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A Cross Sectional Evaluation of Perimenopausal Depression

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Abstract

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 NIMH midlife mood disorders clinic (between March 1990 and January 2004) with perimenopausal major and minor depressions; 2) the impact on these measures 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 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 (6%) women 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 that 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.

Keywords

perimenopause; major depression; minor depression; hot flushes

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Introduction

Recent epidemiologic studies have documented an increased risk of first onset and recurrent major and minor depressions during the menopause transition (MT) compared with the premenopause.[1–4] Several as yet untested hypotheses have been proposed to explain the onset of depression in women during the MT. Depression could be caused by specific endocrine events or physiologic concomitants (e.g., hot flushes) related to the MT. This would not explain, however, why depression is triggered by these events in some women but not 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 MT is a complex series of physiologic events that lasts an average of five years and includes variations in endocrine function that progress from increased estradiol secretion during the early MT, estrogen withdrawal and finally hypogonadism during the perimenopause (i.e., late MT 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 MT 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 MT.

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 (de novo) onset than 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 MT,[7–9] the relevance of a history of PMD or PPD to a woman's risk for depression during the 4 MT 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 two 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 MT (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 non-reproductive- 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?

Methods

Subject Selection

Participants were selected from 395 consecutive women between the ages of 40 and 55 years attending the National Institute of Mental Health midlife mood disorders clinic [between March 1990 and January 2004]. Each woman reported the onset of depression associated with menstrual irregularity (≥ six months but not > one 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 Structured Clinical Interview for DSM-IV (SCID)[11] (n = 112) or Primary Care Evaluation of Mental Disorders (PRIME MD)[12] supplemented with a past history form[12;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 Scheduled for Affective Disorders and Schizophrenia-Lifetime Version.[15] [Complete SCID interviews were not available in four 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 six week screening. [Plasma FSH levels of 14 IU/L represent two 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 four 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 three screening visits over a six week interval. During the first visit, participants completed a semi-structured 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 the Daily Rating Form (DRF),[16] a 21-item self-report scale. The DRF rates the severity of symptoms on a six 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 four weeks throughout the screening; and to quantify the level of functional impairment in each woman (determined by the number of days during four 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

1. Demographics, Historical Variables, Symptom Ratings: At each clinic visit, we administered the following rating scales: 1) the Beck Depression Inventory (BDI)[17] (average scores and the number of women with scores of ≥ 16, a standard cut-off score indicating clinically significant symptoms, 2) the Center for Epidemiologic Studies-Depression Scale (CES-D)[18] (mean scores), and 3) VAS symptom inventory rating the severity (range: none to extreme) of 23 mood and behavioral symptoms (previously described.[14]) including the following: 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.
2. 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.

3. Stage of Reproductive Aging: All women were classified into one of four STRAW stages (-3 through +1a) as follows: stage -3: regular menstrual cycles and one elevated (> 2 SD) FSH levels; stage -2: regular menstrual cycles, but with variable cycle lengths (> or < 7 days) and elevated plasma FSH levels; stage -1: at least two skipped cycles as well as an interval of amenorrhea (≥ 60 days) and elevated plasma FSH levels; and +1a: up to one year of amenorrhea and elevated 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 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's 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 Chi square 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: a) women with current major versus those with minor depression, b) women with recurrent versus first onset major or minor depression, and c) 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 (one-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 BDI and CES-D scores, a significantly greater proportion of BDI scores ≥ 16 (Chi square = 22.1, $p < 0.001$), 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) (Chi square = 12.3, df = 3, $p = 0.006$; Fisher exact test, $p = 0.003$, $p < 0.008$ 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 two variables - lack of motivation ($p = 0.003$) and feelings of letting people down (guilt) ($p = 0.009$) - 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, $z = 5.4$, p (one-tailed) < 0.002].

First-Onset versus 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 numbers 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 stage -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, $p < 0.0001$). 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% compared to the expected prediction rate of 57% [binomial comparison, $z = 2.4$, p (one-tailed) $=.008$].

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, $z = 2.1$, p (one-tailed) $= 0.02$].

Discussion

Many assumptions are made about the cause and characteristics of depression occurring during the MT, but little is actually known. Our data and those of recent studies[3;15;16] dispel several prevalent myths about 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 MT 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 MT.

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 number (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.[14]

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 (SSRIs),[14;17–24] their profiles of basal plasma hormone levels (with the exception of plasma FSH levels,[25]), or their reports of negative life events.[26] Thus although hot flushes are frequent occurrences in depressed perimenopausal women (as they also are in non-depressed 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 MT (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 non-significant 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, prevents 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 MT;[3;7–9;27;28] 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.[29–31]

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.[16] 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 perimenopausal 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.[16] and others,[3;7–9;32;33] the co-morbidities 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 MT. Thus, the hormonal events that characterize the late MT 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 MT are frequent events, 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[34;35] or presage differential treatment response characteristics.[36] 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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References

1. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the study of women's health across the nation (SWAN). J Affective Disord 2007;103:267–272.
2. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition. The Harvard study of moods and cycles. Arch Gen Psychiatry 2006;63:385–390. [PubMed: 16585467]
3. Freeman EW, Sammel MD, Lin H, et al. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63:375–382. [PubMed: 16585466]
4. Bromberger JT, Assmann SF, Avis NE, et al. Persistent mood symptoms in a multiethnic community cohort of pre- and perimenopausal women. Am J Epidemiol 2003;158:347–356. [PubMed: 12915500]
5. Stearns V, Ullmer L, Lopez JF, et al. Hot flushes. Lancet 2002;360:1851–1861. [PubMed: 12480376]
6. Ohayon MM. Severe hot flashes are associated with chronic insomnia. Arch Intern Med 2006;166:1262–1268. [PubMed: 16801508]
7. Stewart DE, Boydell KM. Psychologic distress during menopause: associations across the reproductive cycle. Int J Psychiatry Med 1993;23:157–162. [PubMed: 8359998]
8. Soares CD, Almeida OP. Depression during the perimenopause. Arch Gen Psychiatry 2001;58:306. [PubMed: 11231840]
9. Feld J, Halbreich U, Karkun S. The association of perimenopausal mood disorders with other reproductive-related disorders. CNS Spectrums 2005;10:461–470. [PubMed: 15908900]
10. Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertil Steril 2001;76:874–878. [PubMed: 11704104]
11. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured clinical interview for DSM-IV axis I disorders - patient edition. New York, N.Y.: Biometrics Research Department, New York State Psychiatric Institute; 1996.
12. Hirschfeld RMA. The mood disorder questionnaire: a simple, patient-rated screening instrument for bipolar disorder. Prim Care Companion. J Clin Psychiatry 2002;4:9–11.
13. Spitzer RL, Williams JBW, Kroenke K, et al. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD patient health questionnaire obstetrics-gynecology study. Am J Obstet Gynecol 2000;183:759–769. [PubMed: 10992206]
14. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol 2000;183:414–420. [PubMed: 10942479]
15. Ozturk O, Eraslan D, Mete HE, et al. The risk factors and symptomatology of perimenopausal depression. Maturitas 2006;55:180–186. [PubMed: 16581210]
16. Richards M, Rubinow DR, Daly RC, et al. Premenstrual symptoms and perimenopausal depression. Am J Psychiatry 2006;163:133–137. [PubMed: 16390900]
17. Cohen LS, Soares CN, Poitras JR, et al. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. Am J Psychiatry 2003;160:1519–1522. [PubMed: 12900318]
18. Rasgon NL, Altshuler LL, Fairbanks LA, et al. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. J Clin Psychiatry 2002;63(suppl 7):45–48. [PubMed: 11995778]
19. Soares CD, Almeida OP, Joffe H, et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58:529–534. [PubMed: 11386980]
20. Ladd CO, Newport DJ, Ragan KA, et al. Venlafaxine in the treatment of depressive and vasomotor symptoms in women with perimenopausal depression. Depress Anxiety 2005;22:94–97. [PubMed: 16094663]
21. Stearns V, Beebe KL, Iyengar M, et al. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. J A M A 2003;289:2827–2834.

22. Suvanto-Luukkonen E, Koivunen R, Sundstrom H, et al. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. Menopause 2005;12:18–26. [PubMed: 15668596]
23. Soares CN, Poitras JR, Prouty J, et al. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. J Clin Psychiatry 2003;64:473–479. [PubMed: 12716252]
24. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. Clin Obstet Gynecol 1977;4:31–47.
25. Schmidt PJ, Murphy JH, Haq N, et al. Basal plasma hormone levels in depressed perimenopausal women. Psychoneuroendocrinology 2002;27:907–920. [PubMed: 12383452]
26. Schmidt PJ, Murphy JH, Haq NA, et al. Stressful life events, personal losses, and perimenopause-related depression. Arch Womens Ment Health 2004;7:19–26. [PubMed: 14963729]
27. Novaes C, Almedia OP. Premenstrual syndrome and psychiatric morbidity at the menopause. J Psychosom Obstet Gyn 1999;20:56–57.
28. Freeman EW, Sammel MD, Liu L, et al. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry 2004;61:62–70. [PubMed: 14706945]
29. Gaynes, BN.; Gavin, N.; Meltzer-Brody, S., et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Agency for Healthcare Research and Quality. 2005 [Accessed Nov 9, 2006]. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/peridepr/peridep.pdf
30. Garvey MJ, Tuason VB, Lumry AE, et al. Occurrence of depression in the postpartum state. J Affective Disord 1983;5:97–101.
31. Munk-Olsen T, Munk Laursen T, Bocker Pedersen C, et al. New parents and mental disorders: a population-based register study. J A M A 2006;296:2582–2589.
32. Morse CA, Dudley E, Guthrie J, et al. Relationships between premenstrual complaints and perimenopausal experiences. J Psychosom Obstet Gyn 1998;19:182–191.
33. Freeman EW, Sammel MD, Rinaudo PJ, et al. Premenstrual syndrome as a predictor of menopausal symptoms. Obstet Gynecol 2004;103:960–966. [PubMed: 15121571]
34. Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999;341:1329–1335. [PubMed: 10536124]
35. Demyttenaere K, Bonnewyn A, Bruffaerts R, et al. Comorbid painful physical symptoms and depression: prevalence, work loss, and help seeking. J Affective Disord 2006;92:185–193.
36. Papakostas GI, Petersen TJ, Iosifescu DV, et al. Somatic symptoms as predictors of time to onset of response to fluoxetine in major depressive disorder. J Clin Psychiatry 2004;65:543–546. [PubMed: 15119918]

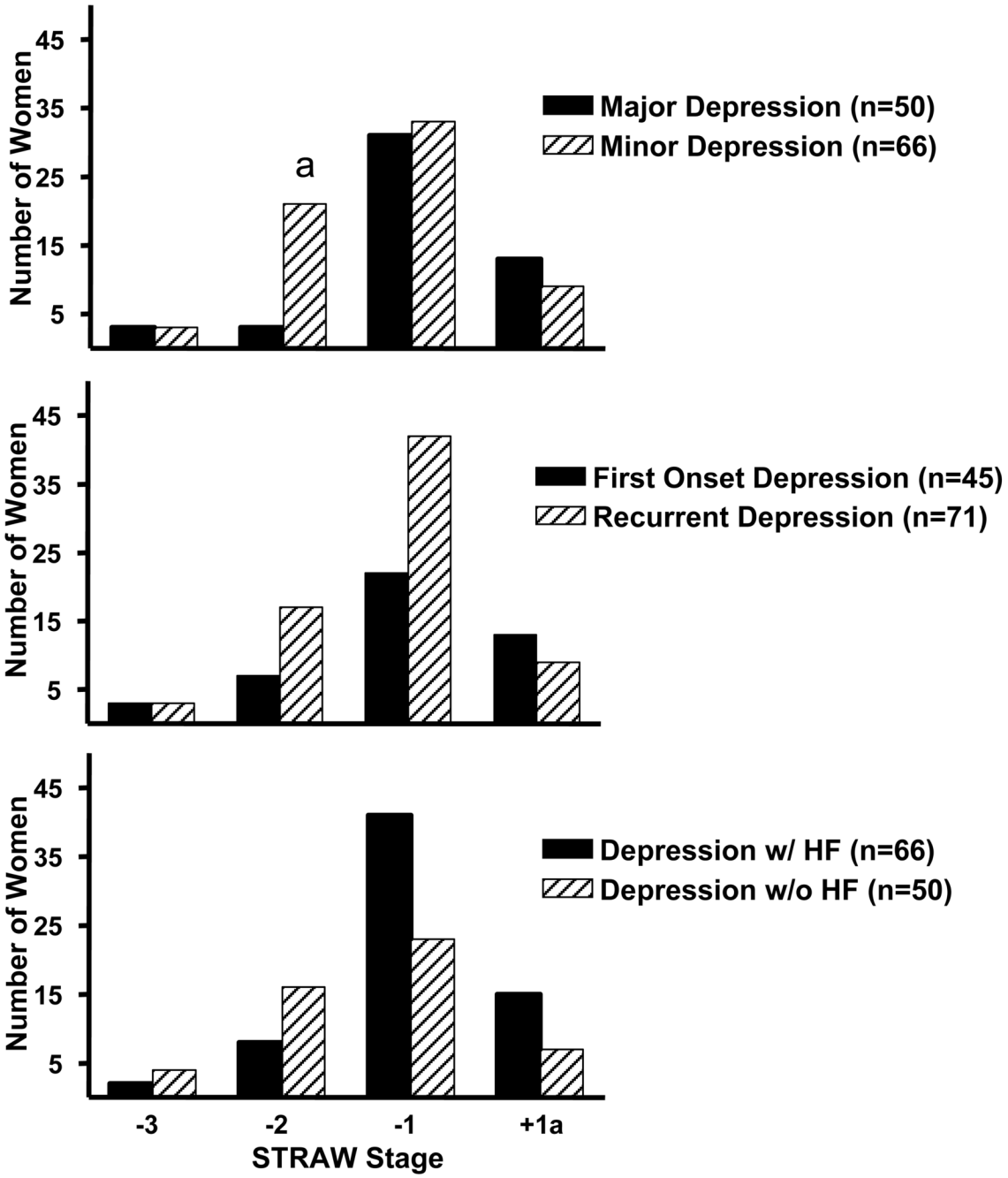

Figure I.

Numbers of depressed perimenopausal women in each STRAW stage were compared across three groups: (1) women with major versus minor depression, (2) first onset versus recurrent depression, and (3) women with and without hot flushes

Criteria for STRAW Stages:

Stage -3: regular menstrual cycles and one 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 two skipped cycles as well as an interval of amenorrhea (≥ 60 days) and elevated plasma FSH levels; and stage +1a: up to one year of amenorrhea and elevated FSH levels. STRAW = Stages of Reproductive Aging Workshop.

Between Group Comparisons:

a - minor depression versus major depression stage -2 Chi square = 12.3, df = 3, p = 0.006; post-hoc Fisher Exact test, p =.003

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

Individual uncorrected 2×2 Chi square 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; 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 six comparisons.

Otherwise all comparisons p = NS

Within Group Comparisons (multinomial):

1) major depression - the number of women in stage -1 was significantly greater than numbers in stages +1a -2, -3 (Z = 4.3–6.1 [range]; p =.003 – <.001 [range]); number of women in stage +1a was significantly greater than 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 numbers in stages -3 and +1a (Z = 2.3–6.3 [range]; p =.02 – <.001 [range]); whereas numbers of women in stages -1 and -2 was not significantly different (p = 0.1)

2) 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)

3) depression with hot flushes (HF) - greater numbers of women were in STRAW stages -1 (compared to +1a: Z = 3.8; p <.001, to -2: Z = 5.8; p <.001 and -3: Z = 8.7; p <.001), and stage +1a (compared to -3: Z = 3.4; p <.001)

depression without hot flushes (HF) - 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 stage -2 (compared to -3: Z = 2.9; p =.004 and to +1a: Z = 2.0; p =.052)

Table 1

Demographic Characteristics of Women with Perimenopausal Depression (n = 116)

	Perimenopausal
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)
[a] Plasma FSH (IU/L):	
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 (%):	
No. of Women in Stage -3	6 (5.0)
No. of Women in Stage -2	24 (20.7)
No. of Women in Stage -1	64 (55.2)
No. of Women in Stage +1a	22 (19.0)
Current Major Depression, N (%)	50 (43.1)
Duration mean (SD)	20.9 (11.7)
Current Minor Depression, N (%)	66 (57.0)
Duration mean (SD)	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 inter-assay 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.

Table 2

Characteristics in Perimenopausal Women with Depression - Mean (SD)[a]

	Age y	Mean FSH IU/L	SD FSH IU/L	CES-D[b] score	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 were unavailable in 14 women.

[c] Student's t-test with Bonferroni adjustment: major vs. minor depression - CES-D: [$t_{100} = 6.0$, $p = .001$]; BDI: [$t_{114} = 5.5$, $p < .001$].

[d] Student's t-test with Bonferroni adjustment: major vs. minor depression - # of days of impairment: [$t_{114} = 3.5$, $p = .001$]; maximum impairment score: [$t_{114} = 2.5$, $p = .13$; without Bonferroni adjustment $p = .02$].

Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiologic Studies-Depression Scale; FSH = follicle-stimulating hormone.