ill, Wolf says.

"That's where the irony comes in," she says. "Because researchers are hardly ever permitted to conduct trials on pregnant women, we end up experimenting on pregnant women all the time, because we can't accumulate a solid fund of evidence. So we just stick with the old standards, or we introduce new things without doing trials on them."

When a woman gets pregnant, her pre-existing medical conditions don't disappear, says UT Southwestern's Spong. She lists a litany of conditions — autoimmune disorders, diabetes, hypertension, infections, asthma, preterm labor, gestational hypertension or hyperemesis -- for which there are few therapies that are specifically developed for or tested on pregnant women.

"If someone comes into pregnancy on anti-hypertensive medicines, commonly they will continue on some type of anti-hypertensive medicine during pregnancy," Spong says. "However, we don't have information about how that medicine should be dosed in pregnancy."

She says when women are pregnant, their blood volume doubles and their liver and kidney function change. No one knows how that affects the medication.
Fig. 1. Treatment algorithm. \(^a\) Additional risk–benefit information and patient Fact Sheets available at Mother to Baby (mother-tobaby.org). \(^b\) Patients with a family history of bipolar disorder (item 4 of the Mood Disorder Questionnaire [MDQ]) require monitoring for antidepressant induced activation. EPDS, Edinburgh Postnatal Depression Scale.
Lithium in Pregnancy

Ebstein’s Anomaly

- Normal heart
  - Right atrium
  - Tricuspid valve

- Ebstein’s anomaly
  - Atrial septal defect
  - Right atrium
  - Displaced tricuspid valve allows blood back into right atrium
Ebstein’s Anomaly

• Baseline risk 0.005%
• Nora 1874
  • 2 of 118 babies born to mothers taking Lithium (1.69%)
  • RR 400
• 1994 Cohen review
  • 2:1000 (0.2%)
  • RR 40
• Folate 5mg daily supplementation (Clark and Wisner 2018)
Pregnancy Complications with Lithium in the Mother (23.5%)

- Gestational Diabetes
- Diabetes Insipidus
- Polyhydramnios/oligohydramnios
- HTN
- Toxemia

Diav-Citron 2014
Pregnancy Complications with Lithium in the Neonate (19.3%)

- Respiratory compromise
- Tachycardia
- Transient hypothyroidism
- Tremor
- Sedation
- Cardiac arrhythmia
- Jaundice
- Hypoglycemia
- Sleepiness

Diva-Citron 2014
Lithium Review

• Munk-Olsen 2018
  • N=727 lithium pregnancies
  • N=21,397 unexposed pregnancies
• Major malformations
  • 7.4% vs. 4.3%
• Major cardiac malformations not statistically significant)
  • 2.1% vs 1.6%
• Increased risk neonatal admissions within one month
  • 27.5% vs 14.3%
Lithium Dosing in Pregnancy

• Wesseloo et al Br J Psych 2017
• N=113
Lithium Monitoring in Pregnancy

- Wesseloo 2017, Degliannidisis 2014
  - Use BID dosing to minimize peak levels
  - Check levels monthly until 34 weeks
    - Special care with preeclampsia, HG
  - Fetal echo 16-18 weeks
  - Check levels weekly 34 weeks to delivery
  - Increase hydration at delivery
  - Recheck 24 hours after delivery and with every dose change
    - or 2x per week for 1st 2 weeks
  - Decrease to pre-pregnancy levels within 2-3 weeks
  - Keep blood level >0.8 after delivery d/t high risk relapse
Lithium with Breastfeeding

• Moretti 2003
  • N=11, samples varied 1 day to 15 mos
  • Wide variability of amount of lithium in breastmilk (0-30% of mother’s levels)
  • No infants with adverse effects

• Other studies have reported up to 40% in breastmilk
Lithium with Breastfeeding

• Monitor infant for
  • Cyanosis
  • Elevated TSH
  • Lithium toxicity
  • Restlessness/sedation
  • Difficulty feeding

• Consider checking infant TSH/BUN/creatinine Q6-8weeks
Anticonvulsants in Pregnancy

• Valproic Acid and Carbamazapine
• Don’t use unless you have to
• VPA with 7 times higher risk of ASD
  • 6.3% vs 0.9%
• Baker 2015 Neurology
  • IQ at 6 years
    • VPA with 9.7 IQ points lower on all sub scales
    • CBZ with reduced verbal abilities
    • No effect with lamotrigine
Anticonvulsants

• Teratogenicity – 1st trimester
  • Neural Tube Defects
    • 0.5% - 1% risk for carbamazepine
    • 1% - 9% risk for valproate
    • 0.03% general population
      • Risk may be dose related, increase with multiple AED use, and associated with higher maternal plasma conc.
  • Orofacial Clefts
  • Minor malformations
    • Rotated ears, depressed nasal bridge, short nose, elongated upper lip, fingernail hypoplasia
Carbamazepine

- Craniofacial defects (11%)
- Fingernail hypoplasia (26%)
- Intrauterine growth retardation
- Transient cholestatic hepatitis
- Urinary tract abnormalities
- Cardiovascular abnormalities

- Fetal Vitamin K deficiency
  - Take 20mg daily oral Vitamin K
  - Pediatric dose of Vitamin K 1mg IM

Yonkers et al. 2004
Valproic Acid with Breastfeeding

- Serum levels low in infants
- Reported adverse effects
  - Thrombocytopenia and anemia n=1
- Check levels and LFTs in infants
Carbamazepine with Breastfeeding

- 32-80% maternal serum CBZ in breast milk
- Active metabolite poorly excreted into breast milk
- Monitor growth and lethargy
- Check maternal and infant serum levels
- Reported adverse events
  - Cholestatic hepatitis
  - Mild neuromotor impairment
  - Seizure
The National Pregnancy Registry for Atypical Antipsychotics is dedicated to evaluating the safety of atypical antipsychotic medications that may be taken by women during pregnancy to treat a wide range of mood, anxiety, or psychiatric disorders. The goal of this Registry is to gather information on the safety of these medications during pregnancy, as current data is limited.

TO PARTICIPATE CALL TOLL-FREE: 1-866-961-2388

All pregnant women between the ages of 18-45 with a history of psychiatric illness are eligible to enroll in the registry. If you are interested in participating in the National Pregnancy Registry, please call the toll-free number above or fill out this Patient Interest Form to be contacted by a member of our research team. All information is kept strictly confidential.
Second Generation Antipsychotics in Pregnancy

• MGH National Pregnancy Registry for Atypical Antipsychotics
  • Cohen et al 2016 AJP
  • N=214 with SGA use
    • 3 babies with malformations (1.4%)
  • N=89 comparison
    • 1 baby with malformations (1.1%)
  • OR = 1.25
Second Generation Antipsychotics in Pregnancy

- Huybrechts 2016 Medicaid registry

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Control</th>
<th>SGA</th>
<th>Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1.3M</td>
<td>9258</td>
<td>733</td>
</tr>
<tr>
<td><strong>Congenital Malformations per 1000</strong></td>
<td>32.7</td>
<td>44.5</td>
<td>38.2</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>1.36</td>
<td>1.17</td>
<td></td>
</tr>
</tbody>
</table>
Second Generation Antipsychotics in Pregnancy

• Dosing may need to increase
  • Increased CP450 (2D6 and 3A4) in second trimester

• Freeman 2018
  • No difference in weight gain with SGA and controls
  • But pts taking SGAs with increased weight at baseline
Second Generation Antipsychotics in Pregnancy

• Long term outcomes
  • Peng 2013
    • N=76 controls and SGA exposed
    • 2 months deficits cognitive, motor, social-emotional, adaptive skills
    • No differences at 12 months
  • Shao 2015
    • No differences at 2 months
Second Generation Antipsychotics and Breastfeeding

• Uguz 2016
  • 27 reports, 206 infants
    • Low RID olanzapine
    • Moderate RID quetiapine, ziprasidone, aripiprazole
    • AP levels undetectable in plasma infants
Lamotrigine in Pregnancy

• No increased risk of congenital malformations
  • Risk of MCM 2.0-2.9% by 4 registries
• 2008 study demonstrated 6x increased risk of cleft palate
  • NOT REPLICATED
• No increased risk PTB or SAB
• Baby IQs not decreased
Lamotrigine in Pregnancy

FIGURE 1. Ratio of Lamotrigine Serum Level to Daily Dose During Pregnancy and the Postpartum Period

Serum-Level-to-Dose Ratio

Weeks of Gestation

0 10 20 30 0 3 6

Months Postpartum

Patient 1
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8

Clark 2013

\(^a\) Ratio was calculated using the following formula: lamotrigine level (\(\mu g/mL\)) \(\times\) 100/prescribed daily lamotrigine dose (mg).
Managing Lamotrigine Pregnancy

• Clark 2013
  • Check optimized lamotrigine level before pregnancy
  • Check levels Q4weeks
    • Increase dose 20-25% as needed
Managing Lamotrigine Pregnancy

• Clark 2013
  • If dose increased 4 or more times, decrease dose 20-25% at delivery
  • If dose increased less than 4 times, check levels Q1-2 weeks
    • Monitor for postpartum toxicity
      • Nausea, diploid, ataxia, dizziness
  • Alternatively, decrease dose over 2 weeks after delivery to prepregnancy dose
Lamotrigine and Breastfeeding

• Milk:plasma ratio 41-60%
  • Wide variation

• Infant plasma concentrations
  • 6-50% of maternal serum level
  • Unsure if maternal dose dependent
  • Infants with immature forms of UGT

• Case reports
  • Infant apnea (1)
  • No reports related rash
Lamotrigine and Breastfeeding

• Lamotrigine concentration lower in serum of nursing than cord blood
• No long term neurodevelopment risk at 6 years old
Bipolar disorder is common in women of childbearing age
  • So is pregnancy

Be aware of misdiagnosis and overlap of symptoms

Interview

Assessment

Plan

Treat postpartum psychosis aggressively as a psychiatric emergency
  • Not be confused with intrusive thoughts but monitor closely
Review-Pharmacology

Must weigh risks of disease with risks of medication use

With all medications in pregnancy, monitor for increased metabolism decreasing blood levels

Lithium has less risk of cardiac malformations than previously thought

Valproic Acid and Carbamazepine with increased teratogen risk, avoid when possible

Lamotrigine has reassuring data in pregnancy but levels vary with breastfeeding

Levels in breastmilk vary

The atypical antipsychotics have reassuring data both for pregnancy and breastfeeding

Although no adverse outcomes consistently found
• Individual treatment decision for each patient
  – Risks
    • Medications to mom
    • Medications to fetus
    • Untreated bipolar illness to mom
    • Untreated bipolar illness to fetus
  – Benefits
    • Medications to mom
    • Treated bipolar disorder

• Screen during pregnancy and postpartum
• Gather collateral
• Assess family unit stability
  • Include partner and family if available and appropriate
• Safety Planning
• Educational of colleagues
• Utilize nonpharmacological treatments
  • Individual Psychotherapy
  • ECT
  • Family/Couples Therapy

• Pregnancy Categories (A,B,C,D,X) are no longer in use

• Monitor for postpartum psychosis
  • Emergency

• Read studies

• Know resources
• “We discussed the risks, benefits, and alternatives to psychiatric medications, including ______, in pregnancy/lactation. We have also discussed the risks of untreated illness during pregnancy/lactation. The patient endorses understanding, was engaged in discussion, was able to ask questions, and from the visit today appears to have capacity to understand and is able to make an informed decision. Ms. X (and her partner) elect to __________.”
Online Resources

• Internet:
  • www.womensmentalhealth.org
  • http://www.postpartum.net/
  • http://www.postpartumprogress.com/
  • http://postpartumstress.com/
  • Http://www.beyondtheblues.info
  • https://the-periscope-project.org/
  • https://www.mcpapformoms.org/
  • http://www.motherisk.org/prof/index.jsp
  • https://toxnet.nlm.nih.gov/pda/lactmed.htm

• Apps
  • PPD ACT
  • MGH Perinatal Depression Scale
  • Mothertobaby
  • LactMed
  • Reprotok
Day Treatment Program
Adult Partial Hospitalization & Intensive Outpatient Programs

✓ Affective disorders adults PHP/IOP
✓ Co-occurring disorders adults PHP/IOP
✓ Chemical dependency IOP
✓ Affective disorders adolescents PHP/IOP
✓ Chemical dependency IOP

• Monday through Friday
  • Patients sleep at home
• Partial Hospitalization Program
  • 8:30am to 2:30pm
  • 5 days a week
• Intensive Outpatient Program
  • 8:30am to 12:30pm
  • 3 days a week

✓ Integrative treatment
  ✓ Group therapy
    ✓ DBT, CBT, ACT
  ✓ Nutrition
  ✓ Yoga
  ✓ Recreation therapy
  ✓ Music therapy, art therapy
✓ Individual therapy
✓ Medication management
References

• Bhat A, Cerimele JM, Byatt N. Pregnant and Postpartum Women with Bipolar Disorder: Taking the Care to Where They Are. Psychiatric Services 2018.
• Clark et al. Does screening with the MDQ and EPDS improve identification of bipolar disorder in an obstetrical sample? Depress Anxiety, 2015
• Clark CT et al. Lamotrigine dosing for pregnant patients with bipolar disorder. Am J Psychiatry 2013
• Cohen LS et al. A reevaluation of risk of in utero exposure to lithium. JAMA 1994
• Jablensky AV et al. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry 2005
• Kim HG. Drowning In Plain Sight. JAMA 2012
• Munk-Olsen T et al. First-trimester lithium exposure increases risk for birth defects. Lancet Psychiatry 2018
• Peng M et al. Effects of prenatal exposure to atypical antipsychotics on postnatal development and growth of infants: a case-controlled, prospective study. Psychopharmacology 2013
References

• Moretti ME et al. Monitoring lithium in breast milk: An individualized approach for breast-feeding mothers. Ther Drug Monitoring. 2003
• Uguz F and Sharma V. Mood stabilizers during breastfeeding: a systematic review of the recent literature. Bipolar Disorder 2016
• Wisner KL et al. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry, 2013
• Wesseloo et al Lithium dosing strategies during pregnancy and the postpartum period. Br J Psychiatry 2017