Treating bipolar disorder during pregnancy

Optimal outcomes require careful preconception planning, medication risk/benefit analysis

Ms. M, age 31, has bipolar I disorder and takes lamotrigine, 200 mg/d, and aripiprazole, 10 mg/d. She was first hospitalized at age 20 for a manic episode and was discharged on lithium, 1,200 mg/d. She was hospitalized again at age 25 for a depressive episode that occurred after she stopped taking lithium because of undesirable side effects. She was switched to lamotrigine, 200 mg/d, which she tolerated well. Aripiprazole, 10 mg/d, was added 1 year later to address emergence of mild mood elevation symptoms.

During a recent follow-up appointment, Ms. M expresses interest in getting pregnant in the next 6 months. Her mood has been stable for 5 years and she asks if she should stop taking her medications in preparation for pregnancy. What would you recommend?

Because the typical age of onset for bipolar disorder (BD) is late adolescence or early adulthood, women are at risk for new onset or recurrence of mood episodes throughout their peak reproductive years. This article updates practitioners on the treatment of BD during pregnancy, including preconception planning and the risks and benefits of medication use during pregnancy. We also cover treatment considerations during the postpartum period, such as prophylaxis of mood episodes and mood stabilizer treatment for women who breast-feed.

Prenatal planning

Ideally, “prenatal planning” should begin long before women with BD prepare to have children. Because one-half of pregnancies in the United States are unplanned and manic episodes may result in impulsivity...
and increased sexual activity, all women of reproductive age with BD should be counseled about birth control and risks of unplanned pregnancies. Discussions about risks of in utero exposure to psychotropics should occur when medications are first prescribed. Because certain mood stabilizers, (eg, carbamazepine) may decrease efficacy of oral contraceptives by inducing cytochrome P450 (CYP450) enzymes, women taking these medications also should be counseled about additional methods of birth control.2

Oral contraceptives also may affect mood stabilizer levels through similar mechanisms. Because of CYP450 induction, lamotrigine serum levels are lower during the 3 “active” weeks of exposure to exogenous estrogen. During the “pill-free” last week, lamotrigine levels may increase up to 54%.3

Because mood stabilizers such as valproate are associated with teratogenic risks, women with BD should be asked about contraception at every visit.4 Valproate also has been associated with an increased risk of menstrual cycle irregularity. Some studies have shown that even before initiating mood stabilizers, women with BD have a higher incidence of menstrual cycle irregularity than women without BD, which suggests the link between polycystic ovarian syndrome (PCOS) and BD may be independent of medications and part of the endophenotype.5

The importance of prenatal vitamins should be discussed. The recommended folate dosage for women planning to become pregnant is 0.4 to 1 mg/d and 0.8 to 5 mg/d for women with either a previous pregnancy with neural tube defects or those taking an antiepileptic medication.6

Table 1 summarizes recommendations to improve prenatal planning in women with BD. Goals include:

• meeting with the patient at least 3 months before conception to review current menstrual cycle functioning. If your patient exhibits any signs or symptoms of PCOS, consider referral to a gynecologist
• meeting with patient and partner/significant supports to discuss treatment decisions
• optimizing the patient’s mood before conception, preferably for at least 3 to 6 months
• prescribing monotherapy at the lowest therapeutic dose if clinically feasible
• assessing the patient’s personal preferences and beliefs regarding medication use during pregnancy and breast-feeding
• assessing the patient’s capacity to understand the risks and benefits of medication continuation/discontinuation during pregnancy, including risk for relapse, current literature on teratogenicity, perinatal complications, and neurodevelopmental studies. Document that the patient provides informed consent.

**Table 1**

<table>
<thead>
<tr>
<th>Pregnancy and BD: Medication management guidelines</th>
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<tbody>
<tr>
<td><strong>Comprehensive prenatal counseling</strong> should begin at least 3 months <strong>before</strong> pregnancy. Folate supplementation is advised.</td>
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<tr>
<td><strong>Medication should be avoided</strong> if clinically feasible (particularly during the first trimester). Avoid abrupt discontinuation. Increase psychosocial and clinical supports.</td>
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<tr>
<td><strong>If medication is pursued:</strong></td>
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<tr>
<td>• Use minimum effective dose</td>
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<td>• Monotherapy is preferable</td>
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<tr>
<td>• Avoid changing effective medications unless there is significant safety or clinical advantage</td>
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<tr>
<td>• Increase frequency of clinical monitoring as indicated</td>
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<tr>
<td><strong>Comprehensive postpartum counseling</strong> should begin before and be reinforced throughout pregnancy, emphasizing:</td>
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<tr>
<td>• importance of sleep</td>
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<td>• postpartum prophylaxis</td>
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<tr>
<td>• risks/benefits of breast-feeding</td>
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<tr>
<td>• importance of social support and identification of support structure, including psychoeducation session with support team</td>
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**BD:** bipolar disorder

**Source:** Adapted from reference 7

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**Clinical Point**

Because mood stabilizers are associated with teratogenic risks, ask women with BD about contraception at every visit.

**Table 2**

<table>
<thead>
<tr>
<th>Comprehensive postpartum counseling should begin before and be reinforced throughout pregnancy, emphasizing:</th>
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**CASE CONTINUED**

**Medication decisions**

Ms. M’s first question is, “Should I stop taking my medications?” Ms. M and her psychiatrist review the risks and benefits of medication exposure during pregnancy (Table 2) and decide against discontinuing all medications.
because of her history of relapse when she stopped lithium. Because Ms. M’s mood has been stable for 5 years, she and her psychiatrist decide to limit her medications to lamotrigine monotherapy at her current dose, and agree to slowly taper aripiprazole. One week later, Ms. M calls and states she has a positive pregnancy test and is wondering if she should stop aripiprazole all at once. Ms. M is advised to continue with the original plan to slowly taper aripiprazole.

Medication risks/benefits
Women with BD have a high rate of relapse associated with abrupt discontinuation of pharmacotherapy during pregnancy. As such, patients and their partners and families should be cautioned against rapid discontinuation of medications. The risk to mother and fetus is particularly high for women with a history of recurrent, severe mood episodes. These patients face not only a high risk of recurrence of mood episodes, but also the inherent danger of impulsivity, poor self-care, and suicidal-ity associated with mania, depression, and mixed states. In these cases, continuing a medication (other than known teratogens such as valproate) that has effectively stabilized mood may be preferred to discontinuation; these decisions are made after careful risk/benefit assessment.

Carefully reviewing the patient’s history is essential to assessing the risks and benefits of tapering medications before pregnancy. Consider the frequency and severity of your patient’s mood episodes, and whether a switch in mood state was rapid or had a prodromal phase. If a patient currently has a stable mood, a history of mild to moderate mood episodes, a history of prodromal symptoms (eg, gradually increasing sleep disturbances and mood deterioration), and no history of rapid switches, gradually discontinuing medications before or during pregnancy may be considered. However, encourage women to enlist their partners and family members to monitor for warning symptoms and advocate for early medication intervention. Because insomnia is a sign of relapse for many patients, educate women and their families about the importance of maintaining a regular sleep/wake cycle and alerting care providers if this cycle changes.

Mood stabilizers with the greatest risk for teratogenicity are valproate, carbamazepine, and lithium. Valproate is associated with a 6% to 13% risk of congenital malformation, including neural tube defects (1% to 2%) and cardiac or craniofacial defects. Risks increase at doses >800 mg/d. Potential perinatal complications associated with valproate include heart rate deceleration, abnormal tone (hypotonia or hypertonia), and growth retardation. Neurobehavioral sequelae include lower IQ scores and increased risk of autism.

Carbamazepine is associated with a 2% to 5% risk of congenital malformation, including neural tube defects and cardiac or craniofacial defects. Perinatal complications associated with carbamazepine include vitamin K deficiency. The neurobehavioral sequelae of carbamazepine are controversial; most prospective studies do not suggest long-term cognitive deficits. It is strongly recommended that...
valproate and carbamazepine be avoided, if possible, in women with BD who plan to become pregnant in the near future.

Prospective studies of lithium have shown a 2.8% rate of congenital malformations, which is much lower than the 11% rate found in retrospective studies.14 Ebstein’s anomaly—downward displacement of the tricuspid valve—is estimated to occur in .05% to 0.1% of infants exposed to lithium, which is 10 to 20 times the base rate, but a low absolute risk.11

It is recommended women taking lithium during pregnancy complete a fetal high resolution ultrasound and echocardiogram at 16 to 18 weeks.11 Perinatal complications associated with lithium include prematurity, hypotonia, hypothyroidism, hepatic abnormalities, respiratory distress, and nephrogenic diabetes insipidus.15 When prescribing lithium, divided doses are recommended to maintain a stable serum level. Serum lithium levels should be monitored frequently, and higher doses may be needed because of increased glomerular filtration rate and plasma volume throughout pregnancy.10 Because of fluid shifts at delivery—including blood loss during delivery and postpartum diuresis and diaphoresis—there is a risk of lithium toxicity at this time. Some researchers have suggested suspending lithium treatment during labor or 24 to 48 hours before planned induction or Caesarean section may lower this risk, with re-administration after delivery when medically stable.16 Women should be followed closely for signs of lithium toxicity and have lithium levels monitored as clinically indicated.16 There is insufficient data to support any neurobehavioral sequelae of utero exposure to lithium; however, there are few long-term follow up studies using standardized measures.17

Lamotrigine is associated with a 1.9% to 4.6% rate of congenital malformations, including cleft lip/palate (8.9/1,000 vs 0.5 to 1.2/1,000 baseline).4 Studies suggest that rates of malformations (cardiac, genitourinary, gastrointestinal, neural tube defect) are dose-dependent: 1.3% at dosages <100 mg/d, 1.9% at 100 to 200 mg/d, and 5.4% at >200 mg/d.18 Because cleft lip and palate are formed by late second trimester, it is recommended to attempt to keep the lamotrigine dose <200 mg/d during the first and second trimesters. Higher doses of lamotrigine may be needed in the third trimester because of increased renal clearance.19 There is insufficient data to support any lamotrigine-associated neurobehavioral effects, and unlike studies of valproate, follow-up evaluations of lamotrigine-exposed children have not shown lower IQs.20

Evidence about the reproductive safety of other mood stabilizers used in BD is limited. A recent population-based cohort study did not show increased risk of major malformations in children exposed to topiramate, gabapentin, or oxcarbazepine during the first trimester of pregnancy.21 Topiramate often is used in combination with other mood stabilizers for weight control, and studies suggest that polypharmacy with topiramate, especially at higher doses and with valproate, increases the risk of major congenital malformations, especially cleft lip and cleft palate.22 Consequently, topiramate is not recommended for women planning to conceive.

**Antipsychotics.** Although there is increasing information about outcomes of neonates exposed to atypical antipsychotics during pregnancy, the literature still is limited. The greatest number of studies have evaluated olanzapine, risperidone, and quetiapine and show the rate of congenital malformations is 0.9% to 4.1%, which
is consistent with general population rates.\textsuperscript{23-26} Perinatal complications associated with these atypical antipsychotics include neonatal extrapyramidal syndrome (EPS), possible neonatal adaptation/withdrawal syndrome, and an increased risk of the infant being either large or small for gestational age. Because atypical antipsychotics may increase the risk of metabolic syndrome, women should be counseled about the possible increased risk for gestational diabetes with these medications. None of these drugs have been associated with neurobehavioral sequelae, but long-term follow-up studies of exposed infants are lacking.

For aripiprazole, asenapine, ziprasidone, iloperidone, and lurasidone there is insufficient data about rate of congenital malformations, obstetric complications, and neurobehavioral sequelae. However, perinatal complications associated with these medications include risk of EPS and withdrawal symptoms.\textsuperscript{25,26}

\textbf{CASE CONTINUED}

\textbf{Worsening mood symptoms}

During pregnancy, Ms. M’s mood is stable on lamotrigine, 200 mg/d, and she participates in individual interpersonally oriented psychotherapy to address anxieties related to becoming a mother. However, late in her third trimester, Ms. M reports worsening symptoms, including depressed mood, insomnia, fatigue, and poor motivation. She also learns her mother had an episode of postpartum depression. Ms. M and her doctor discuss the risks of postpartum relapse, but she declines additional medication for prophylaxis because she is concerned about its impact on breast-feeding.

Two days after delivery, Ms. M complains of increased insomnia and depressed mood, and her husband reports she is not getting out of bed. She describes thoughts and images of throwing her baby out the window, and feels her thoughts are controlled by something outside of herself. Ms. M suspects her husband is having an affair.

\textbf{Clinical Point}

Some researchers have suggested suspending lithium during labor may lower the risk of lithium toxicity.
Postpartum risks
All women with BD should be counseled regarding prophylaxis with mood stabilizers during the postpartum period. Women with BD are at high risk of mania and psychosis postpartum, particularly those with a personal or family history of postpartum psychosis. Postpartum psychosis frequently presents with an abrupt onset, shortly after delivery (Table 3, page 62). Although it may present with the classic symptoms of mania or psychotic depression, it also may have features of delirium.27

Clinicians should immediately implement treatment with mood stabilizers and antipsychotics to manage acute psychotic symptoms, while also ruling out medical causes or comorbidities. Hospitalization should be considered. Aggressive treatment of insomnia will help stabilize mood. Electroconvulsive therapy can be used in treatment-refractory or urgent cases.10

Lastly, because approximately 4% of women with postpartum psychosis commit infanticide, all mother/child interactions should be closely supervised.27

In small prospective studies, use of lithium within 48 hours of delivery decreased the risk of relapse of postpartum psychosis within the first 3 months.26,29 In lower-risk patients who have discontinued pharmacotherapy during pregnancy, restarting medication before or immediately after delivery should be considered. At the same time, it is important to minimize sleep disruption, particularly postpartum. Psychoeducation—ideally begun in the preconception counseling visit—is extremely important for emphasizing the need for postpartum sleep.

Breast-feeding concerns
Data on risks of infant exposure to medications through breast milk are largely limited to case reports and case series. All mood-stabilizing medications have been found to pass into breast milk at varying concentrations.28 If a patient chooses to breast-feed, she should inform her pediatrician of this decision, and she and her support system should be educated about signs of neonatal toxicity. Ideally, the psychiatrist should liaise with the patient’s pediatrician, especially when infants are premature, because the child’s liver metabolism may be immature, leading to higher serum drug levels and in some cases drug accumulation. Encourage patients to consider bottle feeding, either their own breast milk, pumped and stored, or formula. This will allow others to assist with feedings and the patient to have more consistent sleep, which could stabilize mood.

Lamotrigine concentrations in breast milk are highly variable.30 Lamotrigine is processed through glucuronidation, a process that is immature in neonates. One study found serum lamotrigine levels in infants were 23% to 33% of maternal serum levels and milk/plasma ratios were highly variable, ranging from 6% to 147%.30 Infants exposed to lamotrigine in breast milk should be monitored for rash and signs of thrombocytosis, and if clinically indicated, lamotrigine levels should be checked.30 Valproate has a low infant serum/maternal serum ratio; there are rare case reports of hepatotoxicity and thrombocytopenia. Although valproate can be reinitiated because of its lower breast milk concentration, it is not a drug of choice in reproductive-age women because of the many issues described above, including risks during pregnancy, PCOS, and effect on oral contraceptives.

Carbamazepine serum levels in breast-feeding infants range from 6% to 65%; hepatic dysfunction, sedation, and poor feeding have been reported in infants in rare instances.31 Historically, lithium has been considered incompatible with breast-feeding, but recent reports suggest with careful monitoring it may not be contraindicated. In 10 mother/infant pairs, lithium levels in breast milk and infant serum diminished over time, with no adverse neonatal effects.32 However, if an infant does breastfeed, it may be important to monitor thyroid-stimulating hormone, blood urea nitrogen-to-creatinine ratio, and ECG in both mother and infant, especially if the mother is taking high doses of lithium.

The safety of breast-feeding while treated with atypical antipsychotics is largely un-
known. Case reports indicate low transmission of these medications into breast milk.\(^{28}\)

**CASE CONTINUED**

Ms. M is admitted for psychiatric hospitalization because of worsening psychotic symptoms, poor self-care, and persistent thoughts of harming her baby. She agrees to restart aripiprazole, which is titrated to 20 mg/d. Breast-feeding is not pursued. She is discharged in 10 days after she no longer has thoughts of harming her baby, delusions, or psychotic or suicidal ideation. She and her family agree to close supervision by her family and outpatient follow-up.

References

Related Resources

- The Hospital for Sick Children. Pregnancy and breastfeeding resources. www.motherisk.org/women/pregnancyResources.jsp.

Drugs Brand Names

- Aripiprazole • Abilify
- Asenapine • Saphris
- Carbamazepine • Equetro, Tegretol
- Gabapentin • Neurontin
- Iloperidone • Fanapt
- Lamotrigine • Lamictal
- Lithium • Eskalith, Lithobid
- Zonisamide • Topamax

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Clinical Point

Women with BD who choose to breast-feed should be taught to identify signs of neonatal toxicity.

Bottom Line

All women of child-bearing age with bipolar disorder should be counseled about reproductive issues. Medication management should begin with counseling before pregnancy, with the goal of minimizing medications and doses during pregnancy if feasible. Medications with lower risks of teratogenicity include lamotrigine, atypical antipsychotics, and based on newer, prospective studies, lithium. Valproate and carbamazepine should be avoided during pregnancy if clinically feasible.