Bipolar Disorders

3

Verinder Sharma

3.1 Introduction

Bipolar disorder is a common disabling illness that usually begins in late adolescence or young adulthood [1, 2]. The disorder is commonly subdivided into bipolar I, bipolar II, and subthreshold bipolar disorder. Bipolar I disorder is equally common in men and women; however, bipolar II disorder appears more common in women. According to the World Mental Health Survey Initiative, bipolar disorder has a lifetime prevalence of 2.4%, of which more than half of the cases have a diagnosis of subthreshold bipolar disorder [3]. There are gender differences in the manifestation of bipolar disorder as women are more likely to have rapid cycling, mixed episodes, and suicide attempts. Women with bipolar disorder are also more likely to have comorbid thyroid disease, bulimia, and post-traumatic stress disorder [4]. Recently published large sample studies on bipolar disorder have found overrepresentation of women, suggesting a change in the prevalence of the disorder in two genders [5].

The illness course in women is impacted by reproductive events, particularly childbirth, leading to clustering of mood episodes during the reproductive life cycle [6]. The postpartum period is associated with increased risk of first onset of hypo/mania as well as depression [7–9]. Women with preexisting bipolar disorder are at risk of recurrence of hypo/manic, depressive, and mixed episodes in spite of the prophylactic use of psychotropic drugs [10]. Pregnancy, on the other hand, is thought to have a variable effect on the course of the disorder. The effect of pregnancy on the illness course in untreated women has not been studied prospectively; however, data from retrospective studies and population-based cohort studies have

V. Sharma (✉)
Departments of Psychiatry and Obstetrics and Gynecology, London, ON, Canada
e-mail: vsharma@uwo.ca

M. Percudani et al. (eds.), *Key Topics in Perinatal Mental Health*,
https://doi.org/10.1007/978-3-030-91832-3_3

suggested that pregnancy may have a positive effect [11]. Thus, management of bipolar disorder during and after pregnancy requires understanding of the course of treated and untreated illness, as well as risks associated with the use of psychotropic drugs for the mother and the fetus or neonate. Peripartum management of bipolar disorder is further complicated by diagnostic challenges, paucity of controlled pharmacologic or psychotherapeutic data, and concerns about the safety of psychotropic drugs during lactation.

In this chapter, I review the screening, and diagnostic assessment of bipolar disorder followed by a discussion of its management prior to, during, and after pregnancy. Due to the lack of data on the role of psychotherapy, treatment discussion mainly focuses on pharmacotherapy. In order to avoid duplication, topics such as safety of drug use during pregnancy, the postpartum period, and lactation are not discussed in detail. Similarly, discussion of the diagnosis and treatment of puerperal psychosis is omitted.

3.2 Screening and Diagnostic Evaluation

Women are commonly screened for depression during and after pregnancy. The American College of Obstetricians and Gynecologists recommends screening at least once during the perinatal period for depression using a standardized, validated tool [12]. There are several compelling reasons that women should be screened for hypo/manic symptoms during pregnancy and the postpartum period [13]. A study of 10,000 women who underwent screening using the Edinburgh Postnatal Depression Scale (EPDS) between 4 and 6 weeks postpartum found that nearly 23% had bipolar disorder [14]. Several studies using the Highs scale have reported that 9.6–46.1% of women have hypomanic symptoms in the postpartum period [15, 16]. Some of these women have bipolar disorder because the hypomanic symptoms are followed by episodes of depression. Symptoms of hypo/mania are particularly common among women referred to perinatal clinics for postpartum depression. In one study, more than half of the women referred with a diagnosis of postpartum depression met the DSM-IV criteria for bipolar disorder—bipolar disorder not otherwise specified (29%), bipolar II disorder (23%), and bipolar I disorder (2%) [17]. Some women experience a change in diagnosis from major depressive disorder to bipolar disorder due to the first onset of hypo/mania in the postpartum period [8, 9]. Screening for bipolar disorder is necessary to prevent psychiatric hospitalization in the first few weeks after delivery [18]. Also, failure to detect and diagnose maternal bipolar disorder may lead to inappropriate treatment and increase the risk of harm to self or the newborn [19].

Reluctance to seek mental health treatment and a denial or rejection of bipolar diagnosis further contribute to diagnostic delay. The lack of awareness among clinicians of the common occurrence of hypo/manic symptoms may affect receipt of accurate diagnosis. Some delay is unavoidable because a diagnosis of bipolar disorder requires presence of hypo/mania; however, proper screening and diagnosis may mitigate risks associated with inappropriate treatment. For example, women at risk of developing bipolar disorder due to a history of bipolar disorder or puerperal

psychosis in a first-degree family member can be identified and monitored for emergence of hypo/manic symptoms. Clinical features such as younger age at illness onset, de novo depression after childbirth, onset of depression immediately after delivery, atypical symptoms of depression, current psychotic symptoms, mixed features, and history of bipolar disorder in first-degree family members should alert clinicians to consider bipolar disorder a differential diagnosis in women presenting with a depressive episode after delivery [20].

According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines, all women with depressive symptoms should be screened for bipolar disorder during pregnancy and the postpartum period. Validated screening tools such as the Mood Disorder Questionnaire (MDQ) alone or in conjunction with the EPDS are useful [21, 22]. The MDQ is the most studied screening tool for bipolar disorder in the peripartum population. A positive screen requires endorsement of 7 or more of the 13 items, occurrence of items during the same period of time, and "moderate" or "serious" problem as a result of the endorsed items. An alternate scoring method (endorsement of seven or more items only) is more appropriate for bipolar II, or otherwise specified bipolar and related disorder because patients with these diagnostic subtypes are unlikely to say "yes" to question 3 of the MDQ. The Highs scale is another tool that has also been studied in the postpartum population [23]. Unlike the MDQ that assesses lifetime occurrence of hypo/manic symptoms, the Highs scale focuses on these symptoms in the postpartum period.

A positive screen for bipolar disorder should be followed by clinical assessment to confirm or exclude a diagnosis of bipolar disorder. A positive screen may also occur in cases of major depressive disorder with mixed features.

Women should also be screened and evaluated for psychiatric disorders that commonly co-occur with bipolar disorder such as anxiety disorders, obsessive–compulsive disorder, and substance use disorder. Simple screening questions for obsessive–compulsive disorder are "*Do you have unpleasant thoughts, urges, or images that repeatedly enter your mind? "Do you feel driven to perform certain behaviors or mental acts over and over again?*" The Generalized Anxiety 7-item (GAD-7) scale is a validated tool to screen for anxiety symptoms [15]. Clinical evaluation should include questions about family history because women with a history of bipolar disorder in the family are at a high risk of switching from major depressive disorder to bipolar disorder in the postpartum period. A population-based study from Denmark found increased relative risk of postpartum psychiatric disorders in first-time mothers who had a family history of bipolar disorder (hazard ratio = 2.86, 95% CI = 1.88–4.35) [24].

3.3 Preconception Care and Counselling

Since 50% of pregnancies are unplanned in women with bipolar disorder, it is important to consider the safety of medication use during pregnancy when prescribing mood stabilizers for women of reproductive age [25]. Valproic acid should not

be used in women of reproductive age because first trimester use of the drug has been associated with increased risk of neural tube defects, lower IQ, and autism spectrum disorders [26]. Moreover, valproic acid is not effective in preventing postpartum mood episodes in women with bipolar disorder [27]. Drugs such as topiramate, lamotrigine, or carbamazepine can affect pharmacokinetics of birth control drugs and thereby cause contraceptive failure [28].

The goal of preconception counselling is to improve pregnancy outcomes through risk assessment, psychoeducation, health promotion, and intervention. Women with bipolar disorder should be offered counselling at least 3 months prior to considering pregnancy or immediately upon discovery of pregnancy [29]. An important task of preconception counseling is confirmation of diagnosis of bipolar disorder and its subtype. A thorough psychiatric evaluation should be carried out to clarify the illness course including the frequency, severity, duration, and dominant polarity of mood episodes as well as duration of euthymic intervals, psychiatric and physical comorbidities, and hospitalizations. Risk assessment should identify women at high risk of suicide due to the personal history of serious attempts, or family history of completed suicide. Medication history including patterns of response to psychotropic medications, time to relapse following discontinuation of medications, and time to respond with reintroduction of medications should be obtained.

Women should be informed of the effect of pregnancy and postpartum on the course of bipolar disorder, as well as the effect of untreated bipolar disorder on pregnancy outcomes, and risk–benefit analysis of medication use. Decisions about whether or not to start, continue, discontinue, or modify medication should be made collaboratively with the patient and involvement of a partner or family member, if possible. Some women may require discontinuation of typical antipsychotics and risperidone in order to increase the likelihood of conception, as these medications often increase serum prolactin levels and thus interfere with ovulation. Modifiable risk factors such as obesity, tobacco use, and poor diet quality should be addressed [29]. Women dependent on alcohol or drugs should be advised to cease use of these substances, and when necessary should be referred to detoxification services. Preconception counselling should provide an opportunity to shore up social supports.

Reasons for seeking preconception counselling are varied. Due to the potential risk of genetic transmission of bipolar disorder to offspring, women with or without psychiatric illness may seek counseling to decide whether or not to pursue pregnancy. As childbirth is associated with increased risk of first onset of depression, mania, or puerperal psychosis, even women with no history of psychiatric illness should be offered follow-up during and after pregnancy. Sometimes women are referred because they wish to have a medication-free pregnancy. Women who have been clinically stable for 4–6 months, and are at low risk for recurrence can have their mood stabilizer tapered off prior to pregnancy [29]. Medication-free pregnancy may not be an option for those who have severe and frequent mood episodes, mania-preponderant illness, or history of frequent psychiatric hospitalizations, serious suicide attempts, and substance use disorder. Women taking valproate should be

recommended to switch to a different psychotropic drug. An opportunity to discuss the effectiveness of current medication in managing/preventing peripartum recurrences is another common reason for preconception counselling. The risk of mood instability following changes to the drug regimen has to be carefully weighed against the risk associated with the continuation of medications. Every effort should be made to simplify the drug regimen and preference given to mood stabilizing drugs. Antidepressants should be avoided particularly in women with bipolar I disorder.

3.4 Treatment During Pregnancy

3.4.1 General Considerations

Depression is the most common presentation of bipolar disorder during pregnancy. Several studies have found higher rates of depression in the first trimester compared to other trimesters. Abrupt discontinuation of psychotropic drugs, particularly antidepressants, may cause withdrawal symptoms and also increase the risk of recurrence of mood episodes. Abrupt cessation of alcohol use or drugs upon discovery of pregnancy can produce withdrawal symptoms including anxiety, depression, and insomnia. Sleep disturbance due to severe nausea and vomiting that normally peaks in the first trimester may contribute to depression. Thus, it is important to clarify whether mood changes are symptoms of bipolar disorder or are due to withdrawal from medications/substances. Bipolar mood episodes in pregnancy are usually recurrences in the context of preexisting illness; however, hypo/mania can also have first onset during pregnancy. It is unclear how commonly bipolar disorder has first onset during pregnancy.

Similar to valproic acid, carbamazepine is a teratogen and should be avoided. Also, carbamazepine is a strong inducer of hepatic enzymes and may lower the levels of coadministered drugs and necessitate dose increases [30]. According the National Institute for Health and Care Excellence (NICE) guidelines, lithium should be avoided during the first trimester unless antipsychotic medications have been ineffective, and a discussion about the risks and benefits of lithium has taken place with the patient [31]. Polypharmacy ($\geq$2 psychotropic drugs) for bipolar disorder is common during pregnancy. Use of antidepressants may increase the likelihood of polypharmacy as additional psychotropic drugs are needed to manage emerging symptoms of hypo/mania. Concomitant use of mood stabilizers may not be sufficient to prevent antidepressant-led mood instability. Moreover, polypharmacy may increase the risk of adverse outcomes for the mother and her fetus [32, 33]. If possible, an attempt should be made to simplify the drug regimen by gradually tapering antidepressants and benzodiazepines. Thus, preference should be given to continuation/optimization of drugs with broad spectrum of efficacy in the management of bipolar disorder. Decisions about medication use should be made on a case-by-case basis in collaboration with the patient. Drugs selected for acute treatment of mood episodes in pregnancy should ideally be effective in the prevention of mood or

psychotic episodes in the postpartum period. For women who plan to breastfeed, safety of medication during lactation is an important consideration.

Therapeutic monitoring of drugs, particularly with a narrow therapeutic range such as lithium, is necessary during the perinatal period. A study by Wesseloo et al. found serum lithium levels decreased during the first and second trimesters followed by a gradual return to preconception levels starting in the third trimester [34, 35]. They recommended close monitoring of serum lithium levels until 34 weeks of pregnancy, followed by weekly measurements until delivery and then twice weekly for the first 2 weeks postpartum. At our clinic we recommend a flexible monitoring schedule guided by serum levels rather adherence to a rigid monitoring protocol.

Since sleep loss is a symptom as well as a trigger of mood episodes especially hypo/mania, use of a drug such as quetiapine may produce quicker results than optimization of a drug like lithium. Due to increased clearance during pregnancy, lamotrigine doses may need adjustment to maintain therapeutic concentration [36]. Similarly, doses of atypical antipsychotic drugs may need adjustments due to the induction of cytochrome P450 system. In the postpartum period, the doses of these medications may require readjustment to avoid toxicity and/or improve tolerability.

3.4.2 Acute Treatment

Working in collaboration with the patient, a comprehensive and individualized treatment plan should be developed. The key goals of acute treatment should be to achieve full remission and limit the duration and consequences of mood episodes. Currently, there are no data on the acute treatment of bipolar depression during pregnancy. In general first-line options for bipolar I depression include quetiapine, lithium, lamotrigine, and lurasidone. Lamotrigine is not associated with weight gain and is less likely to cause sedation. Lamotrigine is generally well tolerated; however, it is associated with an uncommon (>0.1%) but potentially serious skin rash. Due to the slow titration of lamotrigine, it may take a few weeks before patients experience improvement of their depression. Lamotrigine is effective in preventing mood episodes during pregnancy [37]. A small study using the Danish registries did not find a significant difference in the risk of psychiatric hospitalization rates among women treated with lamotrigine versus those who took lithium during pregnancy (7.3% versus 15.3% respectively, adjusted OR 0.83; 95% CI 0.22–3.14) [34]. A recent systematic review and meta-analysis concluded that in utero exposure to lamotrigine was associated with significantly lower rates of congenital malformations (OR 1.15; 95% CI 0.62–2.16 and OR 1.25; 95% CI 0.89–1.74, respectively) compared to disease-matched controls and healthy controls. Adverse pregnancy outcomes in the lamotrigine group were not significantly increased compared to the general population group [38]. A recent meta-analysis found that in utero exposure to lithium was not associated with statistically significant increased risks for pregnancy or delivery outcomes. Lithium was associated with a significantly increased

risk (27.5% vs. 14.3%) for neonatal hospitalization within 4 weeks postpartum [39]. First-trimester exposure to lithium was specifically associated with an increased risk of major malformations, but not major cardiac malformations. These findings align with accumulating evidence that the absolute risk of malformations is much smaller than reported in earlier studies [40].

Quetiapine is the most commonly prescribed neuroleptic in the USA [41], however, there are no data on its use in the acute treatment of bipolar mood episodes in pregnancy. The drug is generally well-tolerated but some women find it difficult to fulfill childcare responsibilities due to excessive sedation. In higher doses it may cause postural hypotension and dizziness that could be problematic, particularly in the perinatal period [42]. Quetiapine use during pregnancy is associated with increased risk of gestational diabetes. The pooled risk ratio for major malformations in infants exposed to quetiapine in the National Pregnancy Registry for Atypical Antipsychotics at Massachusetts General Hospital was estimated at 1.03 (95% CI = 0.89–1.19) [43], suggesting no increased risk of malformations with first trimester exposure to quetiapine compared with the general public. A recent clinically focused review of second-generation antipsychotics reached a similar conclusion that in utero exposure to quetiapine is not associated with increased risk of major congenital malformations. Similarly, the available data overall do not suggest a clinically important increased risk for other pregnancy outcomes such as miscarriage, stillbirth, and small for gestational age [44].

A systematic review reported on use of electroconvulsive therapy (ECT) in 169 pregnant women with depression, bipolar disorder or psychotic depression [45]. Most women were in their second trimester of pregnancy. The mean number of ECT's was 9.4. Adverse events including fetal heart rate reduction, uterine contractions, and premature labor were reported for 29% of women. The overall child mortality rate was 7.1%; therefore ECT should be recommended as a last resort treatment.

3.4.3 Maintenance Treatment

The goals of maintenance treatment should be to prevent recurrence of mood episodes, manage comorbidities, minimize residual symptoms, promote medication adherence, reduce risk of self-harm, and improve functioning during pregnancy. Regular follow-up visits should be scheduled and frequency of visits increased if needed. More frequent visits are necessary in the third trimester to identify and manage prodromal/early symptoms of 'postpartum' mood or psychotic episodes. Psychoeducation about the illness and its management including strategies to promote sleep opportunities should be an integral part of the overall treatment plan. Regular tracking of mood and sleep should be encouraged to detect early symptoms of mood episodes.

Maintenance treatment planning requires an understanding of the impact of pregnancy on the course of bipolar disorder. Most of the research evidence in this

regard comes from studies of discontinuation of mood stabilizing medications that have shown a very high risk of illness recurrence during pregnancy. However, there is evidence from non-clinical samples, retrospective studies and studies of hospitalization rates that pregnancy may have a protective effect [11]. Prospective longitudinal studies controlling for diagnostic subtypes, illness course and current treatment are needed to clarify the effect of pregnancy on the course of bipolar disorder [46].

A prospective observational study of women who continued or discontinued their mood stabilizers, found that 71% had at least one recurrence during pregnancy [47]. Among women who discontinued the mood stabilizer the recurrence risk was twofold greater, the time to recurrence more than fourfold shorter and the proportion of time being ill during pregnancy was five times greater compared to those who stayed on the treatment. Interestingly, 33.3% of participants who maintained treatment had a recurrence of hypo/mania versus 19.4% of those who discontinued treatment suggesting that the unopposed use of antidepressants may have increased the risk of hypo/manic episodes. The researchers found a diagnosis of bipolar II disorder, and use of antidepressants predicted risk of recurrence. Women who discontinued the medications were more likely to be taking multiple psychotropic medications, had a longer duration of illness, were more likely to have illness onset before age 15 and had significantly higher rates of rapid cycling. They were also more likely to be taking antidepressant medications (66.1% vs.18.5%) and have a diagnosis of bipolar II disorder.

Another study by Viguera et al. found preponderance of hypo/manic and mixed states compared to depression during pregnancy in women with bipolar I disorder (13.13% vs. 8.88%) [10]**.** These results highlight the challenges clinicians encounter in managing bipolar depression during pregnancy. This is especially the case for bipolar II disorder due to the paucity of treatment data relative to bipolar I disorder. Quetiapine is the only first-line recommended drug. Lithium, lamotrigine, sertraline, and venlafaxine are second-line recommended drugs. The role of antidepressants in the treatment of bipolar II disorder remains controversial due to concerns about the risk of switching, cycling, and induction of mixed states.

Different clinical scenarios are encountered when assessing women during pregnancy. Some women present with a history of bipolar disorder while others have a history of undiagnosed or misdiagnosed bipolar disorder. For some women, first onset of hypo/mania during pregnancy may be the beginning of bipolar disorder. Women taking a mood stabilizer or an atypical antipsychotic drug whose mood is stable should continue with the same drug (s) after delivery. Women with recurrences despite maintenance treatment should be evaluated for potential contributing factors including antidepressant treatment, substance use, and dose of mood stabilizing medication, treatment adherence, and hypothyroidism. Changes should be made to the drug regimen accordingly. Some women wish to have a medication-free pregnancy but are agreeable to take medication in the postpartum period. Psychoeducation, regular symptom monitoring, sleep optimization, and assessment immediately after delivery should be the treatment strategy for these women.

3.5 Postpartum Period

3.5.1 General Considerations

Women with bipolar disorder are at a greater risk of occurrence of hypo/mania in the postpartum period than during pregnancy [48]. However, similar to pregnancy, the depressive/mixed episodes are the dominant polarity. Viguera et al. found 52% of women with bipolar I or II disorder despite treatment had illness episodes during the first 6 months postpartum [10]. A retrospective study of women who were medication-free during their pregnancies found 75% had at least one postpartum episode. Of these, nearly 60% had depression, 16% had hypo/mania and the rest mixed episodes [49]. A systematic review and meta-analysis by Wesseloo et al. reported a relapse risk of 35% (95% CI = 29, 41) in the postpartum period [50]. The relapse rate was significantly higher among women with bipolar disorder who were free of medications during pregnancy (66%, 95% CI = 57, 75) compared to those who were treated with psychotropic drugs (23%, 95% CI = 14, 37). The authors concluded that continuation of pharmacotherapy during pregnancy was effective in reducing the postpartum risk of recurrence in women with bipolar disorder or postpartum psychosis.

The postpartum period is also associated with an increased risk of first onset of hypo/mania. A prospective study by Sharma et al. found that 6.5% of women with major depressive disorder experienced a DSM-IV defined episode of hypomania during the first 6 months [9]. Another study reported that nearly 35% of women with a diagnosis of major depressive disorder had an episode of hypo/mania (defined as a score of ≥6 on the Altman Self-Rated Mania scale) during the first 3 months postpartum. Similarly, women with first onset of other psychiatric disorders are at an increased risk of developing bipolar disorder [18]. In spite of the common occurrence of hypo/manic symptoms in the postpartum period, misdiagnosis of bipolar disorder as major depressive disorder appears common. Failure to obtain history of hypo/manic symptoms may result in underdiagnosis of bipolar disorder. Misdiagnosis of bipolar disorder as unipolar postpartum depression among women attending specialized perinatal clinics is particularly high. From the aforementioned discussion, it is clear that all women with a major depressive episode should be screened for bipolar disorder. Women with psychiatric disorders who have postpartum onset are at a particularly high risk of developing bipolar disorder and should be monitored for emergence of hypo/manic symptoms during follow-up.

Abrupt cessation of exclusive breastfeeding has been associated with onset of mixed mania [51, 52]. Some women also experience worsening/recurrence of mood symptoms upon resumption of menstrual periods.

3.5.2 Acute Treatment

Drug treatment of bipolar postpartum depression has been largely overlooked [53]. The Polish Psychiatric Association recommends quetiapine alone or in

combination with an antidepressant for depression [54]. A retrospective study of quetiapine in 18 patients found 83% were "very much" or "much" improved when assessed using the Global Impression Scale [55]. The quetiapine median dose was 75 mg daily (12.5–500 mg). A study of extended release quetiapine in a median dose of 137.5 mg daily was also effective but only 15 of 26 participants completed the study [56]. It is unclear whether the concomitant use of quetiapine is protective against antidepressant-induced emergence of hypo/mania. Lamotrigine, lurasidone, or lithium are other options for acute treatment of bipolar postpartum depression. Factors to consider while selecting a suitable drug include effectiveness and tolerability of previously tried medications, suicide safety assessment, and nature of current psychiatric comorbidity. Since all psychotropic drugs are excreted in breast milk to varying degrees, decisions about the use of drugs should be made after a thoughtful analysis of potential risks and benefits. Postpartum hypo/manic episodes should be treated in the same manner as non-postpartum episodes [29].

3.5.3 Prophylactic Treatment

The prophylactic treatment should aim to (1) prevent recurrences of mood episodes, (2) prevent hypo/mania in women at risk of developing bipolar disorder, (3) reduce the risk of psychiatric hospitalization after delivery, (4) prevent harm to the mother and her baby, and (5) minimize the risk of recurrence of mood episodes beyond the postpartum period. The DSM-5 peripartum onset specifier is a reminder that postpartum episodes can begin during pregnancy. Approximately 60% of cases of postpartum depression begin during or prior to pregnancy [14]. Similarly, puerperal psychosis (generally considered a manifestation of bipolar disorder) can have a prepartum onset as evidenced by symptoms such as feeling euphoric, decreased sleep requirement, feeling active or energetic, or talking more or feeling very chatty [57]. It is, therefore, important that preventative strategies should focus on identification and treatment of mood/psychotic symptoms in late pregnancy. Sometimes it is difficult to distinguish between early times of recurrence and normative changes in sleep, energy, or mood during pregnancy. Prospective charting of symptoms using a mood diary or an app may help early detection of these symptoms. Assertive monitoring is also crucial for identification and management of modifiable risk factors such as sleep loss or the use of antidepressants.

Decisions about pharmacotherapy for prevention of postpartum episodes should be made on a case-by-case basis, taking into consideration the illness course and treatment history [58]. Particular attention should be paid to parity, diagnostic subtype, dominant polarity, sequence of mood episodes (e.g., depression–hypo/mania–euthymic interval [DMI type or the MDI type]), suicide risk assessment, and drug safety [59]. Interestingly, there are no placebo-controlled randomized trials of mood stabilizers in the prevention of postpartum mood episodes in the context of bipolar disorder. A single-blind, nonrandomized trial found valproate plus monitoring was not significantly more effective than monitoring alone for the prevention of

postpartum recurrences. A small prospective study of olanzapine used adjunctively was effective for prevention of postpartum psychosis and bipolar mood episodes [60]. Lithium is generally recommended for prevention of mania or puerperal psychosis; however, there is no evidence that the drug is effective for prevention of depressive episodes. In the absence of controlled data, a personalized, targeted approach guided by a thorough knowledge of the illness course, and treatment history should be applied. For example, lithium may be a better choice in patients with mania-preponderant illness while lamotrigine could be effective in depression-preponderant illness such as bipolar II disorder [61]. Some researchers recommend starting lithium immediately after delivery for prevention of psychosis or mania. Due to its slower onset of action compared to atypical antipsychotics, lithium may not be effective in the prevention of manic episodes occurring immediately after delivery. Antidepressants are commonly prescribed for postpartum depression; however, there are no data on their effectiveness in the prevention of depressive episodes in women with bipolar disorder.

3.5.4 Primary Prevention and Early Intervention

The postpartum period provides a remarkable opportunity for primary and secondary prevention of bipolar disorder for several reasons [62]. First, mood symptoms/episodes are common after delivery and may herald bipolar disorder. Second, women are routinely under the care of health professionals in the peripartum period and are screened for depression. Third, at-risk women including those with major depressive disorder, subthreshold mood episodes, or common psychiatric comorbidities, and a family history of bipolar disorder can be identified. And finally, putative risk factors such as sleep loss, substance use, or antidepressant therapy can be addressed. The relatively short duration of the risk period makes it easier to carry out preventative strategies. Close monitoring and early intervention via a variety of behavioral and pharmacological treatments might reduce the risk of first onset of hypo/mania in the postpartum period.

3.6 Conclusion

Both pregnancy and the postpartum period can affect the course of bipolar disorder. Studies of mood stabilizer discontinuation have found a high risk of recurrence during pregnancy; however, there is some evidence that pregnancy may have a positive effect on the course of bipolar disorder. Illness risk, including recurrences as well as first onset of bipolar mood episodes, is greater after delivery than during pregnancy. The peripartum management of the disorder involves balancing the risks associated with medication exposure versus the risks associated with untreated maternal illness. Due to its association with first onset of hypo/mania or psychosis, childbirth provides a unique opportunity for prevention or early intervention in women at risk of developing bipolar disorder.

References

1. Bauer M, Glenn T, Alda M, Andreassen OA, Angelopoulos E, Ardau R, Baethge C, Bauer R, Bellivier F, Belmaker RH, Berk M, Bjella TD, Bossini L, Bersudsky Y, Cheung EYW, Conell J, Del Zompo M, Dodd S, Etain B, et al. Influence of birth cohort on age of onset cluster analysis in bipolar I disorder. Eur Psychiatry. 2015;30(1):99–105. https://doi.org/10.1016/j.eurpsy.2014.10.005.
2. Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, Whiteford HA. The prevalence and burden of bipolar disorder: findings from the global burden of disease study 2013. Bipolar Disord. 2016;18(5):440–50. https://doi.org/10.1111/bdi.12423.
3. Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011;68(3):241. https://doi.org/10.1001/archgenpsychiatry.2011.12.
4. Baldassano CF, Marangell LB, Gyulai L, Nassir Ghaemi S, Joffe H, Kim DR, Sagduyu K, Truman CJ, Wisniewski SR, Sachs GS, Cohen LS. Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. Bipolar Disord. 2005;7(5):465–70. https://doi.org/10.1111/j.1399-5618.2005.00237.x.
5. Dell'Osso B, Cafaro R, Ketter TA. Has bipolar disorder become a predominantly female gender related condition? Analysis of recently published large sample studies. Int J Bipolar Disord. 2021;9(1):1–7. https://doi.org/10.1186/s40345-020-00207-z.
6. Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, Keck PE. The impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry. 2002;63(4):284–7.
7. Azorin JM, Angst J, Gamma A, Bowden CL, Perugi G, Vieta E, Young A. Identifying features of bipolarity in patients with first-episode postpartum depression: findings from the international BRIDGE study. J Affect Disord. 2012;136(3):710–5. https://doi.org/10.1016/j.jad.2011.10.003.
8. Inglis AJ, Hippman CL, Carrion PB, Honer WG, Austin JC. Mania and depression in the perinatal period among women with a history of major depressive disorders. Arch Womens Ment Health. 2014;17(2):137–43. https://doi.org/10.1007/s00737-013-0408-1.
9. Sharma V, Xie B, Campbell MK, Penava D, Hampson E, Mazmanian D, Pope CJ. A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. Bipolar Disord. 2014;16(1):16–21. https://doi.org/10.1111/bdi.12140.
10. Viguera AC, Tondo L, Koukopoulos AE, Reginaldi D, Lepri B, Baldessarini RJ. Episodes of mood disorders in 2,252 pregnancies and postpartum periods. Am J Psychiatr. 2011;168(11):1179–85. https://doi.org/10.1176/appi.ajp.2011.11010148.
11. Sharma V, Pope CJ. Pregnancy and bipolar disorder: a systematic review. J Clin Psychiatry. 2012;73(11):1447–55. https://doi.org/10.4088/JCP.11r07499.
12. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. ACOG committee opinion no. 757: screening for perinatal depression. Obstet Gynecol. 2018;132(5):e208–12. https://doi.org/10.1097/AOG.0000000000002927.
13. Sharma V, Al-Farayedhi M, Doobay M, Baczynski C. Should all women with postpartum depression be screened for bipolar disorder? Med Hypotheses. 2018;118(March):26–8. https://doi.org/10.1016/j.mehy.2018.06.016.
14. Wisner KL, Sit DKY, McShea MC, Rizzo DM, Zoretich RA, Hughes CL, Eng HF, Luther JF, Wisniewski SR, Costantino ML, Confer AL, Moses-Kolko EL, Famy CS, Hanusa BH. Onset timing, thoughts of self-harm, and diagnoses in postpartum women with screen-positive depression findings. JAMA Psychiatry. 2013;70(5):490–8. https://doi.org/10.1001/jamapsychiatry.2013.87.
15. Sharma V, Sharma P, Sharma S. Managing bipolar disorder during pregnancy and the postpartum period: a critical review of current practice. Expert Rev Neurother. 2020a;20(4):373–83. https://doi.org/10.1080/14737175.2020.1743684.

16. Sharma V, Singh P, Baczynski C, Khan M. A closer look at the nosological status of the highs (hypomanic symptoms) in the postpartum period. Archiv Women's Mental Health. 2020b;24(1) https://doi.org/10.1007/s00737-020-01023-1.
17. Sharma V, Khan M, Corpse C, Sharma P. Missed bipolarity and psychiatric comorbidity in women with postpartum depression. Bipolar Disord. 2008;10(6):742–7. https://doi.org/10.1111/j.1399-5618.2008.00606.x.
18. Munk-Olsen T, Laursen TM, Meltzer-brody S, Mortensen PB, Jones I. Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders. Arch Gen Psychiatry. 2012;69(4):428–34. https://doi.org/10.1001/archgenpsychiatry.2011.157.
19. Kim J-H, Choi SS, Ha K. A closer look at depression in mothers who kill their children: is it unipolar or bipolar depression? J Clin Psychiatry. 2008;69(10):1625–31.
20. Sharma V, Doobay M, Baczynski C. Bipolar postpartum depression: an update and recommendations. J Affect Disord. 2017;219:105–11. https://doi.org/10.1016/j.jad.2017.05.014.
21. Frey BN, Simpson W, Wright L, Steiner M. Sensitivity and specificity of the mood disorder questionnaire as a screening tool for bipolar disorder during pregnancy and the postpartum period. J Clin Psychiatry. 2012;73(11):1456–61. https://doi.org/10.4088/JCP.12m07856.
22. Sharma V, Xie B. Screening for postpartum bipolar disorder: validation of the mood disorder questionnaire. J Affect Disord. 2011;131(1–3):408–11. https://doi.org/10.1016/j.jad.2010.11.026.
23. Glover V, Liddle P, Taylor A, Adams D, Sandler M. Mild hypomania (the highs) can be a feature of the first postpartum week. Association with later depression. Br J Psychiatry. 1994;164(4):517–21.
24. Bauer AE, Maegbaek ML, Liu X, Wray NR, Sullivan PF, Miller WC, Meltzer-Brody S, Munk-Olsen T. Familiality of psychiatric disorders and risk of postpartum psychiatric episodes: a population-based cohort study. Am J Psychiatr. 2018;175(8):783–91. https://doi.org/10.1176/appi.ajp.2018.17111184.
25. Rusner M, Berg M, Begley C. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. BMC Pregnancy Childbirth. 2016;16(1) https://doi.org/10.1186/s12884-016-1127-1.
26. Veroniki AA, Rios P, Cogo E, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, Macdonald H, Tricco AC. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017;7(7) https://doi.org/10.1136/bmjopen-2017-017248.
27. Wisner KL, Hanusa BH, Peindl KS, Perel JM. Prevention of postpartum episodes in women with bipolar disorder. Biol Psychiatry. 2004;56(8):592–6. https://doi.org/10.1016/j.biopsych.2004.07.022.
28. Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010;3(2):183–92. https://doi.org/10.1586/ecp.10.3.
29. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, Sharma V, Goldstein BI, Rej S, Beaulieu S, Alda M, MacQueen G, Milev RV, Ravindran A, O'Donovan C, McIntosh D, Lam RW, Vazquez G, Kapczinski F, et al. Canadian Network for Mood And Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97–170. https://doi.org/10.1111/bdi.12609.
30. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M, Holmes LB. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012;78(21):1692–9. https://doi.org/10.1212/WNL.0b013e3182574f39.
31. National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance; 2014
32. Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez-Diaz S. Fetal effects of anticonvulsant polytherapies: different risks from different drug combinations. Arch Neurol. 2011;68(10):1273–9. https://doi.org/10.1001/archneurol.2011.133.

33. Sadowski A, Todorow M, Brojeni PY, Koren G, Nulman I. Pregnancy outcomes following maternal exposure to second-generation antipsychotics given with other psychotropic drugs: a cohort study. BMJ Open. 2013;3(7):3062. https://doi.org/10.1136/bmjopen-2013-003062.
34. Wesseloo R, Liu X, Clark CT, Kushner SA, Munk-Olsen T, Bergink V. Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: a population-based cohort study. J Affect Disord. 2017a;218(May):394–7. https://doi.org/10.1016/j.jad.2017.04.070.
35. Wesseloo R, Wierdsma AI, Van Kamp IL, Munk-Olsen T, Hoogendijk WJG, Kushner SA, Bergink V. Lithium dosing strategies during pregnancy and the postpartum period. Br J Psychiatry. 2017b;211(1):31–6.
36. Clark CT, Wisner KL. Treatment of peripartum bipolar disorder. Obstet Gynecol Clin N Am. 2018;45(3):403–17. https://doi.org/10.1016/j.ogc.2018.05.002.
37. Newport DJ, Stowe ZN, Viguera AC, Calamaras MR, Juric S, Knight B, Pennell PB, Baldessarini RJ. Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disord. 2008;10(3):432–6. https://doi.org/10.1111/j.1399-5618.2007.00565.x.
38. Pariente G, Leibson T, Shulman T, Adams-Webber T, Barzilay E, Nulman I. Pregnancy outcomes following in utero exposure to lamotrigine: a systematic review and meta-analysis. CNS Drugs. 2017:1–12. https://doi.org/10.1007/s40263-017-0433-0.
39. Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, Gomes T, Howard LM, Khalifeh H, Krohn H, Larsson H, Lichtenstein P, Taylor CL, Van Kamp I, Wesseloo R, Meltzer-Brody S, Vigod SN, Bergink V. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018;5(8):644–52. https://doi.org/10.1016/S2215-0366(18)30180-9.
40. Patorno E, Huybrechts KF, Hernandez-Diaz S. Response: lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med. 2017;377:893–4.
41. Huybrechts KF, Hernández-Díaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, Cohen JM, Panchaud A, Cohen L, Bateman BT. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry. 2016;73(9):938–46. https://doi.org/10.1001/jamapsychiatry.2016.1520.
42. Park Y, Hernandez-Diaz S, Bateman BT, Cohen JM, Desai RJ, Patorno E, Glynn RJ, Cohen LS, Mogun H, Huybrechts KF. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatr. 2018;175(6):564–74. https://doi.org/10.1176/appi.ajp.2018.17040393.
43. Cohen LS, Góez-Mogollón L, Sosinsky AZ, Savella GM, Viguera AC, Chitayat D, Hernández-Díaz S, Freeman MP. Risk of major malformations in infants following first-trimester exposure to quetiapine. Am J Psychiatr. 2018;175(12):1225–31. https://doi.org/10.1176/appi.ajp.2018.18010098.
44. Damkier P, Videbech P. The safety of second-generation antipsychotics during pregnancy: a clinically focused review. CNS Drugs. 2018;32(4):351–66. https://doi.org/10.1007/s40263-018-0517-5.
45. Leiknes KA, Cooke MJ, Jarosch-von Schweder L, Harboe I, Høie B. Electroconvulsive therapy during pregnancy: a systematic review of case studies. Arch Womens Ment Health. 2015;18(1):1–39. https://doi.org/10.1007/s00737-013-0389-0.
46. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatr. 2007;164(12):1817–24. https://doi.org/10.1176/appi.ajp.2007.06101639.
47. Viguera AC. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatr. 2000;157(2):179–84. https://doi.org/10.1176/appi.ajp.157.2.179.
48. Heron J, Haque S, Oyebode F, Craddock N, Jones I. A longitudinal study of hypomania and depression symptoms in pregnancy and the postpartum period. Bipolar Disord. 2009;11(4):410–7. https://doi.org/10.1111/j.1399-5618.2009.00685.x.

49. Maina G, Rosso G, Aguglia A, Bogetto F. Recurrence rates of bipolar disorder during the postpartum period: a study on 276 medication-free Italian women. Arch Womens Ment Health. 2014;17(5):367–72. https://doi.org/10.1007/s00737-013-0405-4.
50. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJM, Kushner SA, Bergink V. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. Am J Psychiatr. 2016;173(2):117–27. https://doi.org/10.1176/appi.ajp.2015.15010124.
51. Schmidt KA, Palmer BA, Frye MA. Mixed mania associated with cessation of breastfeeding. Int J Bipolar Disord. 2016;4(1):18. https://doi.org/10.1186/s40345-016-0059-z. Epub 2016 Sep 5. PMID: 27593209; PMCID: PMC5011067
52. Sharma V. Weaning and mixed mania-A case report. J Hum Lact. 2018;34(4):745–8. https://doi.org/10.1177/0890334418777695.
53. Sharma V, Baczynski C. Is bipolar post-partum depression overlooked? Lancet Psychiatry. 2019;6(11):891–2. https://doi.org/10.1016/S2215-0366(19)30386-4.
54. Rybakowski J, Jerzy Cubała W, Ałeck PG, Rymaszewska J, Samochowiec J, Szulc A, Dudek D. Recommendations of the polish psychiatric association regarding the treatment of affective disorders in women of childbearing age. Part II: bipolar disorder. Psychiatr Pol. 2019;53(2):263–76. https://doi.org/10.12740/PP/103555.
55. Sharma V, Khan M, Sommerdyk C. Quetiapine in the acute treatment of bipolar postpartum depression: a chart review. J Clin Psychopharmacol. 2015;35(6):733–5. https://doi.org/10.1097/JCP.0000000000000415.
56. Misri S, Abizadeh J, Eng B, A., Albert, G., Ryan, D., & Swift, E. An open-label study of quetiapine extended-release in a sample of postpartum women with bipolar II depressive episode. Curr Psychopharmacol. 2015;4(1):17–26. https://doi.org/10.2174/2211556004666150604235028.
57. Heron J, McGuinness M, Blackmore ER, Craddock N, Jones I. Early postpartum symptoms in puerperal psychosis. BJOG. 2008;115(3):348–53. https://doi.org/10.1111/j.1471-0528.2007.01563.x.
58. Albertini E, Ernst CL, Tamaroff RS. Psychopharmacological decision making in bipolar disorder during pregnancy and lactation: a case-by-case approach to using current evidence. Focus. 2019;17(3):249–58. https://doi.org/10.1176/appi.focus.20190007.
59. Koukopoulos A, Reginaldi D, Tondo L, Visioli C, Baldessarini RJ. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. J Affect Disord. 2013;151(1):105–10.
60. Sharma V, Smith A, Mazmanian D. Olanzapine in the prevention of postpartum psychosis and mood episodes in bipolar disorder. Bipolar Disord. 2006;8(4):400–4.
61. Sharma V, Sommerdyk C. Lamotrigine in the prevention of bipolar II postpartum depression. Prim Care Companion CNS Disord. 2016;18(6)
62. Sharma V, Bergink V, Berk M, Chandra PS, Munk-Olsen T, Viguera AC, Yatham LN. Childbirth and prevention of bipolar disorder: an opportunity for change. Lancet Psychiatry. 2019;6(9):786–92. https://doi.org/10.1016/S2215-0366(19)30092-6.