A Cross-Sectional Evaluation of Perimenopausal Depression

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Objective: Overall, the clinical spectrum of depression during the perimenopause is not well characterized. This cross-sectional study examined the following: (1) clinical characteristics of women who presented to the National Institute of Mental Health midlife mood disorders clinic (between March 1990 and January 2004) with perimenopausal major and minor depressions and (2) the impact on these characteristics of either a prior episode of depression or the presence of hot flushes.

Method: Historical variables, reproductive status, symptom ratings, and plasma hormone measures were examined in 116 women between the ages of 40 and 55 years who met research criteria for perimenopause-related depression (a current episode of major or minor depression according to the Structured Clinical Interview for DSM-IV or Primary Care Evaluation of Mental Disorders supplemented with a past history form).

Results: Clinical characteristics did not differ in those women with first-onset (39%) versus recurrent depressions or in those with (57%) and without hot flushes. Depressive episodes clustered in the later stages of the menopause transition and the first year postmenopause. Seven women (6%) reported a past postpartum major depression, and 55% of women reported a history of premenstrual dysphoria (PMD).

Conclusions: We found no evidence that either hot flushes or a previous episode of depression conveys a distinct clinical profile in these women. The clustering of onsets of depression suggests the hormone events that characterize the late menopause transition may be relevant to the onset of this form of depression. Finally, although we observed a high rate of PMD, neither postpartum depression nor PMD are consistent accompaniments of perimenopausal depression.

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Recent epidemiologic studies have documented an increased risk of first-onset and recurrent major and minor depressions during the menopause transition compared with premenopause.[1–4] Several as yet untested hypotheses have been proposed to explain the onset of depression in women during the menopause transition. Depression could be caused by specific endocrine events or physiologic concomitants (e.g., hot flushes) related to the menopause transition. This would not explain, however, why depression is triggered by these events in some women but not in others. Consequently, the onset of depression could reflect a vulnerability to develop recurrent depression in women with a past depression or, in particular, those with a history of depression during other periods of reproductive hormone change. The menopause transition is a complex series of physiologic events that lasts an average of 5 years and includes variations in endocrine function that progress from increased estradiol secretion during the early menopause transition, estrogen withdrawal, and finally hypogonadism during perimenopause (i.e., late menopause transition and first year postmenopause). Additionally, in up to 80% of women, these endocrine events lead to hot flushes[5] that can disrupt sleep[6] and, therefore, increase a woman's risk of developing depression.[2] Thus, the timing of the onset of depression relative to the stages of the menopause transition and their associated endocrine events or the symptomatic accompaniments of depression during the perimenopause (i.e., hot flushes), if uniformly present, could suggest the relevance

of these factors in the onset of depression during the menopause transition.

Historical variables in these women also may help identify factors contributing to the risk for perimenopausal depression. Accompanying endocrine events or hot flushes might have more of an impact in first-onset (de novo) than in recurrent forms of depression. However, studies have not examined whether first-onset depressions during the perimenopause are clinically distinct from recurrent depressions. Similarly, although studies suggest that women with premenstrual dysphoria (PMD) or postpartum depression (PPD) are at greater risk for depression during the menopause transition,[7–9] the relevance of a history of PMD or PPD to a woman's risk for depression during the menopause transition remains unclear.

This study is a preliminary effort to investigate whether a distinct clinical profile can be identified that would suggest factors contributing to the onset of depression in perimenopausal women. We address 2 questions about the clinical characteristics of perimenopausal major and minor depressions. First, what is the clinical presentation of women who develop depression during the perimenopause, including the stage of the menopause transition (defined by the Stages of Reproductive Aging Workshop [STRAW] criteria[10]) during which the depressions developed, plasma levels of follicle-stimulating hormone (FSH), the presence of hot flushes, the presence of past depressive episodes (i.e., both nonreproductive-related and reproductive-related mood disorders), the severity of depression, and overall level of functional impairment? Second, do these clinical characteristics or presenting symptomatologies of perimenopausal depression differ when women are grouped by type of depression (major versus minor), past history of depression, or presence of hot flushes?

METHOD

Subject Selection

Participants were selected from 395 consecutive women between the ages of 40 and 55 years attending the National Institute of Mental Health (NIMH) midlife mood disorders clinic between March 1990 and January 2004. Each woman reported the onset of depression associated with menstrual irregularity (≥ 6 months but not > 1 year of amenorrhea); depressive symptoms, by history, resulted in personal distress or occupational impairment. All women were either self-referred in response to local advertisements or referred by their physicians. Of these 395 women, 116 also met the following criteria: (1) a current episode of major or minor depression evaluated by the Structured Clinical Interview for DSM-IV[11] (SCID) (N = 112) or Primary Care Evaluation of Mental Disorders[12] (PRIME-MD) supplemented with a past history form[13] (N = 4); women presenting prior to 1996 were evaluated with the Structured Clinical Interview for DSM-III-R[14] supplemented by the minor depression module of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version[15] (complete SCID interviews were not available for 4 women; however, PRIME-MDs completed during their initial visit were considered adequate for inclusion in the sample); (2) 3 FSH plasma levels ≥ 14 IU/L obtained at biweekly visits during a 6-week screening (plasma FSH levels of 14 IU/L represent 2 standard deviations above the mean values for the early follicular phase FSH levels in women of reproductive age, consistent with the STRAW criteria[10]); and (3) the absence of a current or recent medical illness confirmed by medical history and laboratory tests including thyroid-stimulating hormone. All women were medication free (with the exception of 4 women on stable thyroid replacement). The protocol was approved by the NIMH Intramural Research Subpanel, and written informed consent to measure plasma hormone levels and mood symptoms was obtained from each woman. Overall characteristics of the study sample are included in Table 1.

Protocol

All women attended at least 3 screening visits over a 6-week interval. During the first visit, participants completed a semistructured interview that detailed presenting symptoms, the duration and level of functional impairment associated with the depression, historical variables including history of PMD, and the characteristics of the menstrual cycle irregularity or amenorrhea. During subsequent visits, blood samples were obtained for the measurement of FSH levels. Finally, on a daily basis for the duration of the screening, women completed a modified Daily Rating Form[16] (DRF), a 21-item self-report scale. The DRF rates the severity of symptoms on a 6-point scale (1 = no symptoms and 6 = extreme symptoms) and was used to confirm the presence of clinically significant hot flushes, operationally defined by an average score of > 2 on the DRF (2 = minimal) during 4 weeks throughout the screening, and to quantify the level of functional impairment in each woman (determined by the number of days during 4 weeks throughout screening in which the women rated functional impairment > 2 [minimal]). Participants were instructed to use the severity scale as a composite of their hot flush frequency and severity.

Outcome Measures

Demographics, historical variables, and symptom ratings. At each clinic visit, we administered the following rating scales: (1) the Beck Depression Inventory[17] (BDI) (mean scores and the number of women with scores ≥ 16, a standard cut-off score indicating clinically significant symptoms), (2) the Center for Epidemiologic Studies-Depression Scale[18] (CES-D) (mean scores), and (3) the visual analog scale (VAS) symptom inventory

Table 1. Demographic Characteristics of Women With Perimenopausal Depression (N = 116)

Characteristic	Perimenopausal Women
Age, mean (SD), y	49.0 (3.4)
Smoking, N (%)	18 (15.5)
Currently married, N (%)	73 (62.9)
Parity, mean (SD)	1.6 (1.2)
Taking thyroid hormone, N (%)	4 (3.4)
Plasma FSH, IU/L[a]	
Mean (SD)	65.6 (35.2)
Standard deviation, mean (SD)[b]	19.7 (12.1)
Confirmed hot flushes, N (%)	66 (57.0)
STRAW criteria, N (%)	
Stage –3	6 (5.2)
Stage –2	24 (20.7)
Stage –1	64 (55.2)
Stage +1a	22 (19.0)
Current major depression, N (%)	50 (43.1)
Duration, mean (SD), mo	20.9 (11.7)
Current minor depression, N (%)	66 (57.0)
Duration, mean (SD), mo	19.4 (11.2)
First-onset depression, N (%)	45 (38.8)
Past major depression, N (%)	39 (33.6)
Postpartum onset, N (%)	7 (6.0)
Past minor depression, N (%)	32 (27.6)
Postpartum onset, N (%)	1 (0.9)
Premenstrual dysphoria, N (%)	64 (55.2)
CES-D score, mean (SD)	22.6 (7.7)
BDI score, mean (SD)	14.7 (6.3)

[a]Assays were performed in duplicate for all hormones and were repeated if the values differed by more than 15%. The interassay and intra-assay coefficients of variation were calculated from the assays performed for each assessment period, with all coefficients being less than 5%.
[b]The standard deviations of the serial FSH levels were calculated for each woman as a measure of the individual variability in FSH secretion.
Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies-Depression Scale, FSH = follicle-stimulating hormone, STRAW = Stages of Reproductive Aging Workshop.

rating the severity (range: none to extreme) of 23 mood and behavioral symptoms (previously described[19]) including inability to enjoy usual activities, excessive worrying, increased appetite or cravings, weight gain, lack of energy, frequent sleep disturbance, problems concentrating, irritability, avoidance of social activities, early morning wakening, preoccupation with physical health, anxiety, tearfulness, emotional numbness, experiencing unpleasant life events, mood instability, emotional detachment, lack of motivation, depressed mood, feelings of letting people down, feeling detached or unreal, mood fragility, and feelings of being unable to cope.

Hormone measures. FSH plasma levels were measured by AxSYM radioimmunoassay (Abbott Laboratories, Abbot Park, Ill.). The mean and standard deviation of the serial FSH levels obtained during each visit were calculated for each woman.

Stage of reproductive aging. All women were classified into one of 4 STRAW stages (–3 through +1a) as follows: stage –3: regular menstrual cycles and 1 elevated (> 2 SD) plasma FSH level; stage –2: regular menstrual cycles, but with variable cycle lengths (> or < 7 days) and elevated plasma FSH levels; stage –1: at least 2 skipped cycles as well as an interval of amenorrhea (≥ 60 days) and elevated plasma FSH levels; and +1a: up to 1 year of amenorrhea and elevated plasma FSH levels.[10]

Statistical Analysis

To address the first question of this study, we employed descriptive statistics to characterize the clinical profile of women with perimenopause-related depression including plasma levels of FSH, scores on the BDI and CES-D, STRAW stage, presence or absence of hot flushes, history of depressive illness, level of functional impairment, and demographics. To address the second question, we examined whether the clinical profile of perimenopausal depression differs as a function of type of depression (major versus minor), past history of depression, or presence of hot flushes. Student t tests with the Bonferroni adjustment were employed to compare dimensional baseline demographic characteristics, symptom rating scores (i.e., BDI and CES-D), and plasma FSH levels (mean and SD) across the groups described above. Chi square analyses (or the Fisher exact test when appropriate) with the Yate's correction were used to compare categorical characteristics. Significant 2×4 χ^2 analyses were explored with repeated 2×2 comparisons with Bonferroni adjustment of the p values. Finally, a multinomial model was used to examine differences in the numbers of women in each STRAW stage within each of the following groups: major depression, minor depression, first-onset depression, recurrent depression, women with hot flushes, and women without hot flushes.

To examine differences in the pattern of presenting symptoms, a stepwise forward discriminant function analysis (DFA) (NCSS, Kaysville, Vt.) was performed to compare the scores on the 23-item VAS symptom rating in the following groups: (1) women with current major versus those with minor depression, (2) women with recurrent versus first-onset major or minor depression, and (3) depressed perimenopausal women with versus those without significant hot flushes. When significant differences were identified by DFA, a binomial test with a z approximation compared calculations of the observed and chance proportions predicted by the DFA (1-tailed tests were employed for the binomial tests since we were interested only in factors that correctly predicted group membership).

RESULTS

Group Comparisons

Major vs. minor depression. Women with major and minor depression did not differ in any measure, with the exception that compared to those with minor depression, women with major depression had significantly higher

Table 2. Characteristics in Perimenopausal Women With Depression, Mean (SD)[a]

Variable	Age, y	Mean FSH, IU/L	SD FSH, IU/L	CES-D Score[b]	BDI Score	No. of Days of Impairment	Maximum Functional Impairment Score
Major vs minor depression							
Current major (N = 50)	49.2 (3.3)	69.7 (35.5)	18.1 (11.7)	27.0 (7.0)[c]	18.0 (16.1)[c]	13.8 (7.9)[d]	4.7 (1.0)[d]
Current minor (N = 66)	48.9 (3.6)	62.6 (35.0)	20.9 (12.3)	19.0 (6.5)	12.1 (5.1)	9.1 (7.1)	4.1 (1.3)
First-onset vs recurrent depression							
First onset (N = 45)	49.0 (3.3)	72.7 (38.7)	22.2 (13.9)	22.6 (8.4)	13.9 (6.9)	11.6 (8.8)	4.2 (1.2)
Recurrent (N = 71)	49.0 (3.5)	61.1 (32.4)	18.1 (10.6)	22.7 (7.5)	15.1 (5.9)	10.8 (6.8)	4.5 (1.2)
Depression ± hot flushes							
Hot flushes (N = 66)	49.2 (3.5)	71.3 (37.0)	18.8 (13.2)	24.0 (8.5)	15.5 (6.7)	11.9 (7.9)	4.5 (1.1)
No hot flushes (N = 50)	48.8 (3.3)	58.2 (31.7)	21.0 (10.5)	20.7 (6.2)	13.5 (5.4)	10.2 (7.3)	4.2 (1.3)

[a]Comparisons were not significant unless indicated by a footnote.
[b]CES-D scores were unavailable for 14 women.
[c]Student t test with Bonferroni adjustment: major vs. minor depression. CES-D score: t = 6.0, df = 100, p = .001; BDI score: t = 5.5, df = 114, p < .001.
[d]Student t test with Bonferroni adjustment: major vs. minor depression. Number of days of impairment: t = 3.5, df = 114, p = .001; maximum impairment score: t = 2.5, df = 114, p = .13, without Bonferroni adjustment p = .02.
Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies-Depression Scale, FSH = follicle-stimulating hormone.

BDI and CES-D scores, a significantly greater proportion of BDI scores ≥ 16 (χ^2 = 22.1, p < .001), and significantly greater impairment (both number of days and maximum impairment rating score) (Table 2). The majority of both major and minor depressions occurred during STRAW stage –1 (Figure 1A). However, the proportion of women in stage –2 was significantly higher in women with minor (N = 21) compared with women with major depression (N = 3) (χ^2 = 12.3, df = 3, p = .006; Fisher exact test, p = .003, p < .008 with correction). In women with major depression, multinomial analyses identified significantly increased numbers of women in stages –1 and +1a compared with stages –2 and –3, with the greatest number in stage –1. In women with minor depression, the numbers in stages –1 and –2 were significantly greater than in –3 and +1a.

The DFA identified significantly higher severity of 2 variables—lack of motivation (p = .003) and feelings of letting people down (guilt) (p = .009)—in women with major compared with those with minor depression. The model identified by the DFA correctly predicted membership in 64% of the group with major and in 69% of those with minor depression. Thus, the overall predictive rate for this model was 66.6% compared with the expected predicted rate of 50.5% (binomial comparison, z = 5.4, 1-tailed p < .002).

First-onset vs. recurrent depression. Women with recurrent major or minor depressions did not differ from those with first-onset depressions in any clinical characteristic measured (Table 2), nor did the number of women in each STRAW stage differ significantly between women with first-onset compared with those with recurrent depression. Multinomial analysis (Figure 1B) of the number of women in each STRAW stage showed that in first-onset depression, a significantly greater number of women were in stage –1 (compared with stages –3, –2, and +1a). The number of women with recurrent depression

also was greatest in stage –1 and, although to a lesser extent, greater in stages –2 and +1a.

Severity scores for the VAS symptom of mood instability distinguished women with first-onset (lower scores) from those with recurrent depression (DFA, p < .0001). The model identified by the DFA correctly predicted membership in 34% of the first-onset and 90% of the recurrent depression group. The overall prediction rate, therefore, was 68.0% compared to the expected prediction rate of 57.0% (binomial comparison, z = 2.4, 1-tailed p = .008).

Depression with and without hot flushes. Women with and without hot flushes did not differ significantly in any clinical characteristic, although there was a trend for the mean ± SD plasma FSH levels to be higher in women with hot flushes (71.3 ± 37.0 IU/L) compared with those without hot flushes (58.2 ± 31.7 IU/L) (t = 2.0, df = 114, p = .048), which did not remain significant after Bonferroni adjustment (Table 2). In women without hot flushes, multinomial analysis (Figure 1C) showed a greater number of women in STRAW stages –1 and –2. Similarly, in women with hot flushes, a greater number of women were in stages –1 and +1a.
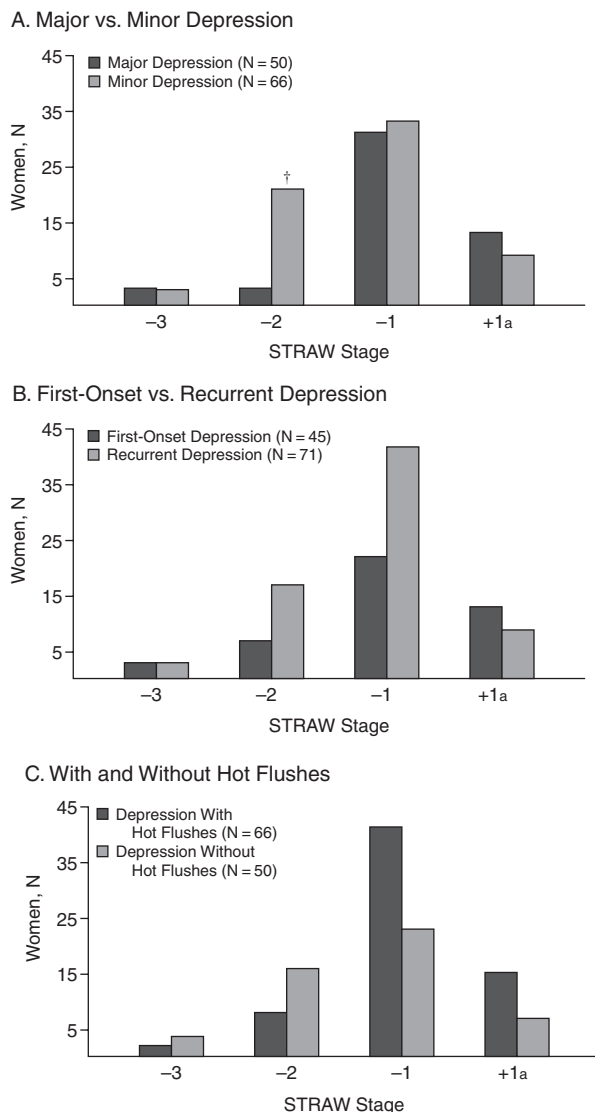
The DFA identified significantly higher severity scores for the symptom of feeling emotionally numb (p < .0001) in women with hot flushes. The model identified by the DFA correctly predicted 42% of the women without hot flushes and 78% of the women with hot flushes. The overall prediction rate was 62.3% compared to an expected prediction rate of 52.6% (binomial comparison, z = 2.1, 1-tailed p = .02).

DISCUSSION

Many assumptions are made about the cause and characteristics of depression occurring during the menopause transition, but little is actually known. Our data and those of recent studies[3,20,21] dispel several prevalent myths about

Figure 1. Number of Depressed Perimenopausal Women in Each STRAW Stage Compared Across 3 Groups: Major vs. Minor Depression, First-Onset vs. Recurrent Depression, and With and Without Hot Flushes[a]

A. Major vs. Minor Depression

B. First-Onset vs. Recurrent Depression

C. With and Without Hot Flushes

Between-Group Comparisons

†Minor depression vs. major depression stage –2 (χ^2 = 12.3, df = 3, p = .006; post hoc Fisher exact test, p = .003).

The distribution of women with and without hot flushes in each STRAW stage differed significantly (χ^2 = 9.3, df = 3, p = .03).

Individual uncorrected 2 × 2 χ^2 analyses were significantly different between women with and without hot flushes in several comparisons as follows: first, significantly more women without hot flushes were in STRAW stage –2, and, second, significantly more women with hot flushes were in STRAW stages –1 and +1a. However, none of the comparisons remained significant when p values were adjusted for 6 comparisons.

Otherwise, for all comparisons p = not significant.

Within-Group Comparisons (multinomial)

(A) Major depression: the number of women in stage –1 was significantly greater than numbers in stages +1a, –2, and –3 (z = 4.3–6.1 [range], p = .003– < .001 [range]); the number of women in stage +1a was significantly greater than the number in stages –3 and –2 (z = 2.7 [both comparisons], p = .008).

Minor depression: the number of women in stages –1 and –2 was significantly different than the number in stages –3 and +1a (z = 2.3–6.3 [range], p = .02– < .001 [range]); whereas numbers of women in stages –1 and –2 were not significantly different (p = .1).

(B) First-onset depression: a significantly greater number of women were in STRAW stage –1 (comparisons with stages –3, –2 [z = 3.1 and 4.6, p = .002 and < .001, respectively], and +1a [z = 1.6, p = .12, trend]).

Recurrent depression: the number of women with recurrent depression was greatest in STRAW stage –1 (z = 3.5–8.0 [range], all comparisons p < .001) and, although to a lesser extent, greater in STRAW stage –2 (comparisons with –3 [z = 3.4, p = .008] and +1a [z = 1.6, p = .11]).

(C) Depression with hot flushes: a greater number of women were in STRAW stages –1 (compared to +1a: z = 3.8, p < .001 and to –2: z = 5.8, p < .001 and to –3: z = 8.7, p < .001) and +1a (compared to –3: z = 3.4, p<.001).

Depression without hot flushes: a greater number of women were in STRAW stages –1 (compared to +1a: z = 3.8, p = .001 and to –3: z = 8.7, p < .001) and –2 (compared to –3: z = 2.9, p = .004 and to +1a: z = 2.0, p = .052).

[a]Criteria for STRAW stages: stage –3: regular menstrual cycles and 1 elevated (> 2 SD) FSH level; stage –2: regular menstrual cycles, but with variable cycle lengths (> or < 7 days) and elevated plasma FSH levels; stage –1: at least 2 skipped cycles as well as an interval of amenorrhea (≥ 60 days) and elevated plasma FSH levels; and stage +1a: up to 1 year of amenorrhea and elevated FSH levels.
Abbreviations: FSH = follicle-stimulating hormone, STRAW = Stages of Reproductive Aging Workshop.

perimenopausal depression. First, a substantial number of women presented to our clinic with first-onset depression in the perimenopause, and many of these women had no evidence of hot flushes accompanying their depressions. Thus, the development of depression during the perimenopause is not simply due to either the distressing consequences of hot flushes or the coincidental occurrence of a recurrent mood disorder. Indeed, the clinical characteristics of perimenopausal depression are not affected by whether the episode is first onset or accompanied by hot flushes.

Second, all depressive episodes clustered in the later STRAW stages of the menopause transition and the first year postmenopause. Thus, these findings and those of others[3] suggest a possible role for estradiol withdrawal and the recent onset of hypogonadism in the development of depressions during the menopause transition.

Finally, PPD was not a prevalent antecedent to, nor consequently a predictor of, perimenopausal depression. In contrast, self-reports of PMD were prevalent and described by over half of the women in our sample. Nonetheless, even self-reported PMD was not uniformly present in

all women. These data demonstrate, therefore, the potential comorbidity in some but certainly not all women between perimenopausal depression and other reproductive endocrine-related mood disorders.

A substantial percentage (39%) of the women in this study presented with their first lifetime episode of major or minor depression. Nonetheless, there were no significant differences in either the symptomatic or hormonal accompaniments of first-onset versus recurrent depression during the perimenopause. Additionally, there were no distinct patterns of clustering of first-onset and recurrent depressions during any of the STRAW stages. These data are consistent with previous studies demonstrating the efficacy of estradiol therapy in depressed perimenopausal women regardless of a past history of depression.[19]

The majority (57%) but certainly not all women with perimenopausal depression reported hot flushes. Indeed, the presence of hot flushes neither significantly differed in first-onset compared with recurrent depressions nor significantly predicted symptom severity or functional impairment. Similarly, the presence of hot flushes predicted neither a distinct profile of presenting symptoms nor the clustering of depressive episodes during a specific STRAW stage. Interestingly, measures of disturbed sleep and early morning wakening also did not distinguish groups of women in this study. Thus, as with a past episode of depression, the presence of hot flushes in perimenopausal depression is not associated with a distinguishing set of hormonal or symptomatic accompaniments. Freeman et al.[3] observed that the increased risk for first-onset depression during the perimenopause was independent of the presence of hot flushes. Previous studies also have reported that perimenopausal depressed women with hot flushes are not distinguished from those without by their therapeutic responses to either estradiol therapy or selective serotonin reuptake inhibitors,[19,22–28] their profiles of basal plasma hormone levels (with the exception of plasma FSH levels[29]), or their reports of negative life events.[30] Thus, although hot flushes are frequent occurrences in depressed perimenopausal women (as they also are in nondepressed perimenopausal women), hot flushes are not necessary accompaniments of depression.

The majority (55%) of women with perimenopause-related depression presented to our clinic in the later stages of the menopause transition (i.e., STRAW stage –1). Although the overall distribution across STRAW stages was similar for the onset of major and minor depression, more women with minor depression presented in STRAW stage –2 and, therefore, earlier in the transition than did those with major depression. Thus, it is possible that the nonsignificant difference in the distributions across STRAW stages reflects that some women with minor depression presented to our clinic earlier in the course of their depressions.

The cross-sectional design of our study, the reliance on retrospective reports of menstrual cycle irregularity and amenorrhea, and the fact that STRAW staging was performed at the time of presentation to our clinic prevent us from precisely determining the specific STRAW stages in which the onsets of depression occurred. Although the majority of women in our study presented within 18 months following the onset of symptoms, it is possible that these self-reports did not accurately reflect the actual onsets of depression. Thus, depression in this study could have started much earlier than we have reported. Nonetheless, all women described the onset of depression in association with menstrual cycle irregularity or amenorrhea—characteristics of the later menopause transition. A more accurate assessment of the relationship between reproductive aging and the onset of depression could be obtained by performing a population-based study rather than a clinic-based study, which relies on women presenting for treatment of a disorder. It is reassuring, however, that a similar pattern of clustering of clinically significant depressive symptoms during the late menopause transition also was observed by Bromberger et al.[1]

We observed that neither a history of postpartum depression nor PMD was a uniform antecedent of depression during the perimenopause. Previous retrospective studies[3,7–9,31,32] have reported a greater than expected frequency of occurrence of other reproductive endocrine-related mood disorders (i.e., PMD and PPD) in women with perimenopausal depression. Based on these observations, PPD has been inferred to be a risk factor for or a predictor of depression during the menopause transition[3,7–9,31,32]; however, in contrast to our study, previous observations were based solely on self-reports and were not confirmed with structured diagnostic interviews. In our sample of well-characterized women with perimenopausal depression, the prevalence of a history of PPD meeting DSM-IV criteria was less than 10%, comparable to reported prevalence rates of PPD in the general population.[33–35]

In contrast to the apparent lack of association between postpartum and perimenopausal depression, we observed that a substantial number of women with perimenopausal depression reported the prior experience of PMD. Previous studies have reported similar findings suggesting a relationship between PMD and perimenopausal depression. In a longitudinal, community-based study of women with no history of depression, Freeman et al.[3] identified that a retrospective self-report of PMD was a significant predictor of perimenopausal depression (defined by high CES-D scores). In a cross-sectional, clinic-based study, however, Richards et al.[21] observed the notable absence of either prospectively confirmed premenstrual-related symptom cyclicity or PMD in the majority of perimenopausal depressed women, although, as a caveat, Richards et al.[21] did observe a higher than expected rate of menses-

related dysphoric symptoms in the women with peri-menopausal depression compared with asymptomatic controls. It remains to be determined in prospective longitudinal studies if an episode of PPD or PMD places a woman at increased risk for developing depression during the perimenopause. As suggested by Richards et al.[21] and others,[3,7–9,36,37] the comorbidities of postpartum, premenstrual, and perimenopausal depressions could distinguish a subgroup of women predisposed to reproductive endocrine-related mood disorders.

In this study, the onsets of depression in perimenopausal women clustered during the later stages of the menopause transition. Thus, the hormonal events that characterize the late menopause transition should not be excluded as potentially relevant in the onset of this form of depression. Future studies of this condition should investigate the possible role of estradiol withdrawal and the onset of a hypogonadal state in the development of depression in these women. Minor depressions occurring during the menopause transition are frequent events and are associated with significant impairment, and, with few exceptions, the clinical presentation is indistinguishable from major depressions that occur at this stage of life. Finally, although the presence of somatic symptoms such as hot flushes in depressed perimenopausal women do not accompany a unique clinical presentation, they still may have clinically important effects and could lead to a delay in diagnosis[38,39] or presage differential treatment response characteristics.[40] Thus, the clinical significance of depression (even minor depression) accompanied by perimenopausal somatic symptoms should not be dismissed as an "appropriate" reaction to the disturbing somatic symptoms.

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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 mfreeman@psychiatrist.com.