The Impact of Reproductive Events on the Course of Bipolar Disorder in Women

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Background: Little is known about the impact of female reproductive hormones on the course of bipolar disorder. This study was designed to assess the influence of reproductive events and hormonal therapies on the course of bipolar disorder in women.

Method: Fifty women with DSM-IV bipolar disorder completed a structured clinical interview to assess the impact of reproductive events on the course of their illness.

Results: The onset of bipolar disorder occurred before menarche in 32% (N = 16) of women; 18% (N = 9) experienced the onset within 1 year of menarche. Most women did not receive an accurate diagnosis of nor treatment for bipolar disorder until after they had children, and therefore the majority were not treated with mood stabilizers during or immediately after pregnancies. Of women with children, 20 (67%) of 30 experienced a postpartum mood episode. Of the women who had postpartum episodes after delivery of a first child, all had episodes after subsequent pregnancies. Having a postpartum mood episode after a first pregnancy significantly increased the risk of a postpartum episode after subsequent deliveries (p = .02). Postpartum episodes were almost exclusively depressive. Increased depressive symptoms during pregnancy were significantly associated with postpartum mood episodes (p = .01). Women who were not using hormone replacement therapy (HRT) were significantly more likely than those who were using HRT to report worsening of symptoms during perimenopause/menopause (p = .02).

Conclusion: These data suggest that hormonal fluctuations are associated with increased risk of affective dysregulation and mood episodes in women with bipolar disorder.

(J Clin Psychiatry 2002;63:284–287)

Received May 24, 2001; accepted Sept. 11, 2001. From the Department of Psychiatry, University of Arizona College of Medicine, Tucson (Drs. Freeman, Smith, Freeman, and Wright) and the Biological Psychiatry Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio (Drs. McElroy and Keck and Ms. Kmetz).

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Freeman, Smith, Freeman, McElroy, Wright, and Keck and Ms. Kmetz have no significant commercial relationships to disclose relative to the presentation.

These data were presented in part at the 41st annual meeting of NCDEU, May 28–31, 2001, Phoenix, Ariz., and at the 40th annual meeting of the American College of Neuropsychopharmacology, December 9, 2001, Kona, Hawaii.

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Sex hormones very likely play important roles in mood disorders. Women have twice the lifetime risk for major depression than men[1] and have a higher prevalence of seasonal affective disorder.[2] Although bipolar disorder is equally prevalent in women and men, women more frequently experience rapid cycling,[3] mixed mania,[4,5] and depressive episodes.[6] Women with bipolar disorder are at especially high risk for relapse during the postpartum period, when the rate of recurrent postpartum mood episodes has been reported to be 25% to 40%.[7] One group of investigators found that pregnancy may be somewhat protective. In a retrospective study by Grof et al.,[8] women with lithium-responsive bipolar I disorder experienced fewer mood episodes during pregnancy. In that study, all pregnancies took place before the women received treatment with lithium prophylaxis for bipolar disorder. In a study of the effects of lithium discontinuation, Viguera et al.[9] found that rates of relapse were similar in pregnant and nonpregnant women but higher in the postpartum. Due to the high rate of postpartum relapse, postpartum prophylactic treatment has been advocated for most patients.[10]

Little is actually known about the impact of female reproductive hormones on the course of bipolar disorder and implications for treatment. Data are particularly lacking regarding the effects of oral contraceptives, menopause, and hormone replacement therapy (HRT). Important associations might exist between course of illness and reproductive events or responses to hormonal treatments.

The hypothesis of this study was that women with bipolar disorder are at risk for worsening of mood symptoms in response to reproductive events across the lifespan, possibly due to hormonal fluctuations. To explore this hypothesis, women with bipolar disorder were recruited to participate in a structured clinical interview to assess the impact of reproductive events and hormonal therapies on the course of their illness.

Table 1. Risk of Postpartum Mood Episodes After Subsequent Pregnancies[a]

	Experienced a Postpartum Mood Episode After Birth of 1st Child (N = 8)		No Postpartum Mood Episode After 1st Child (N = 13)	
Postpartum Experience	N	%	N	%
Experienced a postpartum mood episode after 2nd or later delivery	8	100	6	46
Did not have episode after 2nd or later delivery	0	0	7	54

[a]Considering all women with > 1 child (N = 21).

METHOD

Patients were recruited from the University of Arizona Department of Psychiatry outpatient clinic, inpatient unit, and a community mental health clinic affiliated with the University of Arizona, Tucson (N = 22), and the Biological Psychiatry Program and affiliated clinics at the University of Cincinnati Medical Center, Cincinnati, Ohio (N = 28). After written informed consent was obtained, 50 women with bipolar disorder completed a structured clinical interview designed by the investigators to assess the impact of reproductive events and hormones on the course of their illness. Diagnosis of bipolar I, bipolar II, or bipolar disorder not otherwise specified (NOS) was confirmed using the Structured Clinical Interview for DSM-IV (SCID), mood disorders sections.[11] Patients were asked specific questions about their history of mood symptoms and episodes in relation to pregnancy and the puerperium, use of oral contraceptive pills (OCPs), perimenopause and/or menopause, and HRT. Patients were also asked at what ages they experienced menarche and onset of bipolar disorder (as defined by first mood episode, regardless of polarity). If a woman had more than one child, each pregnancy and postpartum period was individually assessed.

Statistical Analysis

Data were analyzed to assess whether depressive symptoms during pregnancy were associated with an increased risk of postpartum mood episodes and whether a postpartum mood episode after a first pregnancy was associated with postpartum episodes after subsequent pregnancies. Data were also assessed to determine whether the use of HRT was associated with decreased risk of mood symptoms in perimenopause/menopause. Two-tailed Fisher exact tests were performed, and the statistical significance was set at $p < .05$.

RESULTS

Age at Onset and Menarche

Fifty women completed the structured clinical interviews, and diagnoses were as follows: bipolar I (N = 36), bipolar II (N = 13), and bipolar NOS (N = 1). The mean ± SD age of the patients was 43.3 ± 11.4 years at time of participation. Mean age at menarche was 13.2 ± 1.6 years. Mean age at onset of bipolar disorder was 19.8 ± 10.7 years, as defined by the first episode of major depression, mania, or hypomania. The onset of bipolar disorder occurred before menarche in 16 women (32%) and occurred at age 12 or younger in 10 (20%). Nine (18%) experienced the onset of bipolar disorder within 1 year of menarche. Onset at or after 40 years of age was experienced by 3 women (6%).

Pregnancy and Postpartum

Of women with children, 20 (67%) of 30 experienced a postpartum mood episode within 1 month of delivery. For 3 women, an episode of postpartum depression was the first mood episode they had ever experienced. Of the 21 women with more than 1 child, 8 (38%) had postpartum mood episodes after the first pregnancy; 13 women (62%) did not (Table 1). Of the 8 who had postpartum episodes after the first pregnancy, all had a mood episode after a subsequent pregnancy. Of the 13 women who did not have a postpartum episode after the birth of a first child, 6 (46%) had a mood episode after a later pregnancy. Having a postpartum mood episode after a first pregnancy significantly increased the risk of an episode after subsequent deliveries (Fisher exact test [2-tailed], $p = .02$). Postpartum mood episodes reported were almost exclusively depressive, with the exception of 2 episodes of hypomania.

Pregnancy itself did not seem to confer protection against mood symptoms. Of the 30 women with children, 15 (50%) experienced no change or experienced fewer mood symptoms during pregnancy, but half had more symptoms of bipolar disorder during pregnancy. Worsening mood symptoms during pregnancy predicted postpartum relapse. Women who experienced increased symptoms of bipolar disorder during pregnancy were more likely to have a postpartum mood episode than those who did not. Of the women who experienced more mood symptoms during at least 1 pregnancy, all but 1 (14 of 15; 93%) experienced at least 1 postpartum episode. Lack of change or improved course during pregnancy was somewhat protective against the development of a postpartum episode. Of those women, 6 (40%) of 15 experienced 1 or more episodes of postpartum depression in her lifetime, representing a large proportion, but less than the risk of postpartum episodes seen in the sample overall. Increased depressive symptoms during pregnancy were significantly associated with postpartum mood episodes (Fisher exact test [2-tailed], $p = .01$).

In other words, women who did not experience postpartum mood episodes were more likely to report no change or improved course of illness during pregnancy. Of the 10 women who did not experience any postpartum mood episodes, only 1 (10%) experienced increased depressive

symptoms during 1 of her pregnancies. Twenty women experienced at least 1 postpartum mood episode, and 14 (70%) reported increased mood symptoms while pregnant.

Medication Regimens in Pregnancy and Postpartum

Most women in our sample did not receive an accurate diagnosis of bipolar disorder and treatment with psychotropic medication until years after their pregnancies, despite the early onset of mood episodes in many. Of the 30 women with children, 27 were not treated with psychotropic medications before, during, or immediately following their pregnancies. All but 1 of these women reported the onset of mood episodes prior to having children.

One woman continued on divalproex sodium at the same dose during her pregnancies as before becoming pregnant, while another woman decreased her dose of divalproex sodium while pregnant. Of these 2 women who continued divalproex sodium during pregnancy, both experienced postpartum depressive episodes despite treatment with this mood stabilizer during pregnancy. Another woman recalled discontinuing medication during 2 of her pregnancies and restarting postpartum, but she could not specifically state which medications she was on at that time. She experienced episodes of postpartum depression after both of those pregnancies.

Two women were pregnant at the time of interview. One elected to discontinue treatment with lithium and sertraline prior to conception. Another switched from treatment with divalproex sodium and gabapentin to lithium after the first trimester. Of note, when she discovered she was pregnant during her first trimester, she overdosed on her anticonvulsant medications in a suicide attempt.

Oral Contraceptive Pills

The impact of oral contraceptive use on the course of bipolar disorder was equivocal. Thirty-three of the women used OCPs. The majority, 22 (67%) of 33, either reported no change in mood symptoms (N = 17) or did not remember any substantial effect on their mood (N = 5). Four reported improved mood symptoms, and 7 reported worsening mood symptoms associated with OCP use.

Perimenopause and Menopause

Per patient report, 22 women were either currently perimenopausal (N = 9) or postmenopausal (N = 13). Seven women experienced surgical menopause after hysterectomy with removal of both ovaries. One woman had chemotherapy-induced menopause, after treatment with tamoxifen for breast cancer. Three women, all with bipolar I disorder, reported onset of the disorder during or after perimenopause. Two women reported the onset of bipolar disorder while perimenopausal, as defined by the experience of irregular menses and hot flashes, at ages 46 and 48. One woman reported the onset of bipolar disorder at age 46, 6 years after she experienced menopause.

Table 2. Hormone Replacement Therapy (HRT) Use and Bipolar Symptoms

		Worsening Mood Symptoms After Perimenopause	
HRT Status	Total N	N	%
Current use	12	3	25
Never used	8	7	88
Discontinued	2	1	50

Twelve women reported worsening mood, all of whom reported an increase in depressive symptoms, but many also complained of increased irritability (N = 8), hypomania or mania (N = 8), and more frequent cycling (N = 6). Ten reported no change in symptoms with menopause or perimenopause or were unsure of the impact. None of the women reported improvement in the course of their illness during this time.

Twelve women were currently taking HRT, and 2 had used HRT in the past (Table 2). Of the 12 women who were currently using HRT, 3 (25%) reported worsening course of their mood disorder since experiencing perimenopause/menopause and use of HRT (conjugated estrogens N = 1; estradiol N = 1; and conjugated estrogens + medroxyprogesterone N = 1). Of the 2 women who discontinued HRT, 1 did so due to increased depressive symptoms with use of conjugated estrogens + medroxyprogesterone, and 1 discontinued due to development of breast cancer. The women who did not note worsening course of bipolar disorder with concurrent use of HRT were treated with the following: estradiol (N = 1), estradiol + methylprogesterone (N = 1), conjugated estrogens (N = 3), medroxyprogesterone acetate (N = 1), and conjugated estrogens + medroxyprogesterone (Prempro) (N = 2). One woman began treatment with conjugated estrogens + medroxyprogesterone (Premphase) only 3 days prior to the interview and did not note changes in mood. One woman experienced hypomania with the use of a testosterone supplement, which was discontinued.

Of the 8 women who had not used HRT, all but 1 (88%) reported worsening of bipolar symptoms since perimenopause/menopause. One woman who reported worsening of mood, however, was using tamoxifen at the time of interview. Women who were not using HRT were significantly more likely than those who were using HRT to report worsening of symptoms during perimenopause/menopause ($p = .02$).

DISCUSSION

The data from this survey suggest increased risk of mood symptoms at times of reproductive events in women with bipolar disorder. Women with bipolar disorder who participated in this study experienced high rates of postpartum depressive episodes. Women who developed 1 postpartum episode were likely to develop subsequent

postpartum episodes. However, women who did not experience postpartum episodes after the birth of a first child were still at high risk for developing an episode after a later pregnancy. These findings support recommendations that women with bipolar disorder should be treated prophylactically after childbirth.[10] In over half of the women interviewed, mood symptoms worsened during pregnancy and were predictive of postpartum episodes.

Onset of bipolar disorder occurred relatively early in this cohort, in a substantial number at or before the age of menarche. However, an accurate diagnosis of bipolar disorder often occurred decades after the onset of the illness. A shortcoming of this study is that data regarding time of diagnosis of bipolar disorder were not systematically collected. However, the majority of women reported that they had not yet received a diagnosis of nor treatment for bipolar disorder while pregnant and postpartum and that initial treatment was often delayed many years. This finding is consistent with another survey that found substantial delays between onset of affective symptoms and diagnosis of bipolar disorder.[12] As was the case with the cohort studied by Grof et al.,[8] most of the pregnancies included in this study took place before women received treatment with mood stabilizers.

More than half of the women who were perimenopausal or postmenopausal experienced an increase in mood symptoms. In a study of this size, it is difficult to differentiate between the effects of perimenopause/menopause and the use of HRT. However, most women who did not use HRT reported worsening course of illness with perimenopause/menopause, compared to a minority of women who were currently using HRT.

These data support the hypothesis that times of hormonal fluctuation are associated with increased risk of affective dysregulation or mood episodes in women with bipolar disorder. Onset of illness was temporally related to menarche in a substantial proportion of the women. The puerperium was a time of high risk in this group. Pregnancy and perimenopause/menopause were also periods of symptomatic exacerbation in approximately half of the group.

Interpretation of the data is limited by the study design. Patients were asked to recall events and mood symptoms experienced throughout their lifetimes. Furthermore, the relatively small sample size made it impossible to draw definitive conclusions about the impact of oral contraceptives and HRT on the course of bipolar disorder. Despite the limitations of the study, the findings suggest a positive effect of HRT on mood stabilization.

Women were also not asked for longitudinal data about medication use throughout the course of their illness. Specific questions about medication were asked only in respect to use during pregnancy and postpartum. The low number of women who received treatment for bipolar disorder prior to pregnancies and during the postpartum is surprising. For most of the women, treatment with mood stabilizers was not initiated until after they had children.

Also, psychosocial factors that may have been associated with reproductive events were not assessed. Stressful life events and marital discord have been associated with postpartum depression[13] and may contribute to postpartum relapse in bipolar disorder as well. Additionally, information regarding the impact of miscarriages and abortions on mood symptoms was not ascertained.

Although preliminary and descriptive in nature, this study suggests important relationships between hormonal changes and affective instability in women with bipolar disorder. More rigorous prospective data are needed to confirm these findings and expand the available data regarding the course of bipolar disorder throughout the female lifespan.

Drug names: divalproex (Depakote), gabapentin (Neurontin), sertraline (Zoloft), tamoxifen (Nolvadex).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, gabapentin is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder and sertraline is not approved for the treatment of bipolar depression.

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