Bipolar Depression

Pregnancy, Postpartum, and Lactation

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KEYWORDS

• Bipolar depression • Pregnancy • Postpartum • Lactation

KEY POINTS

- Medication management of bipolar depression in pregnancy and lactation is best done by assessing each patient's and family's needs in detail.
- Keeping pregnant patients as psychiatrically stable as possible is the most important principle for clinicians, in conjunction with assessing the various risks and benefits of the medications.
- There is no 100% risk-free situation for patients with psychiatric illness because both illness and medications present potential risks to mother and baby.
- Clinicians serve these patients best by being as transparent as possible about the risk/benefit analysis of each patient's situation with the realization that ultimately the decisions are made by the patient and family.

INTRODUCTION

Pharmacologic treatment of bipolar depression becomes additionally complex during the continuum of pregnancy and the postpartum period for multiple reasons. First, misdiagnosis of bipolar depressive episodes as unipolar depression is common. Mistakenly treating symptoms as if they were part of only a unipolar depression risks triggering manic and psychotic symptoms with documented severe outcomes, potentially including baby harm thoughts, suicide, and (more rarely) infanticide. The diagnosis is often made more difficult due to the inherent disruptions to sleep, energy, and appetite, both before and after delivery. Therefore, treatment begins with an accurate diagnosis, differentiating not only between unipolar and bipolar depressions but also between the subtypes of bipolar disorder (bipolar I disorder, bipolar II disorder, and mixed bipolar disorder). Second, common medications used in bipolar illness

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may cause adverse effects to the developing fetus. Thus, decisions for treatment in the present episode may reverberate for a lifetime, both parents' and child's.

The risks of fetal and maternal exposure to untreated illness must be weighed against the risks of exposure to medications in terms of teratogenicity, obstetric complications, birth outcomes, neonatal outcomes, and neurodevelopmental outcomes. Because of this complexity, clinicians often decide that pharmacologic treatment is incompatible in a pregnant bipolar depressed patient and may recommend discontinuation of bipolar medications. Untreated bipolar depression, however, may also lead to unfortunate outcomes. Furthermore, the impact of the illness and its treatment is not limited to the patients themselves but also includes the fetus or newborn and a patient's other children, spouse, and extended family. These considerations lead to complicated decision-making algorithms for a treating clinician.

Whereas treatment of pregnant women with bipolar disorder has been a neglected area of study in the past, there has been increased attention over the past decade to studies identifying and treating perinatal bipolar disorder.[1–5] With knowledgeable attention to the clinical picture and available evidence, bipolar depression can be managed with a positive outcome.

This article addresses pharmacologic approaches to the treatment of bipolar depression during pregnancy and the postpartum period. The pros and cons of currently available pharmacologic treatments are reviewed and clinical recommendations for the management of medications throughout pregnancy, postpartum, and lactation are provided.

EPIDEMIOLOGY

Bipolar Rates in Women

The National Comorbidity Survey has estimated the lifetime prevalence rate of bipolar disorder at 3.9%[6] among the adult population. In general, the prevalence rate of bipolar I disorder is similar between men and women. According to the World Health Organization,[7] however, the burden of depression is 50% higher in women than in men and is one of the leading causes of disease burden in women across the globe. Women with bipolar disorder tend to experience more depressive episodes during the active phases of illness compared with men.[4,8,9] Furthermore, although the prevalence rate of bipolar I disorder is similar in men and women, the rate of bipolar II disorder is higher in women, and depressive symptoms are 30 times more prevalent than hypomanic symptoms.[4,10–12]

Bipolar Rates During Pregnancy and the Postpartum Period

Pregnancy and the postpartum period is the most vulnerable time in a woman's life for mental health problems or psychiatric hospitalization. This is especially true for women with bipolar disorder. Prospective studies documenting bipolar episodes in pregnancy have reported that up to 70% of women may have an acute mood episode during pregnancy,[13,14] although the postpartum phase may be the most vulnerable.[1] Viguera and colleagues[5] evaluated pregnancy outcomes in 1162 women (2252 pregnancies) with mood disorders (bipolar I disorder – 479 pregnancies, bipolar II disorder – 641 pregnancies, and major depressive disorder [MDD] recurrent – 1132 pregnancies). Of the bipolar women, 23% of them had a mood episode during pregnancy, whereas 52% had an episode during the postpartum period. Depression was the most frequent morbidity. The risk for depression was consistently higher in bipolar patients compared with unipolar depression.[5] Furthermore, there is also evidence that women who have had previous diagnoses of premenstrual syndrome and

premenstrual dysphoric disorder, which identify them as sensitive to hormonal changes, are at higher risk for MDD or bipolar disorder episodes during pregnancy and postpartum.[15]

In a prospective cohort study of 1212 women with bipolar disorder in the United Kingdom, 25% of women with bipolar I had a depressive episode either in pregnancy or postpartum.[16] Similar to previous studies, the onset of mood episodes was less common in pregnancy than during the postpartum period. Women with bipolar II disorder had fewer depressive episodes than bipolar I women, but the rate still remained high. Women with bipolar II, however, were more likely to have depressive episodes during pregnancy and in the late postpartum time compared with women with bipolar I, who were more likely to have episodes of depression in the immediate first 4 weeks postpartum.[16]

Rates of Relapse with Sudden Stopping of Medications

Viguera and colleagues[17] found that after discontinuing lithium, pregnant and nonpregnant women had similar recurrence rates within 40 weeks (52%); however, during weeks 41 to 50 after discontinuation, women in the postpartum period were 2.9 times more likely to have episodes compared with the other women. Furthermore, rapid discontinuation was associated with greater likelihood of recurrences than gradual discontinuation.

In a prospective study of 86 pregnant women with bipolar disorder, Viguera and colleagues[14] found relapse rates of 71% during pregnancy, most of which were depressive episodes. If the mood stabilizer was discontinued, the woman was twice as likely to have an episode, it started 4 times more quickly, and it lasted 5 times as long. Abrupt discontinuation amplified these findings. Recurrence occurred 11 times more quickly than for those who slowly tapered their mood stabilizer.

Risks to Fetus and Neonate with Untreated Maternal Diagnoses of Bipolar Disorder

It is difficult to assess the impact of bipolar disorder, much less untreated bipolar disorder, on fetuses during pregnancy. Most of the data come from registration databases. These are population-based cohorts, as opposed to randomized clinical trials, in which there is little control over other maternal variables, such as smoking, drug use, adverse lifestyles, comorbid conditions, genetic/family history of birth defects, and birth outcomes. Current evidence related to untreated bipolar disorder, however, indicates numerous unfavorable outcomes to mothers and babies These may include placental abruption/abnormalities, preeclampsia, preterm delivery, intrauterine growth restriction, low birth weight, fetal distress, low Apgar scores, congenital defects, stillbirths, and neurodevelopmental difficulties.[18–20] Most of the data used to guide perinatal clinical decision making have been gathered from registries, retrospective chart reviews, and naturalistic cohort and case studies. Safety data about various medications in the perinatal time frame come primarily from the absence of negative reports rather than from the presence of positive studies.

MEDICATIONS

Explanation of the Food and Drug Administration Rating System for Medication Effects in Pregnancy

The current Food and Drug Administration (FDA) teratogenic risk classification system was established in 1979 and, although it has been under proposed revision since 2008, the structure of the current system remains unchanged. The system originated in response to the 1960s thalidomide controversy and rated medications according to static categories of risk A, B, C, D, and X (**Table 1**). In 2004, a lactation risk category

Table 1
Medication impact during pregnancy

Category	Medication	Teratogenic Risk/ Lactation Risk	Comments
Mood stabilizers	Lithium	D/L4	In TM1, slight increased risk of Ebstein anomaly but low absolute risk overall. D/C at start of contractions to avoid toxicity and transient floppy infant. Avoid during lactation if possible due to high excretion in breast milk.
	Carbamazepine (Tegretol)	D/L2	Avoid in pregnancy. Compatible with lactation. Monitor neonate for toxicity.
	Valproate (Depakote)	D/L2	Avoid in pregnancy. Compatible with lactation. Monitor neonate for toxicity.
Anticonvulsants	Gabapentin (Neurontin)	C/NA	Avoid in pregnancy and lactation.
	Lamotrigine (Lamictal)	C/L3	Compatible with pregnancy. Adjust doses in TM2–3. Compatible with lactation with monitoring of neonate due to high excretion in breast milk.
	Topiramate (Topamax)	D/NA	—
Atypical/typical antipsychotics	Lurasidone (Latuda)	B/NA	No known adverse effects in pregnancy. Level of excretion in breast milk unknown.
	Aripiprazole (Abilify)	C/L3	No known adverse effects in pregnancy. Level of excretion in breast milk unknown.
	Risperidone (Risperdal)	C/L3	No known adverse effects in pregnancy. Level of excretion in breast milk unknown.
	Quetiapine (Seroquel)	C/L4	Lowest placental concentration of atypicals. Low excretion in breast milk.
	Olanzapine (Zyprexa)	C/L2	Risk in pregnancy for LGA of fetus. Low excretion in breast milk.
	Ziprasidone (Geodon)	C/L4	No known adverse effects in pregnancy. Level of excretion in breast milk unknown.
	Haloperidol (Haldol)	C/L2	No known adverse effects in pregnancy. Compatible with lactation.
	Chlorpromazine (Thorazine)	C/L3	No known adverse effects in pregnancy and lactation.
	Trifluoperazine (Stelazine)	C/NA	No known adverse effects in pregnancy and lactation.
	Clozapine (Clozaril)	C/L3	Avoid in pregnancy and lactation.

Other Frequently Used Psychiatric Medications During Pregnancy			
Antidepressants	Bupropion (Wellbutrin)	C/L3	Compatible with pregnancy and lactation.
SSRIs	Mirtazapine (Remeron)	C/L3	Compatible with pregnancy and lactation.
SNRIs	Trazodone	C/L2	Compatible with pregnancy and lactation.
	Fluoxetine (Prozac)	C/L2-3	Compatible with pregnancy and lactation
	Paroxetine (Paxil)	D/L2	In TM1, increase in risk for cardiac abnormalities but low absolute risk overall.
	Fluvoxamine (Luvox)	C/L2	Compatible with pregnancy and lactation.
	Citalopram (Celexa)	C/L3	Compatible with pregnancy and lactation.
	Escitalopram (Lexapro)	C/L3	Compatible with pregnancy and lactation.
	Venlafaxine (Effexor)	C/L3	Compatible with pregnancy and lactation.
	Duloxetine (Cymbalta)	C/NA	No known adverse effects in pregnancy and lactation.
	Desvenlafaxine (Pristiq)	C/NA	No known adverse effects in pregnancy and lactation.
Benzodiazepines	Clonazepam (Klonopin)	D/L3	Compatible in low doses with pregnancy and lactation.
	Lorazepam (Ativan)	D/L3	Compatible in low doses with pregnancy and lactation.
	Alprazolam (Xanax)	D/L3	Avoid if possible.
	Temazepam (Restoril)	X/L3	Avoid.
	Sonata (Zaleplon)	C/L3	No known adverse effects in pregnancy and lactation.
	Lunesta (Eszopiclone)	C/NA	No known adverse effects in pregnancy and lactation.
	Ambien (Zolpidem)	C/L3	Compatible with pregnancy and lactation.
	Chloral hydrate	NA	
	Hydroxyzine	NA	

Abbreviations: - D/C, discontinue; LGA, low for gestational age; NA, unknown; M1,2,3 = trimester 1,2,3.

was also added: L1, L2, L3, and L4 (see **Table 1**). Although the intention was noble, the classification system creates difficulties. Some of the difficulties with the current classifications are (1) it generates the misperception that the letters reflect a scale of increasing risk when actually they reflect different risk/benefit balances; (2) the categories do not distinguish between animal and human studies; (3) the categories do not distinguish between the types and severities of the various toxicities; (4) despite more safety data becoming available, the classifications remained static; and (5) commonly, patients and clinicians abruptly discontinue medications based on the classification, which leads to worse pregnancy outcomes. (Only 1 psychotropic has had its classification changed. Bupropion received a new indication for smoking cessation in 1997, leading to a change from category B to C; however, this was based on a new indication not on new data.)

The teratogenic risk categories have remained under revision since 2008. It would eliminate the current categories and instead provide a more clinically relevant framework to manage teratogenic risk and would follow the Motherisk Program model in Canada. The new framework will be based on intrinsic factors, such as scientific evidence in animal and human models, and extrinsic factors, such as clinical conditions and context of care, and provide updated discussions of current data. It will have 3 sections: (1) risk summary, (2) clinical considerations, and (3) therapeutic alternatives and data summary. At this point, however, the old classification system is still in place and provides little guidance for prescribing, which leads to treatment errors by clinicians who have little experience with the perinatal population. Therefore, although it may be helpful to know the classifications of these medications, treatment decisions should be clearly focused on the clinical presentation.

Discussion of Specific Medications and Risks

Pharmacokinetic changes in pregnancy

Pregnancy leads to many pharmacokinetic changes in the body. Understanding these changes is crucial to effectively and safely treat many medical conditions throughout pregnancy. Blood volume gradually increases to a peak increase of 40% to 50% by 32 weeks' gestation.[21,22] This is thought a protective mechanism to prevent hemodynamic instability on delivery; however, this leads to an increase in the volume of distribution of hydrophilic medications, requiring larger doses of such drugs.[21] Serum albumin concentration decreases, which affects medications that are highly protein bound.[21,22] These medications would have significantly higher amounts of unbound drug, requiring a dosage reduction during pregnancy.[21] Afferent and efferent arterioles dilate during pregnancy, leading to a 50% increase in renal blood flow and clearance.[21,22] Increasing renal clearance also increases the elimination rate of drugs that are cleared by the kidneys, producing subtherapeutic concentrations.[21,22] Sodium and water retention is also increased, producing a dilutional effect on plasma sodium concentrations as well as a decrease in peak hydrophilic drug serum concentrations.[21] The progesterone increase during pregnancy causes delayed gastric emptying, which leads to a lower peak concentration as well as longer time to peak concentration of oral medications.[21,22] The metabolism of medications may also be altered in pregnancy.[21,22] Phase I metabolism is affected by alteration of several cytochrome (CYP)450 enzymes.[22] CYP3A4 activity is increased during pregnancy, often requiring dose adjustments in medications metabolized by the enzyme.[21,22] CYP1A2 activity is reduced by 60% to 75%; CYP2C19 activity is reduced by approximately 50%.[22] CYP2D6 is often induced during pregnancy, but the degree of alteration varies on the allele form present.[21,22]

Phase II metabolism is also affected, including urine diphosphate–glucuronyltransferase (UGT) induction.[21,22]

At delivery, plasma volume drops dramatically, predisposing women to toxicity if dosages had been increased throughout pregnancy.[22] Renal clearance and hepatic metabolism return to preconception levels over the course of 1 to 2 weeks.[22–26]

Lamotrigine

Lamotrigine is one of the most widely used mood stabilizers and is one of the most studied among newer agents.[22,24,25,27–29] The alteration of pharmacokinetics in pregnancy has a great impact on women who are on lamotrigine.[22,25,27] Lamotrigine is metabolized by glucuronidation via the UGT pathway in the liver, which is induced during pregnancy.[22,24,25,27,30,31] This induction causes the blood concentration of lamotrigine to be substantially reduced.[22,24,25,27,30] This increase in clearance occurs at pregnancy onset and continues to progress throughout the duration of pregnancy, with clearance increased as much as 330% during the third trimester.[22–25,27] Clearance returns to preconception levels rapidly after delivery, starting within days after delivery, and is complete within 2 to 3 weeks.[22–25,27] The implications of this alteration in clearance could mean some women may not be adequately treated, putting them at an even higher risk for relapse.[31] When used for the treatment of epilepsy, several reports have demonstrated the need to increase lamotrigine doses throughout pregnancy to continue the clinical benefit (absence of seizures), and a more recent observational trial suggested that the same is true when used for bipolar treatment.[25,27,31] Of the 8 women in this trial, 3 required dose increases to continue the clinical benefit, which also suggests that the decreasing concentration of lamotrigine during pregnancy is associated with an increase in symptoms.[31] Although therapeutic drug monitoring for lamotrigine is not standard practice outside of pregnancy, it may be prudent to get blood concentration levels before conception to provide a patient-specific target to aide dose adjustments throughout a pregnancy.[23,27] The American Academy of Neurology supports monthly monitoring of concentrations and consequent dose adjustment during the course of a pregnancy to prevent relapse or postpartum psychosis.[27] This should be followed by rapid de-escalation of the dose back to preconception levels after delivery to prevent toxicity.[23,27,28,31,32] Clinical manifestations of toxicity include blurred vision, ataxia, slurred speech, dizziness, nausea, and malaise.[31,32]

Currently, it is unclear if lamotrigine exposure during pregnancy has an increased risk of major congenital malformations above background rates.[33] The overall risk of major congenital malformations with lamotrigine monotherapy is estimated to be 2% to 3%.[30,33–36] A few reports have suggested a potential increased risk of oral clefts, but other reports and multiple national registries (including 1 from Denmark with more than 830,000 live births) have found no increased risk of major birth defects, including oral clefts.[28–30,32,33,36] Some investigators have also suggested higher rates of major congenital malformations at higher doses (typically more than 200 mg/d), but most reports have not demonstrated a dose-related effect.[23,33,36] Congenital malformation rates have been shown lower with lamotrigine than with valproate and slightly lower than with carbamazepine; however, the rates are significantly higher when lamotrigine is used in combination with valproate compared with lamotrigine monotherapy (10.8% compared with 2.8%).[24,30,33,36] No evidence has suggested an increase in adaptive, emotional, or behavioral functioning or increases in neurodevelopmental disorder diagnoses.[33] Because of the extensive evidence that suggests safety during pregnancy, lamotrigine seems among the safest choices for bipolar disorder management during pregnancy.[33] It is FDA pregnancy category C.[37]

Lamotrigine use during lactation is generally considered acceptable; however, the drug is excreted in breast milk, and infant levels can be up to 50% of the maternal concentration.[28,32] Caution is advised when using high doses of lamotrigine in nursing women as well as in those with small or preterm infants.[32] Infants should be monitored for toxicity, because 1 case report of apnea has been reported.[28]

Clinical pearls

- Lamotrigine clearance is dramatically increased throughout the course of pregnancy. Clearance returns to normal rapidly after delivery.
- Drug concentrations should be monitored closely during pregnancy to ensure continued clinical benefit, and the dosage should be adjusted accordingly. Dosage should be reduced after delivery to prevent toxicity.
- Evidence supports the use of lamotrigine during pregnancy, with most data suggesting no increased risk of congenital malformations.

Valproate

Valproate has demonstrated an increased risk of major congenital malformations and birth defects when used during pregnancy, particularly during the first trimester.[28,33,36] The overall incidence of major congenital malformations is as high as 11%.[30,33,36] Valproate exposure has shown to increase in neural tube defects, spina bifida, craniofacial abnormalities, hypospadias, cardiac defects, and limb defects, and this is a dose-dependent effect (more malformations over 1000 mg/d).[28,30,33,35,36] Folic acid supplementation is recommended starting before conception and throughout pregnancy in hopes of reducing neural tube defects.[28,35,38,39] Conflicting evidence exists regarding this protective benefit, but supplementation is still recommended.[35,38] In 2011, the FDA released a Drug Safety Communication reporting that children exposed to valproate in utero are at increased risk for lower cognitive test scores compared with children exposed to other antiepileptic drugs.[40] Studies have also shown worse neuromotor functioning, worse adaptive and emotional/behavioral functioning, and an increase in autism and autism spectrum disorders in children exposed to valproate in utero.[28,33] Because of the numerous risks associated with use, valproate is FDA pregnancy category D when used for any indication outside of migraine prophylaxis, in which case it is category X (risks clearly outweigh the benefit for this indication).[41]

Valproate is a highly protein-bound drug, and its efficacy is due to the unbound drug that crosses the blood-brain barrier.[22] Clearance of valproate may increase by the end of the third trimester, which can result in reduced serum concentrations.[22] It is has been suggested, however, that the unbound drug concentration remains unaffected.[22] Valproate protein binding decreases during pregnancy, which could explain why free levels may remain unchanged.[22] If a decision is made to use valproate in pregnancy, consider monitoring both free and total valproate levels.[22]

Valproate is excreted into breast milk in small amounts, but there have been case reports of infants having thrombocytopenia and anemia as a result of exposure.[34,36,42] Although most investigators consider valproate use compatible in lactation, the manufacturer recommends caution be used if a woman is breastfeeding while taking valproate.[28,33,41]

Clinical pearls

- Valproate should generally not be used during pregnancy due to well-documented dose-dependent teratogenic risks associated with use.
- Most commonly, valproate use during pregnancy is associated with neural tube defects and spina bifida.

- *Folate supplementation is recommended before conception and throughout pregnancy.*
- Valproate is generally considered compatible with lactation.

Carbamazepine

Carbamazepine exposure during pregnancy is not as teratogenic as valproate exposure.[33] The incidence of congenital malformations is noted to range from 2.2% to 6%.[30,33,35,36] Carbamazepine, like valproate, most commonly increases the risk of neural tube defects and spina bifida.[28,33,36,38] As with valproate, folate supplementation is recommended before conception and throughout pregnancy to minimize these risks, although there are not many data to support this recommendation.[28,30,33,35,38,39] Carbamazepine also has been shown to increase the risk of cardiac abnormalities, cleft palate and other craniofacial defects, and hypospadias.[28,30,33,36,38] Exposure in utero has been associated with higher rates of low birth weight, growth retardation, vitamin K deficiency, and coagulation abnormalities as well as lower Apgar scores.[28,33,35,39,43] The long-term risks of carbamazepine exposure in utero are not clear. One prospective study has demonstrated a dose-dependent effect of worse verbal performance in 3-year-old children who were exposed to carbamazepine during pregnancy; at 6 years of age, this difference was no longer detected.[33] The FDA has determined carbamazepine to be pregnancy category D.[37]

Clearance of carbamazepine may increase during pregnancy, although evidence is conflicting.[22] Some studies have suggested a decline in total carbamazepine concentration during the second and third trimesters, but other studies have found no significant change throughout pregnancy.[22] The total concentration of carbamazepine may decline, but it seems that the unbound concentration may not change.[22,25] If a decision is made to use carbamazepine during pregnancy, both free and total drug levels should be monitored.[22]

Excretion of carbamazepine into breast milk is low, and lactation is generally considered compatible with carbamazepine use.[28,33,34,42] Transient hepatic dysfunction and poor suckling have been reported in infants exposed to carbamazepine through breast milk, so caution should be used.[36,39,42]

Clinical pearls

- Carbamazepine is most commonly associated with neural tube defects and spina bifida, although at rates lower than seen with valproate.
- *Folate supplementation is recommended before conception and throughout pregnancy.*
- *Carbamazepine is generally considered compatible with lactation.*

Oxcarbazepine

Oxcarbazepine does not have much safety data regarding use in pregnancy.[41] Denmark's Medical Birth Registry reported that among 393 pregnancies exposed to oxcarbazepine during the first trimester, there were 11 birth defects (2.9%).[44] Once adjusted for exposure to older antiepileptics, they concluded there was no significant increase in birth defects with exposure to oxcarbazepine above background rates.[44] More evidence needs to be established to draw conclusions about the safety in pregnancy.[45] At this time, oxcarbazepine is labeled FDA pregnancy category C due to the unknown risks.[45]

The pharmacokinetic alteration of oxcarbazepine in pregnancy is better established.[25] Oxcarbazepine is cleared mainly via glucuronidation.[24,25] Lamotrigine is also cleared through this pathway, which is significantly altered during pregnancy.[25] Small studies have confirmed that, like lamotrigine, oxcarbazepine concentrations

decrease during pregnancy.[24,25] The decline is not as great, however, as that of lamotrigine, only a 30% to 40% decline.[25] Clearance seems to return to the preconception rate quickly after delivery.[25]

Oxcarbazepine is excreted into breast milk in small amounts, but evidence is lacking regarding the safety.[45] One case report of a women who switched to oxcarbazepine on delivery and breastfeeding an infant reports no adverse effects to the child through the age of 5.[46] Further studies are needed to establish the safety and risks associated with lactation and oxcarbazepine use.

Clinical pearl

- The risks of oxcarbazepine use in pregnancy and lactation are largely unknown at this time.

Lithium

Lithium remains one of the most efficacious agents used to manage bipolar depression and mania.[47,48] Historically, it was thought that lithium carries a 400-fold increased risk of cardiac defects, including Ebstein anomaly, based on retrospective data through the International Register of Lithium Babies.[33,49] More recent data are conflicting regarding the risk of Ebstein anomaly and other congenital malformations. Observational data have suggested a lower risk for Ebstein anomaly, 0.05% to 0.1%, after exposure to lithium in the first trimester.[28,33–35,38,50,51] This is still an increase from the background rate of 0.005%.[28,33,35,51] In addition, a prospective, observational study of 183 women exposed to lithium during their pregnancy found no significant difference between lithium exposure and no exposure regarding the risk of congenital anomalies, including persistent cardiovascular anomalies.[52] When spontaneously resolving cardiovascular anomalies were included, however, the difference was significant.[52] Alternatively, 1 meta-analysis found no significant increase in the risk of congenital malformations, including Ebstein anomaly, after in utero exposure to lithium.[48] The investigators caution that the sample size was small, however, and larger studies are needed before conclusions can be drawn.[48] A decision to use lithium during pregnancy must consider the risks of untreated mood instability and the potential risks the medication poses to the fetus.[38,47,49] If possible, avoiding exposure until after the eighth week of gestation is ideal to avoid exposure during cardiac formation.[38,39,50] At this time, evidence supports the recommendation to obtain a fetal echocardiogram and level-2 ultrasound during the second trimester in women who received lithium during the first trimester.[28,33–36,39,47,51,52] The FDA has given lithium a pregnancy category D.[37]

Infants exposed to lithium in utero have a higher risk of being large for gestational age as well as an increased risk of prematurity; however, this could be due to the bipolar disorder itself.[33,35,51] Neonatal adverse effects after lithium exposure include polyhydramnios, nephrogenic diabetes insipidus, thyroid dysfunction, floppy infant syndrome, and arrhythmias.[28,33,34,36,39,47,50,51] Neonatal adaptation syndrome has also been reported.[33] Neonatal adaptation syndrome includes hypotonicity, muscle twitching, dyspnea, feeding difficulties, arrhythmias, poor suckling, and cyanosis.[33] This syndrome typically resolves in 1 to 2 weeks and is thought associated with higher maternal lithium concentrations, possibly neonatal toxicity.[33] Because of the potential risk for neonatal toxicity, some investigators suggest stopping or halving the dose of lithium 24 to 48 hours before a planned delivery or at the onset of labor of an unplanned delivery.[33,39] Twice-daily dosing of lithium at the lowest effective dose could also be considered to keep peak serum concentrations lower.[38,39,47] Lithium should be restarted after delivery, once stable.[33] At this time, no data suggest

an increased risk of neurodevelopmental adverse effects, but data remain limited.[28,33,35,38,51]

Lithium is completely eliminated by the kidneys, and clearance is increased during pregnancy.[22,27,51] Like lamotrigine, this could lead to subtherapeutic levels and put women at risk for relapse.[22,27,36] Clearance returns to preconception levels rapidly on delivery, putting women at risk for toxicity in the postpartum period.[22,27,51] Vascular volume drops as much as 40% at delivery, which also increases women's risk of toxicity.[22,27] Holding lithium for 24 to 48 hours before delivery (as discussed previously) has also been suggested to reduce the risk of maternal toxicity.[22,27,28,36,39] Hydration should be maintained throughout delivery, and some women may require intravenous fluids, in particular those with extended labor.[22,28,34] Therapeutic drug monitoring is recommended monthly during pregnancy, weekly during the last month before delivery, and on admission for delivery.[27,34,47,51] The preconception lithium dose can be resumed on delivery with lithium levels checked every few days until normalized.[22,27,28,47]

Lithium is excreted in breast milk, and infant levels have been reported as high as 50% of the maternal level, with most investigators suggesting a range of 20% to 30%.[28,39,51,53] Adverse effects have been reported in infants exposed to lithium through breast milk, although serious events are rare.[36,51] Lethargy, hypothermia, hypotonia, cyanosis, and ECG abnormalities have been reported.[28,36,42,51] Dehydration increases an infant's risk for toxicity and adverse effects as well as the decreased clearance of a premature infant.[39,51] If a decision is made to breastfeed while the mother is taking lithium, frequent monitoring of lithium levels, thyroid function, and renal function is indicated.[28] In general, breastfeeding is not recommended for women taking lithium.[33,42,51]

Clinical pearls

- Lithium exposure during the first trimester increases the risk of fetal cardiac abnormalities. A fetal echocardiogram and level-2 ultrasound are recommended during the second trimester.
- To reduce the risk of toxicity in both mother and infant, lithium doses should be held or reduced around the time of delivery.
- Lithium use is typically not considered compatible with breastfeeding.

Atypical antipsychotics

Atypical (second-generation) antipsychotic use has increased in pregnancy; however, safety data remain limited.[33,54] The evidence currently suggests a low risk of major congenital malformations, with rates ranging from 0.9% to 2.9%.[33] Few reports have suggested an increased risk of cardiovascular defects, such as atrial or ventricular septal defects, but the majority of evidence has found no increased risk of congenital malformations with the atypical antipsychotics.[33,34,49,55,56] The most consistent adverse effect during pregnancy is the weight gain that is commonly associated with use.[28,33,55,56] This weight gain not only increases the risk of obesity, gestational diabetes, hypertension, and metabolic syndrome in the mother but also may increase the likelihood of the infant being large for gestational age compared with typical (first-generation) antipsychotics or placebo.[33,37,55,56] The FDA released a Drug Safety Communication[57] in February 2011 stating the potential risk of withdrawal symptoms and extrapyramidal signs after delivery in infants whose mothers were treated with atypical antipsychotics during the third trimester.[28,33,57] Withdrawal symptoms infants may demonstrate include abnormal muscle tone, tremor, agitation, difficulty breathing, and difficulty feeding.[57] The FDA also reinforces that patients

should not stop taking these medications if they become pregnant without talking to their physician, and they should not be stopped abruptly.[57]

Data are limited on the long-term outcomes of infants exposed to atypical antipsychotics in utero. One prospective controlled study suggests decreased neuromotor performance at 6 months of age after exposure to atypical antipsychotics compared with children exposed to antidepressants or no psychotropic medications.[33] Another study reports delayed development at 2 months of age, but this delay had resolved by 12 months.[28]

Most of the atypical antipsychotics carry an FDA pregnancy category C label with the exception of clozapine and lurasidone, both of which are category B.[37,58]

Atypical antipsychotics are excreted into breast milk in variable amounts.[28] Serum concentrations are typically considered low in the infant, but adverse effects have been reported.[28] The benefits versus risks of continuing an atypical antipsychotic should be evaluated when deciding to use the drug while breastfeeding. The smallest effective dose should be used, and infants should be monitored closely.[28]

Olanzapine Of the atypical antipsychotics, olanzapine is the most studied, and, as a result, some investigators suggest it could be used as a first-line therapy during pregnancy.[59] Animal studies using doses 7 times the maximum human doses suggested no teratogenicity.[55] Most human data have also failed to show an increased risk of birth defects.[36,55,59,60] The rates for spontaneous abortion, stillbirth, prematurity, and major malformations have been reported as consistent with background rates.[36,60] Few reports have suggested low birth weight with olanzapine use; however, a majority of data suggest an increased risk for weight that is large for gestational age.[33,36,60] Olanzapine has the most weight gain associated with use out of the atypical antipsychotic class, which could lead to these metabolic disturbances.[36,39] Olanzapine is excreted in breast milk, and infant doses have been reported to be 0.3% to 4% of the maternal dose.[39]

Quetiapine Most evidence on quetiapine is in the form of case reports and 1 review that included 36 exposures to quetiapine during pregnancy, and no adverse effects were reported.[33] In 1 case report, a woman used quetiapine during her pregnancy and then breastfed the infant with no adverse effects.[36] Animal studies have suggested no increased risk of malformations.[55] The manufacturer's international database, including outcomes for approximately 300 pregnancies, has reports of 14 malformations with no patterns; it is noted that 11 of these women were taking other medications or there was only limited information provided.[55] Quetiapine has the lowest placental transfer of the atypical antipsychotics; however, it has the greatest incidence of sedation, which could be an issue for women trying to be alert to care for their child after delivery.[39] If a woman is clinically stable on quetiapine prior to conceiving, continuing on therapy is a reasonable treatment strategy.[59] Quetiapine is excreted in breast milk, and infant doses have been reported to be 0.09% to 0.43% of the maternal dose.[39]

Lurasidone Currently, the safety data of lurasidone use in pregnancy is unknown; however, animal studies have not demonstrated a teratogenic effect.[33,58] Although lurasidone was not approved at the time and as a result not included in the 2011 FDA Drug Safety Communication, the risk for withdrawal symptoms and extrapyramidal signs after delivery also applies to infants exposed to lurasidone in utero.[58] The amount of drug excreted in breast milk is not known at this time, and breastfeeding is not recommended with use.[58]

Clinical pearls

- Atypical antipsychotics have not shown an increased risk of congenital malformations. The most common effect on infants is a higher likelihood of large weight for gestational age.
- Infants exposed to an atypical antipsychotic during gestation could have withdrawal symptoms or extrapyramidal signs after delivery.
- Breastfeeding is typically not recommended with use of an atypical antipsychotic.
- If a woman is clinically stable on an atypical antipsychotic, the benefits of mood control and risks of relapse and fetal effects must be evaluated if she becomes pregnant.

Electroconvulsive Therapy

Overall, electroconvulsive therapy (ECT) is considered one of the most effective treatments for both MDD and bipolar disorder, with 50% to 75% remission rates. The most recent systematic review of case studies of ECT in pregnancy concluded that contrary to the prior systematic review, ECT should remain an option of last resort for pregnant women.[61] This article looked at 67 studies, a total of 167 cases, and noted that in 29% of cases there were adverse fetal effects, such as fetal heart rate slowing, uterine contractions, and premature labor during a mean of 9.4 administered treatments, half of them in the second trimester. There was a fetal mortality rate of 7.1%. Given the changes in administration of ECT over time, there was no reliable monitoring of fetal effects during and after ECT treatments. This is in contrast to a previous systematic review of 57 reports, 336 cases from 1941 to 2007, which reported only 11 cases of adverse fetal effects and suggested it as a safe alternative to the adverse medication effects needed to treat bipolar disorder.[62]

Despite the uncertainty that ECT is as effective in bipolar depression as it is in unipolar depression, a meta-analysis in 2012 stated that ECT is nevertheless an important treatment consideration for women with bipolar depression during pregnancy due to the risks of switching to mania when using selective serotonin reuptake inhibitors (SSRIs) for depressive symptoms.[63] This article looked at 6 studies of 1105 patients, of whom 316 had ECT for bipolar depression and showed remission rates of 50.9% and 53.3% for unipolar versus bipolar depression. Bipolar patients required fewer ECT treatments. This is important information to consider because treatment of bipolar depression with antidepressants can lead to acute mania, which can be even more difficult to manage during pregnancy.

Psychotherapy

There are few studies evaluating the effectiveness of psychotherapy for treating bipolar disorder in pregnant patients. Richards and Payne[64] reviewed alternative treatments to medications, including psychotherapies, light box therapy, exercise, and nutritional/herbal supplements. They noted that many of these treatments have been validated in the use of bipolar illness or as augmentation strategies, but data in pregnant bipolar patients are limited to nonexistent. Bipolar-specific cognitive behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, group psychoeducation, and systematic care management have all shown efficacy as therapeutic approaches for managing bipolar depression or preventing relapses. For pregnant bipolar depressed women, several researchers have suggested that these evidence-supported psychotherapies are likely beneficial as adjuncts to pharmacotherapy in dealing with psychosocial stressors that are known to have disruptive effects on illness course and increase risk of relapse.[33,65] This may be

especially important when dealing with disruption of sleep and wake schedules or daily social rhythms.[66]

CLINICAL GUIDELINES

First and foremost, the goal is to keep pregnant/postpartum women functioning at their best. This helps in all other realms with both maternal and neonatal outcomes (short and long term), with their other children, with their relationships, with their socioeconomic state in being able to maintain a job if needed, and with prevention of child abuse and neglect.

Secondly, this often necessitates involvement of more support by a spouse/significant other and family than at other times in a patient's life. This may also be a time in a patient's life when psychiatric intervention increases a patient's feelings of shame, humiliation, and worry that the pregnancy will seem imperfect. Thoughtful attention to these issues by a clinician ultimately leads to better adherence and communication with patient and family around the treatment plans.

Third, it is important to appropriately contextualize patient concerns. Clinicians may explain that major and minor episodes of depression are common during pregnancy and the postpartum period for all women, occurring in approximately 10% to 20% of the general population. Therefore, what they are experiencing is something that is shared with many other patients. Furthermore, clinicians may also explain that helpful treatments are available and that prevention and contingency planning are also important.

Fourth, the time when a patient is in the preconception phase is an excellent opportunity to review and potentially reorganize the medication regimen to establish the highest benefit and lowest risk situation before the patient attempts conception.

Fifth, complete a careful and thoughtful initial assessment. Clinicians start with a detailed review of the history, symptoms, and medication trials, keeping in mind that an assessment for undiagnosed bipolar illness is critical. Clinicians should include a review of all additional exposures to the pregnancy (ie, other medications, alcohol use, cigarette use, other substance use, interpersonal partner violence, socioeconomic stressors, personal and family history of birth defects, and developmental syndromes). The review of all past medication trials should include doses and duration and benefits and adverse effects.

Finally, the treatment plan that results from the assessment may occur under either urgent or nonurgent clinical circumstances. In either case, involving the appropriate supportive individuals in a patient's life and nonpharmacologic interventions are critical.

SUMMARY

In summary, medication management of bipolar depression in pregnancy and lactation is best done by assessing each patient's and family's needs in detail (**Box 1**). Keeping pregnant patients as psychiatrically stable as possible is the most important principle for clinicians, in conjunction with assessing the various risks and benefits of the medications. Unfortunately, there is no 100% risk-free situation for patients with psychiatric illness because both illness and medications present potential risks to mother and baby. This is often the most difficult and hard to accept reality for these patients, families, and clinicians. Clinicians serve these patients best by being as transparent as possible about the risk/benefit analysis of each patient's situation with the realization that ultimately the decisions are made by the patient and family.

Box 1
Clinical pearls for pharmacologic treatment of perinatal bipolar depression

- Keep mothers stable—the best prevention of postpartum mood change is to maintain psychiatric stability during pregnancy and through delivery and the postpartum year.
- In all evaluations, ask careful questions about hypomanic, manic, and depressive symptoms. More often patients seek help for depression not elevated mood.
- Pregnancy is not the time to experiment with new medications—each new medication adds an exposure. If patient has a preconception period of time, consider medication changes at that time and contingency plans.
- Discuss risk and benefits of both treatment and illness on patient, fetus, and family. The patient and family ultimately make the decision.
- Be familiar with fetal development and windows of risk during pregnancy.
- Treatment decisions during pregnancy must be made in conjunction with a treatment plan for the postpartum period and lactation.
- Teratogenic classifications and lactation classifications should be considered but with the understanding that they provide incomplete information.
- Consider the impact of illness on the patient's other children, spouse, and family.
- Patients and families do best when they can make informed decisions based on comprehensive discussions with a clinician about risks and benefits.
- Engage patient and family in postpartum planning around child care, patient self-care (including sleep), and lactation.
- When using lithium, discontinue medication when contractions start to prevent maternal and fetal toxicity after delivery.
- If a patient is on an antiepileptic drug before conception, consider use of atypical antipsychotics for the first trimester; if possible, return to the antiepileptic drug in second and third trimesters.
- If lithium or paroxetine has been the most effective medication for a patient, consider changing to a lamotrigine or atypical antipsychotic for first trimester.
- Obtain results of TM1 ultrasound to confirm normal fetal development.
- Discuss patient/spouse/family religious beliefs and beliefs about abortion and miscarriage.

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