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BIPOLAR DISORDERS (R HIRSCHFELD, SECTION EDITOR)

Lithium Use and Non-use for Pregnant and Postpartum Women with Bipolar Disorder

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Abstract

Purpose of Review Despite being recognized as a first-line treatment for bipolar disorder, there is still inconsistent use of lithium in perinatal populations. This article will review data regarding lithium use during the peripartum and provide management recommendations for general psychiatric clinicians.

Recent Findings In contrast to prior data, recent studies indicate that lithium use in pregnancy is associated with either no increased malformations risk or a small increase in risk for cardiac malformations including Ebstein's anomaly. Limited data also show no significant effect on obstetric or neurodevelopmental outcomes. Data regarding infant lithium exposure via breastmilk remains limited.

Summary Lithium is currently under-prescribed and is an important treatment for women with bipolar disorder in pregnancy and the postpartum. Clinicians must weigh the risk of lithium treatment versus the risk of withholding or changing lithium treatment when managing bipolar disorder in this population.

Keywords Lithium · Pregnancy · Postpartum · Psychosis · Bipolar · Breastfeeding

Introduction

Bipolar disorder has a lifetime prevalence greater than 1% in the general population, and in women, bipolar disorder typically presents during child-bearing years (Gentile [1]). In the peripartum period, women with bipolar disorder are at especially high risk for recurrence, with 40–70% suffering an episode postpartum (Reich, Winokur [2] van Gent, Verhoeven [3] Wisner et al. [4], Viguera et al. [5••], Maina et al. [6], Wesseloo et al. [7]). Because bipolar disorder is a chronic disease, psychopharmacologic treatment is typically continuous (Grunze et al. [8]) and lithium is considered the most effective treatment for maintaining mood stability (Geddes, Miklowitz [9]). Even with recent changes in prescribing practices for bipolar disorder, including increased use of second generation antipsychotics, lithium remains frequently prescribed with 26.8% of Danish patients with bipolar disorder filling at least one prescription in 2012 (Bjorklund et al. [10]). Despite this, a majority of women with bipolar disorder either choose to self-discontinue lithium or cannot find a provider who will prescribe it during their pregnancy (Broeks et al. [11], McCrea et al. [12]). A recent Danish study showed only 16% of women with bipolar disorder redeemed at least one lithium prescription during pregnancy and only 6.3% used lithium in the third trimester (Broeks et al. [11]). A smaller study from the UK showed that in women continuously prescribed lithium 3 months before pregnancy, only 33% continued receiving prescriptions beyond the 6th week of pregnancy (McCrea et al. [12]). Although lithium has been the gold standard treatment for bipolar disorder and has been recommended as the first-line mood stabilizer during pregnancy (Larsen et al. [13]), there remains a high variability of information and recommendations regarding its use in the perinatal period.

Much of the inconsistency is based on historical data which overstated lithium's teratogenic risk. In the late 1960s, a registry for fetal teratogenesis reported a 400-fold increase in the risk of Ebstein's anomaly with lithium use during pregnancy, which lead to recommendations that

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it be avoided (Weinstein, Goldfield [14] Goldfield, Weinstein [15], Nora et al. [16]). However, these recommendations did not take into account statistical limitations of registry studies including a bias favoring positive associations. Additionally, prior to recent FDA reforms in drug safety rating procedures, lithium was labeled a category D medication indicating evidence of human fetal exposure risk without providing appropriate context as to its benefits (Gruber [17]). More recently, multiple experts in the treatment of peripartum bipolar disorder have recognized the essential role that lithium plays in managing bipolar disorder during the peripartum (Clark, Wisner [18], Yonkers et al. [19], Osborne [20], Poels et al. [21••]). Yet, this practice has not yet extended to the broader field. Clinicians must be able to make evidence-based decisions regarding lithium use in pregnant and postpartum women which requires both a more accurate understanding of fetal exposure risks as well as the risks of not using the medication in women who may otherwise benefit from it.

Risks Related to Bipolar Disorder during the Perinatal Period

Since the 1980s, multiple researchers have inquired as to how pregnancy affects the natural course of bipolar disorder in women. Kendell et al. noted that there was a low rate of psychiatric hospitalization of pregnant women with bipolar disorder, but that the rate of hospitalization increased significantly within 3 months of parturition (Kendell et al. [22]). While compelling in its description of risk for severe episodes in the peripartum, use of psychiatric hospitalization as a primary outcome measure may not have been sensitive enough to detect less severe mood relapse and therefore was a major limitation of this study. Later, Grof et al. retrospectively compared intraindividual relapse rates during 9-month blocks pre, intra, and post-partum in a sample of 28 pregnant women with lithium-responsive bipolar disorder and found that the pregnancy block had significantly fewer and shorter episodes than either comparison block (Grof et al. [23]). This study also had significant limitations including a small number of cases, retrospective design, and narrow inclusion criteria.

Multiple more recent studies suggest that pregnancy has no effect on relapse rates of mood disorders, and that in fact, lithium discontinuation itself may contribute to risk of recurrence (Viguera et al. [24•] Baldessarini et al. [25], Llewellyn et al. [26]). Stevens and colleagues recently published a review article of 22 studies to better understand the recurrence rates of mood disorders in pregnancy, and determined that it is still uncertain whether the course of depression or bipolar disorder is influenced by pregnancy. They did find that pregnant women with major depression or bipolar disorder on maintenance pharmacotherapy had a significantly lower risk of mood episodes during pregnancy ($p < 0.01$) (Stevens et al. [27]). This group also found that in six studies that specifically looked at lithium use and pregnancy (total $n = 200$), there was a 66% relative risk reduction of a mood episode during pregnancy in women with bipolar disorder who continued lithium maintenance during pregnancy versus those that discontinued lithium (Stevens et al. [27]). For women with bipolar disorder who discontinued lithium because of pregnancy compared with women with bipolar disorder that discontinued lithium for other reasons, Viguera and colleagues found that there was a similar rate of mood episode recurrence during pregnancy or equivalent period, but that post-partum recurrences were nearly 3 times more frequent than recurrences in the non-pregnant women during that equivalent period (Viguera et al. [24•]). One could conclude that the postpartum time period itself increases vulnerability, and perhaps prophylactic mood stabilization may prevent both antepartum and postpartum mood episode relapses (Poels et al. [21••]).

Maternal bipolar disorder has significant clinical impact on both mother and fetus throughout the peripartum. Mood episodes during pregnancy are associated with increased maternal morbidity and mortality due to related alcohol, tobacco, and illicit-substance use, poor self-care, and suicide (Nguyen et al. [28], Orsolini et al. [29], Taylor et al. [30]). Further, mood episodes in pregnancy are associated with poor prenatal care in the peripartum period and compared with controls, pregnant women with bipolar disorder are more likely to experience placental abnormalities and antepartum hemorrhages (Jablensky et al. [31]). Maternal bipolar disorder and affective psychosis have also been associated with preterm birth, low birthweight, and small for gestational age fetuses (Lee, Lin [32], Khan et al. [33], MacCabe et al. [34].)

Maternal bipolar disorder has also been linked with difficulties with maternal infant bonding and inability to care for the baby (Khan et al. [33], Viguera et al. [5••], Jones et al. [35]). Postpartum, women with bipolar disorder have at least a 1 in 5 risk of suffering a mood disorder recurrence 1–2 weeks following delivery and approximately 1 in 2 risk of experiencing a mood episode up to 6 months postpartum (Munk-Olsen et al. [36], Jones, Craddock [37], Di Florio et al. [38]). Women who discontinue mood stabilizers during pregnancy have a particularly high incidence of relapse of any mood episode, especially depressive or mixed states with the rate of relapse as measured by Viguera et al. being 85.5% for women who discontinue compared to 37% for those who remained on their medication (Viguera et al. [5••]). Severity of illness, characterized by factors such as early age of onset and number of prior illness recurrences, predicted illness recurrence (Viguera et al. [5••]), as well as a perinatal history of depression or affective psychosis (Di Florio et al. [39]). Women with bipolar disorder are 100-times more likely to develop postpartum psychosis, the most severe postpartum mood disorder, as compared with women without a psychiatric history. A consistent

relationship has been described between postpartum psychosis and bipolar disorder, including evidence from genetic studies (Di Florio et al. [40]), suggesting it is a variant of bipolar disorder and not a primary psychotic disorder (Bergink et al. [41••]). Chronically mentally ill women are more likely to commit infanticide due to postpartum stressors or symptom exacerbation (Pariser [42], Spinelli [43]) and postpartum psychosis is associated with increased risk of infanticide and suicide (Kendell et al. [22]).

Lithium and Obstetric/Neonatal Risks

Lithium readily and completely crosses the placenta which results in fetal exposure to lithium during the antenatal period. The potential teratogenicity of lithium therapy has been investigated since the 1960s, with a focus on its effects on fetal organ development, specifically cardiac development. Although previous data estimated a 400-fold increase in the risk of Ebstein's anomaly (Nora et al. [16]), more recent data has shown that the risk of this malformation of the tricuspid valve that leads to regurgitation and atrialization of the right ventricle, is much lower than previously described (McKnight et al. [44]). In 2014, Diav-Citrin and colleagues [45••]) in their prospective observational study comparing 183 lithium exposed pregnancies to disease-matched nonteratogenic-exposed pregnancies found no difference in major malformations including cardiovascular anomalies after excluding malformations that spontaneously resolved. In 2017, Patorno and colleagues' registry-based cohort study ([46••]) compared 663 women who were exposed to lithium during pregnancy to an unexposed group of pregnant women and found a dose-dependent increased risk of cardiovascular malformations with first trimester lithium exposure compared to controls. This study found the risk of cardiac malformations to be approximately one additional case per 100 live births in the exposed group, and found no association between lithium exposure and noncardiac malformations. In a 2018 large international meta-analysis, Munk-Olsen and colleagues [47••] compared 727 lithium-exposed pregnancies to 21,397 pregnancies in women with mood disorders but not exposed to lithium and showed that there was no association between lithium exposure during pregnancy and major pregnancy complications or delivery outcomes. There was a small increased risk of overall singular and combined structural defects, syndromes, sequences, and associations—such as cardiovascular defects, neural tube defects, hypospadias, and epispadias (OR 1.71), but they did not find any association for major cardiac malformations, including atrial and atrioventricular septal defects and Ebstein's anomaly. Importantly, although this was a relatively large sample, the study still lacks the power to demonstrate a less robust positive association between lithium use and very rare outcomes such as Ebstein's anomaly as there were only 16 observed cases of cardiac malformations in the entire cohort. When considered together, these recent studies indicate that the absolute risk of major malformations for lithium-exposed neonates may be higher than the general population (pooled prevalence 7.4% versus 4.3%), but substantially smaller than previously described.

The data regarding neonatal outcomes in lithium-exposed pregnancies as compared with non-exposed pregnancies is mixed. In regards to preterm birth, the most recently published meta-analysis of six studies with conflicting conclusions found no difference in the lithium exposed versus unexposed groups (Munk-Olsen et al. [47••]). Multiple studies have found associations between high infant lithium levels and lower APGAR scores at 1 min, longer hospital stays and increased NICU admissions (Newport et al. [48], Munk-Olsen et al. [47••]). There have also been case reports describing neonatal lithium toxicity, kidney impairment, jaundice, respiratory difficulties, congenital goiter, and thyroid problems (Frassetto et al. [49], Newport et al. [48], Krause et al. [50], Grandjean, Aubry [51], Kozma [52]). However, these findings were not replicated in larger controlled studies.

Unfortunately, adverse pregnancy outcomes are associated with bipolar disorder whether it is treated or untreated (Boden et al. [53]), and therefore, studies investigating this association are susceptible to confounding by indication. Frayne and colleagues ([54]) conducted a cohort study of 33 women with severe mental illness who were prescribed lithium during their pregnancy, irrespective of whether they continued or discontinued lithium. The cohort was a high-risk obstetrics group with high rates of smoking, medical comorbidities, and antenatal complications. Compared with those women in the study population who stopped lithium, those who remained on lithium throughout pregnancy had increased rates of fetal ultrasound abnormalities like abdominal circumference > 90th percentile which may have been secondary to polyhydramnios (Frayne et al. [54]). Gestational age, APGAR scores, and rates of NICU admission were not affected by psychotropic medication management for women with bipolar disorder, and a difference in head circumference became not significant after adjusting for confounding variables (Wisner et al. [55]). Patorno et al. found that there was an increased risk of neonatal readmission for the lithium exposed group 28 days after delivery which became no longer significant when they used a control group of patients who only had bipolar disorder (Patorno et al. [46••]). Munk-Olsen and colleagues' large meta-analysis showed no increased risk compared to disease matched controls of pregnancy complications or effect on delivery outcomes including preeclampsia, gestational diabetes, fetal distress, postpartum hemorrhage, or cesarean section (Munk-Olsen et al. [47••]). Cohen et al. also found no increased risk of preeclampsia, placental abruption,

growth restriction, or preterm birth with mood stabilizer exposure, including lithium (Cohen et al. [56]).

Lithium and Neurodevelopmental Outcomes

There are a limited number of clinical studies looking at neurodevelopmental outcomes following in utero exposure to lithium and many contain methodological limitations including lack of a control group, use of subjective assessments, and inadequate control of confounding variables. Overall, growth, behavior, and general development have been found to be in the normal range, and although the data is reassuring it is also limited. Effects on neurodevelopment have only been looked at up until 15 years of age and lithium exposure in utero could affect development beyond this (Feldman [57]). Van der Lugt et al. [58] used standardized assessments as well as parental report to examine 15 children aged 3–15 years who had been exposed to lithium during pregnancy for bipolar disorder. Intelligence quotient (IQ), development, behavior, and growth were all within normal range. There was one child with minor neurological dysfunction but without any clinical implications (van der Lugt et al. [58]). Registry data from Schou ([59]) found no difference in a group of mother's retrospective subjective assessments of development in 60 children exposed to lithium compared to 57 non-exposed siblings. Jacobson and co-authors ([60] in a prospective cohort study found no difference in developmental milestones in 22 lithium exposed infants compared to a control group. A small cohort study used a standardized assessment to evaluate total IQ, performance IQ, and verbal IQ at age 4–5 years old between children with in utero exposure to lithium ($n = 20$), non-exposed children of mothers with a mood disorder ($n = 8$), and controls ($n = 11$). No differences were found (Forsberg et al. [61]). A meta-analysis looked at preclinical and clinical studies of lithium and antipsychotic exposure—93% of the studies examined found one or more adverse effects of lithium or antipsychotics on neurodevelopment, however the three clinical cohort studies looking only at lithium found normal development. Many of the studies included in this meta-analysis are difficult to interpret because the comparison group is children from an unaffected population which does not account for many important confounding variables (Poels et al. [62]).

Lithium Management During and in Preparation for Pregnancy

The first step in managing a woman with bipolar disorder during her pregnancy is a detailed risk assessment. The prescriber should consider the statistics for recurrence for women with bipolar disorder as well as the consequences of recurrence during and after pregnancy including but not limited to risks of hospitalization, maternal-infant separation, poor prenatal care, substance use, psychosis, suicide, and infanticide. The risk of relapse and consequences of relapse will be modulated by the individual patient's illness severity and number of prior occurrences, and the prescriber will need to take this into account in developing treatment recommendations. Next, the prescriber should consider known as well as unknown risks of fetal medication exposure, including the potential but likely weak association between lithium and cardiac anomalies such as Ebstein's anomaly. At this point the prescriber can develop a recommendation to present to the patient in the form of a "risk-risk" discussion.

A "risk-risk" discussion involves obtaining informed consent for the offered treatment from the patient including discussing the previously considered risks, benefits, and any alternatives for medication use during pregnancy and postpartum weighed against the risks, benefits, and alternatives of avoiding or changing medication during pregnancy and postpartum. The patient's primary support person should be included in this discussion if possible and the provider should establish a good understanding of both the patient's and her support person's preferences and expectations in regards to managing her bipolar disorder throughout this period. The provider can then offer individualized treatment recommendations, including a description of intended medications (or lack of), a plan should symptoms develop, and the implications for these recommendations for breastfeeding.

After completion of the "risk-risk" discussion and agreement between the patient and provider on a medication strategy, the provider should discuss with the patient and her primary support person a plan for mitigating identified risks. Strategies for mitigating fetal lithium exposure risk may include using the lowest effective lithium level to maintain euthymia, especially in the first trimester, dividing dosing schedule into twice daily provided medication adherence is not compromised (Horton et al. [63], Poels et al. [21••]), level 2 ultrasound with fetal echo in the second trimester to assess for cardiac anomalies and, if necessary, plan an appropriate intervention, delivering in a hospital equipped with a neonatal intensive care unit (NICU), and holding lithium at the time of labor or 24–48 h prior to planned delivery to reduce neonatal complications secondary to higher fetal lithium levels at the time of delivery. Patients should be informed that Ebstein's anomaly is not only rare but is also usually surgically repairable and can be managed around the time of delivery especially with appropriate monitoring and planning (Gentile [64]). Multiple authors have also recommended additional folate supplementation (Yonkers et al. [19], Khan et al. [33]), but at this point evidence remains lacking to validate its protective potential as well as inform appropriate dosing. Strategies for mitigating maternal risk include determining a plan for symptom monitoring, medication adherence, lithium blood level monitoring, protection of sleep especially in the

postpartum, stress management, and social support. Supporting the woman's transition to role as a mother and self-esteem regarding caretaking are also important elements to attend to.

For a patient with known bipolar I disorder who has been stable on lithium, we generally recommend continuing lithium throughout pregnancy to prophylactically prevent mood instability and associated complications. If a patient with bipolar disorder with a remote mood episode has been stable off of medication for at least 6 months, depending on the individual patient, it may be reasonable to hold lithium or use a reduced dose during the time period that the heart is being formed (4–12 weeks) or longer, and have close monitoring for mood instability. Lithium should never be abruptly discontinued and should be restarted immediately postpartum even if it is not used during pregnancy unless there are other contraindications for the individual.

Lithium levels will need to be monitored more frequently and are expected to fall throughout the first and second trimesters due to GFR changes and expanded blood volume (Wesseloo et al. [65••]). Doses may need to be increased by as much as 50% to maintain lithium in the therapeutic range (Westin et al. [66]). A majority of experts recommend obtaining lithium levels every 2–4 weeks during pregnancy until 34 weeks, and then weekly until delivery (Poels et al. [21••], Deligiannidis [67], Ward, Wisner [68], Llewellyn et al. [26], Khan et al. [33], Wesseloo et al. [65••]). Additional monitoring may be needed if complications develop including hyperemesis gravidarum, severe nausea, diuretic use, febrile illness, or preeclampsia. If lithium is used during the first trimester, a level two fetal ultrasound with fetal echo should be performed between 16 and 20 weeks of gestation to monitor for cardiac malformations (Yonkers et al. [19], Poels et al. [21••], Galbally et al. [69]). Some authors recommend decreasing or discontinuing lithium to reduce perinatal complications proximate to delivery (Newport et al. [48], Gentile [64]) while others recommend no change in dosing and monitoring before and 24 h after delivery (Poels et al. [21••], Wesseloo et al. [65••], Deligiannidis et al. [70]).

Lithium Management Postpartum

Following delivery, it is recommended to monitor women for elevations in creatinine, blood urea nitrogen, and thyroid-stimulating hormone (Viguera et al. [71•]) and to avoid medications known to increase lithium levels if possible. The lithium dose should be adjusted appropriately in the postpartum to account for the decrease in vascular volume and changes in GFR and choosing an appropriate dose in the postpartum will need to take into account pre-pregnancy dose (if known) as well as current symptoms. Some women may require a higher level (0.8–1.2) to maintain euthymia in the postpartum than they needed during pregnancy. Lithium levels should be monitored biweekly for first 2 weeks postpartum given creatinine may continue to normalize (Wesseloo et al. [65••]), and then again at 4 weeks postpartum.

Lithium and Breastfeeding

There is currently a lack of sufficient data on infant lithium exposure via breastmilk, with only 36 cases reported in the literature (Galbally et al. [72]). Lithium passes freely between the serum and breastmilk, but there is a wide variation in infant serum levels with estimates falling approximately between 25 and 50% of maternal serum levels (Viguera et al. [71•], Bogen et al. [73], Frew [74], Moretti et al. [75]). Viguera et al. [71•] measured levels in 10 infant-mother pairs and found infant serum levels to be approximately 25% of maternal levels with no serious adverse events. They did find minor elevations in thyroid-stimulating hormone, blood urea nitrogen, and creatinine in lithium-exposed infants, but this resolved with cessation of breastfeeding.

Sleep deprivation is a known risk factor for a mood episode relapse in bipolar disorder (Geddes, Miklowitz [9], Perlman et al. [76]), and specifically in the postpartum leads to an increased risk of postpartum psychosis (Jones et al. [35]). Given that successful breastfeeding often requires overnight waking in order to establish and maintain milk supply as well as to meet the nutritional needs of the infant, this adds additional risk that must be considered. We agree with international guidelines and other authors who state that in general the risks of breastfeeding on lithium outweigh the benefits (Galbally et al. [72], Poels et al. [21••], Grandjean, Aubry [51]).

However, many experts also recognize that lithium is not an absolute contraindication and some recommend that it can be done in certain cases (Pacchiarotti et al. [77]). It may be more reasonable to consider breastfeeding in a woman taking lithium if she is adherent to treatment, is currently clinically stable, and has a full term, healthy infant. Close collaboration with a pediatrician who is supportive of the mother's decision and is aware of monitoring guidelines is needed (Viguera et al. [71••], Yonkers et al. [19]) If a patient decides to breastfeed, supplemental formula feeding especially overnight can minimize the infant's exposure and help protect mother's sleep. TSH, lithium level, and renal function of the breastfed infant should be monitored and any dehydration, illness, or precipitant of a lithium level increase should prompt immediate assessment. Additionally, any changes in infant behavior, sedation, restlessness or difficulty feeding should prompt evaluation by a clinician.

We generally do not recommend switching from lithium to an atypical antipsychotic or alternative mood stabilizer solely because of pregnancy or wish to breastfeed. The high rate of

relapse with lithium discontinuation (Viguera et al. [5••]) and the risk that a patient may not be responsive to an alternate medication present significant potential harms. In support of this, Bergink ([41••]) found that patients with postpartum psychosis or mania had a significantly lower rate of mood episode relapse at 9 months postpartum on lithium compared to antipsychotic monotherapy. Wisner ([4]) found that valproic acid was not significantly more effective in preventing a mood episode postpartum as compared to women with bipolar disorder with monitoring only. Wesseloo ([78]) found that lamotrigine was not inferior to lithium in the prevention of postpartum mood episode relapse, however this may be more applicable to prevention of postpartum depressive episodes than for mania. Second-generation antipsychotics are considered an alternative treatment to lithium in pregnancy if they have proven to be effective for the individual, however prevention of mood episodes in the postpartum using antipsychotics has not been investigated (Poels et al. [21••], Bergink et al. [79]) and there is less evidence overall for maintenance of mood for bipolar disorder using antipsychotics than for lithium (Geddes, Miklowitz [9]). This suggests that when choosing between lithium and an antipsychotic medication for the peripartum, women should continue the medication that has been most effective in controlling their symptoms prior to pregnancy and that lithium is preferred for prophylaxis in the postpartum period (Bergink et al. [79], Bergink et al. [80••]).

Summary and Conclusion

Women with bipolar disorder are at risk of mood episode recurrence both during pregnancy and postpartum and the consequences of recurrence during this time period present significant potential harms to both mother and infant. Lithium is an essential treatment tool for women with bipolar disorder and yet is currently grossly under-prescribed to pregnant and postpartum women. Appropriate use of lithium during pregnancy and postpartum for a woman with bipolar disorder requires a "risk-risk analysis", weighing the risk of treatment versus the risk of withholding or changing treatment. Risks of lithium use during pregnancy include a small potential increase in cardiac malformations including Ebstein's anomaly, although the extent of that risk remains poorly characterized due to statistical limitations in assessing rare outcomes. There does not appear to be a significant effect on obstetric outcomes or on neurodevelopment although data are limited especially in regard to long term outcomes. Monitoring during pregnancy includes a level 2 fetal ultrasound with fetal echocardiogram between 16 and 20 weeks of gestation and regular lithium levels with appropriate dose adjustments to account for pharmacokinetic and vascular volume changes during pregnancy. We recommend not breastfeeding while taking lithium given limited data and potential adverse consequences. A detailed risk mitigation plan should be used for every patient.

Clinical risk-risk assessment

Maternal risk considerations related to illness relapse	*Fetal risk considerations related to lithium exposure*
Severity of illness including age of illness onset, frequency of past mood episodes, severity of past mood episodes, and number of hospitalizations	Potential small increase in risk for major malformations, including cardiac malformations such as Ebstein's anomaly
History of high-risk behaviors including suicide attempts and aggression	If neonatal lithium level is high at delivery, lower 1-min APGAR scores, longer hospital stay, and increased risk for NICU admission
Substance use history	
History of self-neglect including poor adherence to medical or prenatal care	
History of peripartum onset mood episodes or past episodes triggered by fluctuating gonadal hormones	
History of functional impairment	
Level of social support	
Level of treatment engagement and ability to self-monitor	

Risk mitigation strategies

Maternal risk mitigation	*Fetal risk mitigation*
Symptom monitoring plan including frequent visits	Use lowest effective lithium dose to maintain euthymia
Lithium level monitoring every 2–4 weeks with appropriate dose adjustment	Level 2 ultrasound with echocardiogram between 16 and 20 weeks to monitor for cardiac malformations
Medication adherence plan	Plan to deliver in a NICU-equipped hospital
Prenatal care optimization strategies including coordination with patient's OBGYN	Consider holding lithium 24–48 h proximate to delivery and restarting immediately postpartum
Psychotherapy	Consider additional folate supplementation
Self-care including behavioral wellness interventions such as exercise, and stress management	
Plan for sleep protection	
Social support, including involving primary support person in treatment planning	

"Risk-risk" discussion checklist

- Identify and invite primary support person to the discussion, with patient's permission
- Describe the risk context for managing bipolar disorder on and off medication
- Include in discussion specific risks to the individual patient given her psychiatric history and psychosocial factors
- Offer and discuss a treatment strategy including medication and non-medication plans
- Discuss plan for risk mitigation for both mother and fetus/neonate/infant
- Outline plan for symptom monitoring and a plan should symptoms relapse
- Discuss implications for breastfeeding
- Discuss plan for postpartum sleep and overnight neonatal/infant care
- Support the patient's transition to motherhood and confidence in parenting

Lithium monitoring and dose adjustments

During pregnancy	*Postpartum*
Obtain lithium levels every 2–4 weeks	Monitor lithium levels biweekly for the first 2 weeks postpartum and again at 4 weeks postpartum
Expect to increase dose as needed given changes in GFR and blood volume	Expect to decrease dose as needed, utilizing pre-pregnancy dose and current symptoms
Target level is .6–.8, adjust based on individual symptoms and history	Target level 0.8–1.0 even if euthymic
Twice daily dosing schedule preferred, if patient can be medication adherent	Once daily dosing schedule in evening preferred
	Monitor for maternal elevations in creatinine, blood urea nitrogen, and TSH
	Avoid medications known to increase lithium levels if possible

Breastfeeding considerations for lactating women taking lithium

- In general, the risks of breastfeeding on lithium outweigh the benefits, although it is not an absolute contraindication
- If a woman wishes to breastfeed on lithium, we would recommend:
  - Plan to minimize maternal interruptions in sleep overnight
  - Supplemental formula feeding, especially overnight, to maximize maternal sleep and reduce infant lithium exposure
  - Well informed parents and pediatrician who can collaborate effectively
  - Infant blood monitoring of TSH, renal function, and lithium level
  - Close monitoring for signs or symptoms of lithium toxicity in the breastfed infant

Compliance with Ethical Standards

Conflict of Interest Alyson Gorun and Abigail Benudis each declare no potential conflicts of interest.

Alison Hermann has received personal fees from Sage Therapeutics and a co founder and CMO of Iris OB Health.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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