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Does Pregnancy Have an Effect on the Course of the Bipolar Disorder?

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ABSTRACT

Objective: Limited data exist regarding the influence of pregnancy and the postpartum period on the trajectory of bipolar disorder. This study aims to investigate the potential predictive power of pregnancy and/or the postpartum period on future mood episodes in individuals with bipolar disorder.

Methods: The study sample consisted of 92 female participants, with 72 of them having experienced at least 1 pregnancy. To compare the groups, the Mann–Whitney *U*-test was employed. Additionally, logistic regression analysis was conducted to identify potential predictor variables associated with the cumulative number of mood episodes throughout the life span.

Results: Women who had an affective episode during pregnancy had an earlier onset of bipolar disorder than women who did not have an affective episode during pregnancy ($P = .001$). The frequency of affective episodes was higher in women with a pregnancy history than in women without a pregnancy history ($P = .036$). Postpartum depression is significantly more common in patients with a history of an affective episode during pregnancy ($P = .003$). The age ($P = .001$) and age at onset ($P = .001$) of bipolar disorder are significantly lower in patients with a history of an affective episode during pregnancy. Overall, it can be said that affective episodes and age predict lifetime episodes in women with bipolar disorder.

Conclusion: According to the results of this study, pregnancy may provide protection against exacerbations of mood episodes during index pregnancy. However, factors such as sleep disturbances, changes in family relationships, and cessation of child support may increase the risk for further episodes.

Keywords: Bipolar disorder, postpartum mood episodes, pregnancy

INTRODUCTION

Bipolar disorder (BD) is a lifelong, relapsing–remitting disease. The gender difference has not been reported so far;[1] however, Del'Osso et al[2] reported an increase in the prevalence of BD in women in recent years. There are some clinical differences between males and females. The age at the onset of BD in women is approximately 5 years later.[3,4] The first period is often a depressive episode with atypical features. In addition, rapid cycling BD is more common in women.[5] Age of menarche is not different between women with and without BD.[6] There are contradictory information about affective exacerbations during pregnancy. While some studies have reported lower or similar prevalence rates during pregnancy,[7-9] some suggest a marked increase in rates of affective exacerbations. Freeman

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et al[10] suggested that pregnancy is a risk factor for mood episodes. One of the well-known causes of manic-depressive exacerbations during pregnancy is the discontinuation of mood stabilizers during pregnancy.[11,12] Prophylactic treatment during pregnancy reduces the relapse risk of mood episodes.[12-15] In women with bipolar disorder who do not use prophylactic treatment, the relapse rate is 40%; however, the rate of relapse in women with bipolar disorder receiving maintenance treatment is 19.4%.[13] Grof et al[7] emphasized the protective effects of pregnancy in lithium-responsive women with bipolar disorder type I. The duration and the number of episodes during pregnancy are significantly lower in the lithium-responsive group. If there is an increase in episodes, it is not certain whether the reason is related to pregnancy or not. The risk of relapse persists during pregnancy, despite prophylactic treatment. In addition to hormonal changes, the number of previous episodes, duration of illness, and social-environmental factors can cause exacerbations during pregnancy.[12]

Women with bipolar disorder are at high risk for relapses. Risk of readmissions in 19 days following childbirth is 37.22% in women with bipolar disorder.[16] The recurrence rates were 2.9 times higher during the postpartum period compared to women in the non-postpartum period.[11] Giving birth is an important risk factor for postpartum episodes of psychiatric disorders.[11,17] During the peripartum period, psychotic symptoms may appear, and in this situation, the assessment of manic and depressive states should be assessed. Marce[18] reported that 29 out of 44 cases with psychotic symptoms had diagnosis of manic episodes. The reported risk of recurrence of any major affective episodes during pregnancy and the postpartum period is approximately 50% for bipolar I disorder and 40% for bipolar disorder.[19] In a review study, the relapse risk was reported 35% for bipolar disorder, and the risk increased to 66% in medication-free patients.[20] About 20%-30% of postpartum exacerbations occur within the first month postpartum in women with BD, and most of these episodes are depressive.[14,21] Akdeniz et al[22] reported that 32% of women with BD experienced at least 1 mood episode during the prenatal period and that the age of onset of BD was earlier in these women.

The presence of a history of postpartum depressive episodes increases the risk of recurrence of depressive episodes, regardless of postpartum periods.[23] In a 4-year follow-up study, patients with first-episode psychosis were evaluated for the prognosis of episodes, and it found that the risk was limited to postpartum periods; however, non-postpartum severe recurrences were observed in 32% of women, mainly in the bipolar spectrum.[24] According to a meta-analysis study, the estimated risk of future relapses is 43.5% in patients with first-episode psychosis, with the remaining women experiencing isolated postpartum psychosis.[25]

There are limited data reporting the effects of pregnancy and postpartum episodes on the course of BD. Our aim in this study is to investigate whether the pregnancy and/or postpartum period are predictive of future mood episodes.

MATERIAL AND METHODS

Participants

Ethical approval for this study was obtained from the local ethics committee (2018/1457). Informed written consent was obtained, and then a diagnostic interview was conducted using the Structured Clinical Interview for DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)). The *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (DSM-5) could not be used in the diagnosis of BD due to the lack of Structured Clinical Interview for DSM-5 training during this time. Between August 2018 and June 2019, 92 female patients with BD who were treated in the outpatient and inpatient clinics of the psychiatry department were included in the study. There are 72 women with at least 1 previous pregnancy history.

Procedure

At the time of the interview, the patients were euthymic. The Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) were applied to all participants. Information on demographic data, obstetric history, and the course of the mood episodes during pregnancy and postpartum were obtained retrospectively. Women between the ages of 18 and 65 with a diagnosis of bipolar disorder who signed the voluntary consent form were included in this study. Acute episodes of depression, mania or hypomania, schizoaffective disorder, mental retardation, illiteracy, and not signing consent forms were the exclusion citeria.

Measures

The HDRS was developed by Hamilton.[26] It is widely used to determine the severity of symptoms in depressive patients. In this study, a 17-question version of the scale with different symptom counts was used. A Likert-type scoring system is used for rating. The Turkish validity and reliability study was conducted by Akdemir et al[27] (1996).

The YMRS[28] consists of 11 items, each of which measures 5-stage symptom severity. In the Turkish validity and reliability study of the scale, the internal consistency coefficient was found to be 79%, the consensus of the researchers among the scale items was 63.3%-95.5%, and kappa values were found between 0.114 and 0.849.[29]

Statistical Analysis

Data was analyzed using Statistical Package for the Social Sciences Statistics software, version 18 (SPSS Inc.; Chicago, IL, USA). Data were not normally distributed according to the Kolmogorov–Smirnov test. Categorical variables are evaluated with the chi-square test, and continuous variables are evaluated with the Mann–Whitney *U*-test. The Spearmen correlation analysis is used to investigate the relationship between the number of total episodes, disease, and patient characteristics. Lastly, linear regression analysis is performed to identify which variables have an impact on the number of total episodes.

RESULTS

The study included 72 patients with a history of previous pregnancy and 21 patients without a history of pregnancy. However, 1 of the patients with a history of pregnancy was excluded from the study because she reported more than 200 episodes. Of the 92 women (55 were diagnosed with bipolar I disorder and 37 were diagnosed with bipolar II), 71 had a history of at least 1 previous pregnancy (out of the 71 participants, 28 were diagnosed with bipolar II disorder, while 43 were diagnosed with bipolar I disorder). All participants were on medication. Equivalent doses of medicines were neither calculated nor noted. Patients did not report medication use during pregnancy, except for those with manic episodes. The first episode was defined as mania in 33 patients, hypomania in 2 patients, and depression in 57 patients. About 26 of the patients were working, and 66 were housewives. While 63 (87.5%) of the patients with a pregnancy history lived in nuclear families, 9 (12.5%) lived in extended families, and 20

(100%) of the patients without a pregnancy history declared that they lived in nuclear families ($P = .096$). There was no difference between the groups with and without pregnancy in terms of comorbid psychiatric disorders, smoking, or substance use. Alcohol use was reported by 12.5% (9) of those with a history of pregnancy and 35% (7) of those without a history of pregnancy ($P = .019$). No significant difference was found between the groups in terms of substance use. Patients with a history of pregnancy were older than those without a history of pregnancy ($P < .0001$). The educational level was significantly higher in those without a pregnancy history than in those with pregnancy history ($P = .001$). The age at onset of BD is significantly earlier in those without a history of pregnancy than in those with a history of pregnancy ($P = .001$). The number of any mood episodes (the number of lifetime mood episodes) were higher in those with a history of pregnancy compared to those without history of pregnancy ($P = .036$). There is no difference between 2 groups in terms of marital status, family history of BD, type of first attack, HAM-D, and YMRS scores (Table 1).

Patients with a history of pregnancy are divided into 2 groups according to the history of any mood episode during pregnancy. The patients with a history of mood episodes during pregnancy were younger than patients without a history of mood episodes during pregnancy ($P = .001$). The age at onset of BD was earlier in women who had an affective episode during pregnancy compared to those who did not have any affective episodes during pregnancy ($P = .001$). There was no significant difference between patients with and without a history of episodes during pregnancy in terms of alcohol, smoking, substance use, or additional psychiatric disorders. The total number of episodes after pregnancy describes all episodes after pregnancy in patients with a history of pregnancy. When patients with and without any mood episodes during pregnancy were compared, no difference was found in terms of episodes after pregnancy. Seventeen (81.0%) of those who had an episode during pregnancy lived in nuclear families, 4 (19.0%) in extended families, and 46 (90.2%) of those who did not have an episode during pregnancy lived in nuclear families and 5 (9.8%) in extended families. The YMRS scores were higher in patients with a history of mood episodes during pregnancy. There is no difference between the 2 groups in terms of educational level, number of lifetime mood episodes, or HAM-D scores (Table 2).

A correlation analysis of the lifetime number of lifetime episodes with variables such as age, age at onset of the disease, number of total episodes during and after pregnancy, number of pregnancies, education, HAM-D, and YMRS scores was performed using the Spearman test. The number of lifetime mood episodes has a low and inverse correlation with age at onset ($P = .001$), a very low correlation with HAM-D scores, and a very strong correlation with total episodes after pregnancy (Table 3).

Linear regression analysis is used to determine which factors predicted the number of lifetime mood episodes. According to the results, age at onset of BD and the number of episodes after pregnancy predicted the number of lifetime mood episodes (Table 4). A significant regression equation was found ($F = 1719.737$, $P < .0001$). The assumptions of error independence were met for analysis (Durbin–Watson = 1.988; adjusted $R^2 = 0.987$). The highest Variance inflation factor (VIF) value for the model was 1.048.

Table 1. Comparison of Some Sociodemographic Data and Some Disease Characteristics in Women With and Without Lifetime Pregnancy

	Lifetime Pregnancy, Negative (n = 21)		Lifetime Pregnancy, Positive (n = 71)		Statistical Analysis		
	N	%	N	%	χ^2	*df*	*P*
Marital status					28.846	2	<.0001
Single	10	47.6	2	2.8			
Married	7	33.3	49	69.0			
Divorced/widow	4	19.0	20	28.2			
Family history of BD	12	57.1	35	49.3	0.399	1	.622
Type of first attack					3.875	2	.133
Mania	4	19.0	29	40.8			
Hypomania	1	4.8	1	1.4			
Depression	16	76.2	41	57.7			
Family type					2.771	1	.096
Nuclear	20	100.0	63	87.5			
Extended	0	0.0	9	12.5			
Comorbid psychiatric disorders	3	15.0	13	18.1	0.102	1	.750
Smoking	10	50.0	29	40.3	0.606	1	.436
Alcohol	7	35.0	9	12.5	5.515	1	.019
Substance use	2	10.0	2	2.8	1.963	1	.161
	Mean	**SD**	**Mean**	**SD**	***U***	***Z***	***P***
Age	31.33	12.216	45.13	11.605	302.000	−4.128	<.0001
Educational level	12.05	3.694	8.44	4.188	389.500	−3.367	.001
Age at onset of BD	21.86	6.295	29.55	10.333	399.000	−3.226	.001
Number of lifetime episodes	9.71	17.816	16.37	25.335	521.500	−2.094	.036
HAM-D	7.43	6.860	7.11	6.703	725.500	−0.187	.852
YMRS	3.33	6.688	2.21	3.865	702.500	−0.430	.668

BD, bipolar disorder; HAM-D, Hamilton Depression Scale; YMRS, Young Mania Rating Scale.

Table 2. Comparison of Some Sociodemographic Data and Some Disease Characteristics in Women With and Without Any Affective Episode During Pregnancy

	Episode During Pregnancy, Negative (n=50)		Episode During Pregnancy, Positive (n=21)		Statistical Analysis		
	N	%	N	%	X^2	*df*	*P*
Marital status					1.146	2	.620
Single	2	4.0	0	0.0			
Married	35	70.0	14	66.7			
Divorced/widow	13	26.0	7	33.3			
Family history of BD	22	44.0	13	61.9	1.681	1	.300
Type of first attack					5.466	2	.056
Mania	24	48.0	5	23.8			
Hypomania	0	0.0	1	4.8			
Depression	26	52.0	15	71.4			
Family type					1.162	1	.281
Nuclear	46	90.2	17	81.0			
Extended	5	9.8	4	19.0			
Comorbid psychiatric disorders	9	17.6	4	19.0	0.020	1	.888
Smoking	22	43.1	7	33.3	0.594	1	.441
Alcohol	5	9.8	4	19.0	1.162	1	.281
Substance use	1	2.0	1	4.8	0.432	1	.531
Postpartum depression	8	16.0	11	52.4	9.987	1	.003
	Mean	**SD**	**Mean**	**SD**	***U***	***Z***	***P***
Age	48.14	11.707	37.95	7.671	266.000	−3.341	.001
Educational level	8.26	4.280	8.86	4.028	510.500	−0.317	.751
Age at onset of BD	31.94	10.555	23.86	7.241	278.000	−3.193	.001
Number of lifetime episodes	14.41	23.685	21.04	28.974	411.500	−1.436	.131
Number of episodes after pregnancy	13.42	23.616	19.05	29.137	521.000	−0.051	.960
HAM-D	6.82	6.706	7.81	6.809	485.000	−0.628	.530
YMRS	1.26	2.562	4.48	5.344	362.500	−2.376	.017

BD, bipolar disorder; HAM-D, Hamilton Depression scale; YMRS, Young Mania Rating Scale.

DISCUSSION

The mean age of women with a lifetime pregnancy history was significantly higher than that of those without pregnancy. Having children may enable patients to comply with regular outpatient follow-ups. In those with lifetime pregnancies, the age of onset of BD was found to be significantly later. This may be associated with the onset of episodes during pregnancy. We have found that the age of onset of BD in women who had any mood episodes during pregnancy was significantly lower than that of those who did not have an affective episode during pregnancy. This finding suggests that gestational periods may be associated with mood episodes. In the study of Akdeniz et al,[22] the age of onset of BD in women who reported a mood episode in the peripartum period was found to be significantly lower than that of those who did not report any episodes in the peripartum period.

Educational level of women with a history of pregnancy is significantly lower than that of women without pregnancy. Women with a history of pregnancy may have been married at an early age and could not continue their education, or they may have married at

Table 3. Correlation Analysis Results of Age, Age at Onset, Number of Total Episodes During and After Pregnancy, Number of Pregnancies, Education, HAM-D and YMRS Scores with the Number Lifetime Mood Episodes

	Number of Lifetime Episodes		
	N	*r*	*P*
Age at onset of BD	71	−0.380	.001
Number of total episodes during pregnancies	71	0.203	.089
Number of total episodes after pregnancies	71	0.929	<.0001
Age	71	−0.039	.747
Education	71	0.005	.964
HAM-D	71	0.290	.014
YMRS	71	0.161	.181

HAM-D, Hamilton Depression Scale; YMRS, Young Mania Rating Scale.

Table 4. Regression Analysis Results of Number of Total Episodes (Age, Age at Onset of Bipolar Disorder, Number of Total Episodes After Pregnancies, Number of Total Episodes During Pregnancies, HAM-D, YMRS, Postpartum Depression)

	β	SE	95% CI	*P*
Age at onset of bipolar disorder	−0.109	0.35	−0.179 to −0.040	.002
Number of total episodes after pregnancies	0.987	0.14	0.959-1.016	<.0001

an early age and had children because they did not continue their education.

In patients with bipolar disorder, the rates of alcohol dependence and alcohol abuse are 27.6% and 16.1%, respectively.[30] The risk of alcohol use disorder is higher in women than in men.[31] In this study, alcohol use is reported by 4 patients. Alcohol use is significantly higher in women without a history of pregnancy. However, in terms of alcohol use, there was no statistical difference between the groups with and without pregnancy-related episodes. According to this result, we may suggest that being married may be a protective factor for alcohol use.

In this study, 21 out of 72 (29.2%) bipolar women defined at least 1 mood episode during pregnancy. It is not known whether they received maintenance therapy during pregnancy. Many factors have been identified in this regard, such as duration of illness, age at onset, rapid cycling, mixed episodes, previous history of suicide, unplanned pregnancy, and discontinuation of mood stabilizers.[12] In the study by Viguera et al,[12] the prevalence of at least 1 episode during pregnancy was found to be 37% in those receiving prophylactic treatment. Accordingly, our results were below these rates. Some studies have reported that the risk of hospital readmission during pregnancy is lower than during the postpartum period.[16,17] Our results are consistent with those of Akdeniz et al.[22] In that study, 32% of the patients described an affective episode during the pregnancy. In a review article, the recurrence rate during pregnancy in women with bipolar disorder is reported as 19%. Considering the prospective studies, the recurrence rate was found to be 17%.[15]

Of the patients who had mood episodes during pregnancy, 33.3% (n = 7) had manic, 42.9% (n = 9) had depressive, and 23.8% (n = 5) had both depressive and manic episodes. Consistent with previous studies, most of the episodes during pregnancy were reported as depressive type in our study.[7,14,22,32] In this study, 56% (n = 41) of patients described their first episode as depressive. This result is consistent with the literature.[33–35] The first episode of a depressive episode in bipolar disorder is associated with a longer disease course, frequent episodes, higher rates of depressive episodes, psychotic symptoms and stressful life events, and increased risk of suicide.[33,34] Although not statistically significant ($P = .56$), the first episode was the depressive type in 71.4% of patients with a history of pregnancy. Viguera et al[12] reported that the depressive first episode may be related to maintenance discontinuation but not to recurrences. Therefore, episodes during pregnancy may be related to the discontinuation of mood stabilizers, or, alternatively, patients with the first episode of depressive episode bipolar disorder may be prone to any affective episodes due to hormonal changes.

In our study, the number of lifetime episodes was found to be significantly higher in women with a history of pregnancy than in women without pregnancy. Unlike our study, Stevens et al[15] reported that there is no significant differences between pregnant and nonpregnant women in terms of lifetime manic and depressive episodes. Additionally, they found no differences in the total number of days ill between 2 groups. Considering patients who were pregnant possibly discontinue maintenance therapy. In addition to interruption of the prophylactic treatment, childbirth,[16] and sleep disturbances,[36] the exacerbation of an episode may have increased the subsequent episodes.[37] It is not significant between patients with and without an episode during pregnancy. Gilden et al[38] reported that total bipolar episodes were higher in patients with at least 1 episode during pregnancy or postpartum period. According to the results of this study, pregnancy may be protective for exacerbations of any mood episodes during the index pregnancy period; however, factors like sleeping disturbances, changes in family relationships, and cessation of maintenance may increase the risk of subsequent episodes.

Correlation analysis was performed with variables such as lifetime episode frequency, current age of the patient, age at onset of disease, number of pregnancies, and episodes during pregnancy. In women with lifetime pregnancies, lifetime episode frequency was found to be correlated with the age of onset of illness and the number of episodes after pregnancy. A negative, moderate correlation was found between the early onset of the disease and the number of episodes ($r = -0.370$, $P = .001$). In the study of Stevens et al,[15] no significant difference was found between the age of onset of the disease in pregnant and nonpregnant women. On the contrary, 2 studies found a correlation between the age of early onset and the number of episodes, similar to our study.[11,22]

Prevalence of postpartum depression varies in the literature. For instance, postpartum depression in mothers who give birth to full-term babies is reported to be 19% in Germany[39] and 10%-19% in Japan.[40] In mothers with premature labor, the prevalence increased up to 40%.[41] In adolescent mothers, the prevalence is reported at 26%.[42] Many factors contribute to the development of postpartum depression, such as stressful life events, being a single mother, having more than 1 child, and most importantly, a previous history of psychiatric disorders.[43] Postpartum depression is a subcategory of major depressive disorder that increases mortality and morbidity, such as increased risk of suicide, impaired attachment, and impaired breastfeeding.[44,45] Postpartum depression is approximately 4 times more common in bipolar disorder than unipolar depression (OR 2.48) and is seen in 23.6% of women with bipolar spectrum disorder and 7% of women with unipolar mood disorder (OR 3.33).[46] Additionally, postpartum depression occurs at younger ages in bipolar disorder than in unipolar depressive disorder.[47] Prenatal depression is associated with postpartum depression.[43,47] In this study, 20 out of 72 patients described postpartum depression. The rate of postpartum depression was found to be significantly higher in women who had an attack during pregnancy (57.9%, n = 11, $P = .001$). Out of 7 patients who had experienced a mood episode during their first pregnancy, 6 (85.7%) women experienced a further or subsequent episode during the postpartum period. The odds ratio to experience a mood episode during the first postpartum period among patients who had experienced an episode during their first pregnancy was 9.6.[22] Munk-Olsen et al[17] reported that the risk of postpartum psychiatric disorders is reduced in subsequent pregnancies. Primiparity is also an important risk factor for first-episode psychiatric symptoms, especially in bipolar disorder. Additionally, as the time interval increases between first and second pregnancies, the risk of postpartum psychiatric disorders increases.[48]

Overall, patients with bipolar disorder using prophylactic pharmacotherapy during pregnancy had a significantly lower relapse rate.[20] However, despite preventive treatment, affective exacerbations remain high among women with bipolar disorder.[20,49] Of the women with bipolar disorder (N = 41), 24.4% relapsed during pregnancy, despite prophylaxis use by the majority throughout pregnancy. The postpartum relapse rate was highest in women with bipolar disorder who experienced mood episodes during pregnancy (60.0%).[13] In this study, postpartum depression in women with an episode during pregnancy was significantly higher than in women without an

episode during pregnancy. About 8 of 50 women without an episode during pregnancy described postpartum depression, and 11 of 21 women with an episode during pregnancy described postpartum depression. Depressive episode during pregnancy is another important risk factor for postpartum depression.[50] In the latter group, postpartum depressive episodes may be part of the continuum of pregnancy-related depression. Rommel[24] et al reported that 32.1% of women (n = 34) with postpartum psychosis experienced at least 1 nonpuerperal episode during the 4-year follow-up. Fourteen of these women experienced hypomanic/manic episodes, and 11 of them experienced depressive and anxiety episode. The recurrence of non-puerperal episodes is lower following postpartum psychosis.

In this study, when variables such as age, presence of postpartum depression, number of pregnancies, and number of episodes during pregnancy were evaluated together in the linear regression analysis, it was found that the age of onset of the disease and the episodes after pregnancy predicted the number of episodes throughout life. This finding supports the results of Stevens et al's[15] study. In that study, they reported that a significant proportion of pregnant patients had moderate disease severity rather than euthymia. In addition, in this study, the YMRS scores of patients who reported attacks during pregnancy were within normal limits but were found to be significantly higher than those who did not have a pregnancy attack. This may be due to discontinuation of drug use during pregnancy to avoid possible teratogenic side effects of drugs, the development of tolerance to drugs, and fluctuations in pregnancy-related estrogen levels, as suggested by Meinhard et al.[51] In addition, Rommel et al reported that postpartum psychosis does not predict episodes out of the postpartum period; however, they suggested a possible link between postpartum psychosis and bipolar spectrum disorders. Also, they reported that postpartum recurrences were more severe. They concluded that the postpartum period does not predict the severity of future episodes.

This study has limitations related to recall in terms of being a cross-sectional study and including questions about remembering the past. Another limitation is the relatively small number of participants in the study. Other limitations include a lack of information on diseases that may occur during pregnancy, psychosocial risk factors, and mode of delivery, which may be related to the episode.

CONCLUSION

According to the results of our study, age at the onset of the disease and postpartum episodes were found to predict lifetime episodes. This may be related to many social and biological factors, such as discontinuation of medications during pregnancy and breastfeeding, hormonal changes, increased responsibilities related to child and family, and the effects of family relationships. Cohort studies evaluating these factors are needed.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Adnan Menderes University (Approval no: 2018/1457, Date: 06.08.2018).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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