Menstrual Dysfunction Prior to Onset of Psychiatric Illness Is Reported More Commonly by Women With Bipolar Disorder Than by Women With Unipolar Depression and Healthy Controls

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Background: Preliminary reports suggest that menstrual cycle irregularities occur more commonly in women with bipolar disorder and unipolar depression than in the general population. However, it is not always clear whether such abnormalities, reflecting disruption of the hypothalamic-pituitary-gonadal (HPG) axis, are caused by psychotropic treatments or associated with the disorder per se.

Method: The prevalence of early-onset (within the first 5 postmenarchal years) menstrual cycle dysfunction (menstrual cycle length unpredictable within 10 days or menstrual cycle length < 25 days or > 35 days) occurring before onset of psychiatric illness was compared between subjects with DSM-IV bipolar disorder participating in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and subjects with DSM-IV unipolar depression or no psychiatric illness participating in the Harvard Study of Moods and Cycles. Data from the Harvard Study of Moods and Cycles were gathered from September 1995 to September 1997, and data from STEP-BD were gathered from November 1999 to May 2001.

Results: Early-onset menstrual cycle dysfunction was reported to have occurred in 101/295 women with bipolar disorder (34.2%), 60/245 women with depression (24.5%), and 134/619 healthy controls (21.7%). Women with bipolar disorder were more likely to have early-onset menstrual cycle dysfunction than healthy controls ($\chi^2 = 16.58$, $p < .0001$) and depressed women ($\chi^2 = 6.08$, $p = .01$), while depressed women were not more likely to have early-onset menstrual cycle dysfunction than healthy controls ($\chi^2 = 0.81$, $p = .37$).

Conclusions: Compared with healthy controls and women with unipolar depression, women with bipolar disorder retrospectively report early-onset menstrual dysfunction more commonly prior to onset of bipolar disorder. Future studies should evaluate potential abnormalities in the hypothalamic-pituitary-gonadal axis that are associated with bipolar disorder.

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Abnormalities in the hypothalamic-pituitary-gonadal (HPG) axis have been reported in women and men with bipolar disorder and depression,[1–7] similar to findings in epilepsy.[8–11] In women, disruption of the HPG axis usually results in infrequent ovulation, which presents with sporadic and unpredictable menses or frank amenorrhea.[12] Such dysfunction of the menstrual cycle occurs in approximately 15% to 20% of women in the general population.[13–15] Results of several small studies in women with bipolar disorder and depression are contradictory, with some finding that menstrual abnormalities occur more frequently than in healthy women[13,16–20] and others reporting rates similar to that seen in the general population.[21,22] Menstrual dysfunction indicating infrequent ovulation is strongly associated with infertility and can also cause osteoporosis, endometrial hyperplasia, and other medical problems.[12]

Medications that destabilize the HPG axis and interfere with normal menstrual function are used frequently in women with bipolar disorder and in some women with unipolar depression.[23–25] As a result, studies in treated patients make it difficult to determine whether menstrual dysfunction is secondary to psychotropic medication use

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or related to the mood disorder per se. This is particularly relevant in light of recent data indicating that the mood stabilizer valproate induces polycystic ovary syndrome (PCOS) features[16–18,26] and that selected antipsychotic agents cause hyperprolactinemia.[23,27,28] The HPG axis is disrupted in PCOS and hyperprolactinemia, which typically present with menstrual cycle irregularities.[29,30]

Given that psychotropic agents can destabilize the HPG axis and interfere with normal menstrual function in some women with affective illness, information about menstrual cycle patterns prior to initiation of treatment must be obtained in order to avoid potentially misattributing menstrual dysfunction to pharmacologic therapies in some women. Menstrual dysfunction prior to onset of psychiatric illness may be a window into HPG axis function in women with mood disorders and guide in risk assessment related to the development of new-onset reproductive-endocrine abnormalities with use of psychotropic treatments.

We compared the prevalence of menstrual cycle dysfunction that developed before onset of bipolar disorder and unipolar depression with that seen among healthy women. Subjects with bipolar disorder were drawn from the multicenter Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study,[31] while depressed and healthy subgroups were derived from the Harvard Study of Moods and Cycles, a community-based epidemiologic study of women with and without depression.[32] We tested the hypothesis that menstrual cycle dysfunction occurs more frequently in women prior to onset of mood disorders than in healthy controls.

METHOD

Subjects were drawn from 2 large studies that used the same questionnaires to collect data relevant to this analysis, including assessments of menstrual dysfunction, psychiatric disorders, and age at onset of psychiatric illness. Details of study procedures for both studies are reported elsewhere.[31–33] All data involved in the current analysis were collected at study enrollment. Data from the Harvard Study of Moods and Cycles were gathered from September 1995 to September 1997, and data from STEP-BD were gathered from November 1999 to May 2001.

Subjects

Subjects with bipolar disorder were drawn from all 588 women of the first 1000 adult patients who enrolled consecutively in STEP-BD. STEP-BD is a multicenter, naturalistic, prospective follow-up study of adults with bipolar disorder conducted at 20 U.S. academic medical center sites.[31] Routine study data were collected from STEP-BD subjects at baseline and then quarterly by STEP-BD–trained clinicians at each of the treatment centers. A diagnosis of bipolar disorder (type I, type II, or not otherwise specified [NOS]) or schizoaffective disorder (bipolar type) was made at baseline for all STEP-BD–enrolled subjects based on mood modules from the Structured Clinical Interview for DSM-IV (SCID), administered by trained research personnel.[31,34] The bipolar disorder population for this analysis was drawn from 582 women, after excluding 6 women with schizoaffective disorder. Clinical characteristics of female STEP-BD participants are reported elsewhere.[35]

Women with unipolar depression and healthy controls were drawn from the Harvard Study of Moods and Cycles. This community-based prospective cohort study of 976 premenopausal women aged 36 to 45 years with and without a lifetime history of depression was conducted in the greater metropolitan Boston, Mass., area.[32,33] Questionnaires were administered to subjects at study enrollment and then twice annually over a 36-month period by trained personnel. The primary goal of the Harvard Study of Moods and Cycles was to examine the association between a lifetime history of depression and subsequent transition to menopause in women who were premenopausal at study enrollment. SCID mood modules[34] were administered by trained research personnel at the baseline visit to determine the presence or absence of a lifetime history of major depressive disorder or dysthymia so that participants could be classified as depressed or healthy controls.[32] Women with a history of depression comprised approximately one third of the 976 subjects. For the current analysis, the healthy control population was drawn from 643 women with no lifetime history of depression or bipolar disorder, and the depressed subgroup was derived from 333 women who had a history of major depressive disorder (N = 318) or dysthymia (N = 15). Further details pertaining to this study population and study procedures are described elsewhere.[32,33]

Procedures

At baseline, all women participating in STEP-BD and the Harvard Study of Moods and Cycles completed self-report questionnaires about their gynecologic history. The study questionnaires included an identical set of questions that asked specifically about menstrual cycle patterns "during the first 5 years after menarche and before pregnancy or oral contraceptive use." These questions included information about the length of menstrual cycles and whether menstrual cycles were predictable within 10 days. For the purpose of this analysis, early-onset menstrual dysfunction was operationalized as a history of either unpredictable cycles (unpredictable within 10 days) or abnormal menstrual cycle length (average < 25 days or > 35 days)[36] within the first 5 postmenarchal years and before pregnancy or oral contraceptive use. This definition of menstrual dysfunction is consistent with those definitions used in other studies that have assessed the preva-

lence of oligo-ovulation defined clinically by menstrual cycle dysfunction.[16–18,21,22]

Subjects were excluded from the analysis if they were missing menstrual cycle data or, in the bipolar and depression cohorts, if they had fewer than 5 years between menarche and the first illness episode (Figure 1). The final analysis was conducted on 295 women with bipolar disorder, 245 with unipolar depression, and 619 healthy controls, which included 50.7%, 73.6%, and 96.2% of women from the original cohorts of 582, 333, and 643 eligible subjects, respectively. The cohorts of women with bipolar disorder and unipolar depression were restricted to those with at least 5 years between menarche and onset of psychiatric illness because our research question focused on menstrual cycle dysfunction associated with the psychiatric illness per se, rather than menstrual abnormalities that may have resulted from use of psychotropic medications. The 5-year cutoff was used because the menstrual history questionnaire specified this time frame for early-onset menstrual dysfunction.

Written informed consent was obtained from all subjects in both STEP-BD and Harvard Study of Moods and Cycles, and the research protocols were approved by the local institutional review board at each of the 20 participating STEP-BD sites and by the Brigham and Women's Hospital Institutional Review Board for the Harvard Study of Moods and Cycles.

Statistical Analysis

The prevalences of postmenarchal menstrual cycle dysfunction prior to onset of bipolar disorder and preceding onset of the first depression episode were compared with the prevalence of menstrual dysfunction during the first 5 years after menarche in healthy controls using χ^2 techniques. Characteristics associated with early-onset menstrual dysfunction were examined using χ^2 techniques (or Fisher exact tests for small cell sizes) for categorical outcomes and analysis of variance, Student t tests, or, for non-normal data, Mann-Whitney nonparametric tests for continuous measures. Logistic regression models were built using early-onset menstrual dysfunction as the dependent measure. All statistical analyses were conducted using the SAS System (Version 8.01; SAS; Cary, N.C.), and statistical significance was set at the $\alpha = .05$ level.

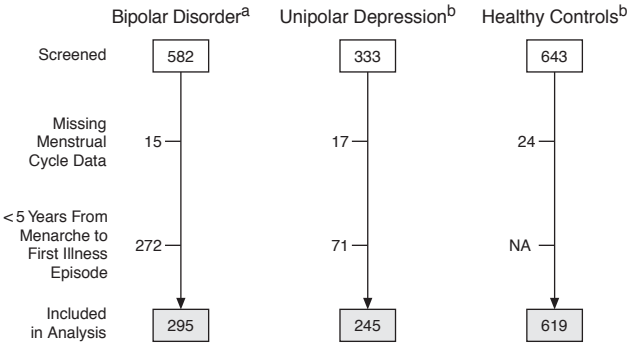
RESULTS

Subjects

Characteristics of the 295 women with bipolar disorder, 245 with unipolar depression, and 619 healthy controls included in the analysis are listed in Table 1. The study populations differed in their age at assessment; ethnicity; marital, educational, and employment status; age at menarche; and body mass index (BMI). Bipolar and depressed subjects reported menarche at a younger age, were more likely to be obese (BMI ≥ 30 kg/m^2), and were less likely to be married than healthy controls at the time of assessment. Compared with depressed women and healthy controls, bipolar patients were a little older at assessment and less likely to be working or to have achieved graduate level education (Table 1).

The mean (± SD) age at onset of illness was 27.2 ± 8.6 years for women with bipolar disorder and 29.4 ± 7.7 years for those with unipolar depression ($p = .002$). Within the bipolar subgroup, 194/295 (65.8%) had type I, 88/295 (29.8%) had type II, and 13/295 (4.4%) had bipolar disorder NOS. The depressed subgroup reported 2.3 ± 2.2 episodes of depression during their lifetime.

Figure 1. Number of Subjects Included in the Analysis and Reasons for Exclusion by Group



[a]Bipolar subjects were drawn from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[31]
[b]Depressed and healthy subjects were drawn from the Harvard Study of Moods and Cycles.[32]

Prevalence of Early-Onset Menstrual Cycle Dysfunction

Early-onset menstrual dysfunction was reported to have occurred in 101/295 women with bipolar disorder (34.2%), 60/245 women with depression (24.5%), and 134/619 healthy controls (21.7%) (Figure 2). Early-onset menstrual dysfunction was therefore reported to have occurred more commonly in women with bipolar disorder than in healthy controls ($\chi^2 = 16.58$, $p < .0001$), while women with depression were not more likely to have reported early-onset menstrual dysfunction than healthy controls ($\chi^2 = 0.81$, $p = .37$). Early-onset menstrual dysfunction was also reported more commonly in women with bipolar disorder than in those with unipolar depression ($\chi^2 = 6.08$, $p = .01$).

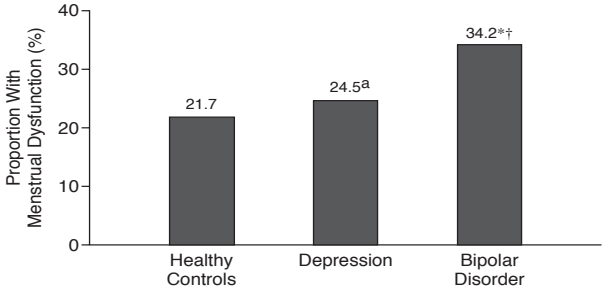
Further analyses were undertaken to examine whether differences in age, ethnicity, BMI, age at menarche, or marital, educational, and employment status between the 3 cohorts might explain the increase in early-onset menstrual dysfunction seen in the bipolar population.

Table 1. Demographic Characteristics in Women With Bipolar Disorder (N = 295), Women With a Lifetime History of Depression (N = 245), and Healthy Controls (N = 619)[a]

Characteristic	Women With Bipolar Disorder (N = 295)	Women With a History of Depression (N = 245)	Healthy Controls (N = 619)	Statistical Test Result	p
Age at assessment, mean ± SD, y	42.3 ± 11.3	40.6 ± 2.6	40.2 ± 2.5	F = 18.5	< .001
Caucasian[b]	277 (95.8)	231 (94.3)	593 (95.8)	χ^2 = 10.2	.0014
Body mass index				χ^2 = 37.6	< .0001
< 25 kg/m^2	152 (51.5)	147 (60.3)	417 (67.4)		
25–29.9 kg/m^2	63 (21.4)	53 (21.7)	138 (22.3)		
≥ 30 kg/m^2	80 (27.1)	44 (18.0)	64 (10.3)		
Age at menarche				χ^2 = 35.5	< .0001
≤ 10 y	26 (8.8)	17 (6.9)	18 (2.9)		
11 y	56 (18.9)	40 (16.3)	68 (11.0)		
12–13 y	170 (57.6)	147 (60.0)	382 (61.7)		
14 y	27 (9.2)	25 (10.2)	75 (12.1)		
≥ 15 y	16 (5.4)	16 (6.5)	76 (12.3)		
Marital status[b]				χ^2 = 98.6	< .001
Never married	77 (26.9)	40 (16.3)	95 (15.4)		
Married	128 (44.8)	169 (69.0)	472 (76.3)		
Disrupted marriage	81 (28.3)	36 (14.7)	52 (8.4)		
Educational status[b]				χ^2 = 36.9	< .0001
≤ High school	43 (15.0)	17 (6.9)	40 (6.5)		
≥ Some college	189 (66.1)	138 (56.6)	344 (55.6)		
Graduate school	54 (18.9)	89 (36.5)	235 (37.9)		
Employment status[b]				χ^2 = 45.3	< .0001
Full/part-time work	129 (45.1)	193 (78.8)	514 (83.0)		
Interrupted employment[c]	113 (39.5)	14 (5.7)	4 (0.7)		
Homemaker	36 (12.6)	28 (11.4)	93 (15.0)		
Other[d]	18 (6.3)	10 (4.1)	8 (1.3)		

[a]Data shown as N (%) unless otherwise noted.
[b]Data missing in ≤ 9 subjects with bipolar disorder.
[c]Leave of absence, unemployed, or disabled.
[d]Student or retired.

Figure 2. Prevalence of Early-Onset Menstrual Cycle Dysfunction Retrospectively Reported by Women With Bipolar Disorder (N = 295), Women With Depression (N = 245), and Healthy Controls (N = 619)



[a]Depression vs. healthy controls, p = .37.
*Bipolar disorder vs. healthy controls, p < .0001.
†Bipolar disorder vs. depression, p = .01.

Although the bipolar cohort included subjects with a wider age range than the depressed and control populations, age at the time of assessment had no effect on the results because the findings were similar when subjects with bipolar disorder were restricted to the 82 women who were in the same 36- to 45-year-old age group (29/82, 35.4%) as the depressed and control subgroups (χ^2 = 7.64, p = .006 vs. healthy controls and χ^2 = 3.67, p = .055 vs. depressed subjects).

Table 2 lists the unadjusted odds ratios and 95% confidence intervals (CIs) for the association between the primary exposure variable of psychiatric diagnosis and other explanatory variables in a logistic regression model with early-onset menstrual dysfunction as the dependent measure. In unadjusted models, women with bipolar disorder were 1.9 times more likely to report early-onset menstrual dysfunction (95% CI = 1.4 to 2.6, p < .001) than healthy controls. Other characteristics significantly associated with reporting of early-onset menstrual dysfunction were menarche age ≥ 15 years (p = .03), marital status (p = .003 for never married and p = .002 for disrupted marriage compared with married subjects), and interrupted employment (p = .005).

Table 2 shows a multivariable logistic regression model with early-onset menstrual dysfunction as the dependent measure that adjusted for psychiatric diagnosis, age, ethnicity, BMI, age at menarche, and marital, educational, and employment status. After adjusting for all demographic characteristics that differed between these populations, women with bipolar disorder remained 1.7 times more likely to report early-onset menstrual dysfunction than healthy controls (95% CI = 1.1 to 2.4, p = .01). Other factors independently associated with reporting of

Table 2. Effect of Psychiatric Illness (bipolar disorder, N = 295, and unipolar depression, N = 245, versus healthy controls, N = 619) and Other Variables on Reporting of Early-Onset Menstrual Cycle Dysfunction

	Unadjusted Model			Adjusted Model[a]		
Characteristic	OR	95% CI	p Value	OR	95% CI	p Value
Bipolar disorder	1.9	1.4 to 2.6	< .001	1.7	1.1 to 2.4	.01
Unipolar depression	1.2	0.8 to 1.7	.35	1.2	0.8 to 1.7	.35
Age at assessment	1.0	1.0 to 1.0	.44	1.0	…	.26
Non-Caucasian[b]	1.5	0.9 to 2.6	.11	1.3	0.7 to 2.2	.37
Body mass index						
25-29.9 kg/m^2	1.3	0.95 to 1.8	.10	1.4	1.0 to 1.9	.07
≥ 30 kg/m^2	1.2	0.9 to 1.8	.25	1.1	0.8 to 1.7	.55
Marital status[b]						
Never married	1.6	1.2 to 2.3	.003	1.5	1.03 to 2.1	.03
Disrupted marriage	1.8	1.3 to 2.7	.002	1.6	1.03 to 2.4	.04
Educational status[b]						
≤ High school	1.3	0.9 to 2.1	.20	1.2	0.8 to 2.0	.37
Graduate school	0.9	0.6 to 1.1	.29	1.0	0.7 to 1.3	.74
Age at menarche						
≤ 10 y	1.3	0.7 to 2.3	.41	1.0	0.5 to 1.8	1.0
11 y	1.1	0.8 to 1.7	.59	1.0	0.7 to 1.5	.87
14 y	1.3	0.8 to 1.9	.29	1.4	0.9 to 2.1	.18
≥ 15 y	1.6	1.05 to 2.5	.03	1.8	1.1 to 2.8	.01
Employment status[b]						
Interrupted employment[c]	1.8	1.2 to 2.6	.005	1.1	0.7 to 1.8	.69
Homemaker	1.2	0.8 to 1.8	.35	1.4	0.9 to 2.1	.13
Other[d]	1.2	0.6 to 2.6	.57	1.1	0.5 to 2.4	.81

[a]Logistic regression model adjusted for age at assessment, ethnicity, marital status, educational status, employment status, age at menarche, and body mass index. Reference population includes healthy women who had a body mass index < 25 kg/m^2, experienced menarche at age 12–13 years, were married, had at least some college education, and were working full- or part-time.
[b]Data missing in ≤ 9 subjects with bipolar disorder.
[c]Leave of absence, unemployed, or disabled.
[d]Student or retired.

early-onset menstrual dysfunction in the adjusted model were having a disrupted marriage, having never married, and having onset of menarche at age 15 years or older. However, despite these associations, the relationship between bipolar disorder and retrospective reporting of early-onset menstrual dysfunction remained strong.

Characteristics of Subjects With and Without Early-Onset Menstrual Cycle Dysfunction

Demographic, psychiatric, and gynecologic characteristics of subjects who had early-onset menstrual dysfunction were examined separately within the bipolar, unipolar depressed, and healthy control groups. For all 3 subgroups, menstrual cycle irregularities at the time of assessment were more common among those who reported early-onset menstrual dysfunction ($p \leq .05$ for all comparisons).

Among women with bipolar disorder, those who reported early-onset menstrual dysfunction were more likely to have been diagnosed with type I (74.3%) rather than type II or NOS (25.7%) disease than those without menstrual dysfunction (61.3% type I, 38.7% type II/NOS; $p = .03$). There was no difference between the bipolar patients who did and did not report early-onset menstrual dysfunction in age at onset of psychiatric illness, prevalence of rapid-cycling disease, mixed episodes, or type of first episode of illness (depressive vs. manic).

Among depressed patients, age at onset of psychiatric illness did not differ between those who did and did not report early-onset menstrual dysfunction. Compared with women who did not report menstrual abnormalities, early-onset menstrual dysfunction was associated with obesity in women with a history of depression (28.3% vs. 14.7%, $p = .04$), but not in those with bipolar disorder or healthy controls.

Healthy controls who reported early-onset menstrual dysfunction were more likely to have never married than those without menstrual dysfunction (22.4% vs. 13.4%, $p = .03$). There were no differences in age at study enrollment, age at menarche, ethnicity, or educational or employment status between those who did and did not report early-onset menstrual dysfunction within the 3 subgroups of women with bipolar disorder, women with depression, and healthy controls.

DISCUSSION

In this study, early-onset menstrual dysfunction was retrospectively reported by 34.2% of women with bipolar disorder, which was significantly more common than the 24.5% and 21.7% prevalence of early-onset menstrual dysfunction reported by women with depression and by healthy controls, respectively. The higher prevalence of

menstrual dysfunction reported by women with bipolar disorder during the first 5 postmenarchal years preceded the onset and treatment of their illness, thus eliminating the possibility that psychotropic medications interfered with the HPG axis to disrupt ovulation and cause menstrual cycle abnormalities.

The menstrual cycle is controlled by pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, through luteinizing hormone (LH) and follicle-stimulating hormone from the anterior pituitary.[29] Menstrual cycle irregularities typically reflect abnormalities in the neuroendocrine control of the cycle.[29] The association between bipolar disorder and menstrual dysfunction raises the possibility that neurotransmitter changes occurring in women with bipolar disorder may interfere with the functional activity of the GnRH pulse generator, which has been seen in women with epilepsy.[37] Abnormalities in pulsatile release of GnRH are suggested by studies in bipolar patients showing elevated basal plasma LH concentrations and an increased LH response to GnRH administration.[4,5,7] In contrast, the HPG axis appears to be functionally intact in depressed patients, based on studies showing normal basal LH levels and LH response to GnRH stimulation.[2,38,39]

Ours is the first large study to examine the prevalence of early-onset menstrual dysfunction in women with bipolar disorder and depression. Our findings that women with bipolar disorder report an elevated prevalence of early-onset menstrual dysfunction are consistent with several small studies in this population that report menstrual dysfunction in up to 82% of women with bipolar disorder, although menstrual abnormalities were not seen as frequently in our patients as in some other studies.[16–19] Our results contradict other studies that report such abnormalities in approximately 20% of women with bipolar disorder,[21,22] which is consistent with estimates in the general population.[13–15]

Our study focused on menstrual dysfunction that was reported to have been present before onset of psychiatric illness and use of psychotropic treatments that can disrupt normal menstrual function.[26–28] Several small retrospective studies have also found that menstrual dysfunction occurs more often than expected prior to onset of bipolar disorder.[16,18,19] Other studies have not evaluated the prevalence of menstrual dysfunction preceding psychotropic medication use but reported only menstrual abnormalities occurring while on valproate and lithium treatment.[17,21,22]

The large number of bipolar, depressed, and control subjects in our study permits us to examine specific characteristics associated with early-onset menstrual dysfunction separately by group. Among women with bipolar disorder, menstrual abnormalities were reported to have occurred more commonly prior to onset of type I disease, rather than type II or NOS type. To our knowledge, this specific clinical characteristic of bipolar disorder has not been evaluated previously in relation to menstrual abnormalities. Our results contradict studies that found an association between menstrual dysfunction and the rapid-cycling subtype of bipolar disorder.[40]

In this study, a larger proportion of women with bipolar disorder than those with depression were excluded on the basis of onset of their mood disorder within the first 5 years after menarche. We excluded women with < 5 years between menarche and onset of a mood disorder because the specific wording of the questionnaires asked about menstrual patterns in the first 5 years after menarche and we wanted to restrict the study subjects to those who would not have been taking psychotropic medications during this time period. However, when we loosened this requirement and reanalyzed the data, restricting the study population to those who had a minimum of 1 year between menarche and onset of psychiatric illness, the results did not change. With 67.2% of the bipolar cohort included in the analysis, 148/391 women (37.8%) reported early-onset menstrual dysfunction. This result was not meaningfully different from the 34.2% of women with bipolar disorder who reported early-onset menstrual dysfunction when the population was restricted to those with at least 5 years between menarche and onset of bipolar disorder.

Because of the requirement for a 5-year interval between menarche and onset of psychiatric illness, the current study does not address whether women who developed depression or bipolar disorder prior to or proximate to menarche were more likely to have early-onset menstrual dysfunction independent of psychotropic medications. Further studies are needed to determine whether our findings are generalizable to those with earlier onset of a mood disorder.

Our study subjects were derived from 2 separate studies, which may influence the comparability of the 3 subpopulations. However, despite differences in demographic characteristics between the bipolar, depressed, and control populations, our findings of an increased prevalence of early-onset menstrual dysfunction reported by the bipolar patients persisted after adjustment for these demographic characteristics. The results of the adjusted model suggest that, although menarche at an older age and being unmarried are also associated with early-onset menstrual dysfunction, these effects are independent of and do not explain the strong association between bipolar disorder and early-onset menstrual dysfunction. A potential residual confounder that we are unable to control for is that the STEP-BD bipolar cohort was derived from a study population recruited to a multicenter, hospital-based study for treatment of their psychiatric illness, rather than the single-center, community-derived populations of depressed subjects and healthy controls who participated in the Harvard Study of Moods and Cycles. However, there is no reason to believe that willingness to

seek care for a psychiatric illness would be associated with menstrual irregularities that were present many years prior. Future community-based studies are needed to account for these complex sociodemographic issues.

Our results also suggest that women with unipolar depression are not significantly more likely to have reported early-onset menstrual dysfunction than healthy controls; this is consistent with some,[21] but not other smaller studies that report a doubling of the risk for such menstrual abnormalities in women with depression.[13,20] Unlike previous studies in women with depression,[13,20,21] our study examined whether menstrual dysfunction was more common prior to onset of depression and its treatment.

In all 3 groups in our study, there was an association between reporting of early-onset menstrual dysfunction and current menstrual cycle irregularities. The association between early-onset and current menstrual cycle abnormalities can be interpreted in several ways. It is possible that women with current menstrual cycle abnormalities are more likely to recall prior menstrual cycle abnormalities. It is also plausible that menstrual cycle irregularities that present early in the postmenarchal years may persist over time or that having early-onset menstrual dysfunction may increase the likelihood of subsequent menstrual irregularities. Prospective studies are required to determine whether early-onset menstrual dysfunction in women with mood disorders persists and whether those who have menstrual cycle abnormalities prior to onset of psychiatric illness are more likely to develop treatment-emergent menstrual irregularities when they are treated with psychotropic medications.

In summary, our results indicate that, compared with healthy controls and women with unipolar depression, women with bipolar disorder are more likely to report that they had early-onset menstrual dysfunction before onset of bipolar disorder. Our study raises the possibility that neurotransmitter effects on GnRH release, which are specific to bipolar disorder, may contribute to the association between early-onset menstrual dysfunction and bipolar disorder. Prospective studies of women with bipolar disorder and unipolar depression are required to further evaluate potential HPG axis abnormalities associated with bipolar disorder. Future studies may also inform risk assessment for the development of reproductive abnormalities with use of antiepileptic drugs and antipsychotic agents among those with baseline abnormalities of the HPG axis and menstrual cycle.

Drug names: lithium (Lithobid, Eskalith, and others), valproate (Depacon and others).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene Freeman, M.D., at marlenef@email.arizona.edu.