A Follow-Up Study of Premenstrual Syndrome

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Background: Previous data suggest that premenstrual syndrome (PMS) and affective disorder are related. The purpose of this preliminary study was to ascertain (1) whether women with PMS have an increased risk for future major depressive episodes compared with controls and (2) whether PMS is a stable diagnosis over time.

Method: Patients with prospectively confirmed PMS, along with retrospective DSM-IV premenstrual dysphoric disorder, and asymptomatic controls were studied at 5- to 12-year follow-up using a structured clinical interview. Additionally, those women who still had regular cycles and were medication-free were asked to complete 2 months of prospective daily ratings.

Results: Women with PMS (N = 27) had a nonsignificantly higher incidence of new-onset depressive episodes (DSM-III-R and Schedule for Affective Disorders and Schizophrenia-Lifetime Version [SADS-L] criteria) during a 5- to 12-year follow-up compared with controls (N = 21). Differences in incidence disappeared when patients and controls without prior history of depression were compared. Prospective ratings completed during follow-up confirmed original diagnoses of PMS patients (N = 7) and controls (N = 11).

Conclusion: While preliminary, these results suggest that the higher rate of major depression in patients with PMS during follow-up reflects the higher risk attendant to the history of major depression that existed at baseline. Additionally, at least in a small subsample, PMS appears to be a stable diagnosis over time.

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Several types of data suggest that premenstrual syndrome (PMS) and affective disorder are related: (1) symptoms of PMS are similar to those of depression, particularly atypical depression[1]; (2) treatments used for major depressive disorder (e.g., antidepressants) are effective in the treatment of PMS[2]; (3) higher prevalence rates of major depressive disorder are seen in women with PMS compared with controls[3,4]; and (4) women with PMS may be more likely to develop affective disorders than will controls during follow-up.[5] Evidence for this last observation comes from Wetzel et al.,[5] who reported that 18% of a sample of college students with "premenstrual affective syndrome" presented with new-onset affective disorder during a 4-year follow-up, and from Graze et al.,[6] who observed that scores on the depressive subscale of the Premenstrual Assessment Form were significantly correlated with depression during a 2- to 4-year follow-up period.[6]

This article describes a follow-up study of patients with prospectively confirmed PMS and controls and addresses the following questions: Is PMS a stable diagnosis, or does it serve as a prelude to other psychiatric disorders? Does having premenstrual syndrome increase a woman's risk for future major depressive episodes? Do women with PMS continue to meet criteria for the syndrome over time?

METHOD

Subject Selection

All subjects had participated in studies at the National Institute of Mental Health (NIMH) as either patients or asymptomatic controls in PMS studies 5 to 12 years prior to the follow-up interview. The potential subject pool comprised all former patients and controls: of the 89 patients, 27 (30%) were successfully contacted, and of 73 controls, 21 (29%) were successfully contacted. All subjects that we contacted agreed to participate.

Original Clinic Admission

During their original participation in our studies, patients (N = 27) and controls (N = 21) completed 2 to 3 months of prospective daily visual analogue ratings of mood and behavioral symptoms. Patients were confirmed to have PMS if their mean negative mood symptom scores were 30% higher (relative to the range of the visual analogue scale used) during the premenstrual week compared with the postmenstrual week in at least 2 of 3 menstrual cycles. This method correlates highly with the effect size method of determining that the severity criteria for PMS are met.[7] Additionally, these original ratings were reviewed, and all former patients met DSM-IV[8] criteria (retrospectively applied) for premenstrual dysphoric disorder (PMDD). Subjects were defined as normal controls if they exhibited no mood disturbance in relation to their men-

strual cycle and had no history (current or past) of psychiatric disorder. The protocol under which subjects were originally diagnosed and admitted for study was approved by the NIMH Institutional Review Board, and all subjects gave written informed consent to participate in the study.

All subjects underwent a structured diagnostic interview (modified Schedule for Affective Disorders and Schizophrenia-Lifetime Version [SADS-L])[9] when first evaluated for their initial participation in the clinic. At that time, all subjects (both patients and controls) were free of current or recent medical or psychiatric illness, were taking no medications, and had menstrual cycles of regular lengths. Controls had no past history of psychiatric illness.

Follow-Up Admission

Subjects were readmitted and reinterviewed 5 to 12 years after their first evaluation, using the Structured Clinical Interview for DSM-III-R (SCID)[10] and the posttraumatic stress disorder and minor, intermittent, and atypical depression sections of the SADS-L.[9] Because of the nature of the structured interview, it was not possible to blind the interviewer to past history of PMS. However, at the beginning of the interview, the interviewer was blind to past psychiatric diagnoses. In addition, those subjects who at the time of the follow-up interview were still medication-free and having regular menstrual cycles were asked to complete an additional 2 months of prospective daily ratings. Subjects completing prospective ratings were considered to have PMDD if they met the original operational criterion for PMS (see above) and DSM-IV criteria for PMDD by history.

Statistical Analysis

The Student t test was used to compare age and years of follow-up between patients and controls. Comparison of the appearance of new episodes (since the time of initial evaluation) of major depression and other Axis I psychiatric disorders in patients and controls was performed using Yates-corrected chi-square analysis. As the results of this comparison may be biased by the higher prevalence of a history of major depression in the patient group, the Fisher exact test (2-tailed) was used to determine the significance of the differences in the appearance of major depression in those subjects with no such previous history. Additionally, we performed a Kaplan-Meier survival analysis to take into account the number of individuals lost to follow-up. Data are expressed as mean ± standard deviation (SD).

RESULTS

The mean ± SD age of the patients at the time of follow-up (47.1 ± 5.7 years) was significantly higher than that of controls (42.7 ± 7.7 years; $t = 2.29$, $df = 46$, $p = .03$). In contrast, no difference was found in the number of years from initial visit to follow-up in patients (8.5 ± 2.2 years) versus controls (7.6 ± 2.3; $t = 1.44$, $df = 47$, N.S.; Table 1).

At the time of the initial interview, 52% of the patients and none of the controls reported an antecedent history of major depressive disorder. Eleven (41%) of 27 patients and 4 (19%) of 21 controls reported major depressive disorder during the interval between their initial evaluation and the follow-up interview. This difference was not significant (Yates-corrected $\chi^2 = 1.68$, $p = .19$). When data for women with PMS with a past history (prior to study entry) of depression were removed from the analysis, the rates of appearance of depression during follow-up were similar (patients with PMS = 23% [N = 3/13], controls = 19% [N = 4/21]; Fisher exact test, $p = .68$). Also, a higher number of all psychiatric disorders (including major depressive disorder) appeared during the follow-up period in women with PMS, 15 (56%) of 27, compared with controls, 6 (29%) of 21, although this difference did not reach statistical significance (Yates-corrected $\chi^2 = 2.49$, $p = .12$). The non–major depression Axis I diagnoses for PMS patients were dissociative identity disorder, N = 1; alcohol dependence, N = 1; dysthymia, N = 1; and generalized anxiety disorder with agoraphobia, N = 1. For controls, diagnosis were minor depression, N = 1; and simple phobia, N = 1.

The Kaplan-Meier survival analysis of the sample stratified by diagnosis (patients with PMS versus controls, Figure 1) showed no difference in the onset of depression during follow-up (Tarone-Ware $\chi^2 = 2.63$, $df = 1$, $p = .11$), whereas the survival analysis using a past history of major depressive disorder (Figure 2) as the stratification factor showed a significant difference (Tarone-Ware $\chi^2 = 12.86$, $df = 1$, $p = .00$), indicating that the past history of major depressive disorder, not a history of PMS alone, was the significant factor associated with the occurrence of major depressive disorder during the follow-up period.

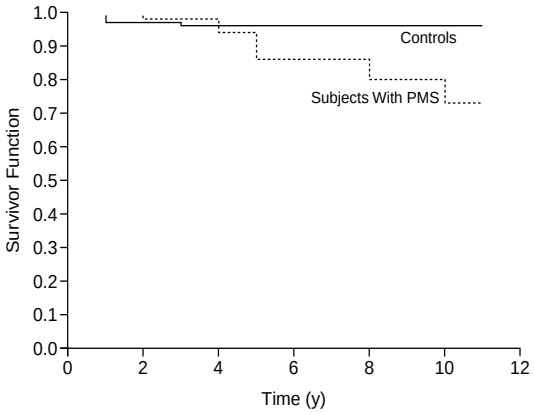
Of the 16 former patients who had regular menstrual cycles at follow-up, only 7 were medication-free. Of these 16 patients, 4 who were receiving medication were being treated with psychotropics (1 with divalproex sodium for bipolar disorder, 3 with SSRIs—2 for major depressive disorder, 1 for PMS). The other patients receiving medications were being treated for a variety of medical disorders (e.g., Sjögren's syndrome, multiple sclerosis, asthma, hypothyroidism). Those 7 patients who were medication-free completed 2 cycles of daily visual analogue ratings. All 7 met criteria for PMS. Of the 17 control women who were premenopausal, 16 were medication-free (1 was receiving oral contraceptives). Eleven of these women completed 2 cycles of the daily ratings. None of the controls met criteria for PMS.

Table 1. Results[a]

Variable	Original Diagnosis: Premenstrual Syndrome (N = 27)	Original Diagnosis: Controls (N = 21)	Statistical Comparison
Age at presentation, mean ± SD, y	37.9 ± 5.1	35.2 ± 7.0	t = 2.23, df = 46, p = .03
Age at follow-up, mean ± SD, y	47.1 ± 5.7	42.7 ± 7.7	t = 2.29, df = 46, p = .03
Time to follow-up, mean ± SD, y	8.5 ± 2.2	7.6 ± 2.3	t = 1.44, df = 14, NS
Subjects with regular menstrual cycles at follow-up	16 (59)	16 (76)[b]	Fisher exact test, p = .2
Subjects perimenopausal or postmenopausal (surgical or natural menopause)	11 (41)	4 (19)	Fisher exact test, p = .13
Subjects with history of major depressive disorder at initial presentation	14 (52)	0 (0)	Fisher exact test, p = .00
Subjects with history of other psychiatric diagnosis at initial presentation	4 (15)[c]	0 (0)	Fisher exact test, p = .11
Subjects with at least 1 episode of major depressive disorder during follow-up period	11 (41)	4 (19)	χ^2 = 1.68, p = .19
Subjects without history of major depressive disorder at initial presentation with at least 1 episode of major depressive disorder during follow-up period	3 (23)[d]	4 (19)	Fisher exact test, p = .68
Subjects with occurrence of psychiatric disorders other than major depressive disorder during follow-up period	4 (15)[e]	2 (10)[f]	Fisher exact test, p = .68
Subjects receiving medication at time of follow-up visit	16 (59)[g]	4 (19)[h]	Fisher exact test, p = .008

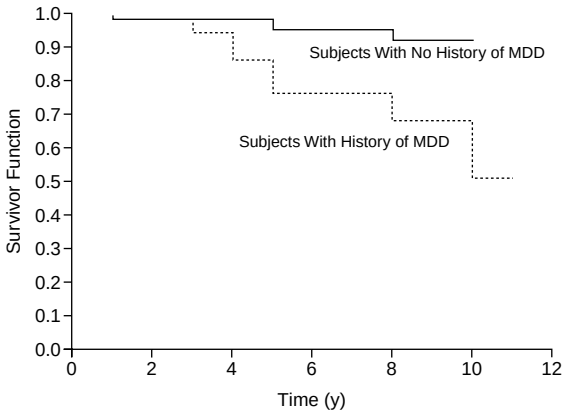
[a]All values shown as N (%) unless otherwise specified. Abbreviation: NS = not significant.
[b]One subject (5%) in control group pregnant.
[c]Generalized anxiety disorder (GAD), N = 2; panic disorder, N = 1; alcoholism, N = 1.
[d]Total N = 13.
[e]Dissociative identity disorder, N = 1; alcohol dependence, N = 1; dysthymia, N = 1; GAD with agoraphobia, N = 1. Although dissociative identity disorder was not diagnosed until the follow-up Structured Clinical Interview for Depression was administered, we presume that this diagnosis antedated the patient's initial presentation.
[f]Minor depression, N = 1; simple phobia, N = 1.
[g]Psychotropic agents, N = 8; oral contraceptives, N = 1; hormone replacement therapy, N = 3; thyroid, N = 1; miscellaneous, N = 3.
[h]Hormone replacement therapy, N = 1; oral contraceptives, N = 1; miscellaneous, N = 2.

Figure 1. Kaplan-Meier Survival Analysis: Subjects With PMS Versus Controls[a]



[a]Tarone-Ware χ^2 = 2.63, df = 1, p = .11.

Figure 2. Kaplan-Meier Survival Analysis: Subjects With Past History of Major Depressive Disorder (MDD) Versus Those With No History of MDD[a]



[a]Tarone-Ware χ^2 = 12.86, df = 1, p = .00.

DISCUSSION

In a 5- to 12-year follow-up of patients with prospectively diagnosed PMS and controls, we observed a nonsignificantly higher rate of subsequent episodes of psychiatric disorders in general and major depression in particular in patients versus controls. PMS patients had a higher lifetime prevalence of affective disorder at baseline (52%) compared with controls (0%), however, and when the data of patients with a previous history of major depression were removed from the analysis, the difference in the onset of new depressions during follow-up between the 2 groups virtually disappeared (23% vs. 19%). These findings were also supported by the survival analysis, which demonstrated the overwhelming significance

of past history of major depressive disorder, compared with the diagnosis of PMS, as the determinant of subsequent episodes of major depressive disorder. Thus, although a type II error may have prevented us from detecting the higher rate of major depressive disorder in patients as significantly different from that of controls, our data suggest that, absent a prior history of affective disorder, a woman with PMS is not more likely to develop major depression compared with normal control subjects. While preliminary, these data are consistent with a recent study by Kendler et al.,[11] who found that genetic and environmental risk factors for PMS were only weakly related to those for major depression.[11] The stability of the diagnosis of PMS over time is suggested by the observation that all 7 women with PMS who completed the prospective ratings at follow-up continued to meet criteria for PMS, compared with none of the controls.

This study has a number of obvious limitations: the sample size, particularly of those providing prospective ratings at follow-up, is small; the proportions of originally diagnosed subjects recruited for follow-up are similarly modest, thus potentially introducing a selection bias; the times to follow-up, while comparable across groups, are variable; and the psychiatrist performing the SCID at follow-up could not be completely blinded to group classification. Additionally, a higher proportion of women with PMS were menopausal at follow-up, and there was a higher number of comorbid medical conditions in this group; these higher numbers, however, may inflate the apparent number of cases of depression in women with PMS, thus further strengthening one of the main conclusions in this paper, i.e., women with PMS are not more likely to experience affective episodes absent an antecedent history of affective disorder. Despite limitations, our findings, particularly if replicated, have several significant clinical and research implications: (1) consistent with the findings of Kendler et al.[11] (and despite high comorbidity with major depression), PMS is not merely a forme fruste of major depression, perhaps explaining why it is responsive to therapies not traditionally employed in the treatment of affective disorder (e.g., leuprolide acetate); (2) studies of the concomitants and treatments of PMS should make certain that the variance observed is not accounted for by the presence and/or absence of history of affective disorder; and (3) if the stability of the diagnosis over time that we observed is confirmed in larger samples, it would complement the already observed intercycle consistency in the nature and severity of symptoms[12] in further suggesting the validity of PMS as a distinct syndrome.[13]

Drug names: divalproex sodium (Depakote), leuprolide acetate (Lupron).

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