Article

A Longitudinal Evaluation of the Relationship Between Reproductive Status and Mood in Perimenopausal Women

Peter J. Schmidt, M.D.

Nazli Haq, M.A.

David R. Rubinow, M.D.

Objective: Mood and reproductive function were prospectively evaluated in asymptomatic premenopausal women to determine whether the onset of depression was temporally linked to the perimenopause.

Method: Twenty-nine asymptomatic, regularly cycling women were monitored longitudinally for an average of 5 years until at least 6 months of amenorrhea occurred. Outcome measures included mood ratings and menstrual diaries completed daily, the Structured Clinical Interview for DSM-IV, and plasma levels of follicle-stimulating hormone obtained at 3–6-month intervals. The number of episodes of depression and their timing relative to the final menstrual period were determined. Differences in outcome measures between women who did and did not become depressed during the perimenopause were determined by Student's t test, chi-square tests, and Fisher's exact test.

Results: The authors observed 11 episodes of new-onset depression in nine of the 29 women. In the 24 months surrounding the last menstrual period nine episodes of depression were observed. Six of the nine women who became depressed during the study had no prior depressive episodes. For the 24 months surrounding the final menses, the risk for onset of depression was 14 times as high as for a 31-year premenopausal period of time. Women who developed depression during the perimenopause were not distinguished from those who remained asymptomatic on the basis of symptom profile, duration of the perimenopause, endocrine measures, or past historical variables.

Conclusions: These preliminary data suggest that events related to the late perimenopause may be associated with an increased susceptibility to develop depression in some women.

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Epidemiologic studies have clearly demonstrated that the majority of women do not develop a depression at the menopause (1–3). However, in the women who do become depressed during midlife, the temporal relationship between the last menstrual period and the onset of depression has not been established. For depressed perimenopausal women there is an underlying assumption that hormonal events related to the perimenopause are involved in the pathophysiology of their depression, supported, albeit indirectly, by studies indicating the therapeutic efficacy of estradiol in this condition (4, 5). While these studies suggest the psychotropic action of estradiol in perimenopause-related depression, they do not inform us about the role of declining ovarian estradiol secretion in the onset of depression in some perimenopausal women. Several community- and clinic-based studies have documented that perimenopausal women report more depressive symptoms than either pre- or postmenopausal women (6–10), suggesting, therefore, that the perimenopause may be a time of increased susceptibility to depression.

Attempts to identify predictors identifying women who become depressed at this time have pointed to several variables associated with depression, including the following: past episodes of depression (8, 11), longer duration of the perimenopause (defined by menstrual cycle irregularity) (12), presence of hot flushes (12, 13), retrospective reports of premenstrual syndrome (7, 11, 14, 15), history of smoking (7, 15), lower parity, and being unmarried (15). Nonetheless, several constraints have compromised efforts to define more precisely the relationship between the last menstrual period and the onset of depression. For example, both cross-sectional and repeated cross-sectional studies suffer low sensitivity consequent to long unsampled intervals (e.g., 9 months) (1) and the use of scales that inquire about the presence of depressive symptoms only during the 1–2 weeks before the subject's interview, e.g., Center for Epidemiologic Studies Depression Scale (CES-D Scale) (16). Thus, depressive episodes could occur that would not be detected during the interviews and could confound efforts to determine the relationship between endocrine changes and mood.

Studies cannot examine the temporal contiguity of mood disturbance and altered reproductive function at a distance; indeed, inferences about this relationship can be confidently drawn only with use of a longitudinal prospective design employing the appropriate diagnostic and symptom rating instruments. In this study we present preliminary results from a group of asymptomatic, regularly

menstruating premenopausal women whose reproductive status and mood were monitored prospectively and regularly until 6 months of amenorrhea ensued.

Method

Subject Selection

Asymptomatic women who had regular menstrual periods (22 to 35 days) and were between the ages of 40 and 50 years were recruited through newspaper advertisements to participate in a study of the effects of the perimenopause on mood and behavior. Written informed consent was obtained. All subjects completed 3 months of daily ratings on visual analogue scales of sadness, anxiety, and excessive worry to confirm the absence of premenstrual syndrome (PMS); i.e., no subject met the severity criterion of a 30% or greater change in pre- versus postmenstrual symptom ratings relative to the range of the scale employed by the subject (17). Over 200 women were screened by telephone, 79 came to our clinic to be screened, and 29 women were entered into the study. Dropouts were largely due to an inability to make a commitment to completing the ratings, the presence of mood symptoms, and a wish to start hormone replacement therapy within the next 1–2 years. Only one woman was excluded from the study because of evidence of PMS symptoms on her daily symptom ratings. This low rate of exclusion reflects the impact of the extensive screening that was performed on the telephone and during the first interview regarding any potential confounding mood and behavioral symptoms linked to the menstrual cycle. Additionally, several women were excluded because of abnormal findings in their histories or their results on the physical examination, laboratory tests, chest X-ray, or ECG.

At intake all subjects had normal physical and laboratory findings. Additionally, no subject had a current (within the past 2 years) axis I psychiatric illness, but subjects could have a past history of depression, identified by the administration of a structured diagnostic interview, the Structured Clinical Interview for DSM-IV (SCID) (18) and a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (19), instruments designed to identify both current and lifetime episodes of psychiatric illness.

Protocol

Each subject was seen every 6 months in the National Institute of Mental Health outpatient clinic during a visit scheduled between days 3 and 6 of her menstrual cycle (after the onset of menses). As the menstrual cycle became irregular, periods of amenorrhea ensued, or hypoestrogenic symptoms such as hot flushes appeared, the frequency of visits was increased from every 6 months to every 3 months. Outcome measures included measurements of both reproductive status and mood and behavior. The reproductive measures included plasma levels of follicle-stimulating hormone (FSH), which were determined between menstrual cycle days 3 and 6 (at the time of the clinic visits), and a diary of menstrual cycle length, which was completed daily throughout the study. Normal gynecologic examinations performed approximately yearly were required throughout the study, and periodic physical examinations and laboratory testing (e.g., routine thyroid function tests) were performed by the investigator or the woman's personal physician. Self-reports of exit-type events (defined as real or perceived losses of personally relevant objects, such as death of a loved one, divorce, loss of a loved one, child moving from home) and unpleasant events were recorded at 6-month intervals. The mood and behavior measures were 1) daily self-ratings of symptoms on visual analogue scales (identical to those employed during the 3 months of the screening phase) measuring sadness, anxiety, and excessive worry and 2) upon the initial self-report of the presence of hot flushes, a modification of the daily rating form (20) that monitored the severity of both daytime and nighttime hot flushes on a 6-point Likert-type scale (1=not present, 6=severe). In addition to the daily symptom self-ratings, the SCID was completed at 6-month or 3-month intervals at each clinic visit during the follicular phase. Finally, at any time in the study when the subject described feeling depressed, the SCID was repeated.

The subjects were monitored until they had at least 6 months of amenorrhea, with exceptions as follows: 1) two asymptomatic women, one of whom had a hysterectomy for severe fibroids (and hence no further menses) after 3 years in the study and remained in the study until her plasma FSH levels were higher than 40 IU/liter and the other of whom moved out of the state and was lost to follow-up after 3 months of amenorrhea and 2) five women who became depressed during the study and required referral for treatment, which occurred between 2 and 6 months after their last menses (to be discussed). All women who became depressed were counseled about therapeutic options, and a referral for treatment at an outside facility was made if clinically indicated or if requested by the woman. Otherwise, none of the subjects received any active treatment as part of this protocol.

We addressed the following questions in this study: 1) Is the time close to the last menstrual period associated with an increased rate of depressive episodes relative to the early perimenopause? 2) Does the duration of the perimenopause, as measured by the duration of menstrual cycle irregularity or by the latency from an elevated early-follicular-phase plasma FSH level until the last menstrual period, predict the onset of depression? 3) Is the onset of depression predicted by the duration of the late perimenopause, as defined by the criteria of the Stages of Reproductive Aging Workshop (STRAW) (21), i.e., the duration of the time from two or more missed cycles and ≥60 days of amenorrhea until the final menstrual period? 4) Does a past history of premenstrual syndrome, major depression, or minor depression predict the onset of depression during the perimenopause? and 5) Is the development of hot flushes or prospectively confirmed PMS a uniform accompaniment of perimenopausal depression?

Outcome Measures

The following information was obtained on each subject: 1) the final menstrual period, defined as the last date of menses preceding a period of at least 6 months of amenorrhea, 2) the number and age at onset of episodes of either major or minor depression that occurred before the subject entered the study, as reported during the administration of the SCID, 3) the number of episodes of major or minor depression identified (by the administration of the SCID) during this study, 4) the date at onset of menstrual cycle irregularity, defined by the date of onset of the menses at the beginning of a time period in which menstrual cycle intervals were shorter than 21 days or longer than 35 days for 3 consecutive months, 5) the date after which a woman missed two or more menstrual cycles and had 60 or more days of amenorrhea (the beginning of late perimenopause according to the STRAW criteria), 6) the presence of hot flushes, as defined by self-report and confirmed by scores on the daily ratings of hot flushes of 2 or greater on a 6-point self-rating scale (1=no hot flushes, 2=minimal severity) (20), and 7) the presence during the 2–4 years before the final menstrual period of significant premenstrual mood changes, defined by a 30% or greater change in the average premenstrual mood rating from the average postmenstrual rating relative to the range of the scale employed by each subject. The absence of significant premenstrual symptoms was defined by a pre-post difference in symptom ratings of less than 10%. Each past or new episode of minor or major depression was characterized with respect to the patient's age as well as the date of onset relative to the subject's final menstrual period. Finally, plasma FSH levels

proximate to the dates of the onset of menstrual cycle irregularity and the onset of depression were examined.

Statistics

Outcome measures in the women who did and did not become depressed during the perimenopause were compared by Student's t test (two-tailed) and chi-square analysis (or Fisher's exact test).

One woman reported a postpartum depression that occurred 36 years before her final menstrual period, and this episode served to define the years of risk for depression onset in this study (i.e., 36 years before the final menstrual period). We examined the risk of onset of depression during each of the following three time periods: 36–6 years before the final menstrual period, 5–2 years before the final menstrual period, and the year before and after each woman's final menstrual period. Thus, the number of months at risk (29 women multiplied by 12 months per year multiplied by the number of years in each time period) was calculated and divided into the number of recorded episodes of depression for each time period. The relative risk of experiencing an episode of depression during each of these times was expressed relative to a 500-month period of risk.

Results

Subject Characteristics

In this preliminary study, 29 women were monitored until at least 6 months of amenorrhea occurred. The average age of the women entering the study was 48.0 years (SD=2.6, range=42–54), and the average age at study completion (after 6 months of amenorrhea) was 53.3 (SD=2.5, range=48–57). Thus, on average we followed the women for a mean of 5.2 years (SD=2.3, range=1.4–10.6). All but one woman were followed for at least 2 years. At baseline, nine women had histories of depression (six women had past histories of major depression, and three others had past histories of minor depression); three of the six women with histories of major depression had had postpartum depression. All women were from the Washington, D.C., suburban area and were of middle-class background. Of the 29 women, about half (N=15) were married and most (N=27) were Caucasian. Thirteen reported exercising regularly, 20 reported using vitamin or mineral supplements (e.g., multivitamin, vitamin E, calcium, folic acid, vitamin B complex, vitamin C), and four reported prior use of antidepressant or anxiolytic medication. During the study none of the women received formal psychotherapy or counseling and, with the exception of one woman who intermittently received alprazolam from her family physician while depressed, none of the women took antidepressant or anxiolytic medication. Moreover, with the exception of two women taking stable replacement doses of thyroid hormone, none of the women reported any significant medical illnesses or took any medications with potential psychotropic effects. Six of the nine women who developed a depression during this study and eight of the women who remained asymptomatic reported a history of mood disorder in a first-degree relative (n.s., Fisher' exact test). Finally, five of the nine women who became depressed during the study required referral for treatment, which occurred between 2 and 6 months after the last menses.

The average age at the last menstrual period was 52.5 (SD=2.4), and the average age at the onset of menstrual cycle irregularity was 51.3 (SD=2.1). All women were selected on the basis of being asymptomatic and having regular menstrual cycle functioning (by history) at baseline. Several women, however, had plasma FSH levels greater than or equal to 14 IU/liter at the first visit. On average there were 4.1 years (SD=2.2) between the first FSH level of 14 IU/liter or higher and the final menstrual period, an average of 1.3 years (SD=1.0) between the onset of three consecutive months of menstrual cycle irregularity and the final menstrual period, and an average duration of the late perimenopause (STRAW criteria) of 20.6 months (SD=21.8). The average FSH level at the onset of menstrual cycle irregularity was 32.5 IU/liter (SD=23.9), and at the onset of the final menstrual period it was 47.5 IU/liter (SD=30.6, range=3–119). The subject who had an FSH level of 3 IU/liter at the time of her final menstrual period had no preceding interval of menstrual cycle irregularity.

Timing and Type of Depressive Episodes

Eleven episodes of new-onset depression (major: N=1, minor: N=10) were documented with the structured interview in nine of the 29 women. Nine episodes occurred within the 12 months before or after the last menstrual period, and two occurred before the onset of menstrual cycle irregularity (6 and 12 months before, respectively). The latter two episodes also occurred in the context of recent (within 2 months) elevations of FSH levels (≥14 IU/liter). Six of the nine women who became depressed during the study had no prior depressive episodes and, therefore, had first-onset depressions. Of the remaining three women who became depressed, two reported past episodes of major depression and one reported a past episode of minor depression.

The calculated risk of an episode of depression (per 500 months) during the 24 months surrounding the final menstrual period was 6.5, compared to values of 1.4 and 0.46 during the periods 2–5 years and 6–36 years before the final menstrual period, respectively.

Variables Associated With Depression

As shown in Table 1, there was no difference between the women who did and did not develop a depression during the 24 months surrounding the final menstrual period on the following measures: parity, family history of mood disorder, smoking history, age at onset of menstrual cycle irregularity, duration of menstrual cycle irregularity before the final menstrual period, FSH level at either the onset of menstrual cycle irregularity or the last menstrual period, duration of the late perimenopause, and age at the final menstrual period. Additionally, the reports of regular exercise, use of vitamin or mineral supplements, and presence of medical illnesses did not distinguish the women who

TABLE 1. Characteristics of Women Who Did and Did Not Develop Depression During the 24 Months Surrounding the Final Menstrual Period

Characteristic	Depressed (N=9)[a]		Not Depressed (N=20)	
	Mean	SD	Mean	SD
Number of children	2.3	1.3	1.7	1.1
Age at onset of menstrual cycle irregularity (years)[b]	51.3	1.4	51.3	2.4
Age at final menstrual period (years)	52.9	1.5	52.4	2.7
Duration of menstrual cycle irregularity before final menstrual period (years)	1.3	0.8	1.3	1.1
Latency between first elevated follicle-stimulating hormone (FSH) level (≥14 IU/liter) and final menstrual period (years)	5.0	2.5	3.8	2.1
Duration of late perimenopause (months)[c]	20.4	13.0	20.7	25.2
Plasma FSH level at onset of menstrual cycle irregularity (IU/liter)	23.3	14.6	36.8	26.5
Plasma FSH level at final menstrual period (IU/liter)	46.7	37.9	47.9	27.8
	N		N	
Positive smoking history[d]	3		1	
Past depression	3		6	
Onset of premenstrual syndrome during perimenopause	1		1	
Hot flushes[e]	8		11	
Family history of depression	6		8	

[a] Eleven episodes of depression occurred, one episode of major depression and 10 episodes of minor depression, diagnosed with the Structured Clinical Interview for DSM-IV (18).
[b] Menstrual cycle irregularity was defined as menstrual cycle intervals shorter than 21 days or longer than 35 days for 3 consecutive months.
[c] Late perimenopause was defined by the criteria of the Stages of Reproductive Aging Workshop (STRAW) (21), i.e., the interval from two or more missed cycles and ≥60 days of amenorrhea until the final menstrual period.
[d] p=0.08, Fisher's exact test.
[e] p<0.01, Fisher's exact test, Yates corrected.

developed a depression during the perimenopause. Finally, in the women who became depressed, neither the number of exit-type nor unpleasant events during the 6 months before the onset of depression differed from the number of these events reported at other times in the study.

Of the nine women with a past history of depression before study entry, only three developed a depression during the study. None of the three women with previous postpartum depression developed depression during the perimenopause.

We observed only two women who met the criteria for PMS during this study, and only one of these women developed a depression. Several other women met the criteria for significant premenstrual mood changes in isolated months, but these women also were represented in both the depressed and nondepressed groups. Finally, 19 (66%) of the 29 women in this study experienced hot flushes at some time during the study. Eight of the nine women who developed depression during the study reported hot flushes of varying levels of severity. The proportion of women who reported hot flushes was significantly higher for the women who developed depression than for those who did not develop depression. Six of the eight depressed women who had hot flushes reported that their onset occurred before (1, 4, 5, 10, 22, or 43 months before) the onset of depression. In the woman who experienced hot flushes 22 months before the onset of depression, her hot flushes stopped at the time that her depressive episode commenced. Two of the eight women reported the onset of hot flushes 10 and 21 months after the onset of depression. Thus, hot flushes often occurred before the onset of depression, but flushes occurred within a year before the onset of depression in only four women and, therefore, were not proximate to the onset of depression in five of the nine women who became depressed.

Discussion

This study yielded three major findings: 1) the 24 months surrounding the final menstrual period are associated with an increased risk for the onset of depression, 2) neither a past psychiatric history nor PMS is a necessary antecedent or accompaniment of perimenopause-related depression, and 3) hot flushes, although frequently associated with depression, are not a uniform accompaniment of depression during the perimenopause. The observed 14-fold increase in the rate of onset of depression during the 24 months surrounding the final menstrual period, relative to the 31 years we used as a comparison time period, suggests an increased risk of depression in women during both the late perimenopause and the early postmenopause relative to the premenopause. Moreover, we also observed an increase, albeit considerably smaller, in the risk of depression (relative to the same 31 comparison years) during the 4 years prior to the year before the final menstrual period—suggesting an increased risk also during the early perimenopause relative to the premenopause. It is interesting that the two episodes of depression that developed before the 2 years around the final menstrual period, during the early perimenopause, both occurred in the context of recently elevated plasma FSH levels, suggesting a potential linkage of these depressions to the endocrine events of the perimenopause. Although

suggested, an endocrine cause for the depressions we observed cannot be concluded from these preliminary data. Regardless of any inferences about a specific etiology, the depressive episodes were clustered around the final menstrual period and were more common during these 24 months than during the previous years (during both the years that were prospectively examined and the longer period of recall examined in the structured interviews). Our data, therefore, identify the events related to the final menstrual period as important in the onset of depression in these women. The observed episodes of depression were not randomly distributed during the prospective component of the study, and therefore, it is unlikely that these episodes reflect the effects of chance or of a few outlier values. Finally, our data are consistent with those from several studies that have identified the perimenopause but not the postmenopause as a time of increased risk for developing depressive symptoms (7–10, 13, 22).

The increased rate of depression we observed reflected the onset of minor depressions, not major depressions. All episodes of depression met standardized diagnostic criteria for a syndrome of depression characterized by persistent symptoms and personal impairment. Nonetheless, it could be argued that the presence of minor depression is not a clinically significant mood disorder and, instead, represents a ubiquitous change in mood that may merely reflect life stresses. Additionally, it is possible that the recall of minor depression is more impaired by the passage of time than is recollection of major depression and that a lack of recall led to the reporting of more episodes during the prospective component of the study than were reported in the diagnostic interview for the years before the study. However, the episodes of minor depression clustered around the final menstrual period and were not evenly distributed throughout the average of 5 years during which the women were followed prospectively. Only three women recalled the presence of a minor depressive episode in their pasts, and this number suggests that these episodes of minor depression diagnosed by structured interviews are not ubiquitous experiences in a person's life. Moreover, recent evidence confirms the clinical importance of minor depressions. Studies have suggested that major and minor depression share important features, including heritability, morbidity, and treatment response characteristics (23).

We believe that this study is unique since we employed a diagnostic interview capable of both establishing the diagnosis of depression and validly surveying a longer intervisit interval than that sampled by many of the standardized cross-sectional rating scales of depression used in prior studies of the menopause and mood, e.g., the CES-D Scale (covering days to weeks). Additionally, the reliance on a fixed cutoff point on a standardized mood rating scale, such as the commonly employed versions of the CES-D Scale, compromises sensitivity for detecting depressive syndromes; the reported sensitivity of these instruments is approximately 75% (24–26).

Prior community- and clinic-based studies have identified several potential antecedents of perimenopausal depression, including past episodes of depression (8, 11), the presence of PMS (7), a prolonged perimenopause (12), and hot flushes (13). We were unable to identify any variable that was uniformly associated with the onset of depression. We did not observe more onsets of depression in women with a past history of depression (diagnosed by structured clinical interview). In fact, of the depressions that were observed, similar percentages occurred in the women with no prior history of depression (six of 20) and in those with a past history (three of nine), the small number of subjects notwithstanding. Nor did the three women with postpartum depression develop perimenopause-related depression, a fact that suggests that the presence of one episode of a mood disorder related to reproductive endocrine functioning (i.e., postpartum depression) does not predict the uniform occurrence of depression during a subsequent period of hormonal change (the perimenopause).

Prior studies employing retrospective reports of the onset of PMS have suggested that it accompanies and, possibly, predicts depression during the perimenopause (7, 11, 14, 15). We believe that our study is the first to prospectively evaluate, by means of daily symptom ratings, self-reports of the onset of PMS in women entering the perimenopause, and for these women PMS only rarely accompanied perimenopausal depression. In fact, in the women who became depressed during the perimenopause, only one woman met the criteria for PMS or premenstrual dysphoric disorder (PMDD) in the 4 years before the final menstrual period, and two additional women met the criteria for significant premenstrual cyclicity intermittently in three to five menstrual cycles over the course of the 4 years before the final menstrual period. Some reports suggest that the severity and duration of premenstrual symptoms worsen with age. We did not include anyone in the current study group with a diagnosis of PMS or PMDD, and only two women developed PMS or PMDD (one who developed depression and one who did not). We cannot, therefore, assess whether preexisting PMS is a risk factor for perimenopausal depression. It is, nonetheless, clear that the onset of PMS is not a uniform accompaniment of the perimenopause, nor is it a necessary antecedent to perimenopausal depression.

Finally, hot flushes are frequently reported to accompany depression in the perimenopause (12, 13) and are viewed as potentially causal. Thus, hot flushes would be hypothesized to disturb sleep and contribute to daytime mood symptoms, consistent with the domino theory. For this relationship to be tenable, the reported hot flushes would have to occur before the onset of depression (i.e., as a precipitant of depression). In contrast, in this study hot flushes were not uniformly present in all women and, when present, did not necessarily precede the depression.

Although eight of the nine women reported the onset of hot flushes at some point during the perimenopause, the pattern of the relationship varied considerably; the onset of hot flushes ranged from several years before to several years after the onset of the depression. Only four of the women who developed a depression during the perimenopause reported the onset of hot flushes proximate to the development of their depression. Thus, hot flushes appear to be neither a necessary nor sufficient accompaniment of depression during the perimenopause, and perimenopausal depression cannot be dismissed as epiphenomenal to hot flushes.

The majority of the women in this study remained asymptomatic throughout the perimenopause. Nonetheless, our data suggest that events surrounding the final menstrual period may predispose some women to develop depression. Although several factors could precipitate depression in these women, endocrine events are suggested indirectly by studies reporting estradiol's efficacy in perimenopausal-onset depression and by the stage of the perimenopause (i.e., late perimenopause) during which the depressions appeared. The late perimenopause is characterized by more prolonged hypogonadism than the early perimenopause, during which estradiol secretion may be increased. Indeed, the late perimenopause may represent the phase of the perimenopause most correctly characterized by estradiol "withdrawal," in contrast to either the postmenopause or the early perimenopause (27, 28). Thus, the timing of appearance of the depressions observed in this study suggest an endocrine mechanism related to the late perimenopause (estradiol withdrawal and recent onset of prolonged hypogonadism) in the pathophysiology of perimenopausal depression. Alternatively, hot flushes have been identified as frequent correlates of mood symptoms in epidemiologic studies of perimenopausal depression. Our data confirm that flushes are a frequent accompaniment of depression, but the timing of hot flushes in relation to depression does not support the inference that hot flushes are causally connected to depression. Finally, even if either hormonal events or hot flushes were the proximate cause of depression, these events did not precipitate depressions in the majority of the women in this study.

We could not identify characteristics that predicted depression. Indeed, in the women who developed depression during the perimenopause, the reported number of exit-type or unpleasant events in the 6 months preceding the onset of depression did not differ from the numbers of these events reported at other times during the study. Additionally, regular exercise, use of vitamins or minerals, presence of concurrent medical illness, use of psychoactive medication, or a family history of mood disorder did not predict the development of depression during the perimenopause. Notably, a past history of depression, whether related to reproductive endocrine change (i.e., postpartum depression or PMS) or not, also failed to predict the onset of perimenopausal depression. As a caveat, however, we should point out that our inability to identify predictors of the onset of depression may reflect the small number of subjects examined. An additional limitation of this study is our inability to prospectively confirm the incidence of depression during other periods of life in our study group. Clearly, however, the strength of this study is the use of the longitudinal monitoring of both mood and reproductive functioning necessary to adequately establish a temporal linkage between the changes in both of these measures. If these preliminary data are confirmed, future studies must identify the basis for this susceptibility to depression and the specific events related to the perimenopause that trigger the onset of depression in this group of women.

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