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Brief report

Reproductive cycle-associated mood symptoms in women with major depression and bipolar disorder

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Abstract

Background: We sought to determine the prevalence of, and association between, reproductive cycle-associated mood symptoms in women with affective disorders. We hypothesized that symptoms would correlate with each other across a woman's reproductive life span in both major depression (MDD) and bipolar I disorder (BP).
Methods: 2412 women with, MDD or BP were asked standardized questions about mood symptoms prior to menstruation, within a month of childbirth and during perimenopause. Lifetime rates for each of these symptom types were determined and an odds ratio was calculated correlating each of the types with the others.
Results: Of 2524 women with mood disorders, 67.7% reported premenstrual symptoms. Of those at risk, 20.9% reported postpartum symptoms and 26.4% reported perimenopausal symptoms. The rates did not differ between women with MDD and BP but were significantly different from women who were never ill. The symptoms were significantly correlated in women with MDD with odds ratios from 1.66 to 1.82, but were not in women with BP.
Limitations: This is a secondary analysis of a sample that was collected for other purposes and is based upon retrospecitve reporting.
Conclusions: Reproductive cycle-associated mood symptoms were commonly reported in women with mood disorders and did not differ based on diagnosis. In MDD, but not BP, the occurrence of these symptoms was trait-like as the presence of one predicted the occurrence of the others. Further prospective study is required to clarify the determinants of this trait.

Keywords: Major depression; Bipolar disorder; Premenstrual; Postpartum; Perimenopausal

1. Introduction

Gender clearly plays a role in the risk of the development of major depression (MDD) with a lifetime prevalence rate as high as 21% in women compared with 12.7% in men (Kessler et al., 1994; Alonso et al., 2004).

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There is evidence that in at least some women, reproductive cycle-associated hormonal changes may trigger depressive episodes in MDD as well as mood episodes in women with bipolar disorder (BP). For example, the prominent gender difference in MDD begins in adolescence, a time of hormonal change: prior to adolescence the rates of, MDD are equal in girls and boys (Kessler et al., 1994). Evidence also comes from the relationship between the premenstrual period and depressive symptoms, which when severe enough constitute the syndrome of premenstrual dysphoric disorder (PMDD). Women with PMDD appear to be at higher risk for depression as well as other mood disorders (reviewed in Yonkers, 1997). Several studies have found that women with BP report premenstrual depressive symptoms (Roy-Byrne et al., 1986; Rasgon et al., 2003) though Leibenluft et al. found no association with rapid cycling BP and premenstrual worsening (Leibenluft et al., 1999). Further, treatment of postpartum and perimenopausal depression with estrogen has been shown in some studies to be therapeutic (Ahokas et al., 2001; Sichel et al., 1995; Gregoire et al., 1996; Ahokas et al., 2000; Schmidt et al., 2000; Soares et al., 2001). The postpartum time is well known to be a period of high risk in women with BP for the development of not only postpartum psychosis (see below) but also postpartum depression (Freeman et al., 2002). Finally, the rate of depression in women appears to decrease after menopause to approximately the same rate found in men (Bebbington et al., 1998; Jorm, 1987). Relatively few studies have examined the effect of perimenopause on BP the few that have reported that this reproductive period was associated with generally worsened mood symptoms (Freeman et al., 2002; Blehar et al., 1998; Sajatovic et al., 2006). These and other observations suggest a potential relationship between hormones and mood although much about the interaction remains to be clarified.

There are, in general, three reproductive cycle time periods during which women may experience significant mood symptoms: premenstrual, postpartum and perimenopausal. Premenstrual mood changes include premenstrual dysphoric disorder (PMDD) which has a strict set of research criteria described in the Diagnostic and Statistical Manual of Mental Disorder-4th edition (DSM-IV) and is thought to occur in 3–8% of the general population (Endicott, 2000; Wittchen et al., 2002) as well as the less severe but more common (up to 80% of the general population; Pearlstein et al., 1990) premenstrual syndrome (PMS) which has no well-defined criteria. PMDD requires social or occupational disfunction as well as confirmation by 2 months of prospective ratings. Postpartum mood changes include three different types of syndromes: (1) postpartum blues which lasts less than 2 weeks and generally produces relatively mild symptoms, postpartum blues is thought to occur after as much as 80% of all live births; (2) postpartum depression, which meets the criteria for a major depressive episode as defined by the DSM-IV. Postpartum depression occurs after approximately 10–20% of all live births (Campbell and Cohn, 1991; Robinson and Stewart, 1986); and (3) postpartum psychosis which is a rare (0.05–0.1% of all live births; Gitlin and Pasnau, 1989) but severe syndrome that is usually associated with BP and resembles a manic episode. The perimenopausal time is well known to produce intermittent depressive symptoms such as low mood, poor concentration and irritability and may carry a higher risk for major depressive episodes in women with a previous history of MDD (Avis et al., 1994; Cohen et al., 2005). All of these syndromes have in common a precipitous change in estrogen and progesterone levels: the drop in estrogen and progesterone levels that occurs during the luteal phase of the menstrual cycle, the drop in estrogen and progesterone levels that occurs after labor and delivery and finally, fluctuations in estrogen and progesterone that occur during the perimenopausal time as ovulation becomes irregular and ultimately ceases.

It has been hypothesized that women with hormonally triggered mood disturbances have abnormalities within the gonadal steroid system. As multiple studies have shown (reviewed in Payne, 2003) this does not appear to be the case; the mood disturbances appear to take place in the context of normal levels and functioning of gonadal steroids. In contrast, change in hormonal levels has been correlated with mood symptoms in women with a history of hormonally triggered symptoms in several studies. Schmidt et al. (1998) showed that women with PMDD experienced a recurrence of their mood symptoms when estrogen or progesterone was given after symptom stability induced by leuprolide, a gonadotropin releasing hormone analog. Similarly, Bloch et al. (2000) showed that women with a history of postpartum depression had a recurrence of depressive symptoms when high doses of estrogen and progesterone were precipitously dropped. Finally, Daly et al. (2003) observed 18 women with perimenopausal depression who experienced spontaneous improvements in their symptoms in conjunction with a decline in plasma FSH levels (indicating a restoration of ovarian function).

Although it is clear that all women are not *a priori* vulnerable to hormonally related events, particular subgroups of women may experience naturally occurring hormonal changes as triggers for mood symptoms including depression. Further, it may be that not all

women with mood disorders have a vulnerability to reproductive cycle-associated events, but rather a subset of such women do.

Despite evidence that women who experience reproductive cycle-associated symptoms are more likely to have a history of a mood disorder, there are few estimates of the prevalence rates of these symptoms in women with MDD and BP. While a number of studies have tested the idea that reproductive cycle-associated symptoms are correlated with each other (see Discussion), most of these have been in community-based samples with poorly defined histories of psychiatric diagnoses. Further, to our knowledge, there have been no such studies of correlation of symptoms in women with BP.

We therefore sought to analyze retrospectively two large data sets collected as part of multi-site genetics studies in recurrent, early onset MDD and BP disorder, specifically examining the rates of mood symptoms premenstrually, postpartum, and during the perimenopausal time period in women with MDD and BP. We also tested the hypothesis that the presence of one type of reproductive cycle-associated symptom would predict the presence of the other types in both MDD and BP.

2. Methods

2.1. Sample

The sample consisted of women who participated in two multi-site psychiatric genetics studies, one studying MDD and the other BP. The Genetics of Recurrent Early-Onset Depression (GenRED) study is a six-site project which collected 680 pedigrees with 971 affected sibling pairs with recurrent, early-onset MDD. All sites for both studies were in the United States. Criteria for enrollment included a proband with recurrent early-onset (<30 years old) DSM-IV MDD with at least one sibling with recurrent MDD with onset <40 years old. Seventy-nine percent of the affected subjects were female (Levinson et al., 2003). The second sample was collected by the NIMH Genetics Initiative Bipolar Disorder Collaborative. This study began in 1989 as a four-site project and expanded to ten sites in 1999. The data used in this analysis come from samples collected from 1999 to 2003. Inclusion criteria focused on BPI probands with at least one sibling with BPI disorder. Fifty-three percent of the affected subjects were female (McInnis et al., 2003; Dick et al., 2003).

Subjects were recruited for both of the studies through various means including newspaper, magazine and radio advertising as well as from clinical settings. After complete description of the study to the subjects, written informed consent was obtained. Diagnoses were based upon an interview conducted by trained research clinicians (masters or doctoral level) using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), or DIGS (see below). Collateral information from family informants and medical records were obtained whenever possible. Final diagnoses were made at each site by two clinicians who reviewed all available data using a best-estimate diagnosis procedure based on the DSM-IV.

The total combined sample included 2524 women. Of these, 1747 had a diagnosis of MDD (both recurrent and single episode), 665 had BPI disorder, 112 had Bipolar II (BPII) disorder and 163 were never mentally ill. The 163 women who were classified as never mentally ill were relatives of participants in the genetics studies who also completed the entire DIGS interview. 75.4% (N=2025) of the sample had a previous pregnancy and 32.0% (N=860) of the sample indicated they had experienced menopause.

2.2. Interview

The DIGS (Nurnberger et al., 1994) was used as part of the diagnostic process in both the NIMH Bipolar study and the GenRED study, though the former used the 3.0 version, while the latter used the 3.0 modified for mood disorder studies (3.0 GenRED). Interrater reliability has been shown to be 0.85–0.96 for mood disorders (Nurnberger et al., 1994). Both versions included the same questions about mood symptoms prior to menstruation, during and after pregnancy, and during the perimenopausal time. These questions were as follows: “Have you ever noticed regular mood changes in the premenstrual or menstrual period?; Have you ever had any severe emotional problems during a pregnancy or within a month of childbirth?; Have you ever had any severe emotional problems associated with menopause?”. Clinicians were allowed flexibility in their interview in order to obtain enough information to accurately answer the questions. The question about mood symptoms during or after pregnancy allowed for affirmative answers that included during pregnancy only, both during and after pregnancy, and after pregnancy only. Since we were interested in mood symptoms that may have been triggered by the hormonal changes associated with childbirth, we only included women who had symptoms solely after pregnancy and within a month of childbirth as positive for postpartum mood symptoms and excluded those that indicated that they had symptoms both during and after pregnancy.

2.3. Statistical analysis

Lifetime rates of each of the symptoms (premenstrual, postpartum, and perimenopausal mood symptoms) were calculated for the following diagnostic categories: MDD, BPI, BPII, and no diagnosis (never mentally ill). MDD included both recurrent and single-episode diagnoses. The Chi-square statistic (with Yates correction) was then used to compare rates in each of the major mood disorder categories to the no diagnosis category.

The General Estimating Equation (GEE) (Zeger and Liang, 1986) was used to calculate an odds ratio correlating each of the types of symptoms with the others. The GEE uses logistic regression and takes into account potential correlation between observations when multiple members of the same family are considered. The GEE was also used to evaluate whether premenstrual mood symptoms predicted having either postpartum or perimenopausal symptoms or both. The sample for these analyses included women with either MDD or BPI who had a previous pregnancy and who had experienced menopause. All analyses were controlled for duration of illness and number of live births.

Because the sample size for women with BPI who had undergone both pregnancy and menopause was relatively small ($N=197$) compared with the sample of women with MDD ($N=509$), we carried out an additional analysis examining whether premenstrual mood symptoms predicted postpartum mood symptoms in the larger sample of women who had a previous pregnancy (BPI, $N=517$; MDD, $N=1282$). The GEE was again used and the analysis was controlled for duration of illness and number of live births.

3. Results

3.1. Prevalence of reproductive cycle-associated mood symptoms

Table 1 displays the rates of premenstrual, postpartum, and perimenopausal mood symptoms by diagnosis. Both percentage and exact numbers of women who reported these symptoms are displayed since the exact number of women who could potentially experience each set of symptoms varied by history of pregnancy and menopause. Premenstrual mood symptoms were reported in 67.7% of women with mood disorders while only 33.7% of women without a psychiatric diagnosis reported them ($\times^2=76.62$, $df=1$, $p=0.0001$). Among women with mood disorders, 20.9% reported postpartum mood symptoms compared with 2.8% of women with no diagnosis ($\times^2=26.8$, $df=1$, $p=0.0001$). 26.4% of women with either MDD or BPI reported experiencing perimenopausal mood symptoms while 12.5% of women with no diagnosis reported this experience ($\times^2=4.60$, $df=1$, $p=0.032$). While a larger portion of women with BPII reported perimenopausal symptoms, the number of women with this diagnosis who had entered perimenopause was quite small ($N=26$). Although the women classified as never mentally ill are not true controls since they are relatives of women with mood disorders, the rate of reproductive cycle-associated mood symptoms in this group provides an idea of the frequency of symptoms as elicited by the DIGS in women without a history of mood disorder.

3.2. Co-occurrence of hormonally triggered symptoms

Table 2 displays the odds ratios for associations between the various reproductive cycle-associated mood symptoms (premenstrual, postpartum, and perimenopausal mood symptoms) as well as between premenstrual mood symptoms and either postpartum or perimenopausal mood symptoms or both in MDD and BPI (Table 2). A total of 509 women with a diagnosis of MDD had had a previous pregnancy and had experienced menopause while 197 women with BPI had met these criteria. Table 2 shows that in women with MDD each of the types of symptoms significantly co-occurred with each of the others and that having premenstrual mood symptoms predicted having either postpartum or perimenopausal mood symptoms. Premenstrual mood symptoms also appeared to predict having both postpartum and

Table 1
Prevalence of reproductive cycle-associated mood symptoms in women with affective disorders

Diagnosis	Premenstrual Mood Symptoms		Postpartum Mood Symptoms		Perimenopausal Mood Symptoms	
	N	%	*N*	%	*N*	%
Major Depression	1196/1747	68.5%	260/1283	20.3%	144/558	25.8%
Bipolar I	433/665	65.1%	113/514	22.0%	57/220	25.9%
Bipolar II	79/112	70.5%	19/83	22.9%	11/26	42.3%
No Diagnosis	55/163	33.7%	4/145	2.8%	7/56	12.5%

Table 2
Associations between reproductive cycle-associated mood symptoms in women with major depression and Bipolar I disorder

Symptom type	Major Depression $N=509$				Bipolar I Disorder $N=197$			
	OR	p	Z score	95% Confidence Interval	OR	p	Z score	95% Confidence Interval
Premenstrual–Postpartum	1.82	0.018	2.37	1.11–2.99	1.41	0.317	1.00	0.72–2.76
Premenstrual–Perimenopausal	1.69	0.018	2.36	1.09–2.60	1.50	0.227	1.21	0.78–2.91
Postpartum–Perimenopausal	1.66	0.043	2.03	1.02–2.72	0.72	0.406	−0.83	0.32–1.58
Premenstrual–Either	1.80	0.003	3.00	1.22–2.64	1.50	0.847	1.39	0.85–2.67
Premenstrual–Both	2.35	0.055	1.92	0.98–5.63	2.17	0.288	1.06	0.52–9.03

Controlled for live births and duration of illness.

perimenopausal mood symptoms with an odds ratio of 2.35, however the p-value was not significant (0.055). In contrast, Table 2 shows that in women with BPI, none of the symptoms significantly co-occurred and premenstrual mood symptoms did not predict having postpartum and/or perimenopausal mood symptoms.

Because of the smaller sample size for BPI, we wondered whether a failure to detect statistically significant associations between reproductive cycle-associated symptoms might be an artifact of reduced power. We thus examined the association between premenstrual mood symptoms and postpartum mood symptoms in an expanded sample of all women with a previous pregnancy (BPI, $N=517$; MDD, $N=1282$). The results did not differ in the expanded sample (Table 3). In women with BPI, premenstrual mood symptoms still did not predict postpartum mood symptoms at a statistically significant level.

We explored several potential artifactual explanations for our findings. First, we tested whether premenstrual mood symptoms were associated with physical health problems or with a course of illness characterized by frequent, brief episodes. Course of illness was designated as part of the best estimate diagnosis procedure and required agreement between at least 2 clinicians reviewing the case. Course of illness categories included: Remitting (well periods longer than mood episodes), Double/Chronic, Frequent/Brief and Other. We found that there was no difference between women who had premenstrual mood symptoms and those who did not in the frequency of endorsing multiple health problems before age 30 (8.12% vs. 9.24%, $\times^2=0.42$, $p=0.66$). There was also little difference between women with MDD who had premenstrual mood symptoms and those who did not in the frequency of experiencing a "frequent, brief" course of illness (2.3% vs. 0.8%, $\times^2=3.62$, $p=0.06$) (this information was not available in the NIMH Genetics Initiative for Bipolar Disorder data). We also compared women who had a history of all three types of symptoms (premenstrual, postpartum, and perimenopausal symptoms) to women who had none of the symptoms: There were no significant differences in the rates of endorsing multiple health problems (9.7% vs. 6.1%, $\times^2=0.68$, $p=0.17$), or in having a "frequent, brief" course of illness (4.2% vs. 0%, $\times^2=0.577$, $p=0.45$) in women with MDD (data not available for women with BP). Second, based on the finding by Murphy-Eberenz et al. (2006) that younger women were more likely to report perinatal mood episodes than older women, we examined whether age influenced the findings, and divided the sample based on whether a woman was less than or greater than 50 years old. This did not alter the associations in either of the samples (data not shown). Third, we examined whether women who stated they were depressed at the time of the interview were more likely to report reproductive cycle-associated mood symptoms. Although there was no difference in the rates of reported symptoms in women with MDD, in women with BPI both premenstrual (depressed 34.8%, not depressed 26.4%, $p=0.04$) and perimenopausal symptoms (depressed 44.8%, not depressed 24.1%, $p=0.007$) were more commonly reported in women who were depressed at the time of the interview. Therefore, we reanalyzed the association between different types of symptoms in both women with MDD and BPI who reported that they were *not* currently depressed at the time of the interview. Our results did not change (data available by request). For example, premenstrual symptoms significantly predicted postpartum symptoms in women with MDD (odds ratio 1.83, $p=0.048$) but not in women with BPI (odds ratio 1.18, $p=0.69$).

Table 3
Associations between premenstrual and postpartum mood symptoms in women with a previous pregnancy

Diagnosis	OR	p value	Z score	95% Confidence Interval
MDD (N=1282)	1.73	0.001	3.37	1.25–2.39
BPI (N=517)	1.35	0.206	1.27	0.85–2.14

4. Discussion

Our major findings are (1) the rates of premenstrual, postpartum and perimenopausal mood symptoms do not

differ between MDD and BP, however, these symptoms were more prevalent in women with mood disorders than in women who have never been mentally ill; (2) premenstrual, postpartum, and perimenopausal mood symptoms did tend to co-occur within individuals with MDD; and (3) in contrast, premenstrual, postpartum and perimenopausal mood symptoms did not significantly co-occur within individuals with BP.

This study had a number of strengths. First, this is the largest sample size ($N=2524$) ever reported on in a study of reproductive cycle-associated mood symptoms. Second, all subjects were rigorously assessed using a well-validated instrument, the DIGS. Third, our results did not appear to be influenced by recall bias as age of subjects did not alter the findings. Fourth, the association in MDD of premenstrual, postpartum and perimenopausal mood symptoms was specific as the presence of premenstrual mood symptoms did not predict other unrelated symptoms such as headache, multiple medical problems or a frequent, brief course of illness.

Previous studies of the prevalence of reproductive-associated mood symptoms have found that these symptoms are typically associated with mood disorders and in particular MDD (reviewed in Payne, 2003). However, most examined the rates of MDD or BP in women with a particular type of reproductive-associated mood symptom—few studies have examined the rates of these symptoms specifically in a sample of women diagnosed with MDD or BP. One exception is the Blehar et al. (1998) study which examined the rates of premenstrual, postpartum, and perimenopausal symptoms in BPI women who participated in an earlier phase of the NIMH Genetics Initiative Study (this sample was not included in the analysis of this study) and found that in a sample of 186 women, premenstrual symptoms were present in two-thirds of the sample, perinatal *and* postpartum symptoms were present in 49% (note: our study examined postpartum symptoms only), and perimenopausal symptoms were present in 19% . Our findings are consistent with these results. Blehar et al. did not examine correlation between different types of reproductive cycle-associated mood symptoms.

Several previous studies have found an association between premenstrual mood symptoms and other reproductive cycle-associated episodes, particularly during the perimenopause. Stewart and Boydell (1993) found that 44 women with "high psychologic distress" attending a menopause clinic were more likely to report a past psychiatric diagnosis, as well as premenstrual and postpartum mood symptoms. Chuong and Burgos (1995) found that 43% of 190 women with PMS had a history of postpartum depression or postpartum blues compared with 12% of the controls. Women with a past psychiatric history were specifically excluded. Morse et al. (1998) found that a history of premenstrual complaints predicted a more difficult "menopausal transition" in 291 women. Psychiatric history was not evaluated. Binfa et al. (2004) found that a history of PMS was a strong predictor of perimenopausal symptoms (OR 3.6) in 300 Chilean women. Again, psychiatric history was not evaluated. Most recently, Freeman et al. (2004) examined a population based cohort of 436 women primarily in their 40s. Women with premenstrual syndrome at study entry were more likely to experience perimenopausal mood symptoms after adjusting for age, race, diagnosis of MDD, and estradiol use with an odds ratio of 2.34.

In the only study to specifically examine women with MDD, Gregory et al. (2000) studied 72 women with MDD and found associations between retrospective mood ratings during premenstrual and perimenopausal time periods, as well as during the postpartum and perimenopausal time periods. There was no association between mood symptoms during the premenstrual and postpartum time periods. This study was limited by the small sample size.

Our results in MDD are consistent with these prior findings of association between reproductive cycle-associated mood symptoms in various populations. What remains unclear is the underlying reason for the lack of association among reproductive cycle-associated symptoms in women with BP. We initially thought that the non-significant associations were a result of the smaller sample size of women with BP. However, increasing the sample size to approximately the same size as that for MDD (by examining the association between premenstrual and postpartum symptoms in women with a previous pregnancy) did not change the nonsignificant odds ratio. Our observations show that reproductive cycle-associated symptoms are common in women with BP, however, the presence of one type of symptom does not predict the presence of another type. There are a number of possible explanations for this observation including the possibility that diagnosis and treatment of BP prevents some types of reproductive cycle-associated symptoms. In support of this possibility is the fact that most women with BPI disorder receive life-long treatment of their mood disorder, whereas some women with MDD may take antidepressants only briefly or intermittently. Unfortunately, information about previous medication treatment was not collected so we were not able to determine if this factor influenced our results. Another possibility is that factors other than hormonal change, such as sleep deprivation, play a role

in the development of reproductive cycle-associated symptoms. For example, the sleep deprivation experienced postpartum has been shown to be a potential trigger for postpartum psychosis (Sharma and Mazmanian, 2003) in some women with BP. We would not expect that postpartum mood episodes triggered by sleep deprivation would correlate with a history of premenstrual mood changes or necessarily predict perimenopausal mood symptoms.

The fact that women experience twice the rate of MDD as compared with men but have an equivalent prevalence of BPI may be related to the finding that reproductive cycle-associated symptoms are correlated with each other, only in women with MDD and not BP. One possibility is that the hormonal changes that women experience throughout their reproductive lifetime constitute a "risk factor" for some women who develop MDD, thus explaining the increased prevalence of MDD in women. In other words, some women may have a genetic vulnerability for the development of MDD that only manifests in the setting of reproductive-cycle related hormonal change. The genetic vulnerability for BPI is likely to be at least partly different than that for MDD, and may be uninfluenced or less influenced by hormonal change.

Limitations of this study include the fact that this is a secondary analysis of a sample that was collected for other purposes. Similarly, the interview used is retrospective in nature and was not designed to specifically examine reproductive cycle-associated symptoms. We thus did not collect information that might have influenced the interpretation of these results such as clinical significance of symptomatology, age of onset of menses, duration of or use of psychiatric medication treatment, especially during the reproductive years, or use of oral contraceptive pills or hormone replacement therapy. The use of retrospective reporting for premenstrual mood syndrome (PMS) and PMDD has been shown to have limited reliability (Rubinow et al., 1984). However, timing and frequency of symptoms is critical to making these (PMS and PMDD) diagnoses; it remains unclear whether the report of the mere presence of particular types of mood symptoms, on which the present analyses are based, is reliable. Women who are currently depressed may be more likely to recollect past depressive symptoms such as reproductive cycle-associated mood symptoms. Indeed, we found that women with BPI (but not MDD) who were depressed at the time of the interview were more likely to report a history of premenstrual and perimenopausal symptoms. This finding did not appear to influence our results since a reanalysis using only non-depressed women led to the same associations between symptoms in women with MDD and lack of associations in women with BPI. Diagnoses of PMDD or postpartum depression cannot be made from the information gathered—it therefore remains unclear if the association patterns observed would remain the same if a more detailed interview was used that allowed for more specific clinical diagnoses. Finally, the samples in this study are highly familial and therefore may not be representative of most patients with MDD or BPI. If genetic predisposition plays a role in the trait of reproductive cycle-associated mood symptoms, then these samples may show elevated rates of these types of symptoms.

In summary, reproductive cycle-associated symptoms appear to be commonly reported in women with both MDD and BP. In MDD, but not necessarily in BP, the occurrence of reproductive cycle-associated symptoms across a woman's reproductive life span appears to be trait-like as the presence of one type of reproductive cycle-associated symptoms predicts the occurrence of other types of reproductive cycle-associated symptoms. Further study is required to clarify the determinants of this trait.

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