Bipolar Disorder
Level 1 Case Conference
Facilitator's Guide

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Pre-Assessment Learning

- Khan, S. J., Fersh, M. E., Ernst, C., Klipstein, K., Albertini, E. S., & Lusskin, S. I. (2016). Bipolar disorder in pregnancy and postpartum: principles of management. Current psychiatry reports, 18(2), 13.
- Mother To Baby Fact Sheet: Critical Periods of Fetal Development: https://mothertobaby.org/fact-sheets/critical-periods-development/

Optional Supplemental Reading

- Anderson, Eric L., and Irving M. Reti. "ECT in pregnancy: a review of the literature from 1941 to 2007." Psychosomatic medicine 71.2 (2009): 235-242.
- Deligiannidis, K. M., Byatt, N., & Freeman, M. P. (2014). Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. Journal of clinical psychopharmacology, 34(2), 244.
- Fornaro, Michele, et al. Lithium exposure during pregnancy and the postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes. *American Journal of Psychiatry* 177.1 (2020): 76-92.

Overview
The goal of this module is to utilize a clinical case presentation to broaden learners' knowledge of the management of bipolar disorder in the perinatal period. This session is designed to last 60 minutes but can be modified for a longer or shorter session. The session is best utilized for psychiatry residents who have some clinical experience with the management of bipolar disorder. Prior to the session, residents should read the articles included in the pre-reading section of this module.

Session

- **Clinical Vignette Part 1: read aloud (3 min)**
- **Residents divide into working groups and discuss questions 1-4 (10 min)**
- **Choose one group per question to guide a brief discussion (15 min)**
- **Clinical Vignette Part 2: read aloud (2 min)**
- **Residents return to working groups and discuss questions 5-13 (10 min)**
- **Choose one group per question to guide a brief discussion (15 min)**
- **Wrap up (5 minutes)**

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Learning Objectives

1. Describe the relative magnitude of relapse risk for individuals with bipolar disorder during pregnancy and the postpartum period.
2. Understand factors that influence the risk-risk discussion of pharmacologic treatment of perinatal individuals with bipolar disorder.
3. Consider pharmacodynamic and pharmacokinetic changes of pregnancy and their application to lithium monitoring in the perinatal period.
4. Describe the current data informing the reproductive safety of second-generation antipsychotics during the perinatal period.
5. Review non-pharmacologic treatments of bipolar disorder and their application to the perinatal period.

Clinical Vignette Part 1

Ms. H is a 27-year-old G1 female at 31 weeks gestation with a h/o bipolar disorder I who was referred to psychiatric care upon discharge from inpatient psychiatric treatment.

Ms. H describes a history of mood lability starting in adolescence and was formally diagnosed with bipolar disorder at age 21. After a series of 1–2-day periods where she would be "full of energy" despite sleeping only 1-2 hours at a time, she had a more prolonged episode where she was "like the energizer bunny, didn't sleep for days" and reports being loud, boisterous, and hypersexual. "It's like I was on drugs, only I wasn't." During that time, she reports feeling like she was receiving messages from people around her during everyday encounters (i.e., when the coffee barista gave her a red cup, she felt like she was receiving a message that she was in danger). She was hospitalized and started on lithium and quetiapine with good effect. Since then, she has remained on a maintenance regimen of lithium 900mg and quetiapine XR 400mg at bedtime. At age 25 she attempted a lithium taper; however, this was aborted when she was hospitalized with depression and suicidal ideation. During a subsequent hospitalization last year for depression, she was also started on ECT (3x week for several weeks, then weekly for "a long time," then monthly thereafter), which has been very effective.

Ms. H self-tapered her medications and stopped seeing her long-time psychiatrist upon learning she was pregnant. At that time, she was estimated to be approximately 12 weeks gestation and desired a "natural pregnancy." While her ECT provider did tell her that ECT is "safe" in pregnancy, he felt unable to continue treatments due to not having access to on-site obstetrics support. Ms. H reports that shortly after discontinuing her medication and ECT treatments she noticed she felt more down, was frequently tearful and more easily overwhelmed. After talking with her fiancé, she attributed these feelings to "expected ups and downs," however as the weeks passed her symptoms worsened. She began ruminating about death, started smoking cigarettes after years without use, and was frequently calling off work due to not feeling like she could "face the day." Ms. H reports that the withdrawal and irritability she exhibited took a toll on her relationship and her partner moved in with his parents temporarily. At her 28-week obstetric visit she admitted to her obstetrician that she was having transient periods where she had a belief that her fetus was "not real." Her obstetrician referred her for an emergency psychiatric evaluation. She required PRN medications in the emergency room for agitation, and from there she was hospitalized for stabilization.

Ms. H has been in a relationship with her current partner for about 18 months. Her mother, whose own mother had bipolar disorder, lives nearby and checks on Ms. H frequently. Ms. H is currently working part time as a nanny but also receives financial support via social security disability for her mental illness.

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Discussion Questions

1. Consider the role of her previous outpatient psychiatrist. Prior to pregnancy, what risk factors and protective factors might have informed her risk of relapse during pregnancy? Given that Ms. H disengaged from treatment upon becoming pregnant, what opportunities (if any) did the psychiatrist have to address her perinatal mental health needs?
   Facilitator elicits the following:

Risk Factors: Encourage learners to consider Ms. H's severity of illness, which likely could be described as severe based on the following factors:

- h/o multiple inpatient hospitalizations, last was only 1 year ago
- h/o suicidal ideation
- presence of psychotic symptoms during mood episodes
- h/o decompensation when medication was tapered in the past
- h/o of ECT

Protective Factors:

- Partnered (fiancé)
- Supportive family
- Current employment
- Financial stability via SSD
- Prior adherence to medications and appointments.

Regarding Ms. H's previous outpatient care, optimal psychiatric care of reproductive-aged women necessarily includes proactive and collaborative discussion of the patient's family planning goals, contraceptive needs, and preconception planning. When prescribing medication treatment, potential teratogenic effects should be discussed. In the event where a patient is either trying to conceive or not using reliable contraception, a full and personalized preconception planning discussion should include potential risks of the patient's underlying illness, risks of the patient's prescribed medications, and a plan for how to best minimize these risks. Of note, a woman's risk for relapse is increased if she does not continue maintenance medication. One prospective study found that among women with BD who were euthymic at birth, those who discontinued their mood stabilizer had twice the risk of relapse than those who remain on medication. Rapid discontinuation (tapering off within 2 weeks) was associated with greater risk of relapse than those who tapered more gradually.[1] While some early studies have suggested an association between first trimester lithium use and cardiac abnormalities, more recent data shows lower magnitude of risk than originally reported. Lithium is also highly effective in preventing relapse at throughout the peripartum period. Finally relapse during the peripartum is not only precipitated by hormonal fluctuations but also psychological and social changes. It is thus important to discuss non-pharmacological strategies for maintaining wellness. Such considerations could include modifying or reducing work hours, postponing non-essential projects or bolstering emotional and physical support from one's community. Among the most important modifiable risk factors is protection of sleep. Sleep physiology is altered during the peripartum. Nighttime feedings during the postpartum period further contribute to poor sleep quality. Sleep disruption is a commonly reported precursor to a mood episode thus a discussion about breastfeeding plans should be discussed. Formula feeding should be considered and planning for additional help with nighttime feedings is critical to ensure a peripartum mother is getting as much continuous sleep as possible.

[1]Viguera AC, Whitfield T, Baldessarini RJ, et al: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry 164(12):1817-1824, 2007

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Given the fact that Ms. H was engaged in outpatient care prior to pregnancy, her treating psychiatrist had an opportunity to provide Ms. H with pertinent information and collaborate with her on a treatment plan *prior to* her pregnancy. Once Ms. H did not return to care, best practice would also include appropriate outreach attempts to gauge her safety and explore barriers to treatment.

2. Ms. H self-tapered her medications upon learning she was pregnant at approximately 12 weeks gestation. What teratogenic concerns regarding lithium or quetiapine might have been discussed at that time?
Facilitator elicits the following:

At 12 weeks gestation, Ms. H was nearing the end of the first trimester and beyond the period of highest risk for major malformations. While important components of fetal development continue well beyond the first trimester, at 12 weeks the fetal heart and stomach are fully formed, neural tube closure has occurred, and the oral palate is formed.

Recent data suggests that the risk of cardiac or overall malformations with use of lithium exists at a much lower magnitude than previously reported. Discontinuing lithium at 12 weeks gestation is unlikely to affect the level of risk in any meaningful way. Quetiapine is not thought to increase risk of birth defects.

May be helpful to review the fact sheet on "critical periods of development" freely available on the website of the organization Mother To Baby: https://mothertobaby.org/fact-sheets/critical-periods-development/

3. Consider the treatment Ms. H received in the emergency department. If you were caring for Ms. H in the ED, how might you approach agitation management in the setting of pregnancy?
Facilitator elicits the following:

- Prioritize verbal de-escalation techniques, such as providing the patient with personal space, using a calm demeanor with a soft-spoken voice, identifying the patient's wants and feelings, and communicate in an honest, straightforward, transparent manner.
- In the situation where the patient does not respond to verbal de-escalation attempts and is engaging in behavior that puts her or other's safety at risk, medication may be necessary. Just as in non-acute settings, there is no "one best" medication to use in this situation, but the clinician must weigh available options in terms of likelihood of effectiveness, degree of information available about that option, and potential side effects to the patient.
- As stated in the "Emergencies Progressive Case Conference" module (see 5 Hour Essentials Course): *Psychosis, mania, and agitation in pregnancy are not good for mother or fetus. It is important to treat them, and most of the medications we use for agitation in the emergency setting are well-studied older medications about which we have considerable evidence for safety in pregnancy. If you need them, you can safely use Haloperidol or Olanzapine, for example, or lorazepam, for acute agitation needs. Remember that the golden rule in pregnancy is minimum dose of as few medications as possible – so be sure to think about why you are using each medication and give them only if there is an indication.*
- In the rare situation when restraints are needed, careful positioning on the left side is essential for patients in their 2nd or 3rd trimester of pregnancy in order to prevent vena cava syndrome.

4. Describe potential negative consequences for Ms. H due to illness recurrence during pregnancy.
Facilitator elicits the following:

- exposure to underlying illness
- exposure to tobacco use
- negative impact on her relationship with her boyfriend
- potential impact on her employment due to missed work
- exposure to PRN medications

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- exposure to antenatal depression
- increased risk for suicide
- increase risk for mood episode in the postpartum period (note that while mania is a concern in the postpartum period, the most common type of postpartum mood episode for individuals with bipolar disorder is a major depressive episode)
- increased risk for postpartum psychosis

Clinical Vignette Part 2: post-hospitalization outpatient appointment

During her 2 weeks inpatient stay, she was restarted on her pre-pregnancy doses of lithium (900mg at bedtime) and quetiapine XR (400mg at bedtime) as well as several doses of lorazepam for acute anxiety in the first few days of treatment.

Li level measured in interim between hospital discharge and this appointment was 0.65. Historically, her Li level on maintenance treatment has ranged between 0.8 and 1.0.

On today's appointment, Ms. H reports she is "a little better." Her delusional beliefs have remitted, and she is no longer ruminating about death. However, she continues to feel depressed and anxious. She states she has been unable to return to work after the hospitalization as she "just can't bear to deal with it all." She hasn't reached out to her fiancé or other supports as she just can't get motivated to do so. She often feels hopeless and has guilty ruminations about not being able to "tough it out" without medication. She worries that she will be a terrible mother.

Discussion Questions

5. Consider why Ms. H's Li level is below her typical range on her maintenance dose. What are some potential contributors? How might these contributors affect your decision-making around Li management?
Facilitator elicits the following:

- Most likely her lower Lithium level is secondary to increased clearance during pregnancy. GFR and intravascular volume increase substantially over the course of pregnancy and result in a 30-50% increase in lithium clearance. Of note, after delivery, lithium clearance quickly returns to pre-pregnancy rates.
- It would also be prudent to inquire about medication adherence given previous reluctance to take medication in pregnancy.
- Recommended monitoring strategy during pregnancy includes:
    - Monthly early in pregnancy
    - Weekly starting at 4 weeks prior to expected delivery.
    - Any time the patient is at risk for dehydration (hyperemesis) or impaired renal function (preeclampsia)
    - At 24-48 hours after delivery
- It is likely that Ms. H will require incremental dose increases of lithium during pregnancy. These dose adjustments should consider both her lithium level and her clinical presentation.
- If incremental dose increases have been made, consider returning patient to pre-pregnancy maintenance dose immediately after delivery.

6. How might you counsel Ms. H about the reproductive safety of lithium when used in the 3rd trimester of pregnancy?
Facilitator elicits the following:

- Lithium has NOT been found to increase the risk of preeclampsia, gestational diabetes, preterm birth, low birth weight or postpartum hemorrhage. There are case reports of polyhydramnios in pregnant individuals taking lithium, however no clear association.
- Reversable neonatal effects associated with lithium use in late pregnancy include:
    - Hypothyroidism (likely related to untreated maternal hypothyroidism)

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  - Nephrogenic diabetes insipidus
  - Cardiac arrhythmias
- Signs of neonatal lithium toxicity include
  - respiratory difficulties
  - hypotonicity
  - lethargy
  - tremor
- Limited data regarding longer-term developmental outcomes of children exposed in utero to lithium are reassuring.

7. What are some relative contraindications for use of lithium during pregnancy?
Facilitator elicits the following:

A mother's unwillingness to have frequent lithium blood draws poses a relative contraindication due to the risk of lithium toxicity or lack of therapeutic benefit. Complications such as hyperemesis gravidarum (risk of dehydration), pre-eclampsia, other illnesses that affect renal function, and polyhydramnios may lead to lithium toxicity in the patient or child. Other complications such as oligohydramnios or abnormalities in amniotic fluid volume may increase the likelihood of lithium-associated fetal nephrotoxicity.

8. Ms. H asks you if it is safe to continue quetiapine going forward in her pregnancy. How might you describe the risks and benefits of this treatment?
Facilitator elicits the following:

Second generation antipsychotics (SGAs), including quetiapine, are increasingly used for the treatment of bipolar disorder. For Ms. H, quetiapine has also been a medicine that she has historically tolerated and has likely contributed to her periods of stability. Data on the safety of SGAs during pregnancy is limited as compared to SSRIs, however what has been reported is generally reassuring and does not indicate that SGAs are major teratogens. Most studies of this class report combined data rather than one specific medication, although it is reported that quetiapine has the lowest placental transfer compared to olanzapine and risperidone, however may present a higher risk of gestational diabetes than some other SGAs.

There is evidence for risks associated with SGAs including: prematurity, low and high birth weight and neonatal symptoms such as abnormal muscle movements. While one study (Peng et al 2013) did show an association between SGAs and delayed development at 2 months of age, this difference was no longer significant by 12 months of age.

Based on the above information, the psychiatrist should have a discussion with Ms. H that includes the risk of under-treated disease vs. the risk of quetiapine. If Ms. H does decide to continue quetiapine, she should be screened for gestational diabetes (usually as part of her prenatal care) and have regular monitoring of her weight. The psychiatrist should counsel Ms. H about monitoring for sedation, particularly in the postpartum period when she will need to care for her infant's needs throughout the day and night.

Facilitator should also alert learners to the National Pregnancy Registry for Atypical Antipsychotics (https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry). Patients or clinicians can call or email the registry to enroll patients in this large registry study.

9. Is ECT a possibility for Ms. H? How might you counsel her about ECT?
Facilitator elicits the following:

ECT is a treatment option for pregnant patients and has been helpful for Ms. H in the past. ECT does have evidence of efficacy in pregnancy, and risks of adverse effects are low. ECT during pregnancy does require the availability of obstetrical monitoring and support and ideally access to NICU care.

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10. What non-pharmacologic measures would you discuss with Ms. H?
Facilitator elicits the following:

Every patient with bipolar disorder should have an individualized perinatal relapse prevention plan that is developed in collaboration with the patient, obstetrical and pediatric providers. It is important to be mindful of the patient's social and financial resources while developing this plan. The plan should include a description of medication prophylaxis, potential intervention strategies in case of relapse as well as strategies to enhance wellness such as:

- Individual psychotherapies such as cognitive behavioral therapy, family-focused treatment, interpersonal and social rhythm therapy have evidence to support their utility in bipolar disorder.
- Nutrition and exercise
- Prenatal vitamin with folic acid
- Additional folic acid supplementation in pregnant individuals on some anticonvulsant mood stabilizers (valproate and carbamazepine)
- Cessation of substances
- Strategies to optimize sleep (planning support for night feeding, maintaining circadian rhythm, sleep medication)
- Psychosocial support (prenatal support groups, doula support, psychoeducation)
- Instrumental support in newborn care (postpartum doula, night nanny, etc.)

11. How might you counsel Ms. H about her risk of symptom recurrence in the postpartum period and potential preventative strategies?
Facilitator elicits the following:

Ms. H should be counseled that the postpartum period is a time when persons with bipolar disorder are at high risk of recurrence of illness. Continuation of her medication postpartum with close monitoring by her psychiatrist is an important preventative strategy. Furthermore, continuation of non-pharmacologic measures, as described above, should be recommended.

Ms. H should also be counseled that the risk for relapse in the postpartum period includes an increased risk of postpartum psychosis. She should know that while her risk is elevated, it is still low in absolute terms. The psychiatrist should counsel Ms. H and her family members of symptoms of postpartum psychosis such as delusional beliefs, disorganized behavior, and hallucinations. Severe insomnia may represent an early symptom of postpartum psychosis.

Among the most important modifiable risk factors is protection of sleep. Sleep physiology is altered during the peripartum. Nighttime feedings during the postpartum period further contribute to poor sleep quality. Sleep disruption is a commonly reported precursor to a mood episode thus a discussion about breastfeeding plans should be discussed. Formula feeding should be considered and planning for additional help with nighttime feedings is critical to ensure a peripartum mother is getting as much continuous sleep as possible

12. Ms. H expresses a strong desire to breastfeed and asks you if it will be safe for her and her baby. What advice might you offer?
Facilitator elicits the following:

While Lithium is not an absolute contraindication to breastfeeding, there is significant risk to the infant. Numerous reports exist of infants who were breastfed during maternal lithium therapy without any signs of toxicity or impaired development. Data does suggest, however that Lithium exposure through lactation can adversely affect the infant when its elimination is impaired, such as in dehydration or prematurity. Collaboration with and close monitoring by the pediatrician is essential, and Ms. H should be counselled that this might include monitoring infant serum levels, BUN, Cr and TSH. It can be recommended to Ms. H that Lithium can be an option if she has a full-term infant, she has reached and maintained illness stability and has identified a collaborative pediatrician.

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Data on the safety of quetiapine is more limited but overall reassuring. As Ms. H is taking quetiapine during pregnancy, it can be hypothesized that the exposure to the infant will be small as compared to his or her exposure during gestation.

If Ms. H does decide to breastfeed, she should be counselled to monitor her infant for drowsiness and to inform her pediatrician of any medications she is taking. Ms. H should also be counselled that breastfeeding potentially can interfere with the possibility for support persons to assist with night-time feedings and allow her to get more consolidated sleep hours.

13. After discussing a treatment plan, Ms. H calls to let you know that at her f/u Obstetric visit, her OB provider voiced concerns about her medication regimen. She is now second-guessing her choices and would like to discuss this with you. How might this be approached?
Facilitator elicits the following:

This question speaks to the importance of coordination of care between providers during the perinatal period (including obstetricians, pediatricians, psychiatrists, psychotherapists). At times, proactively facilitating communication may increase the consistency of the feedback to the patient by providing space for consideration of different perspectives and education around recommendations. If differences of opinion between providers remain, continued communication may provide a supportive context for the patient to understand these different perspectives and make decisions based upon her own values and understanding.

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