Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

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Context: Transition to menopause has long been considered a period of increased risk for depressive symptoms. However, it is unclear whether this period is one of increased risk for major depressive disorder, particularly for women who have not had a previous episode of depression.

Objective: To examine the association between the menopausal transition and onset of first lifetime episode of depression among women with no history of mood disturbance.

Design: Longitudinal, prospective cohort study.

Setting: A population-based cross-sectional sample.

Participants: Premenopausal women, 36 to 45 years of age, with no lifetime diagnosis of major depression (N=460), residing in 7 Boston, Mass, metropolitan area communities.

Main Outcome Measure: Incidence of new onset of depression based on structured clinical interviews, Center for Epidemiologic Studies Depression Scale scores, and an operational construct for depression.

Results: Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

Conclusions: The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier have a significant risk for first onset of depression. Further studies are needed to determine more definitively whether other factors, such as the presence of vasomotor symptoms, use of hormone therapy, and the occurrence of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes seen during this period may affect many women as they age and may lead to a significant burden of illness.

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TRANSITION TO MENOPAUSE has long been considered a period of increased risk for depressive symptoms. However, the extent to which this period is one of increased risk for major depressive disorder is less clear. Some[1,2] but not all,[3,4] studies suggest an association between the menopausal transition and significant psychosocial impairment with concomitant vulnerability to depressive symptoms. These inconsistent findings may be due at least in part to variability in study designs and other methodological limitations. For example, there has been little uniformity with respect to selection of study participants, with some studies targeting specialized menopause clinics, while others have included subjects from community-based samples. Another source of inconsistency across some studies has been the definition of menopausal status. Menopausal status has frequently been assigned based on 1 single criterion (eg, age) or by a combination of various criteria including age, presence of menopause-related symptoms, hormone levels, or history of menstrual cycle irregularity. Last, some studies have lacked a standardized assessment of psychiatric symptoms or disorders and/or rigorous criteria to delineate severity of depressive episodes.[5-7]

The Harvard Study of Moods and Cycles is a population-based prospective study of premenopausal women with and without a lifetime history of major depression. The specific aim of the initial study was to examine the association between lifetime history of major depression and the decline in ovarian function as measured by an earlier transition to the menopause based on prospectively assessed reproductive endocrine and menstrual cycle changes.[8] The design of the study included prospective documentation of menstrual cycle changes and new onset of psychiatric morbidity over

time as women approached the menopausal transition. In the current report, we examine the association between the menopausal transition and the onset of first lifetime episode of depression within the group of women from the original cohort who had no history of mood disturbance.

METHODS

Participants in the Harvard Study of Moods and Cycles were selected from a population-based cross-sectional sample of women 36 to 45 years of age residing in 7 Boston, Mass, metropolitan area communities. After achieving a 73% response rate to a self-administered questionnaire that assessed menopausal status and past and current depressive symptoms, 4161 women composed the target population used to identify a sample with and without a lifetime history of major depression. Details regarding data collection and other characteristics of the target population can be found elsewhere.[8-10] Briefly, about 30% each of women initially screened with and without depression were eventually enrolled in the Harvard Study of Moods and Cycles. Among the remaining women not enrolled, about half were unwilling to make the sizable commitment required for participation in this prospective study. The remaining subjects were ineligible for enrollment because of pregnancy, menopausal status, misclassification of depression status, mania or psychoses, or loss to follow-up after the initial screening assessment. Thus, a sample of women who did (n=333) and did not (n=643) meet criteria for past or present major depression, based on structured clinical interviews for *DSM-IV* (*Structured Clinical Interview for* DSM-IV, *Outpatient Version* [*SCID*]),[11] were prospectively followed up with respect to changes in mood and menstrual status.[8]

The Brigham and Women's Hospital Human Subjects Research Committee (Boston) approved the study protocol. Study procedures were fully explained to all participants prior to their written consent. On enrollment, in-person interviews were conducted with all study participants regarding their demographic and lifestyle characteristics, menstrual and reproductive history, and past and current medical conditions at study entry. Telephone interviews were conducted every 6 months during a 36-month period, and a self-administered questionnaire was mailed to participants approximately 72 months after study enrollment to track menstrual and medical history changes. We restricted the current analysis to the cohort of women with no lifetime history of major depression.

DEFINING THE PERIMENOPAUSAL TRANSITION

The World Health Organization defines the perimenopause as the time immediately preceding the menopause, beginning with endocrine, biologic, and clinical changes, and ending a year after the final menstrual period.[12] At each follow-up interview, we determined whether a study participant had remained premenopausal or had entered the menopausal transition. A participant was classified as having initiated this transition at the time of the follow-up interview if any of the following events occurred during the previous period: an absolute change of 7 days or greater in menstrual cycle length as compared with cycle length reported at study enrollment; a change in menstrual flow amount (≥2 flow categories [eg, from light or moderately light to moderately heavy or heavy]) or duration (absolute change of ≥2 days); or self-report of skipped periods. These menstrual cycle changes were used to indicate the menopausal transition; similar methods had been previously used in the Massachusetts Women's Health Study,[13,14] the Seattle Midlife Women's Health Study,[15] and other related epidemiologic research.[16] The criteria are also consistent with a more recent construct used to characterize the menopausal transition as proposed by the Stages of Reproductive Aging Workshop.[17]

We also had an opportunity to examine self-reported vasomotor symptoms during the last period of follow-up and whether the use of hormonal therapy (ie, oral contraceptives or hormone therapy) had been initiated to alleviate hot flushes or symptoms of menstrual irregularity. If so, subjects were categorized as having initiated a "hormone-modulated" perimenopause, in contrast to "natural perimenopause." This information was obtained using a menstrual, reproductive, and general medical history questionnaire completed at the last follow-up interview.

ASSESSMENT OF LIFE EXPERIENCES AND NEW ONSET OF DEPRESSION

Information regarding the presence of significant adverse life experiences was collected with the Life Experience Survey (LES), a questionnaire assessing the presence of 57 events in the past 6 months, with the impact of these events rated on a 7-point scale.[18] Consistent with previous studies, we submitted for analysis the sum (absolute value) of the negatively rated items as our index of negative life stress, with higher scores indicating higher levels of negative events.[19] In assessing the influence of LES on the association between the perimenopausal transition and risk of new onset of depression, we used the most recent LES questionnaire that preceded both the menopausal transition and new onset of depression. We used a trichotomous distribution (none, 1 or 2, ≥3 negative life events) when adjusting for LES in our logistic models and a dichotomous variable (none, ≥1 negative life events) when assessing the effect modification of LES on our association of menopausal transition and new onset of depression.

During the first 3 years of follow-up, new onset of depression was defined based on telephone-administered *SCID* interviews. The last follow-up occurred between 59 and 92 months from study enrollment and took into consideration the period following the initial 36 months of follow-up. At that point, assessment of depressive symptoms during the past month was based on self-reported Center for Epidemiologic Studies Depression Scale[20] (CES-D) scores; the occurrence of depression at other times was captured based on responses to 3 questions about experiences subjects may have had including (1) a 2-week period of feeling depressed or down nearly every day, (2) a loss of interest or pleasure in things usually enjoyed, or (3) having been bothered by depressed mood more than half of the time. Subjects were considered to have had a new episode of depression if they had CES-D scores of 16 or higher or responded positively to at least 1 of the 3 questions mentioned earlier. The occurrence of a more severe episode of depression was considered if the CES-D scores were higher than 24 or if the subjects positively endorsed questions 1 and 2 mentioned earlier. The operational definition for depression used during the last follow-up assessment had shown high sensitivity and specificity when data were compared with those of women enrolled in the Harvard Study of Moods and Cycles who met *DSM-IV* criteria for major depressive disorder based on *SCID* interviews.

STATISTICAL ANALYSIS

To identify potential confounders, we compared the distribution of age, education, parity, and prior use of oral contraceptives between those who did and did not transition to the perimenopause. We used unconditional logistic regression to examine the relationship between menopausal transition and first onset of depression. Women who did and did not make the menopausal transition were not matched on any covariates. However, differences between the 2 groups by age at study enrollment were controlled for in the logistic regression models. We also assessed

the risk of new onset of depression within the perimenopausal subjects stratified by presence or absence of vasomotor symptoms and by occurrence of natural perimenopause (without any hormonal intervention) or hormonally modulated perimenopause. Additionally, we stratified all subjects by history of adverse life events and examined the relationship between menopausal transition and any first onset of depression within each group. Vasomotor symptoms among perimenopausal subjects were also examined by this stratification.

RESULTS

Of the original 643 cohort members, we excluded 31 women who were taking oral contraceptives at study enrollment because they could not be assessed for onset to perimenopause; 17 women who became menopausal; and 7 women who were lost to follow-up after baseline enrollment. Of the remaining 588 women, we also excluded 128 who failed to provide the last follow-up interview because critical information on the presence of vasomotor symptoms was only obtained at that follow-up visit. Thus, based on the criteria established for menopausal transition, 134 women remained premenopausal at the end of the last follow-up period, while 326 women had entered the perimenopause.

As presented in **Table 1**, women who entered the menopausal transition were similar to those who remained premenopausal with respect to education, parity, and history of oral contraceptive use. However, as expected, women who entered the perimenopause were older than women who remained premenopausal.

Premenopausal women with no lifetime history of major depression who entered the perimenopause were nearly twice as likely to develop depressive symptoms as women with no history of depression who remained premenopausal, after adjustment for age at study enrollment and history of negative life events as recorded on LES (**Table 2**). Entering the menopausal transition was more strongly associated with risk of new onset of depression in women who reported the presence of vasomotor symptoms (hot flushes). We further stratified the group of women who entered the perimenopause based on use of hormonal therapy to ease perimenopausal symptoms or to regulate menstrual cycles. A similar association between menopausal transition and risk of new onset of depressive symptoms was observed in those women whose transition occurred with and without hormonal intervention. A greater percentage of women with "severe" first onset of depression were naturally perimenopausal (ie, without reporting use of hormonal interventions); however, the small numbers in each subgroup could potentially explain this difference.

Table 3 shows that women with a history of negative life events were at a significantly increased risk of developing a first episode of depression as they transitioned to perimenopause compared with those who remained premenopausal. This increased risk did not appear to be attributable to the presence of vasomotor symptoms.

Table 1. Characteristics of Women Who Did and Did Not Transition to the Perimenopause

Characteristic	No. (%)	
	Premenopausal	Transitioned
Age at study enrollment, y*		
36-37	20 (14.9)	36 (11.1)
38-39	47 (35.1)	62 (19.0)
40-41	30 (22.4)	80 (24.5)
42-46	37 (27.6)	148 (45.4)
Education		
≤High school graduate	7 (5.2)	24 (7.4)
Some college/vocational school	20 (14.9)	62 (19.0)
College graduate	55 (41.1)	108 (33.1)
Graduate school	52 (38.8)	132 (40.5)
Parity		
Nulliparous	44 (32.9)	95 (29.2)
1-2 Live births	42 (31.3)	106 (32.5)
≥3 Live births	48 (35.8)	125 (38.3)
Prior use of oral contraceptives		
Never	48 (35.8)	87 (26.7)
Use for ≤1 y	14 (10.5)	49 (15.0)
>1 y of use	72 (53.7)	190 (58.3)

*$P<.05$ based on χ^2 assessments.

COMMENT

Several epidemiologic studies have now demonstrated the substantial prevalence of mood disorder in women at distinct periods across their life cycle. The current investigation demonstrated high rates of serious mood disturbance in premenopausal and perimenopausal women (9.5% and 16.6%, respectively), consistent with some prevalence estimates from other community-based samples[21,22] but higher than other prevalence estimates for women in the same age group.[23]

Recent reports have consistently documented that the perimenopause is a time of increased risk for the development of depressive symptoms in women. Results from a multiethnic community-based cohort of premenopausal and perimenopausal women (SWAN study) showed that mood symptoms and irritability are more likely to occur in perimenopausal than in premenopausal women. In addition, reports of persistent mood symptoms remained higher among perimenopausal women after adjustment for potential confounding factors such as vasomotor symptoms and sleep disturbances.[24] In a recent community-based study by Freeman and colleagues,[25] an increased likelihood of depressive symptoms (as assessed by CES-D scores) was noted among women transitioning to menopause and a decreased likelihood, after onset of frank menopause (based on increasing follicle-stimulating hormone profile). Similarly, Schmidt and colleagues[26] prospectively assessed 29 premenopausal women until the occurrence of amenorrhea for at least 6 months. The risk observed for new episodes of depression was significantly higher during the 24 months surrounding the final menses.

Other investigators have previously suggested an increased risk for depressive symptoms during the transition to perimenopause.[1,4,24] However, in most studies, menopausal status has been defined solely on menstrual regularity or age and, in some cases, information regarding presence of vasomotor symptoms. Information regarding concurrent hormone therapy (if any) used to alleviate such symptoms has not been systematically studied.[1,2]

Table 2. Risk of First Onset of Depressive Symptoms in Premenopausal and Perimenopausal Women With No Lifetime History of Major Depression

At Outcome or End of Follow-up	Any First Onset, No. (%)	Adjusted OR (95% CI)*	Severe First Onset, No. (%)†	Adjusted OR (95% CI)*
Premenopausal (n = 95)‡	19 (20.0)	1.0	9 (9.5)	1.0
Perimenopausal (n = 326)	106 (32.5)	1.8 (1.0-3.2)	54 (16.6)	1.9 (0.9-4.0)
No vasomotor symptoms (n = 169)§	52 (30.8)	1.8 (0.9-2.5)	23 (13.6)	1.6 (0.7-3.7)
Vasomotor symptoms (n = 135)	49 (36.3)	2.2 (1.1-4.2)	26 (19.3)	2.5 (1.1-5.8)
Unknown vasomotor symptoms (n = 22)	5 (22.7)	1.0 (0.3-3.3)	5 (22.7)	2.7 (0.8-9.1)
"Hormone-modulated" perimenopause (n = 49)‖	17 (34.7)	2.0 (0.9-4.5)	5 (10.2)	1.1 (0.4-3.7)
Natural perimenopause (n = 277)	89 (32.1)	1.8 (1.0-3.2)	49 (17.7)	2.0 (0.9-4.4)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age at study enrollment and proximate Life Experience Survey[18] scores.
†Women classified as severe if they had (1) *Structured Clinical Interview for* DSM-IV*, Outpatient Version*[11]–confirmed depression from an earlier follow-up interview, (2) self-reported at last follow-up being depressed most of the day nearly every day and also indicated a loss of pleasure in things usually enjoyed, or (3) scored higher than 24 on the Center for Epidemiologic Studies Depression Scale.
‡Of the original 134 subjects who stayed premenopausal, included were 95 women with no vasomotor symptoms.
§Vasomotor symptoms defined as, on average, once a week or more awoke with hot flushes.
‖Defined as taking hormonal therapy to ease perimenopausal symptoms or to regulate menstrual cycles.

Table 3. Risk of First Onset of Depressive Symptoms in Premenopausal and Perimenopausal Women by History of Adverse Life Events

	No History of Adverse Life Events		History of Adverse Life Events	
At Outcome or End of Follow-up	Any First Onset, No. (%)	Adjusted OR (95% CI)*	Any First Onset, No. (%)	Adjusted OR (95% CI)*
Premenopausal (n = 90)†	22 (9.1)	1.0	68 (19.1)	1.0
Perimenopausal (n = 321)‡	73 (19.2)	1.9 (0.4-10.1)	248 (36.3)	2.4 (1.2-4.6)
No vasomotor symptoms (n = 156)§	38 (15.8)	1.3 (0.2-8.4)	118 (30.5)	1.9 (0.9-3.8)
Any vasomotor symptoms (n = 125)	26 (19.2)	0.9 (0.1-8.7)	99 (36.4)	2.5 (1.2-5.2)

Abbreviations: See Table 2.
*Adjusted for age at study enrollment.
†Of the original 134 subjects who stayed premenopausal, included were 90 women with no vasomotor symptoms and who also completed the Life Experience Survey.
‡Of the original 326 subjects who became perimenopausal, 321 had completed the Life Experience Survey.
§Some subjects (n = 18) did not complete information on vasomotor symptoms; 22 women developed new onset of depression prior to completing information on vasomotor symptoms.

Our study suggests an increased risk for the development of a first episode of depression among women entering the perimenopause. To our knowledge, this prospective documentation of increased risk for depression among women without a history of depression is unique, particularly given our more rigorous efforts to define menopausal status and to characterize the presence of significant depression.

In the current study, the increased risk for depression during the menopausal transition appeared to be accentuated by the presence of vasomotor symptoms. This association between vasomotor symptoms and occurrence and severity of reported depression, particularly among perimenopausal women, is consistent with some,[27] but not all,[24,25] previous investigations. The relationship between hot flushes and depression during the menopausal transition is not yet fully understood and may result from a number of factors. Hot flushes frequently lead to a significant sleep disruption, severe enough to adversely affect daytime functioning and to impact quality of life.[28] Thus, the presence of mood disturbances during the perimenopause could be secondary to hot flush–induced sleep disturbance—the so-called domino theory.[29] Alternatively, the occurrence of depression and hot flushes during the perimenopause may represent a distinct phenomenon caused by changes in the reproductive hormonal milieu to which some, but not all, women are particularly sensitive.[12,30] This hypothesis is supported by evidence suggesting that both estrogen and serotonin may modulate hypothalamic thermoregulatory function. Thus, abrupt changes in neuromodulatory function and/or in reproductive-hormone levels could contribute to the constellation of mood and vasomotor symptoms seen in some perimenopausal women.[31,32]

Women in the current sample who entered the menopausal transition and who concurrently initiated hormonal therapies to alleviate symptoms or to regulate their cycles demonstrated a similar risk for developing any depressive symptoms but a somewhat decreased risk of developing depression (ie, severe depressive symptoms) compared with those who did not take these agents. This difference could easily be due to chance, given the small numbers; however, there is growing evidence to suggest that estrogen-based preparations (oral contraceptives, hormone therapies) may have an ameliorative effect on mood, particularly in perimenopausal subpopulations,[33-35] aside from a well-established positive impact on vasomotor symptoms.[36] Given the various effects of estrogen on the central nervous system,[37,38] hormonal therapies may have

a direct and positive impact on mood independent of any effect on vasomotor symptoms.[33,39]

The putative ameliorative effects of estrogen on mood are also particularly noteworthy given the recent reports from the Women's Health Initiative study and the extent to which these reports have influenced clinical care with respect to use of estrogen in women at various stages of reproductive life—and not only in postmenopausal women.[40-42] The Women's Health Initiative study has prompted important safety issues with respect to the use of hormone therapy in nonsymptomatic, postmenopausal women. However, the extrapolation of these findings may have also affected the use of estrogen for its primary indication—the treatment of vasomotor symptoms in symptomatic, younger women.[43,44] The findings described in the current report may underline the importance of still considering estrogen-based therapies for the treatment of symptomatic, perimenopausal women. The putative association of vasomotor symptoms and risk for depression in this subpopulation also underscores the importance of identifying safe and efficacious nonhormonal strategies for the treatment of symptomatic, perimenopausal women who are unable or unwilling to use estrogen preparations.[45-48]

In the current study, we also noted a greater risk for developing depression among women who experienced major life events proximate to the inception of perimenopause, regardless of concurrent vasomotor symptoms. When we assessed the proportion of LES assessments that were antecedent, as opposed to subsequent, to the menopausal transition, we observed that a similar proportion reported negative (defined as ≥1 item) life events (72.6% and 77.5%, respectively). Furthermore, among women with LES assessments prior to perimenopause, 32% reported any first new onset of depressive symptoms compared with 28% of women with LES assessments subsequent to perimenopause. Thus, our association of menopausal transition and risk of new onset of depression is not likely due to an association between negative life events and new onset of depression. These results are also consistent with previous findings[49] and with diathesis-stress models of depression onset[50] where, in this case, a changing hormonal environment during perimenopause may lower the threshold for depression should negative life events be encountered. These results also support the hypothesis that many factors may contribute to an increased risk for new onset of depression among perimenopausal women, with vasomotor symptoms and life events appearing to independently contribute to the increased risk of depression in this group of women.

The current study has some important methodological limitations. First, data used to prospectively assess and classify subjects as having "depression" were not based solely on structured clinical interviews. However, previous work with the initial cohort of women with and without history of depression revealed that by using the same construct to characterize the occurrence of depression, we observed adequate sensitivity with respect to the diagnosis of major depression as compared with the *SCID*.[9] Second, the presence of vasomotor symptoms was determined based on self-reported questionnaires. It has been suggested that women experiencing hot flushes may underestimate the frequency or severity of these symptoms, particularly if the assessment is retrospective.[51] Ideally, investigations should include the use of hot flush composite scores,[45,48,52] which are accompanied by objective measures of core body temperature variations.[53]

Third, women were interviewed every 6 months through the initial 3 years of follow-up. However, between the 36-month interview and the last follow-up assessment, there was a substantially larger interval—between 59 and 92 months. Therefore, the third limitation of the study was our inability to assess a more precise temporal relationship between menopausal transition and new onset of depression among those women who made the transition to perimenopause and also developed new onset of depressive symptoms during this larger interval. However, when we limited the analysis to the first 36 months of follow-up, we still observed that 7.2% of women who made the perimenopausal transition developed new onset of depression compared with 2.9% of women who remained premenopausal (odds ratio, 2.7 [95% confidence interval, 1.0-6.9]; $P=.04$).

Last, as noted in Table 3, we were unable to collect information from all participants with respect to vasomotor symptoms and their association with new onset of depression among perimenopausal women with or without a history of adverse life events. Although subtle increased risk for developing depression was noted among those perimenopausal women who had reported both heightened frequency of adverse life events and vasomotor symptoms, it is possible that missing data contributed to an underestimation of the relative contribution of vasomotor symptoms for the occurrence of depression in this subpopulation. Prospective studies where missing data are minimized would be able to more completely clarify this issue.

Despite the fact that most women do not develop depression during the menopausal transition, the current study suggests that, relative to women who remain premenopausal, similarly aged women who begin the transition to menopause appear to be at an increased risk for first onset of depression even in the absence of a history of depression. If confirmed by other studies, this finding will carry important public health implications. In the United States only, approximately 1.5 million women may reach menopause each year. A spectrum of symptoms and syndromes has been extensively described in women during the menopausal transition including severe vasomotor symptoms, loss of bone density, sexual dysfunction, a decline in cognitive function, and a potential increased risk for cardiovascular disease.[54-56] Thus, the comorbidity of these problems with perimenopause-associated depression could affect many aging women, leading to a compounded burden of illness.

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