

Predictors of recurrence of bipolar disorder during pregnancy and postpartum periods in a sample of Egyptian women

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Introduction

Pregnancy and postpartum are periods of increased risk for women with bipolar disorder to develop new episodes. The aim of this study was to evaluate factors that are supposed to be associated with recurrence of bipolar I disorder among euthymic women with a history of bipolar I disorder, which could be used as predictors of this disorder in that period.

Methods

Eighty-three pregnant women with a history of bipolar I disorder were followed through their pregnancy and postpartum periods for possible recurrence of a new episode. All women were assessed using the Mini International Neuropsychiatric Interview. Factors that may contribute to recurrence were assessed prospectively. These included the age of patients, age of onset of bipolar disorder, duration of illness, number of previous attacks, number of previous pregnancies, prior episodes in pregnancy or postpartum, complications during pregnancy and labor, pregnancy type, prior hospitalization, prior suicidal attempts, time since last episode (in months), and continuation of medications.

Results

Of euthymic bipolar females, 65% had recurrence of a new episode, either during pregnancy (33.73%) or 4 weeks postpartum (31.32%). Discontinuation of medications, longer duration of illness, more number of previous attacks, more number of previous pregnancies, more prior episodes in pregnancy, more complication during pregnancy, more complication during labor, unplanned pregnancy type, and prior hospitalization were associated with recurrence of bipolar disorder during pregnancy and postpartum.

Conclusion

Multiple factors were associated with risk of recurrence of bipolar I disorder during pregnancy and postpartum. Consideration of these factors while planning treatment for women with a history of bipolar disorder may decrease the risk of recurrence during pregnancy and postpartum.

Keywords:

bipolar disorder, postpartum, predictors, pregnancy, risk factors, women

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Introduction

Bipolar disorder is common among women of childbearing age [1]. Bipolar disorder in women presents special diagnostic and treatment challenges to the clinician [2]. The issue of whether bipolar illness improves during pregnancy is controversial [3–6], but, in any case, pregnancy is not protective for all women with bipolar disorder [6]. The postpartum period is a time of increased risk of illness onset and exacerbation of mood episodes in women with bipolar disorder [7]. As many as 40–67% of women with bipolar disorder report experiencing a postpartum mania or depression [8].

Viguera *et al.* [9] in 2007, found that discontinuation of ongoing maintenance treatment carries a very high risk of recurrence of bipolar disorder. However, the treatment of bipolar disorder during pregnancy or in those women who wish to conceive is challenging and poses a unique set of dilemmas, given the risk of teratogenicity and perinatal complications of some psychotropic medications

used to treat bipolar disorder and incomplete reproductive safety data for agents frequently used to manage the illness. In contrast, the decision to breastfeed must also take the adverse impact of sleep deprivation in triggering mood episodes [8,10,11] into account.

The aim of this study was to prospectively evaluate factors that are supposed to be associated with recurrence of bipolar I disorder, among relatively large samples of euthymic women with a history of bipolar I disorder. Knowing these factors could help in using them as predictors of bipolar disorder during that period.

Materials and methods

Eighty-three euthymic (at least 8 weeks before their last menstrual period) pregnant women who had a history of bipolar disorder type I were enrolled in this large prospective, observational study, during the period between January 2006 and June 2010, at the Neuropsychiatry Outpatient Clinic at Tanta University Hospital.

Euthymic women who had a history of bipolar I disorder and were planning to be pregnant or had unplanned pregnancy and seeking specialized psychiatric consultation were recruited for the study.

Patients were excluded if they met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for schizophrenia, schizoaffective, or organic mental disorder or mental retardation. All the patients provided a written informed consent to participate in this study.

The patients were followed through the end of pregnancy and 4 weeks postpartum, regardless of their decisions with regard to the continued use of psychotropic medication.

All the patients initially received individual evaluations by the first author (M.A.E.-H.), including clinical assessment using the Mini International Neuropsychiatric Interview [12] to establish diagnosis. This interview was translated and validated into Arabic by Ghanem *et al.* in 1999 [13].

Demographical and clinical characteristics of interest were recorded at baseline, including current age, estimated age at onset of bipolar disorder, number of prior episodes and previous hospitalizations, occurrence of suicidal attempts, time since the last episode, and treatment history.

The potential risks and benefits of continuing or stopping treatment, and the potential teratogenicity of mood stabilizing, antipsychotic, and antidepressant drugs, their potential adverse effects on neonates, and maternal and potential fetal risks associated with discontinuing treatment were discussed with the patients. Patients who decided to continue medication used the same drugs that brought them into remission prescribed by their treating doctor. These drugs included mood stabilizers, with or without antipsychotics, and antidepressants.

The patients were followed by the first author at the first study visit at each trimester and at any time the patient or her family felt any psychiatric symptom, to ascertain the presence of significant symptoms and their clinical severity (mild, moderate, or severe) and current treatments (drugs, doses, apparent benefits, and adverse effects).

The recurrence of a new bipolar episode was determined by the second (H.E.S.) and third (A.B.) authors, who were blind to the patient's psychiatric history including treatment status.

Statistical analysis

SPSS 16 software (SPSS Inc., Chicago, Illinois, USA) for Windows was used for data analysis. The statistical significance level was defined as *P* value less than 0.05. The chi-square analysis was used to compare categorical variables and analysis of variance was used to compare quantitative variables. Pearson's correlation coefficient was used to find out the correlation of recurrence of bipolar disorder and the time of recurrence (being antepartum or postpartum), and variables supposed to be associated with risk of recurrence.

Results

Patient characteristics

This study included 83 women whose age ranged from 20 to 35 years with a mean age of 25.33 ± 3.20 years. All participants were married; their years of education ranged from 6 to 16 years with a mean age of 12.89 ± 2.445 years, and 95% of them were multiparous. Only 24 (29%) women were employed outside home and 31 women (37%) continued medication during pregnancy and postpartum (Tables 1 and 2).

Risk and timing of recurrences during pregnancy and postpartum

Among the participants, 54 (65%) had recurrence of bipolar disorder, 28 (33.73%) during antepartum, and 26 (31.32%) during postpartum period. Among cases who had recurrence during the antepartum period, one had recurrence during first trimester, 11 during second trimester, and 16 during third trimester.

Among the patients who had antepartum recurrence (28 women), 16 had depressive episode, one had manic episode, eight had mixed episode, and three had hypomania. In postpartum cases (26 women), nine had depressive episode, two had manic episode, 14 had mixed episode, and one had hypomania.

Participants who had recurrence of bipolar disorder during pregnancy and postpartum did not differ on many demographical characteristics. These included current age, marital status (all were married), years of education, and employment outside home (Tables 1 and 2).

The age at the onset of bipolar disorder, which ranged from 16 to 31 years, with a mean age of 20.55 ± 2.80 years, did not statistically differ among who had recurrence of bipolar disorder ($P > 0.05$) or not (Table 1).

Table 1 Demographic characteristics of patients and control

	Total sample	Relapse during pregnancy and postpartum (<i>n</i> = 54)	Normal pregnancy and postpartum (<i>n</i> = 29)	<i>P</i>
Age (years) (mean $\pm$ SD)	25.33 $\pm$ 3.20	26.02 $\pm$ 3.073	24.46 $\pm$ 3.185	0.164
Education (years)	12.89 $\pm$ 2.445	12.59 $\pm$ 2.68	13.45 $\pm$ 1.84	0.129
Age at onset (years)	20.55 $\pm$ 2.80	20.80 $\pm$ 3.81	20.24 $\pm$ 2.42	0.629
Duration of illness (years)	4.78 $\pm$ 2.47	5.1957 $\pm$ 2.696	4.2703 $\pm$ 2.10355	0.034*
Number of previous attacks	3.24 $\pm$ 1.98	3.72 $\pm$ 2.29	2.65 $\pm$ 1.31	0.001*
Number of previous pregnancies	2.17 $\pm$ 0.90	2.33 $\pm$ 0.790	1.97 $\pm$ 1.013	0.002*
Time since last episode (months)	10.08 $\pm$ 4.283	10.22 $\pm$ 4.14	9.83 $\pm$ 4.60	0.692

SD, standard deviation.

*significant difference at 0.05.

Table 2 Comparison of some clinical features in patients and control

	Total sample		Recurrence during pregnancy and postpartum (n = 54)		Normal pregnancy and postpartum (n = 29)		P
	Yes	No	Yes	No	Yes	No	
Employment outside home	24	59	15	39	10	27	0.803
Continuation of medications	31	52	14	40	17	12	0.005*
Prior episodes in pregnancy	32	51	27	27	5	24	0.004*
Complications during pregnancy	42	41	38	16	4	25	0.000*
Complications during labor	24	59	21	33	3	26	0.010*
Pregnancy type (planned or not)	31	52	11	43	20	9	0.000*
Prior hospitalization	34	49	27	27	7	22	0.034*
Prior suicidal attempts	20	63	12	42	8	21	0.600

*significant difference at 0.05.

Duration of illness, which ranged from 1 to 13 years, was more in those who had new episodes during pregnancy or postpartum with statistically significant difference ($P < 0.05$) (Table 2).

Number of previous episodes, which ranged from 1 to 11 episodes, were more in those who had new episodes during pregnancy or postpartum with statistically significant difference ($P < 0.05$) (Table 2).

Number of previous pregnancies ranged from 0 to 5 times. It was significantly more in those who had recurrence of bipolar disorder ($P < 0.05$) (Table 2).

Time since the last bipolar episode ranged from 3 to 24 months. Time since the last episode was not significantly different in those who had recurrence or not ($P > 0.05$) (Table 2).

Recurrence of bipolar disorder was significantly more in those who stopped medication ($P < 0.05$). Of those who continued medications, 14 (45.16%) had new bipolar disorder episode, but 17 (54.83%) had no recurrence. Among those who stopped medications, 40 (76.92%) had recurrence and 12 (23%) had no recurrence.

Prior episodes in pregnancy, complication during pregnancy, and complication during labor were more in those who had recurrence of bipolar disorder during pregnancy and postpartum ($P < 0.05$).

Planned pregnancy correlated significantly with less recurrence of bipolar disorder during pregnancy and postpartum ($P < 0.05$).

Earlier hospitalization during previous episodes correlated significantly with less recurrence of bipolar disorder during pregnancy and postpartum ($P < 0.05$).

Prior suicidal attempts was not significantly different in those who had recurrence or not ($P > 0.05$) (Table 2).

Correlation of recurrence of bipolar disorder with different variables

Many factors did not correlate with the recurrence of bipolar disorder in this study. These factors included the age of participants, age at the onset of bipolar disorder, prior suicidal attempts, and time since the last episode (in months) ($P > 0.05$).

The factors that correlated significantly with recurrence of bipolar disorder included longer duration of illness,

more number of previous attacks, more number of previous pregnancies, more prior episodes during pregnancy, more complication during pregnancy, complication during labor, unplanned pregnancy, prior hospitalization, and discontinuation of medications (Table 3).

Correlates of time of recurrence (antepartum/postpartum)

Pearson's correlation coefficient was made to find out factors that were associated with the time of recurrence (during pregnancy or postpartum period). There was no correlation between the time of recurrence and the age of the patients, duration of illness, number of previous pregnancies, prior episodes in pregnancy, complications during pregnancy, planning pregnancy, prior suicidal attempts, and continuation of medication (Table 4).

Younger age at onset of bipolar disorder, more previous episodes during pregnancy, more complication during labor, more prior hospitalization, and less time since last episode (in months) correlate with postpartum onset (Table 4).

At onset, the age of patients who had antepartum onset ranged from 18 to 31 years with a mean age of 21.46 ± 3.024 years, whereas the age of patients who had postpartum onset ranged from 16 to 26 years with a mean age of 19.35 ± 2.667 years.

Table 3 Pearson's correlation coefficient of recurrence of bipolar disorder with different variables

Recurrence	Pearson's correlation coefficient	Significance
Age (years)	-0.154	0.164
Age at onset (years)	0.054	0.629
Duration of illness (years)	-0.233*	0.034
Number of previous attacks	-0.358**	0.001
Number of previous pregnancy	-0.333**	0.002
Prior episodes in pregnancy	0.321**	0.003
Complications during pregnancy	0.540**	0.000
Complications during labor	0.300**	0.006
Pregnancy type (planned/unplanned)	0.479**	0.000
Prior hospitalization	0.251*	0.022
Prior suicidal attempts	-0.060	0.591
Time since last episode (in months)	-0.044	0.692
Continuation of medications	-0.322**	0.003

*Correlation is significant at the 0.05 level (two-tailed).

**Correlation is significant at the 0.01 level (two-tailed).

Table 4 Pearson's correlation coefficient of time of recurrence (antepartum/postpartum) of bipolar disorder with different variables

Antepartum/postpartum	Pearson's correlation coefficient	Significance
Age (years)	-0.192	0.165
Age at onset (years)	-0.353**	0.009
Duration of illness (years)	0.181	0.191
Number of previous attacks	0.284*	0.038
Number of previous pregnancy	0.264	0.053
Prior episodes in pregnancy	-0.222	0.106
Complications during pregnancy	-0.057	0.682
Complications during labor	-0.296*	0.030
Pregnancy type (planned/unplanned)	-0.211	0.125
Prior hospitalization	-0.148	0.285
Prior suicidal attempts	-0.020	0.887
Time since last episode (in months)	-0.287*	0.035
Continuation of medication	0.063	0.653

*Correlation is significant at the 0.05 level (two-tailed).

**Correlation is significant at the 0.01 level (two-tailed).

The number of previous episodes in patients who had antepartum onset ranged from 1 to 9 with a mean of 3.18 ± 1.634 . The number of previous episodes in patients who had postpartum onset ranged from 1 to 11 with a mean of 4.38 ± 2.467 .

Time since the last episode in the case of antepartum recurrence ranged from 3 to 18 months with a mean of 11.36 ± 4.424 months. In the case of postpartum onset, time since last episode ranged from 6 to 18 months with a mean of 9 ± 3.499 months.

Eleven participants (39%) with antepartum recurrence had previous episodes during pregnancy, whereas 16 (62%) of postpartum cases had previous episodes during pregnancy.

Complication during labor occurred in seven (33%) of antepartum cases and 14 (54%) of postpartum cases.

Discussion

This prospective study tried to evaluate the risk of recurrence of bipolar disorder during pregnancy and postpartum, and to find out possible correlates of this recurrence. Approximately 65% (54 out of 83 cases) of patients had recurrence of bipolar disorder. More than half of recurrences occurred during the antepartum period (28 out of 54 cases) and 48% (26 out of 54 cases) occurred during the postpartum period. Among cases of recurrences in the antepartum period (39%), 11 out of 28 cases occurred during the second trimester, and (57%) 16 out of 28 occurred during the third trimester. These findings suggest that pregnancy is not protective of bipolar disorder. However, it seems that recurrence increases through pregnancy and reaches a maximum in the postpartum period.

The findings of this study provide support to those studies that showed that pregnancy is not protective against risk of recurrence [9,14,15], although it is contra-

dicting with some old reports that found an improvement of bipolar symptoms during pregnancy [16]. This study also confirms the frequently reported findings of increased risk of recurrence of bipolar disorder during the postpartum period [3,5,7].

Risk factors of recurrence during pregnancy and postpartum

This study did not find any association between recurrence of a new episode of bipolar disorder and the age at onset of bipolar disorder, and time since the last bipolar episode. The lack of association between recurrence and these factors may suggest that each of these factors do not play as a risk of recurrence by itself, a matter that needs to be confirmed by other studies.

Absence of such an association between previous suicidal attempts, which may reflect severity of an episode, and recurrence in this study may stem from the religious beliefs that attenuate the value of such factors in Egyptian culture.

Factors that were associated with increased risk of recurrence included discontinuation of medication, more number of previous episodes, more number of previous pregnancies, more prior episodes in pregnancy, more complication during pregnancy and labor, more hospitalization during previous episodes, and unplanned pregnancy. Some of these factors were reported by previous studies, specifically discontinuation of mood stabilizers, earlier onset, more recurrences/year, and increased number of previous episodes [8,17–20]. Confirmation of these findings by further prospective studies will mandate proper intervention to reduce these risk factors, a matter that will have great implication on reducing risk of recurrence of bipolar disorder among women in that critical period of their lives.

Variable correlation with time of recurrence (antepartum/postpartum)

In this study, many factors differentiated antepartum from postpartum onset of recurrence. These included the age at onset, previous episodes during pregnancy, more complication during labor, more prior hospitalization, and time since last episode.

Postpartum onset correlated with younger age at onset, more previous episodes during pregnancy, more complication during labor, more prior hospitalization, and less time since last episode in months. The reverse is true for antepartum onset. Considering the previous factors, it could be suggested that the severity of illness (as indicated by age at onset, previous episodes during pregnancy, prior hospitalization, and the duration of remission) and the stress of labor (as indicated by complications during labor) play a crucial role in precipitating a new postpartum episode.

Some factors, such as the duration of illness, number of previous pregnancy, prior episodes in pregnancy, complications during pregnancy, planning pregnancy, and continuation of medication, although correlated with recurrence of bipolar disorder, were not found to differentiate antepar-

tum from postpartum onset. This finding may suggest that some factors might play a role in increasing the risk of recurrence in general; others, either alone or in association with other factors, play a role in the timing of recurrence. Again, further studies are needed to confirm this finding.

Conclusion and recommendations

This study suggests several predictors of bipolar episodes. Knowledge of these factors has significant clinical implications and could help in treatment and prevention strategies.

Pregnant women with a history of bipolar disorder should be assessed, ideally before conception, but certainly, as early in pregnancy as possible for risk of recurrence. For women at risk, it is important to maintain close contact and regular assessment.

More research is needed to increase our understanding of predictors of relapse, with the intent of improving quality of life and preventing episodes in female patients with bipolar disorder during pregnancy and postpartum.

There is no conflict of interest to declare.

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الملخص العربي

مؤشرات تكرار الاضطراب الثنائي القطب أثناء الحمل وفترة ما بعد الولادة في عينة من النساء المصريات

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الخلفية: تعد فترة الحمل و فترة ما بعد الولادة أوقات خطيرة للنساء اللاتي يعانين من الاضطراب الثنائي القطب حيث تزداد نسبة حدوث نوبات جديدة في تلك الفترات.

الهدف من البحث: تقييم العوامل المحتمل أن تترافق مع تكرار اضطراب ثنائي القطب- النوع الأول، بين النساء اللاتي عانين سابقا من الاضطراب الثنائي القطب، والتي يمكن استخدامها بمثابة مؤشر للاضطراب الثنائي القطب في تلك الفترة.

طريقة البحث: تم هذا البحث على ثلاثة وثمانون من النساء الحوامل اللاتي عانين سابقا من الاضطراب الثنائي القطب- النوع الأول، حيث تم متابعتهم خلال الحمل وفترة ما بعد الولادة لدراسة احتمال تكرار نوبة جديدة اثناء تلك الفترة. وقد جرى تقييم جميع النساء باستخدام المقابلة الدولية العصبية والنفسية (ميني). كما تمت دراسة العوامل التي قد تسهم في تكرار الاضطراب، و شملت عمر السيدة، العمر عند بدء الاضطراب الثنائي القطب، ومدة المرض، وعدد النوبات السابقة، وعدد مرات الحمل السابقة، حدوث نوبات سابقة أثناء الحمل او بعد الولادة، والمضاعفات أثناء الحمل، والمضاعفات أثناء المخاض، نوع الحمل (تم التخطيط له ام لا)، دخول المستشفى أثناء النوبات السابقة، ومحاولات الانتحار السابقة، وقت آخر نوبة، واستمرار استخدام الدواء.

النتائج: أصيبت 65 ٪ من الإناث المشاركات في الدراسة بنوبة إما أثناء الحمل (33.73٪) أو بعد الولادة (31.32٪). وقد ارتبط عدم مواصلة الأدوية، وطول مدة المرض، وزيادة عدد النوبات السابقة، كثرة عدد مرات الحمل السابقة، حدوث نوبات سابقة أثناء الحمل أو بعد الولادة، والمضاعفات أثناء الحمل وبعد الولادة، ونوع الحمل (مخطط له ام لا)، دخول المستشفى أثناء النوبات السابقة، مع تكرار الاضطراب الثنائي القطب خلال الحمل وبعد الولادة.

الخلاصة: هناك العديد من العوامل المرتبطة بخطر تكرار الاضطراب الثنائي القطب خلال فترة الحمل وبعد الولادة. و النظر في هذه العوامل عند وضع الخطة العلاجية للنساء اللاتي عانين من الاضطراب الثنائي القطب قد يساهم في خفض خطر تكرار هذا الاضطراب أثناء الحمل وبعد الولادة.