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*Original article*

# TREATMENT CHALLENGES OF BIPOLAR DISORDER DURING THE PERINATAL PERIOD

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**Abstract**

**Introduction:** The perinatal period presents significant challenges for women with bipolar disorder (BD), who face heightened risks of affective episodes and postpartum psychosis. The clinical management requires balancing maternal mental stability with fetal safety, considering the teratogenic risks of some mood stabilizers.

This study aimed to examine the course of BD during the perinatal period, assess associated risk factors, and evaluate therapeutic interventions.

**Material and methods:** This prospective cohort study included 23 women, diagnosed with BD (ICD-10), over the course of six months. Assessments included the Edinburgh Postnatal Depression Scale (EPDS), Young Mania Rating Scale (YMRS), clinical interviews, and a questionnaire on sociodemographic and risk factors. Patients received combined pharmacological and psychotherapeutic treatment.

**Results:** The EPDS scores showed a low likelihood of depression at baseline, 3, and 6 months (56.5%, 69.6%, 69.6%), with mean scores decreasing from baseline to three months and slightly increasing at six months ($p = 0.81$). The YMRS scale indicated a significant reduction in mania from baseline to six months ($p = 0.038$).

All participants reported risk factors, including history of affective episodes (95.6%), traumatic events, intimate-partner violence (34.8%), substance abuse (26.1%), and unplanned pregnancy (21.7%). There was no significant correlation between risk factors and depression ($p > 0.05$).

**Conclusion:** The findings of the study confirm the increased risk of mood episodes in women with (BD) during the perinatal period. Continuous treatment and long-term monitoring play a vital role in reducing the incidence and severity of affective episodes. Identifying and managing risk factors is crucial for providing effective individualized care during this vulnerable period.

**Keywords:** bipolar, pregnancy, perinatal, treatment, risk, factors

## Introduction

Pregnancy is a period of profound physiological and psychological changes, presenting unique challenges for women with chronic psychiatric disorders, particularly bipolar disorder (BD). Bipolar disorder is a chronic mental health condition characterized by relapsing affective episodes, with an estimated prevalence of 1% in the general population[1]. Onset typically

occurs in early adulthood, often overlapping with peak reproductive years of women 18-30, thus placing women with BD at a significant risk of affective episodes during the perinatal period, encompassing pregnancy and the postpartum year [2].

In the past, pregnancy was considered a period of relative emotional stability for women with BD, with reduced rates of hospital admissions and suicide compared to non-pregnant periods[3]. The myth of the "protective" effect of pregnancy has been potentially perpetuated by the traditional cultural beliefs regarding childbirth and motherhood as blissful periods in a woman's life, as well as by the underrepresentation of the population of pregnant women in research studies and screening programs. However, over the years emerging evidence suggests that the perinatal period is an especially vulnerable period for the mental health of mothers due to the hormonal fluctuations, physiological changes, and the psychosocial stress accompanying childbirth and parenthood, which could particularly contribute to the exacerbation of BD symptomatology[4]. Studies reveal that women with BD have a substantially higher risk of experiencing perinatal mood episodes, with pooled prevalence of 55-60 % for women with BD-I or BD II experiencing recurrence during pregnancy or postpartum[5,6]. Depressive episodes are generally more prevalent than manic episodes, although women with bipolar I disorder have a seven-fold higher risk of experiencing severe manic or psychotic episodes postpartum compared to those with bipolar II disorder[6].

The prominent vulnerability during the postpartum period for patients diagnosed with BD includes the risk of postpartum psychosis, a psychiatric emergency that occurs 100 times more frequently in women with BD compared to the general population[7]. Symptoms typically emerge within the first two weeks postpartum, characterized by rapid onset, cognitive disorganization, hallucinations, and delusions, often accompanied by increased risks of maternal suicide and infanticide, thus being defined as a psychiatric emergency[8]. Prompt recognition of symptoms and timely treatment are critical to mitigating adverse outcomes.

The treatment of BD during pregnancy presents significant challenges, since clinicians must carefully balance the risks of untreated affective episodes against the teratogenic risks of psychotropic medications[2]. Lithium discontinuation, for instance, significantly increases the risk of relapse, particularly in the postpartum period[9]. Untreated BD during the perinatal period, on the other hand, could lead to adverse pregnancy outcomes, deteriorated maternal mental health and fetal development, including impulsive behaviors, poor adherence to perinatal care, adverse birth outcomes such as low birth weight and premature delivery, and exposure to high doses of psychotropic medications in case of acute episodes[1]. Furthermore, maternal mental health especially during the first year postpartum, closely associated with the mother-infant bonding, is detrimental for the future psychosocial, emotional and cognitive development of the child, highlighting the necessity for regular screening, close monitoring and specialized therapeutic interventions[10].

Despite these challenges, comprehensive treatment planning - focused on preconception counseling, medication adjustments, and coordinated psychiatric and obstetric care - can mediate risks and promote maternal and fetal well-being.

Over the past eight years, there has been a growing clinical and research interest in the field of perinatal mental health in North Macedonia, marked by several research studies focusing predominantly on perinatal depression[11-14]. These studies, which involved recruiting patients from the Cabinet for treatment of women during pregnancy and postpartum as well as screening for perinatal depression in recruited patients from several national hospitals for Gynaecology and Obstetrics, have highlighted an increasing trend in the prevalence of perinatal depression across the country, especially pronounced during the COVID-19 pandemic and the postpandemic period[15]. The findings emphasize significant associations between maternal mental health and various risk factors, such as previous depressive episodes, traumatic events, unplanned pregnancies, family and intimate-partner violence, advanced maternal age or

minority and COVID-19 pandemic-related factors. Despite these advancements, no prior research has focused specifically on the perinatal mental health of patients with bipolar disorder and its associations with risk factors. Given that this population represents a particularly vulnerable group, this knowledge gap motivated us to conduct the present study, aiming to evaluate the course of BD during the perinatal period, assess the impact of risk factors, and examine the effectiveness of therapeutic interventions.

**Material and methods**

This prospective cohort study was conducted at the University Clinic for Psychiatry, Skopje, North Macedonia, over the course of 6 months. The study aimed to evaluate the mental health outcomes, in terms of affective episodes during the perinatal period, in patients with bipolar affective disorder (BD), and their association with socidemographic and psychosocial risk factors.

***Participants:*** The study included 23 female patients, recruited from the Cabinet for treatment of women during pregnancy and postpartum at the University Clinic for Psychiatry in Skopje, diagnosed with bipolar disorder in compliance with ICD-10 criteria, prior to the inclusion in the study. Participants, aged 18 to 45 years, were at different stages of pregnancy at the beginning of the study.

***Interventions:*** Participants were treated as outpatients at the Cabinet for treatment of women during pregnancy and postpartum and/or the Day Hospital Unit at the University Clinic for Psychiatry in Skopje. A combined treatment approach was employed, encompassing psychopharmacological therapy and psychosocial interventions delivered by a multidisciplinary team including: a psychiatrist trained in the field of perinatal psychiatry, psychiatry trainees, a clinical psychologist, social worker, and nurse. The psychosocial interventions were delivered in a group and individual setting. Regarding the psychopharmacological treatment, therapy was individually tailored according to the needs and clinical presentation of patients. During the course of the study, there was a regular interclinical collaboration with the University Clinic for Gynaecology and Obstetrics regarding pregnancy and general health follow-ups. All treatments were delivered following the guidelines for antenatal and postnatal care[16]. The mood stabilizer sodium valproate was excluded, and predominantly changed with second generation of antipsychotics with mood stabilizing effect, with or without additional antidepressants or anxiolytic medication. In patients where treatment with lithium was continued or initiated, the plasma concentrations of lithium were monitored monthly until the 34 gestational week, and weekly until delivery, accompanied by regular monitoring of the fluids balance.

***Outcome Measures:*** Participants in this study were evaluated at three assessment points: baseline, at 3 months, and 6 months after the start of treatment. Baseline data collection included a structured psychiatric interview, a sociodemographic questionnaire, and psychodiagnostic assessments using the Edinburgh Postnatal Depression Scale (EPDS) and Young Mania Rating Scale (YMRS) to measure affective symptoms. The EPDS and YMRS were additionally administered at the second (3$^{rd}$ month) and third (6$^{th}$ month) assessment point to evaluate changes in depressive and manic symptomatology over the course of the treatment. Depression symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-reported measure scored on a 4-point scale (0-3; range 0-30, with higher scores indicating greater severity). Originally developed for postnatal use, it is also applicable during pregnancy. A meta-analysis of 36 studies reported optimal sensitivity and specificity at a cut-off of 11, with scores of 13 or higher indicating pronounced symptoms[17].

Symptoms of mania were evaluated using the Young Mania Rating Scale, which is an 11-item clinician-administered tool with five levels of severity[18]. Items were selected based on core symptoms of mania in bipolar disorder, covering the full spectrum from mild to severe.

Ratings were based on the patient's self-report over the past 48 hours and the clinician's observations.

**Results**

The study sample comprised 23 female patients diagnosed with bipolar affective disorder, recruited from the Cabinet for treatment of women during pregnancy and postpartum. Table 1 presents the sociodemographic data. A significantly larger percentage of 69.6% of participants were over 30 years of age compared to other age groups (p = .0060).

The difference observed in patients who were married, accounting for 78.3% compared to other marital status modalities, was significant (p = .0000). Additionally, 69.6% of patients had a stable socioeconomic status (p = .0078), and 87.0% belonged to the Christian faith (p = .0000).

**Table 1.** Presentation of Sociodemographic Data (in %)

| ***Age*** | | | ***Marital status*** | | | | | ***Socioeconomic status*** | | ***Education*** | | | ***Religion*** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≤20 | 20-30 | ≥30 | Married | Unofficial mar. union | Alone | Widow | Divorced | Sustainable | Uunsustainable | Faculty | High school | Elementary school | Christian | Muslim |
| 4.3 | 26.1 | 69.6 | 78.3 | 8.7 | 4.3 | 4.3 | 4.3 | 69.6 | 30.4 | 34.8 | 60.9 | 4.3 | 87 | 13 |

Regarding education, 60.9% have a secondary education level, but the difference compared to other educational modalities was not significant (p = .0764) (Table 1).

The pregnancy-related data show that the largest, though non-significant, percentage of participants (56.5%) have had one pregnancy (p = .1396). A significant percentage of participants (60.9%) have had one completed pregnancy (p = .0069). The majority (78.3%) have had a normal course of pregnancy (p = .0001), and 47.8% delivered via caesarean section (p = .0631) (Table 2).

**Table 2.** Presentation of Variables Related to Pregnancy (in %)

| ***Number of pregnancies*** | | | ***Number of completed pregnancies*** | | | | | | ***Course of pregnancy*** | | ***Mode of delivery*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | >=3 | Ongoing pregnancy | 1 | 2 | >=3 | Miscarriage | Unsuccessful IVF | Normal | Complicated | Ongoing pregnancy | Normal delivery | Preterm birth | Caesarean section | Miscarriage/terminated |
| 56.5 | 8.7 | 34.8 | 4.3 | 60.9 | 21.7 | 4.3 | 4.3 | 4.3 | 78.3 | 21.7 | 8.7 | 13 | 21.7 | 47.8 | 8.7 |

**Table 3.** Presentation of Variables Related to Psychiatric Treatment

| ***Psychiatric treatment*** | **%** |
|---|---|
| Outpatient | 17.4 |
| Outpatient and inpatient | 82.6 |
| ***Psychopharmacotherapy*** | **%** |
| Antipsychotics | 21.7 |
| Antidepressants + Anxiolytics | 4.3 |
| Antidepressants + Antipsychotics | 4.3 |
| Anxiolytics + Antipsychotics | 21.7 |
| Antidepressants + Anxiolytics + Antipsychotics | 17.4 |
| Mood stabilizer | 4.3 |
| Mood stabilizer + Antidepressants + Anxiolytics + Antipsychotics | 4.3 |
| Mood stabilizer + Anxiolytics + Antipsychotics | 8.7 |
| Mood stabilizer + Antipsychotics | 4.3 |
| Mood stabilizer + Antidepressants + Antipsychotics | 8.7 |

Psychiatric treatment of patients was combined (outpatient and inpatient) in 82.6% of cases (p = .0000).

Regarding psychopharmacotherapy, the majority of patients (91.3%) took antipsychotics, either in combination with other therapies (16 patients) or as monotherapy (5 patients) (p = .000, compared to others). Antidepressants were used by 39.1% (in combination), anxiolytics by 34.8%, and mood stabilizers by 30.4%, in combination with other therapies in 6 patients and as monotherapy in one patient (Table 3).

All patients were found to have at least one risk factor.

Table 4 shows the presence of specific risk factors: 34.8% of patients had a family history, experience of domestic violence, or traumatic events; 21.7% had an unplanned pregnancy; 95.6% had past episodes; 30.6% experienced intimate partner violence; and 26.1% reported alcohol or psychoactive substance abuse.

**Table 4.** Presentation of Variables Related to Risk Factors (in %)

| **Family History** | | **Domestic violence** | | **Traumatic events** | | **Unplanned pregnancy** | | | **Had past episode** | | **Intimate partner violence** | | **Alcohol or psychoactive substance abuse** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | Yes | No | Yes | No | Yes | No | Yes | Missing | No | Yes | No | Yes | No | Yes |
| 65.2 | 34.8 | 65.2 | 34.8 | 65.2 | 34.8 | 73.9 | 21.7 | 4.3 | 4.3 | 95.6 | 69.6 | 30.4 | 73.9 | 26.1 |

**Table 5.** Total Score from the EPDS Scale for Postnatal Depression at Baseline, 3 Months, and 6 Months of Treatment in the Perinatal Period (in %)

| ***Postnatal depression at baseline*** | | | | | ***Postnatal depresion after 3 months*** | | | | | ***Postnatal depresion after 6 months*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0-9 | 10-12 | 13-14 | 15-19 | 20-30 | 0-9 | 10-12 | 13-14 | 15-19 | 20-30 | 0-9 | 10-12 | 13-14 | 15-19 | 20-30 |
| 56.5 | 13.0 | 4.3 | 8.7 | 17.4 | 69.6 | 21.7 | 8.7 | 0 | 0 | 69.6 | 8.7 | 4.3 | 4.3 | 13.0 |

During all three assessment points, based on EPDS scoring (baseline, 3 months, and 6 months), the majority of patients, over 50.0%, showed a low likelihood of depression (56.5%, 69.6%, 69.6%). The percentage difference compared to other modalities was significant at p <.05 (p = .00) (Table 5).

At baseline, 17.4% of patients were recorded with severe depression, 13.0% with mild depression, 8.7% with moderate to severe depression, and one patient with moderate depression.

At 3 months, 21.7% of patients were recorded with mild depression and 8.7% with moderate depression.

At 6 months, 13.0% of patients were recorded with severe depression, 8.7% with mild depression, and one patient each with moderate and moderate-to-severe depression (Table 5).

The average EPDS score at baseline was the highest, though not significantly, compared to the averages at 3 and 6 months, at 11.2 ± 8.9, with a high standard deviation indicating greater variability around the mean. The range was 2 to 30. The average score corresponded to mild depression, warranting careful monitoring and further evaluation (Table and Figure 6).

At 3 months, the average EPDS score decreased to 8.0 ± 2.9, with a range of 2 to 14. The average score corresponded to a low likelihood of depression, and clinical assessment was advised if concerns arose (Table 6 and Figure 1).

At 6 months, the average EPDS score increased to 9.9 ± 8.2, with a range of 3 to 29. A high standard deviation was observed, indicating greater variability around the mean. The average score corresponded to mild depression, warranting careful monitoring and further evaluation (Table 6 and Figure 1).

The difference between the average EPDS scores across the three time points was not significant (Friedman test, p = .80968).

**Table 6.** Presentation of Average EPDS Values and Friedman Test

| EPDS | Average - Rank | Sum of Ranks | Average | Std. Dev. |
|---|---|---|---|---|
| EPDS - 0 (baseline) | 2.065217 | 47.50000 | 11.17391 | 8.809355 |
| EPDS - 3 months | 2.043478 | 47.00000 | 7.95652 | 2.915137 |
| EPDS - 6 months | 1.891304 | 43.50000 | 9.91304 | 8.027866 |

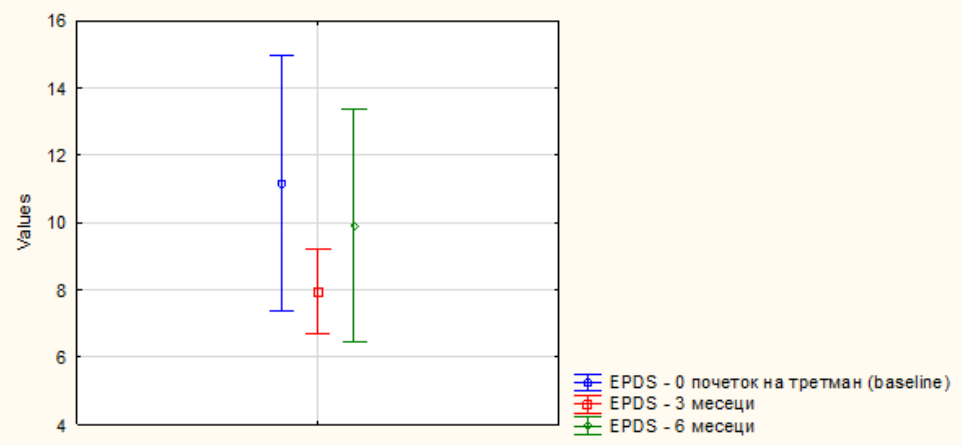


**Fig. 1.** Presentation of Average EPDS Values

**Table 7.** Total Score from the YMRS Scale for Mania Assessment at Baseline, 3 Months, and 6 Months of Treatment in the Perinatal Period

| ***Mania at baseline*** | | | | | ***Mania after 3 months*** | | | | | ***Mania after 6 months*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0-12 | 13-19 | 20-25 | 26-37 | 38-60 | 0-12 | 13-19 | 20-25 | 26-37 | 38-60 | 0-12 | 13-19 | 20-25 | 26-37 | 38-60 |
| 56.5 | 17.4 | 0 | 4.3 | 21.7 | 87.0 | 4.3 | 4.3 | 0 | 4.3 | 87.0 | 0 | 13.0 | 0 | 0 |

During all three time periods, based on YMRS scoring for mania assessment (baseline, 3 months, and 6 months), the majority of patients did not exhibit significant mania (56.5%, 87.0%, 87.0%). The percentage difference compared to other mania modalities was significant ($p < .05$**;**$(p = .00)$.

At baseline, 21.7% of patients exhibited extreme mania, 17.4% mild mania, and one patient had moderate mania. At 3 months, mild, moderate, and extreme mania were recorded in one patient each (4.3%). At 6 months, moderate mania was recorded in 13.0% of patients (Table 7).

The average YMRS score at baseline was the highest compared to the averages at 3 and 6 months, measuring **16.1 ± 20.1**. A high standard deviation indicated greater variability around the mean, with a range of 0 to 58. The average score corresponded to mild mania (Table 8 and Figure 2).

At 3 months, the average YMRS score decreased to **7.0 ± 12.5**, with a range of 0 to 58. A high standard deviation indicated significant variability around the mean. The average score suggested no significant mania (Table 8 and Figure 2).

At 6 months, the average YMRS score further decreased to **6.1 ± 7.3**, with a range of 0 to 23. The average score suggested no significant mania (Table and Figure 8).

The difference between the average YMRS scores across the three time points was significant at **p < 0.05** (Friedman test, p = .037857).

**Table 8.** Presentation of Average YMRS Scores

| YMRS | Average - Rank | Sum of - Ranks | Average | Std. Dev. |
|---|---|---|---|---|
| Young Mania Rating Scale - 0 (baseline) | 2.260870 | 52.00000 | 16.08696 | 20.09277 |
| Young Mania Rating Scale - 3 | 1.913043 | 44.00000 | 7.00000 | 12.48272 |
| Young Mania Rating Scale - 6 | 1.826087 | 42.00000 | 6.08696 | 7.29828 |

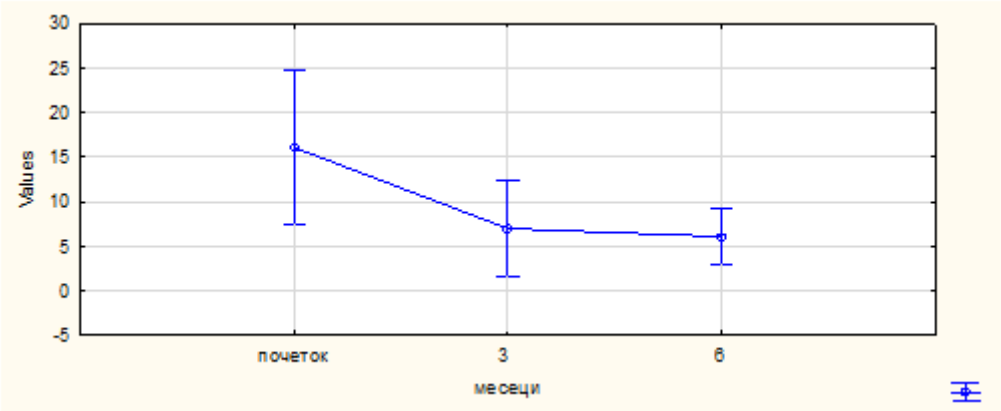


**Fig. 2.** Mean YMRS scores

No association was found between risk factors (domestic violence, alcohol or psychoactive substance abuse, past episodes, unplanned pregnancy, intimate partner violence, stressful conditions, family history) and perinatal depression at the start of treatment, 3 months into treatment, and 6 months into treatment during the perinatal period ($p > .05$ - Chi-square test).

**Discussion**

This prospective cohort study included 23 patients with bipolar affective disorder (BD) treated at the Cabinet for treatment of women during pregnancy and postpartum at the University Clinic for Psychiatry in Skopje, presenting with heterogeneous sociodemographic characteristics. Although younger maternal age during pregnancy has been frequently pointed out in the literature as a risk factor for worsening mental health in patients with BD during the perinatal period[19,20], in the current study, a significantly larger percentage of participants (69.6%) fell into the age group over 30 years. A twofold higher risk of relapse during the perinatal period among women over 30 years (60% compared to 30% of women under 30) was also identified in the study by Doyle *et al.* [1], which can be attributed to biological factors associated with aging as well as psychosocial or clinical differences characteristic to advanced age in mothers.

A significantly larger portion of participants were married (78.3%), had a stable socioeconomic status (69.6%), and had completed high-school education (60.9%). However, these sociodemographic characteristics did not show a statistically significant association with their mental health outcomes during the perinatal period.

An analysis of data related to pregnancy history among the cohort revealed that the majority of recruited patients who sought treatment at the Cabinet for treatment of women during pregnancy and postpartum (60.9%) were primiparas. This finding aligns with a systematic review of studies[21], which demonstrated a significant association between the number of pregnancies and affective episodes, specifically that primiparas have an increased risk of affective episodes during pregnancy and particularly in the early postpartum period. Additionally, primiparas have an elevated risk of developing manic episodes or postpartum psychosis within the first few weeks postpartum[22]. Several factors may contribute to the heightened risk of mental health deterioration during a first pregnancy/childbirth, including increased psychosocial stress associated with entering motherhood, lower confidence in coping with the challenges of this role linked to the stigma surrounding the diagnosis of a chronic mental disorder, concerns about the impact of pharmacological treatment on pregnancy and fetal health, fears about breastfeeding, and sleep disturbances due to newborn care[23].

Among patients included in our study, a significant proportion (47.8%) delivered via Cesarean section. The association between BD, various delivery modalities, and pregnancy outcomes was also explored in the Swedish National Cohort Study[24], which reported that patients diagnosed with BD had approximately 50% higher rates of Cesarean section or instrumental vaginal delivery (vacuum or forceps).

In the group of participants, 82.6% received both inpatient and outpatient care during the course of their illness. Regarding the observation period during the study (the perinatal period), two patients were hospitalized, one toward the end of the third trimester and the other within the first three months postpartum. Literature highlights this period - the last trimester and puerperium - as the most vulnerable for psychiatric deterioration and relapse of affective episodes, with or without psychotic symptomatology in BD patients, with an estimated prevalence ranging from 25% to 94%[25,21]. Biological factors associated with childbirth, particularly the abrupt decline in placental hormones elevated during pregnancy, play a key role. These are further compounded by physiological and social factors such as sleep

deprivation before and after childbirth[26], newborn care, changes in family dynamics, and potentially insufficient social support.

Patients in this study were treated with a combined therapeutic protocol that included psychopharmacotherapy and psychosocial interventions, delivered by a multidisciplinary team at the Cabinet for treatment of women during pregnancy and postpartum. Given the high risk of relapse due to discontinuation of pharmacological therapy during the perinatal period in BD patients, all included participants received pharmacological treatment throughout pregnancy and after delivery, in compliance to evidence-based recommendations. A significant majority of patients (91.3%) received second-generation antipsychotics (SGAs) with mood stabilizing effects, either as monotherapy (21.7%) or in combination with other psychotropic medications depending on the clinical presentation. The use of SGAs in BD patients during the perinatal period is consistent with current clinical recommendations[16], supported by evidence from recent studies evaluating the safety of this class of drugs during pregnancy, which show that SGAs carry an insignificant risk of teratogenic effects, with an absolute risk of congenital malformations of 2.5% compared to 1.9% in unexposed populations [27,28].

Mood stabilizers are typically an indispensable component of the psychopharmacological regimen for treating BD. However, some have proven teratogenic properties and carry an increased risk of congenital malformations in the fetus as well as neurodevelopmental disturbances depending on the gestational age at exposure. The use of sodium valproate/ valproic acid is contraindicated during pregnancy and, according to recent recommendations, in women as well as in men of reproductive age[29], due to its proven teratogenicity and high risk of neural tube defects, intrauterine growth retardation, neonatal toxicity, and neurobehavioral effects in newborns[2]. For this reason, it was discontinued in the therapy of all included patients and predominantly replaced with SGAs.

Despite the estimated higher risk of congenital, primarily cardiac, malformations in the fetus, lithium therapy was continued or included in 30% of patients in the study during certain phases of treatment due to unsatisfactory responses to alternative therapy and relapse prevention in high-risk patients who had previously achieved effective remission with this agent. Robust data from the literature, including clinical studies, systematic reviews, and meta-analyses, highlight the risk of relapse during the perinatal period in BD patients following lithium discontinuation (70% in pregnant *versus* 24% in non-pregnant patients), especially after abrupt discontinuation, with a more pronounced risk in the postpartum period[9]. This supports the protective effect of lithium in preventing relapse during this vulnerable period [30].

Lithium treatment in these patients was conducted according to clear guidelines, including monitoring plasma lithium concentrations every four weeks and weekly after 36 weeks of gestation until the end of pregnancy, along with fluid balance monitoring due to the risk of dehydration[16]. No congenital malformations were recorded in the newborns of the included patients. These findings demonstrate the clinical challenges of managing BD during pregnancy and the necessary skill of clinicians in balancing the risk of maternal relapse against the teratogenic risk of medications.

Identified risk factors for mental health deterioration during the perinatal period were recorded in all participants, including positive family history of BD, family violence, traumatic events (34.8%), intimate partner violence (30.6%), unplanned pregnancies (21.7%), and alcohol or psychoactive substance misuse (26.1%). Nearly all patients reported a history of affective episodes (95.6%). Some participants reported multiple risk factors. Although statistical analysis did not confirm a significant correlation between risk factors for mental health deterioration and the worsening of psychiatric condition during the perinatal period as evaluated through EPDS and YMRS psychodiagnostic instruments, numerous data in the literature highlight the importance of psychosocial factors such as unplanned pregnancy[31,1,32,23], intimate partner violence[33,34], substance and alcohol misuse[35] , family

violence history[36], and family history of BD[19] on the psychological well-being of BD patients.

Unplanned pregnancies, which are disproportionately common among women with bipolar disorder (BD), present significant challenges, exacerbated by behaviors during manic episodes, including impulsivity, risky sexual activity, and substance use[32,1]. These pregnancies often increase the risk of relapse due to abrupt medication changes and elevated psychosocial stress, contributing to potential adverse outcomes for both mother and fetus, including teratogenic risks and neonatal complications [9,31]. The lack of statistical significance regarding the correlation between unplanned pregnancy and mental health outcomes in our study may be attributed to the fact that the majority of participants included were married. While being married does not eliminate the higher risk of unplanned pregnancies in individuals with bipolar disorder, it may serve as a protective factor by facilitating family planning and providing additional support system. Addressing this issue requires the establishment of specialized perinatal mental health services and fostering a knowledgeable and non-stigmatizing attitude of health professionals in order to deliver comprehensive psychoeducation and family planning counselling[23].

The individual history of prior affective episodes during the perinatal period stands out in the literature as the most significant risk factor associated with the risk of relapse during pregnancy or postpartum in BD patients [22,19]. As this is the first study of its kind in our country, and there is no data on the prevalence of affective episodes during pregnancy in BD patients, was as well as no data on the incidence of affective episodes during previous pregnancies assessed in the included participants, this study could serve as a motive for initiating a longitudinal study focused on continuous monitoring of these individuals. This would track the rate of affective episodes during the perinatal period in future pregnancies and assess the history of affective deterioration in the perinatal period as a significant risk factor demonstrated in the results of the cited studies.

Finally, our study confirms the findings from the literature that women with bipolar affective disorder (BD) are at a high risk of experiencing affective episodes during the perinatal period, with depressive episodes being particularly prevalent in the postpartum period. The results from our study align with the existing evidence showing that depressive episodes are more frequent and have a later onset than manic episodes. At six-month follow-up, we observed a slight increase in severe depression cases (13.0%), even after initial improvements at three months, with no registered severe depression in comparison to severe depression being registered in 17.4% of patients at baseline, indicating the potential for recurrent depressive symptoms in this period. This finding is consistent with a study by Perry *et al*., who reported that women with BD experience episodes 3.5 times more frequently during the postpartum period than during pregnancy, with depression being the most common type of episode.

***Study limitations:*** This study has several limitations. Firstly, the relatively small sample size of 23 participants limits the generalizability of the findings, hence a larger study population would allow for broader applicability of the results. Additionally, the study population was exclusively recruited from the Cabinet for the treatment of women during pregnancy and postpartum, which may not fully reflect the diverse range of women with bipolar disorder (BD) in the perinatal period. Future studies should aim to include participants from different institutions within secondary healthcare setting to provide a more comprehensive understanding of the condition and the impact of potentially different treatment strategies. The ongoing monitoring of participants is expected to yield valuable longitudinal data, including psychological outcomes during potential future pregnancies. In our future research, we will strive to include screening for BD symptomatology in perinatal women, which would aid in early detection and appropriate intervention.

## Conclusion

This study contributes to a better understanding of BD during the perinatal period by examining the prevalence of mood episodes, associated risk factors, and the effectiveness of therapeutic interventions in North Macedonia. The results of the study confirm that BD women are at a high risk for mood episodes during the perinatal period. While continuous treatment mitigates severe mood deterioration, BD women remain vulnerable, necessitating long-term monitoring. Although no direct significant correlation was observed in this study, existing literature suggests that risk factors such as unplanned pregnancy, abrupt medication changes, and intimate partner violence are associated with adverse outcomes in BD women during the perinatal period. Understanding and managing these risks is essential for comprehensive BD care. Given the scarcity of regional data, this study delivers information about the current clinical practice and insights into the management of BD. This offers foundation for further development of both the clinical and research practice in the perinatal mental healthcare, improving outcomes for both mothers and their infants.

***Conflict of interest statement***. None declared.

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