American Journal of Psychiatric Rehabilitation | Expert Opinion Article

Maternal And Fetal Outcomes in Bipolar Disorder the Impact of Continuing Vs. Discontinuing Mood Stabilizers During Pregnancy

Zeest Shah[1*], Aleena Khawaj[2], Arooma Sagheer[3], Hira Khan[4], Saad Junaid[5]

[*1,2,3,4,5]Resident Psychiatrists Department of Psychiatry and Behavioural Sciences, MTI Ayub Teaching Hospital, [1*]drzeestshah@gmail.com [2]aleenakhawaj@gmail.com [3]saghiraroma@gmail.com [4]hira.khan.hk194@gmail.com [5]saadjunaid10@gmail.com

Submission Date: 30/12/2025, Revised Dates: 6/1/2026, Accepted Date: 27/1/2026 Publication Date: 6/2/2026

ABSTRACT

Background: The perinatal period presents a major clinical challenge for women with bipolar disorder (BD). Concerns about teratogenic risk often lead to the discontinuation of mood-stabilizing medications, potentially increasing vulnerability to severe mood episodes. However, prospective data on this risk-benefit trade-off, particularly in non-Western health care settings, remain limited.

Objective: To prospectively quantify the risk of mood episode recurrence during pregnancy in women with BD, comparing those who continued mood stabilizers with those who discontinued them around conception or in early pregnancy.

Methods: This prospective observational cohort study was conducted at Ayub Teaching Hospital, Abbottabad, Pakistan, from July 1, 2025, to November 30, 2025. Euthymic pregnant women aged 18–45 years with a DSM-5-confirmed diagnosis of Bipolar I or II disorder and gestational age ≤24 weeks were enrolled. Consecutive sampling was used to recruit 86 women, who were categorized according to treatment status at conception or during early pregnancy: 38 in the continuation group and 48 in the discontinuation group. The primary outcome was the first recurrence of a DSM-5-defined mood episode (depressive, manic, hypomanic, or mixed). Group comparisons were performed using chi-square and Fisher's exact tests. Time to recurrence was analyzed using Kaplan-Meier survival curves and the log-rank test. Multivariable Cox regression was planned to identify independent predictors of recurrence.

Results: The discontinuation group had a significantly higher rate of unplanned pregnancies (64.6% vs 42.1%; $p = 0.04$) and greater baseline illness severity, characterized by a higher proportion of Bipolar II subtype (56.3% vs 31.6%; $p = 0.02$), longer illness duration (≥5 years: 66.7% vs 44.7%; $p = 0.03$), a history of rapid cycling (39.6% vs 18.4%; $p = 0.03$), and prior suicide attempts (33.3% vs 15.8%; $p = 0.04$). Lithium use was more common in continuers (52.6% vs 12.5%; $p < 0.001$). The cumulative incidence of any mood episode recurrence during pregnancy was significantly higher in the discontinuation group (62.5% vs 31.6%; $p = 0.004$), with the excess risk most pronounced in the first trimester (33.3% vs 7.9%). Kaplan-Meier analysis demonstrated a significantly shorter time to recurrence in the discontinuation group (log-rank test, $p < 0.01$).

Conclusion: Discontinuation of mood-stabilizing medication in early pregnancy is associated with a significantly higher and earlier risk of mood episode recurrence. These findings from a Pakistani cohort underscore the need for individualized preconception risk-benefit counseling and integrated perinatal psychiatric care, particularly for women with markers of greater illness severity.

Keywords: Bipolar disorder, pregnancy, mood stabilizers, lithium, recurrence, relapse, prospective cohort, Pakistan.

INTRODUCTION

Bipolar disorder (BD) is a chronic and disabling psychiatric illness that affects approximately 1%–2% of the global population and is characterized by recurrent episodes of mania, hypomania, and depression [1,2]. Because its onset commonly occurs during the reproductive years, BD poses unique challenges for women during the perinatal period, when profound biological, psychological, and social changes can destabilize mood [3]. Pregnancy is not protective against recurrence; for many women with BD, it may actually increase vulnerability to mood episodes [4]. Fluctuating hormone levels, disrupted sleep, medication nonadherence, and psychosocial stress may converge to create a high-risk period for relapse [5,6].

Mood episodes during pregnancy carry important consequences for both mother and fetus, including impaired self-care, poor nutrition, increased suicidality, reduced engagement with antenatal services, and possible adverse fetal effects mediated through stress-related physiological pathways [7]. Mood stabilizers, including lithium, anticonvulsants, and atypical antipsychotics, remain central to relapse prevention in BD [8]. However, their use during pregnancy is complex because of concerns about teratogenicity. Lithium has been associated with a small absolute increase in the risk of cardiac

malformations, whereas some anticonvulsants, especially valproate, carry well-established risks of congenital anomalies and neurodevelopmental impairment [9,10]. As a result, many women and clinicians choose to taper or discontinue these medications before conception or immediately after an unplanned pregnancy is recognized [11]. This decision requires a careful balancing of the risks of medication exposure against the risks of untreated maternal illness [12]. Research from high-income countries has shown that rapid discontinuation of mood stabilizers, particularly lithium, is associated with a marked increase in relapse risk, especially during the first trimester and postpartum period [4,13]. Nevertheless, the applicability of these findings to low- and middle-income countries (LMICs), including Pakistan, remains uncertain because of major differences in health care access, cultural perceptions of mental illness, medication availability, and family support systems [14].

In Pakistan, mental health services remain limited, stigma is substantial, and a considerable proportion of pregnancies are unplanned, placing women with BD at particular risk [15,16]. Prospective local data are lacking. This study was therefore designed to address this gap by comparing the risk and timing of mood episode recurrence during pregnancy among women who continued mood stabilizers versus those who discontinued them around conception or in early pregnancy. We also examined the sociodemographic and clinical characteristics associated with treatment discontinuation and relapse. Our aim was to generate locally relevant evidence to inform integrated obstetric and psychiatric care in this under-resourced setting.

METHODOLOGY

This prospective observational cohort study was conducted from July 1, 2025, to November 30, 2025, at Ayub Teaching Hospital, Abbottabad, Pakistan. The study was a collaborative effort between the Departments of Obstetrics and Gynecology and Psychiatry. Pregnant women aged 18–45 years with a confirmed DSM-5 diagnosis of Bipolar I or II disorder were screened for eligibility. Women were eligible if they were euthymic at enrollment, defined as a score of <8 on the Young Mania Rating Scale (YMRS) and <8 on the Hamilton Depression Rating Scale (HAM-D), and were at ≤24 weeks of gestation. Exclusion criteria included an active mood episode at baseline, a comorbid psychotic disorder, substance use disorder within the preceding six months, severe medical or obstetric illness requiring hospitalization, or inability to provide informed consent.

Consecutive sampling was used to recruit eligible participants from antenatal clinics and the psychiatry outpatient department. The sample size was calculated a priori using a two-proportion comparison. Assuming a recurrence rate of 35% in the continuation group and 65% in the discontinuation group [13], with 80% power and a two-tailed alpha of 0.05, a minimum of 80 participants was required. To account for potential loss to follow-up, 86 women were enrolled.

After written informed consent was obtained, participants underwent a comprehensive baseline assessment, including a structured clinical interview to confirm diagnosis and collect detailed sociodemographic and clinical information. Based on their medication status at the time of conception or during the first trimester, participants were categorized into two groups:

1. **Continuation group (n = 38):** Women who continued their prescribed mood-stabilizing medication throughout the periconception period and early first trimester.
2. **Discontinuation group (n = 48):** Women who discontinued their mood-stabilizing medication before conception or during the first trimester. Discontinuation was defined as complete cessation of pharmacotherapy for at least two weeks.

Participants were followed prospectively throughout pregnancy. Regular assessments, including mood ratings using the YMRS and HAM-D, were conducted monthly or more frequently when clinically indicated. The primary outcome was the first recurrence of a mood episode (depressive, manic, hypomanic, or mixed) as defined by DSM-5 criteria. Time to first recurrence was recorded.

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Baseline sociodemographic and clinical characteristics were compared between groups using independent-samples *t* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. The cumulative incidence of mood episode recurrence was compared using the chi-square test. Time to recurrence was analyzed using the Kaplan-Meier product-limit method, and survival distributions were compared using the log-rank test. A multivariable Cox proportional hazards regression model was planned to identify independent predictors of recurrence while adjusting for potential confounders such as baseline illness severity. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 86 pregnant women with bipolar disorder were enrolled, including 38 in the continuation group and 48 in the discontinuation group. Mean age was comparable between the groups (29.4 ± 4.8 vs 28.1 ± 5.2 years; $p = 0.21$). A significantly higher proportion

of women in the discontinuation group reported an unplanned pregnancy (64.6% vs 42.1%; $p = 0.04$). All participants were married (Table 1).

The discontinuation group had a more severe baseline illness profile. Compared with the continuation group, they had significantly higher proportions of Bipolar II subtype (56.3% vs 31.6%; $p = 0.02$), illness duration of at least 5 years (66.7% vs 44.7%; $p = 0.03$), history of rapid cycling (39.6% vs 18.4%; $p = 0.03$), and prior suicide attempts (33.3% vs 15.8%; $p = 0.04$) (Table 2).
Medication profiles also differed significantly between groups. Lithium use was substantially more common in the continuation group (52.6% vs 12.5%; $p < 0.001$). In contrast, anticonvulsant use (45.8% vs 21.1%; $p = 0.01$), adjunctive antidepressant use (41.7% vs 13.2%; $p < 0.001$), and polytherapy (52.1% vs 26.3%; $p = 0.006$) were all more frequent in the discontinuation group (Table 3).

The cumulative incidence of any mood episode recurrence during pregnancy was significantly higher in the discontinuation group than in the continuation group (62.5% [30/48] vs 31.6% [12/38]; $p = 0.004$) (Table 4). This corresponds to a relative risk of 1.98 (95% CI: 1.19–3.30) for recurrence among women who discontinued medication. The timing of recurrence also differed markedly between groups. The excess risk in the discontinuation group was most pronounced during the first trimester, when 33.3% (16/48) of women who discontinued treatment experienced recurrence, compared with 7.9% (3/38) of women who continued treatment. Recurrence rates in the second and third trimesters were more similar between groups (Table 5; Figure 1).

Kaplan-Meier analysis confirmed a significantly shorter time to mood episode recurrence in the discontinuation group. The log-rank test for equality of survival distributions was statistically significant ($\chi^2 = 7.82$, $p = 0.005$), indicating different survival trajectories during pregnancy (Table 6). The median time to recurrence could not be estimated for the continuation group because fewer than half experienced an event, whereas the median time to recurrence in the discontinuation group was approximately 10 weeks (IQR: 6–14 weeks).

Table 1. Sociodemographic Characteristics of Participants

Variable	Continuation (n = 38)	Discontinuation (n = 48)	*p* value
Mean age (years) ± SD	29.4 ± 4.8	28.1 ± 5.2	0.21
Unplanned pregnancy, n (%)	16 (42.1%)	31 (64.6%)	0.04
Married, n (%)	38 (100%)	48 (100%)	—

Table 2. Baseline Clinical Characteristics

Variable	Continuation (n = 38)	Discontinuation (n = 48)	*p* value
Bipolar II subtype, n (%)	12 (31.6%)	27 (56.3%)	0.02
Illness duration ≥5 years, n (%)	17 (44.7%)	32 (66.7%)	0.03
History of rapid cycling, n (%)	7 (18.4%)	19 (39.6%)	0.03
Prior suicide attempt(s), n (%)	6 (15.8%)	16 (33.3%)	0.04

Table 3. Baseline Treatment Profiles

Treatment variable	Continuation (n = 38)	Discontinuation (n = 48)	*p* value
Lithium use, n (%)	20 (52.6%)	6 (12.5%)	<0.001
Anticonvulsant use, n (%)	8 (21.1%)	22 (45.8%)	0.01
Adjunctive antidepressant use, n (%)	5 (13.2%)	20 (41.7%)	<0.001
Polytherapy (≥2 medications), n (%)	10 (26.3%)	25 (52.1%)	0.006

Table 4. Overall, Mood Episode Recurrence

Outcome	Continuation (n = 38)	Discontinuation (n = 48)	*p* value
Any mood episode recurrence, n (%)	12 (31.6%)	30 (62.5%)	0.004

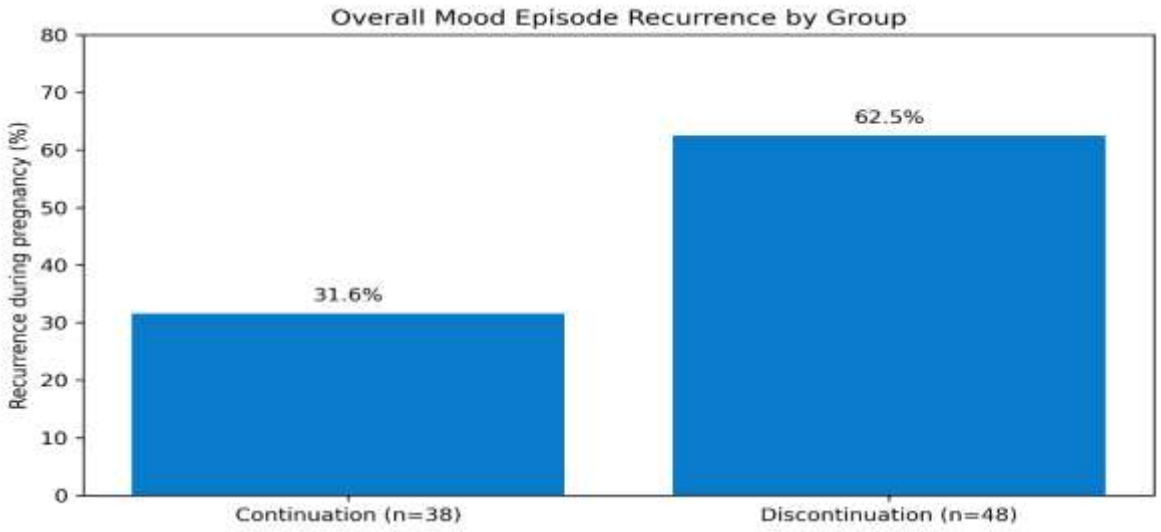


Table 5. Timing of First Mood Episode Recurrence by Trimester

Trimester of recurrence	Continuation (n = 38)	Discontinuation (n = 48)
First trimester (weeks 1–12), n (%)	3 (7.9%)	16 (33.3%)
Second trimester (weeks 13–28), n (%)	6 (15.8%)	10 (20.8%)
Third trimester (weeks 29–40), n (%)	3 (7.9%)	4 (8.3%)

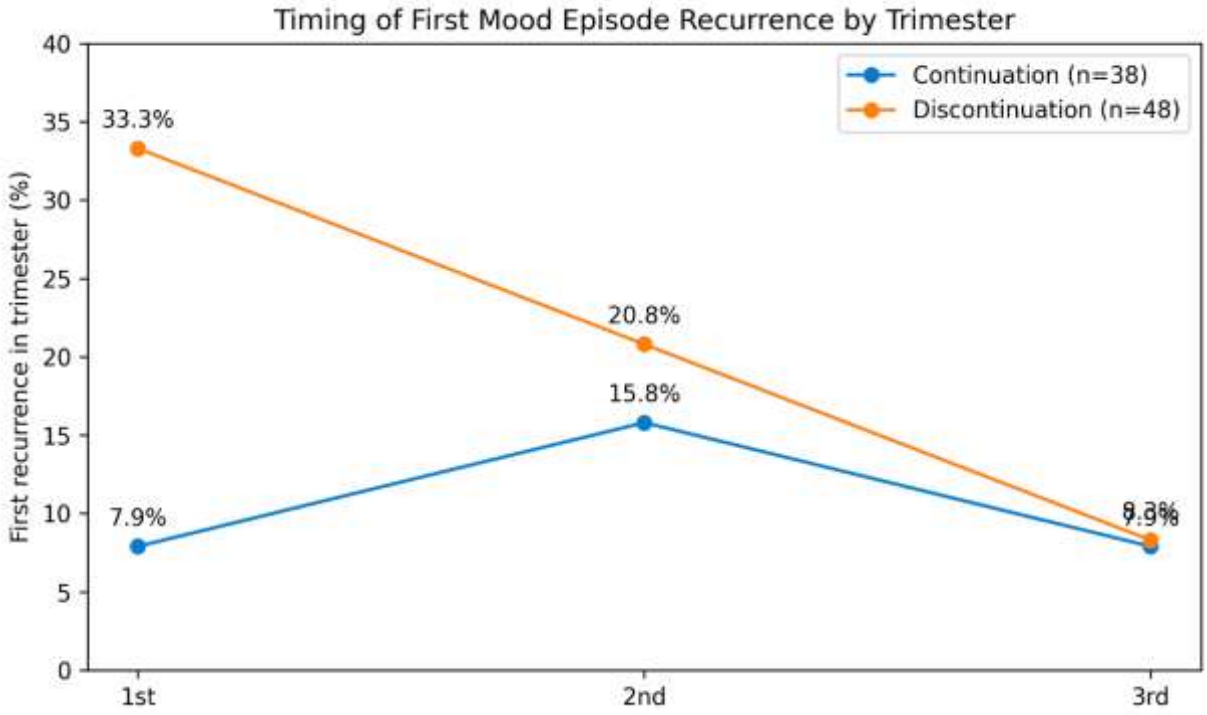
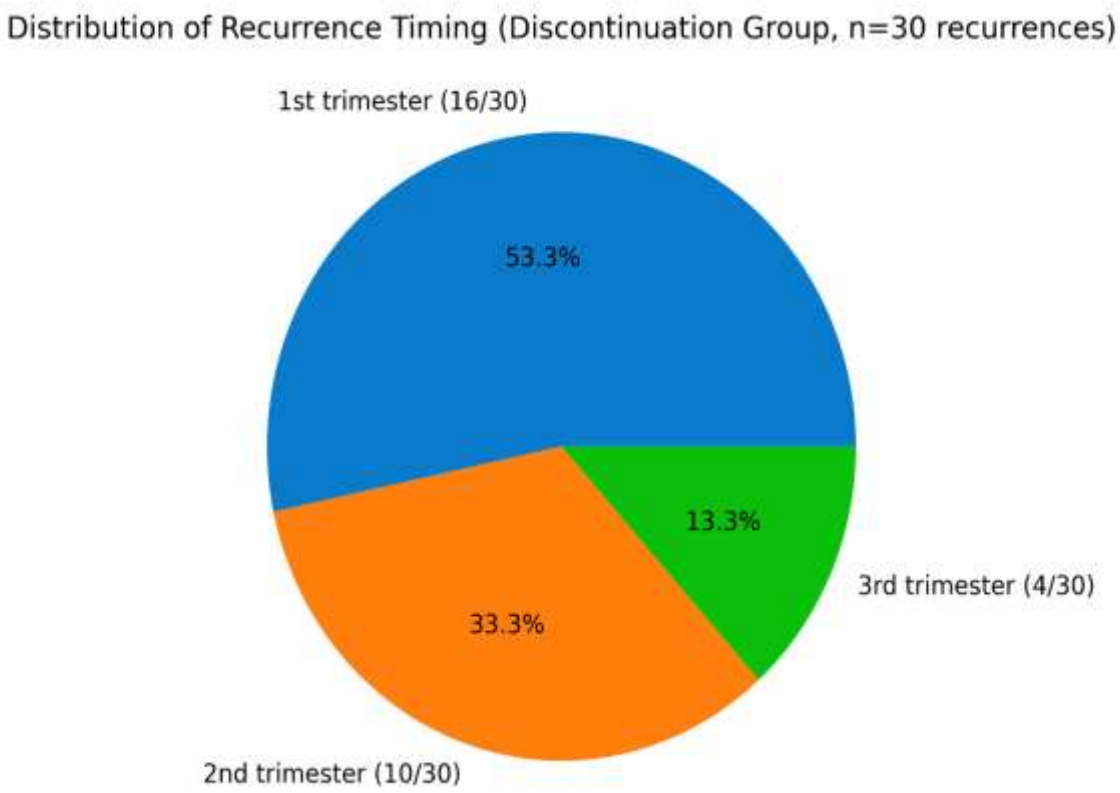


Table 6. Survival Analysis Summary

Analysis	Result
Kaplan-Meier curves	The discontinuation group showed a steeper and earlier decline in survival probability (remaining recurrence-free).
Log-rank test	$\chi^2 = 7.82$, $p = 0.005$ (significant difference between groups)
Median time to recurrence	Continuation group: not reached (>50% remained recurrence-free). Discontinuation group: 10 weeks (IQR: 6–14 weeks).



Discussion

This prospective cohort study from Pakistan provides clinically relevant real-world evidence regarding the risks associated with discontinuing mood stabilizers during pregnancy. Our findings show that women who stopped pharmacotherapy around conception were almost twice as likely to experience mood episode recurrence during pregnancy as those who continued treatment. The excess risk was particularly marked during the first trimester, a period already characterized by substantial physiological and psychological adjustment. These findings are consistent with earlier reports from high-income countries [4,13] and extend that literature to a different cultural and health care context. A major strength of the present study is its prospective design and detailed characterization of the cohort. Importantly, the decision to discontinue medication did not appear random. Women in the discontinuation group had a more severe baseline illness trajectory, including longer illness duration, higher rates of rapid cycling, greater suicidality, and a higher prevalence of Bipolar II disorder. This pattern reflects confounding by indication and is important when interpreting the results [17]. Women with more severe or complex illness may be more likely to stop medication because of fears regarding teratogenicity, concerns about polypharmacy, or unplanned pregnancy that prevents timely preconception planning. Therefore, the higher relapse rate in this group is likely related both to medication discontinuation itself and to underlying clinical vulnerability. The significantly higher rate of unplanned pregnancy in the discontinuation group (64.6%) is a particularly important finding. It suggests missed opportunities for preconception counseling, during which the risks and benefits of different treatment strategies could have been discussed and individualized plans developed. In Pakistan, where psychiatric and reproductive health services are often fragmented, this gap may be especially pronounced [18]. The finding supports stronger integration of mental health counseling into routine reproductive and family planning services. The observed treatment patterns are also noteworthy. Greater lithium use in the continuation group may reflect better preconception planning and greater access to specialist care, as lithium requires careful

monitoring. By contrast, the higher rates of anticonvulsant use and polytherapy in the discontinuation group may indicate attempts to manage more complex or treatment-resistant illness before pregnancy, or prior switching from lithium because of perceived teratogenic risk. The higher use of adjunctive antidepressants in the discontinuation group may further reflect a more unstable pre-pregnancy course, particularly with depressive symptoms [19]. The timing of recurrence has direct clinical implications. The sharp rise in first-trimester relapses among women who discontinued treatment (33.3% vs 7.9%) supports the hypothesis that withdrawal of a stabilizing agent during a period of major hormonal change creates a high-risk window for mood destabilization [20]. The closer recurrence rates observed later in pregnancy may suggest that women who remain well through the first trimester represent a more resilient subgroup, or that physiological changes later in pregnancy provide relative stabilization regardless of medication status [21].

Strengths and Limitations

The main strengths of this study are its prospective cohort design and its focus on an understudied population in an LMIC setting. It provides much-needed locally relevant evidence. However, several limitations should be acknowledged. First, although the study was adequately powered for the primary comparison, the relatively small sample size limited the ability to perform robust multivariable analyses that could fully separate the effects of medication discontinuation from baseline illness severity. Second, because the study was observational and non-randomized, causality cannot be definitively established, and residual confounding by indication remains possible. Third, the single-center tertiary care setting may limit generalizability to women managed in community settings with less access to specialist care. Fourth, the lack of blinded outcome assessment may have introduced observer bias. Finally, follow-up ended at delivery, so postpartum relapse risk, which is known to be high in BD, could not be evaluated [22]. Despite these limitations, the findings have immediate practical relevance. They strongly support proactive, collaborative, and individualized preconception counseling for women of childbearing age with BD. Clinical discussions should move beyond a narrow focus on teratogenicity and instead weigh the risks of both medication exposure and untreated illness. For women with severe illness markers, such as long illness duration, rapid cycling, or previous suicide attempts, the risks of discontinuation may substantially outweigh the risks of continuing a carefully selected medication at the lowest effective dose. Lithium, despite its known risks, remains an important treatment option, and strategies are available to reduce fetal exposure while preserving maternal stability [23]. At the health system level, this study underscores the urgent need for integrated perinatal mental health services in Pakistan. This includes training obstetric clinicians to identify bipolar disorder, establishing clear referral pathways to psychiatric services, and promoting collaborative care models in which maternal mental health is managed alongside routine antenatal care. Reducing the burden of unplanned pregnancy through improved access to family planning for women with severe mental illness is also a critical preventive strategy.

Conclusion

Discontinuation of mood-stabilizing medication during early pregnancy is associated with a significantly higher risk of early and severe mood episode recurrence among women with bipolar disorder in Pakistan. This risk appears greatest among women with markers of more severe baseline illness. These findings challenge the assumption that medication cessation is always the safest strategy during pregnancy and instead support a nuanced, individualized approach to treatment planning. They also highlight the need for integrated perinatal mental health services capable of delivering timely, evidence-based, and patient-centered care to this vulnerable population.

Author Contributions

Zeest Shah conceived and designed the study, supervised data collection, and drafted the initial manuscript. Aleena Khawaja contributed to study design, data acquisition, and manuscript revision. Arooma Sagheer participated in data collection, statistical analysis, and interpretation of results. Hira

Khan contributed to literature review, data organization, and manuscript editing. Saad Junaid assisted with data analysis, interpretation, and final proofreading of the manuscript. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest:

The authors declare that they have no conflict of interest.

Funding:

This research received no external funding.

Acknowledgment

The authors would like to thank the Department of Psychiatry and Behavioural Sciences and the Department of Obstetrics and Gynecology, MTI Ayub Teaching Hospital, Abbottabad, for their support during the conduct of this study. The authors are also grateful to all the participants who generously contributed their time and cooperation to this research.

Future Research Gap

Further research is needed using larger, multicenter prospective cohorts to improve the generalizability of findings and to better adjust for potential confounding factors such as illness severity, medication type, and psychosocial stressors. Future studies should also evaluate maternal and neonatal outcomes in greater detail, assess postpartum relapse risk, and examine the long-term safety and effectiveness of different mood-stabilizing treatment strategies during pregnancy. In addition, qualitative and mixed-methods research may help clarify why women discontinue treatment and how preconception counseling and integrated perinatal psychiatric services can be improved in low- and middle-income settings such as Pakistan.

References

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet*. 2016;387(10027):1561–1572.
2. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;68(3):241–251.
3. Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and ACOG. *Obstet Gynecol*. 2009;114(3):703–713.
4. Viguera AC, Whitfield T, Baldessarini RJ, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry*. 2007;164(12):1817–1824.
5. Payne JL. The role of estrogen in mood disorders in women. *Int Rev Psychiatry*. 2003;15(3):280–290.
6. Bodén R, Lundgren M, Brandt L, Reutfors J, Kieler H. Risks of adverse pregnancy and infant outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population-based cohort study. *BMJ*. 2012;345:e7085.
7. Stein A, Pearson RM, Goodman SH, et al. Effects of perinatal mental disorders on the fetus and child. *Lancet*. 2014;384(9956):1800–1819.
8. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet*. 2013;381(9878):1672–1682.
9. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med*. 2017;376(23):2245–2254.
10. Wesseloo R, Kamperman AM, Munk-Olsen T, et al. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry*. 2016;173(2):117–127.
11. Sharma V, Burt VK, Ritchie HL. Bipolar II postpartum depression: detection, diagnosis, and treatment. *Am J Psychiatry*. 2009;166(11):1217–1221.
12. Di Florio A, Forty L, Gordon-Smith K, et al. Perinatal episodes across the mood disorder spectrum. *JAMA Psychiatry*. 2013;70(2):168–175.
13. Viguera AC, Nonacs R, Cohen LS, et al. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. *Am J Psychiatry*. 2000;157(2):179–184.
14. Patel V, Saxena S, Lund C, et al. The Lancet Commission on global mental health and sustainable development. *Lancet*. 2018;392(10157):1553–1598.
15. Mirza I, Jenkins R. Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: systematic review. *BMJ*. 2004;328(7443):794.
16. Husain N, Chaudhry N, Afridi MA, et al. Life stress and depression in a tribal area of Pakistan. *Br J Psychiatry*. 2007;190:36–41.

17. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615–625.
18. Howard LM, Khalifeh H. Perinatal mental health: a review of progress and challenges. *World Psychiatry*. 2020;19(3):313–327.
19. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Mol Psychiatry*. 2019;24(2):198–217.
20. Jones I, Chandra PS, Dazzan P, Howard LM. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the postpartum period. *Lancet*. 2014;384(9956):1789–1799.
21. Wesseloo R, Liu X, Lambrichts S, et al. Lithium dosing strategies during pregnancy and the postpartum period. *Br J Psychiatry*. 2017;211(1):31–36.
22. McAllister-Williams RH, Baldwin DS, Cantwell R, et al. British Association for Psychopharmacology guidelines for bipolar disorder. *J Psychopharmacol*. 2017;31(5):495–553.
23. Gentile S. Managing bipolar disorder in pregnancy and postpartum. *CNS Drugs*. 2012;26(6):459–480.