ORIGINAL ARTICLE

Associations of Hormones and Menopausal Status With Depressed Mood in Women With No History of Depression

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Context: Whether depressed mood reported in the transition to menopause by women with no history of depression is associated with menopausal status and changes in reproductive hormones is controversial and lacks scientific information.

Objectives: To identify new onset of depressive symptoms and diagnosed depressive disorders in the menopausal transition and to determine the associations of menopausal status, reproductive hormones, and other risk factors with these cases.

Design: A within-woman, longitudinal (8-year) study to identify risk factors of depressed mood.

Setting: A subset of a randomly identified, population-based cohort.

Participants: Premenopausal women with no history of depression at cohort enrollment.

Main Outcome Measures: The Center for Epidemiological Studies of Depression scale (CES-D) was used to assess depressive symptoms, and the Primary Care Evaluation of Mental Disorders (PRIME-MD) was used to identify clinical diagnoses of depressive disorders.

Results: High CES-D scores (≥16) were more than 4 times more likely to occur during a woman's menopausal transition compared with when she was premenopausal (odds ratio, 4.29; 95% confidence interval, 2.39-7.72; $P<.001$). Within-woman change in menopausal status, increased levels of follicle-stimulating hormone and luteinizing hormone, and increased variability of estradiol, follicle-stimulating hormone, and luteinizing hormone around the woman's own mean levels were each significantly associated with high CES-D scores after adjusting for smoking, body mass index, premenstrual syndrome, hot flashes, poor sleep, health status, employment, and marital status. A diagnosis of depressive disorder was 2½ times more likely to occur in the menopausal transition compared with when the woman was premenopausal (odds ratio, 2.50; 95% confidence interval, 1.25-5.02; $P=.01$); the hormone measures were also significantly associated with this outcome.

Conclusion: Transition to menopause and its changing hormonal milieu are strongly associated with new onset of depressed mood among women with no history of depression.

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THERE IS LITTLE SCIENTIFIC information about the extent to which common menopausal symptoms are associated with the changes in reproductive hormones that occur in the transition to menopause. Although there is general agreement that vasomotor symptoms and vaginal dryness are associated with ovarian aging, the report from the National Institutes of Health State-of-the-Science Conference on management of menopausal symptoms concluded that there is only limited evidence about mood symptoms in the perimenopausal years.[1] Whether mood symptoms increase in the perimenopausal years and whether the occurrence of depressed mood is independently associated with ovarian changes or is secondary to vasomotor or other bothersome symptoms remains controversial.[2-4]

Many community-based studies have assessed depressive symptoms in women in midlife and concluded that these symptoms are not associated with natural menopause but with factors such as stress, relationship problems, other menopausal symptoms, or previous depression.[5-8] In contrast, recent epidemiologic studies found an increase in depressive symptoms in perimenopausal women compared with premenopausal women,[9,10] and another study reported an association between menopausal transition and increased risk for clinical depression, particularly in women with a history of depression.[11] Another longitudinal study found a significantly greater risk for episodes of clinical depression around menopause than when the women were premenopausal.[12]

We have similarly found that women in the menopausal transition were up to 3 times more likely to report depressive symp-

toms than were premenopausal women.[13] While a history of depression was the strongest predictor of these findings, the changing hormonal milieu, such as increased levels of estradiol that occur in the early menopausal transition, contributed to depressive symptoms in women approaching menopause. Others have also hypothesized that the cyclic fluctuations of estradiol levels, which may increase in the menopausal transition, are an important factor in the occurrence of depressed mood.[14-16]

We examined which risk factors in a woman approaching menopause are present at the onset of depressed mood compared with the time preceding the symptoms of depression. Based on our previous findings,[13,17,18] we hypothesized that menopausal status (ie, changing from premenopausal status to menopausal transition) and fluctuations and changes in reproductive hormone levels are predictors of new onset of depressed mood.

METHODS

STUDY PARTICIPANTS

Data are from a subset of participants in the Penn Ovarian Aging Study, a population-based cohort of 436 women identified by random-digit dialing to households in Philadelphia County, Pennsylvania, and described in previous reports.[13,17] This study examined 231 women who had no history of depression as reported in the baseline medical history interview, no diagnosis of depressive disorder at baseline using the Primary Care Evaluation of Mental Disorders (PRIME-MD),[19] and scores below the standard cutoff point of 16 at baseline on the Center for Epidemiologic Studies Depression scale (CES-D).[20] These women were followed up for 8 years, starting from their premenopausal baseline at enrollment in the cohort.

At enrollment in the cohort, the women were aged 35 to 47 years and had menstrual cycles in the normal range (22-35 days) for the previous 3 months, an intact uterus, and at least 1 ovary. Exclusion criteria included current use of psychotropic or hormonal medications, including hormonal contraception and hormone replacement therapies; pregnancy or breastfeeding; serious health problems known to compromise ovarian function (eg, diabetes mellitus, liver disease, and breast or endometrial cancer); and alcohol or drug abuse within the past year. The institutional review board of the University of Pennsylvania approved the study, and written informed consent was obtained from all enrolled women.

STUDY DESIGN

Data were collected in 10 assessment periods from 1996 to 2004. The first 6 periods were at 8-month intervals, and periods 7 through 10 were at 1-year intervals for a total of 8 years. Each assessment period included 2 visits, scheduled in the first 6 days of 2 consecutive menstrual cycles or 1 month apart in noncycling women, to obtain blood samples for the hormone assays (a possible maximum of 20 samples per participant).

Trained research interviewers obtained all data in individual in-person interviews at the participants' homes. The structured interview focused on overall health and included demographic background information, menstrual cycle dates, reproductive history, general health status, and health behaviors including smoking, alcohol use, and medications used. A validated menopause symptom list that included 12 common menopausal symptoms was embedded in the structured interview questionnaire.[21]

STUDY VARIABLES

Menopausal Status

Menopausal status was identified at each assessment using menstrual cycle duration, which was determined from the menstrual date at each study visit (conducted within 6 days of bleeding) and the 2 previous menstrual dates recorded at each visit. Confirmatory menstrual dates were obtained from the daily symptom diaries that participants recorded for 1 menstrual cycle at each assessment period, with the diary date used in cases of disagreement.

The definitions of menopausal status were from the consensus statement on a staging system for reproductive aging in women (Stages of Reproductive Aging Workshop [STRAW]),[22] which we previously demonstrated were significantly associated with changes in reproductive hormones and differentiated the earliest stages in the menopausal transition.[17,23] Menopausal status was examined as 2 groups in this study because there were few observations in the late transition stages: premenopausal (defined as regular menstrual cycles in the range of 22-35 days) and transition (defined as commencing with a change in cycle duration in either direction 7 or more days from the woman's personal baseline at enrollment in the cohort[22] and including all women who reported at least 1 menstrual period in the previous 12 months).

Hormone Levels

Nonfasting blood samples for hormone assays were collected at each visit. Assays of estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were conducted in the General Clinical Research Center using commercially available kits (Coat-a-Count; Diagnostic Products, Los Angeles, Calif). All interassay and intra-assay coefficients were less than 5%. The dimeric inhibin B level was measured in serum by Patrick Sluss, PhD, Massachusetts General Hospital, Boston, using a sensitive, 2-site nonisotopic immunoassay (Serotec, Oxford, England). The intra-assay and interassay coefficients were less than 5% and 8.5%, respectively (range, 15-500 pg/mL). Values below the sensitivity threshold (15 pg/mL) were given the threshold value.

The 2 hormone values obtained in each study period were averaged for each subject. The subject's mean value at each study period and her deviation from the average of the 2 hormone measurements (SD) were used in the analyses. In cases where 2 hormone values were not obtained in an assessment period, the single value was used for the mean, and the standard deviation was set at missing for that period. This approach was used to reduce the correlation of the hormone values, to provide a measure of the woman's hormone fluctuations separate from the hormone levels, and to avoid overestimation of the hormone values that would occur by relating 2 hormone measures at each assessment to the single measures of other risk factors. The statistical method allowed for a variable number of assessments per woman, and only 4 women were excluded from the analysis completely because of a missing standard deviation for the hormone measure.

Ninety-nine percent of the hormone values from cycling women were within days 1 to 6 of the menstrual cycle. The influence of cycle day in the hormone measurement was evaluated by testing the cycle day of the 2 hormone values in each period. Inclusion of menstrual cycle day in the models showed that within-subject differences were not significantly associated with the CES-D scores (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.78-1.15; $P = .60$). Log-transformed values were used in all analyses; hormone levels are expressed as geometric means with 95% CIs.

Outcome Variables

The primary outcome measure was the CES-D,[20] a 20-item self-report questionnaire used to assess current depressive symptoms. The standard CES-D cutoff score of 16 or greater was used to define high depressive symptoms. We also examined a clinical diagnosis of depressive disorder as assessed at each period with the PRIME-MD or its self-report version, the Patient Health Questionnaire.[19,24] Both versions are validated diagnostic assessment procedures to yield *DSM-IV* diagnoses in primary care research and practice and to detect depression outcome and changes over time.[25] The Patient Health Questionnaire differentiates only major depressive disorder and other depressive disorders in diagnosis of depression; both diagnoses are included in this study.

Other Risk Factors

The selection of potential risk factors was based on their significance in previous studies[2,4,26-29] and the goals of this study. In addition to hormone levels and menopausal status, the following potential risk factors were evaluated at each assessment: current smoking (yes or no); poor sleep, as reported on the validated St Mary's Sleep Questionnaire[30] (responses to "How well did you sleep last night?" were categorized as poor sleep and good sleep); hot flashes (yes or no), as assessed in the validated symptom list in the interview[21]; premenstrual syndrome (PMS), as constructed from 3 interview questions ("Several days to 2 weeks before your period begins, do you experience irritability, mood swings, or other distress?" "Yes" responders then rated the symptoms as mild, moderate, or severe and rated symptom interference with daily activities on a 4-point scale. Women with severe PMS included only those who rated the symptoms as severe and also rated interference with functioning as severe. Body mass index (calculated as weight in kilograms divided by the square of height in meters) was calculated at each assessment. General health status was assessed with the 12-Item Short-Form Health Survey (SF-12),[31] a validated questionnaire with demonstrated equivalence to the 36-Item Short-Form Health Survey; higher scores indicate better health. Whether a woman was currently employed (yes or no) and marital status (married or living with a partner vs all other participants) were obtained at each assessment. Age was examined initially, but there was no within-woman effect of age in the conditional models ($P = .99$). Nonchanging variables were excluded from these models because they do not contribute information to the conditional logistic regression.[32]

STATISTICAL ANALYSIS

A conditional (fixed-effects) logistic regression model[32] was used to estimate the associations of within-woman changes in risk factors for high CES-D scores. The conditional regression considers each woman as her own control, and each woman was considered to have her own personal risk for reporting the outcome (eg, depressed mood). An increment in risk associated with a change in each risk factor was estimated for each woman by comparing the average level of the covariate when the woman had high depressive symptoms with the previous average covariate level when she did not have depressive symptoms. These individual estimates were then averaged for the study group. The interpretation of the estimated association is the ratio of the average odds of reporting the risk factor at the outcome (eg, depressive symptoms or diagnosed depressive disorder) compared with the average odds of reporting the risk factor when depressive symptoms were not present. An OR greater than 1 indicates an increase in the risk factor variable at the time of the measured outcome (ie, high CES-D scores or diagnosed depressive disorder) compared with the average risk factor value preceding the event (ie, from baseline to onset of depressed mood). An OR less than 1 indicates a decrease in the risk factor at the time of outcome compared with the value before the outcome.

Each woman contributed all data from her cohort enrollment through the first assessment in which she reported the outcome of interest (CES-D score $\geq$16 or a diagnosis of depressive disorder) and included any contiguous assessments that continued to meet the outcome criteria. The outcome observations were compared with all observations before the outcome (identified individually for each subject) . Assessments that followed the measured outcome (high CES-D scores or diagnosed depressive disorder) were excluded in the conditional analysis.

We first estimated the unadjusted associations of the potential risk factors with CES-D scores of 16 or greater. All variables had significance levels of $P<.10$ in the unadjusted analyses and were then estimated in the multivariable model to identify their independent contributions after adjusting for the presence of the other variables. We used a backward elimination strategy to determine whether any of the variables included in the model modified the estimates of other significant associations by 15% or more.[33] Model diagnostics with 2 or more hormones in the models indicated that the regression estimates were highly colinear and consequently uninterpretable; therefore, each hormone was examined separately in the final models. Hypothesized interactions of variables in the models were not significant.

The same strategy was used to model the secondary outcome of *DSM-IV* diagnosis of depressive disorder. The smaller number of women having a diagnosed depressive disorder yielded less reliable analyses, and interpretation of the estimates must consider the possibility of type II error. All analyses were performed using the SAS statistical software package (version 9.1; SAS Institute, Cary, NC). Statistical tests were 2-tailed, with $P \leq .05$ considered significant.

RESULTS

PARTICIPANTS

One hundred sixteen (50%) of the 231 women who had no history of depression at baseline reported a high CES-D score ($\geq$16) during the 8-year follow-up. Forty of these women reported a high CES-D score at 1 assessment only, 16 had high CES-D scores at 2 consecutive assessments, and 35 had high scores at 3 or more consecutive assessments after enrollment in the cohort.

Fifty-nine (26%) of the 231 women met the criteria for a diagnosis of depressive disorder as assessed with PRIME-MD or the Patient Health Questionnaire after enrollment in the cohort: 26 women with major depressive disorder and 33 with other depressive disorders (which were not further differentiated by the Patient Health Questionnaire). All but 7 of these women also reported high CES-D scores during follow-up. In the analysis, 46 women had a diagnosis of depressive disorder at 1 assessment only, 9 had a diagnosis at 2 consecutive assessments, and 4 had a diagnosis at 3 or more consecutive assessments after enrollment in the cohort. **Table 1** gives the first occurrence of cases of high CES-D scores and diagnosed depressive disorders by assessment period.

One hundred eight (47%) of the 231 women had neither high CES-D scores nor diagnosed depressive disorder during the study. These women constituted the no-depression group.

Table 2 gives the study variables at baseline for the group with depressive symptoms (n=116) compared with the no-depression group (n=108). Only 2 variables differed significantly at baseline: smoking, with more smokers in the group with subsequent high CES-D scores ($P=.03$), and baseline CES-D scores. The CES-D scores in both groups were well below the cutoff of 16 that was used to identify possible depression (mean±SE, 8.88±0.41 vs 6.41±0.42, respectively; $P<.001$).

Table 3 shows the study variables at baseline for the group having a subsequent diagnosis of depressive disorders (n=59) and the no-depression group (n=108). Only 2 variables differed significantly at baseline: PMS, with more reports in the subsequent diagnosis group ($P=.04$), and baseline CES-D scores, which were well below the cutoff score in both groups (mean±SD,9.41±0.57 vs 6.41±0.42, respectively; $P<.001$).

Table 1. New Cases of First Onset of High CES-D Scale Scores, or First Episode of *DSM-IV* Depression by Assessment Period

	Assessment Period									
Measurement	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
CES-D scale score ≥16	49	26	13	7	4	3	10	3	1	**116**
DSM-IV diagnoses	19	3	12	9	3	3	1	6	3	**59**

Abbreviation: CES-D, Center for Epidemiological Studies of Depression.

MENOPAUSAL STATUS

All participants were premenopausal at enrollment. At the end of the study, 43% had entered the menopausal transition and 57% remained premenopausal. High CES-D scores were more than 4 times more likely to occur when a woman was in menopausal transition compared with her premenopausal status in unadjusted analysis (OR, 4.29; 95% CI, 2.39-7.72; $P<.001$). Similarly, a diagnosis of depressive disorder was more than twice as likely to occur when a woman was in menopausal transition compared with her premenopausal status (OR, 2.50; 95% CI, 1.25-5.02; $P=.01$).

HORMONE LEVELS AND DEPRESSED MOOD

The change in the women's own levels of FSH, LH, and inhibin B (comparing levels at the assessment when high CES-D scores occurred with the mean levels before the occurrence of high CES-D scores) and the variability around her mean levels of estradiol, FSH, and LH (comparing the variability at the assessment when high CES-D scores occurred with the variability before this outcome) were significantly associated with the high CES-D scores in unadjusted analysis. The unadjusted associations of these hormone measures with the outcome of diagnosed depressive disorder were also significant (**Table 4** and **Table 5**).

Table 2. Study Variables at Baseline for the High CES-D Scale Score and No Depression Groups*

Variable	CES-D Scale Score ≥16 Group†‡ (n = 116)	No Depression Group (n = 108)	*P* Value
CES-D scale score, mean (SE)	8.88 (0.41)	6.41 (0.42)	<.001
Age, mean (SE), y	41.79 (0.32)	42.20 (0.33)	.37
BMI, mean (SE)	29.11 (0.74)	29.42 (0.75)	.77
Physical health, mean (SE)§	50.90 (0.64)	51.49 (0.66)	.52
Estradiol level, pg/mL‖	33.97 (30.10-38.33)	34.50 (30.38-39.19)	.86
FSH level, ng/mL‖	7.00 (6.51-7.53)	7.27 (6.74-7.84)	.49
Inhibin B level, ng/mL‖	57.82 (51.13-65.37)	62.27 (54.86-70.69)	.41
LH level, mIU/mL‖	2.79 (2.54-3.07)	2.73 (2.47-3.01)	.75
Poor sleep	15 (13)	11 (10)	.52
Severe PMS	18 (16)	11 (10)	.24
Current smoker	44 (38)	27 (25)	.03
Hot flashes, yes	34 (29)	19 (19)	.07
Race			
African American	49 (42)	46 (43)	.96
White	67 (58)	62 (57)	
Marital status			
Married or living with partner	74 (64)	71 (66)	.76
Other	42 (36)	37 (34)	
Employed	102 (88)	101 (94)	.15

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D, Center for Epidemiological Studies of Depression; CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PMS, premenstrual syndrome.
SI conversion factor: To convert estradiol to picomoles per liter, multiply by 3.67.
*Data are given as number (percentage) of participants unless otherwise indicated.
†Defined as new cases with CES-D scale scores of 16 or higher.
‡Identified during 8 years of follow-up.
§The 12-Item Short-Form was used to evaluate this participants' condition.
‖Hormone values were measured in menstrual cycle days 1 to 6 and are shown as geometric means with 95% confidence intervals.

Table 3. Study Variables at Baseline for Diagnosed Depressive Disorders and No Depression Groups*

Variable	*DSM-IV* Depressive Disorder Group† (N = 59)	No Depression Group (n = 108)	*P* Value
CES-D scale score ≥16, mean (SE)	9.41 (0.57)	6.41 (0.42)	<.001
Age, mean (SE), y	41.16 (0.44)	42.20 (0.33)	.06
BMI, mean (SE)	30.48 (1.07)	29.42 (0.78)	.43
Physical health, mean (SE)‡	50.63 (0.94)	51.49 (0.70)	.46
Estradiol level, pg/mL§	36.47 (30.82-43.14)	34.50 (30.43-39.12)	.61
FSH level, ng/mL§	6.88 (6.22-7.61)	7.27 (6.75-7.83)	.39
Inhibin B, ng/ml§	58.18 (48.94-69.17)	62.27 (54.91-70.62)	.53
LH level, mIU/mL§	2.70 (2.36-3.08)	2.73 (2.47-3.01)	.89
Poor sleep	5 (8)	11 (10)	.72
Severe PMS	13 (22)	11 (10)	.04
Current smoker	22 (37)	27 (25)	.10
Hot flashes, yes	17 (29)	19 (19)	.14
Race			.55
African American	28 (47)	46 (43)	
White	31 (53)	62 (57)	
Marital status			.96
Married or living with partner	39 (66)	71 (66)	
Other	20 (34)	37 (34)	
Employed	54 (92)	101 (94)	.63

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D, Center for Epidemiological Studies of Depression; CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PMS, premenstrual syndrome.
SI conversion factor: To convert estradiol to picomoles per liter, multiply by 3.67.
*Data are given as number (percentage) of participants unless otherwise indicated.
†Identified during 8 years of follow-up.
‡The 12-Item Short-Form was used to evaluate this participants' condition.
§Hormone values were measured in menstrual cycle days 1 to 6 and are shown as geometric means with 95% confidence intervals.

OTHER RISK FACTORS

The unadjusted associations of smoking, hot flashes, BMI, and PMS with high CES-D scores were statistically significant and remained significant in the multivariable model (Table 4). Other unadjusted associations with CES-D scores were as follows: change from employed to unemployed status: OR, 5.33; 95% CI, 160-1.70; *P*=.006; change from married or living with partner to living with no partner: OR, 3.09; 95% CI, 1.22-7.70; *P*=.02; decrease in physical health: OR, 0.97; 95% CI, 0.94-1.00; *P*=.07; and increase in poor sleep: OR, 1.89; 95% CI, 0.89-3.97; *P*=.10. These risk factors were not significant in the adjusted models.

Table 5 gives unadjusted associations of the same risk factors with diagnosed depressive disorders. The unadjusted associations with diagnosed depressive disorders of the remaining risk factors were as follows: change from employed to unemployed status: OR, 19.71; 95% CI, 2.15-180; *P*=.008; change from married or living with partner to living with no partner: OR, 3.05; 95% CI, 1.05-8.86; *P*=.04; decrease in physical health: OR, 0.97; 95% CI, 0.93-1.00; *P*=.048; and increase in poor sleep: OR, 3.68; 95% CI, 1.22-11.15; *P*=.02. These risk factors were not significant in the adjusted models.

Table 4. Odds Ratios (ORs) of Study Variables for Onset of Depressive Symptoms (CES-D Scale Score ≥16) From the Final Multivariable Model for 116 Participants

Variable	OR*		95% CI	*P* Value
	Unadjusted	Adjusted		
Menopausal stage				
Premenopausal	Reference	Reference		
Transition	4.29	5.44	(2.56-11.59)	<.001
Estradiol				
Mean	1.10	1.06	(0.63-1.78)	.83
SD†	1.30	1.36	(1.02-1.80)	.03
BMI	1.15	1.27	(1.07-1.50)	.007
Hot flashes, yes	1.92	2.16	(1.07-4.33)	.03
PMS, yes	0.05	0.34	(0.12-0.92)	.03
Smoking, yes	0.24	0.23	(0.06-0.90)	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D, Center for Epidemiological Studies of Depression; CI, confidence intervals; PMS, premenstrual syndrome.
*In this within-subject analysis, an OR greater than 1 indicates that a woman is more likely to report the presence of the risk factor at the time of reporting a high CES-D scale score; an OR less than 1, a women is less likely to report the risk factor at the time of a high CES-D scale score.
†Refers to odds per 1 unit change in standard deviation (SD) of the hormone. The SD is the deviation of the hormone measures around the subject's mean, calculated for each subject at each assessment period.

ADJUSTED ASSOCIATIONS

After adjusting for all other risk factors in the model, on average a woman was more than 5 times more likely to be in menopausal transition at the time of reporting high CES-D scores than she was before the onset of depressive symptoms (OR, 5.44; 95% CI, 2.56-11.59; *P*<.001; Table 4). The woman's variability of estradiol around her own mean levels was significantly greater at the time of reporting the high CES-D score than before the onset of depressive symptoms (OR, 1.36; 95% CI, 1.02-1.80;

Table 5. Odd Ratios (ORs) of Study Variables for Onset of Diagnosed Depressive Disorders From the Final Multivariable Model for 59 Participants

Variable	OR*		95% CI	*P* Value
	Unadjusted	Adjusted		
Menopausal stage				
Premenopausal	Reference	Reference		
Transition	2.50	1.60	(0.62-4.15)	.34
Estradiol				
Mean	0.79	0.93	(0.36-2.40)	.88
SD†	2.22	2.45	(1.54-3.89)	<.001
BMI	1.37	1.81	(1.30-2.52)	<.001
Hot flashes, yes	2.02	1.34	(0.42-4.25)	.63
PMS, yes	0.60	0.47	(0.09-2.51)	.38
Smoking, yes	1.66	2.30	(0.26-20.6)	.46

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence intervals; PMS, premenstrual syndrome.

*In this within-subject analysis, an OR greater than 1 indicates that a woman is more likely to report the presence of the risk factor at the time of reporting a high Center for Epidemiological Studies of Depression (CES-D) scale score; an OR less than 1, a women is less likely to report the risk factor at the time of high CES-D scale score.

†Refers to odds per 1 unit change in standard deviation (SD) of the hormone. The SD is the deviation of the hormone measures around the subject's mean, calculated for each subject at each assessment period.

Table 6. Odds Ratios (ORs) of Hormones From the Final Multivariable Model for Onset of Depressive Symptoms (CES-D Scale Score ≥ 16) for 116 Participants

Hormone*	OR		95% CI	*P* Value
	Unadjusted	Adjusted		
Estradiol				
Mean	1.10	1.06	(0.63-1.78)	.83
SD†‡	1.30	1.36	(1.02-1.80)	.03
FSH				
Mean	4.38	4.58	(2.03-10.35)	<.001
SD†‡	1.90	2.09	(1.70-3.41)	<.001
Inhibin B				
Mean	0.34	0.37	(0.20-0.66)	<.001
SD†‡	1.32	1.20	(0.89-1.60)	.21
LH				
Mean	2.98	3.00	(1.52-5.93)	.002
SD†‡	1.57	1.57	(1.18-2.22)	.005

Abbreviations: CES-D, Center for Epidemiological Studies of Depression; CI, confidence intervals; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

*Each hormone was examined separately in the final model because of high colinearity of the hormones.

†Standard deviation (SD) is the deviation of the hormone measures around the subjects' mean, calculated for each subject at each assessment period.

‡Refers to odds per 1 unit change in SD.

P=.03). Compared with the woman's own measures before her high CES-D scores, on average the women were 1.27 times more likely to have an increase in BMI (*P*=.007), 2.16 times more likely to report hot flashes (*P*=.03), 66% less likely to report severe PMS (*P*=.03), and 77% less likely to report smoking (*P*=.04) at the time of the high CES-D scores.

Table 7. Odds Ratios (ORs) of Hormones From the Final Multivariable Model for Diagnosed Depressive Disorders for 59 Participants*

Hormone	OR		95% CI	*P* Value
	Unadjusted	Adjusted		
Estradiol				
Mean	0.79	0.93	(0.36-2.40)	.88
SD†‡	2.22	2.45	(1.54-3.89)	<.001
FSH				
Mean	10.22	9.33	(2.55-3.41)	<.001
SD†‡	1.89	1.81	(1.33-3.09)	.006
Inhibin B				
Mean	0.34	0.49	(0.20-1.17)	.11
SD†‡	1.32	1.11	(0.73-1.67)	.64
LH				
Mean	2.98	4.47	(1.75-11.42)	.002
SD†‡	1.57	1.19	(0.85-1.70)	.33

Abbreviations: CI, confidence intervals; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

*Each hormone was examined separately in the final model due to high colinearity of the hormones.

†Standard deviation (SD) is the deviation of the hormone measures around the subjects' mean, calculated for each subject at each assessment period.

‡Refers to odds per 1 unit change in SD.

Estimates of the same set of variables showed that the strongest risk factor for the new onset of diagnosed depressive disorders was the increased variability of estradiol (around the woman's own mean levels) at the time of the diagnosed disorder (OR, 2.45; 95% CI, 1.54-3.89; *P*=<.001; Table 5). Compared with the woman's own measures before the diagnosis of depressive disorder, on average the woman was 1.81 times more likely to have an increase in BMI (OR, 1.81; 95% CI, 1.30-2.52; *P*<.001). The risk factors of hot flashes, PMS, and smoking were not significant in the adjusted model and were also not significant in the unadjusted analysis of this outcome. This may be a result of the smaller sample size of women with a diagnosis of depressive disorder and possible type II error.

ADJUSTED HORMONE ASSOCIATIONS

Each of the hormone measures was estimated separately in the adjusted models because of multicollinearity. At the time of high CES-D scores, a woman was more likely to have an increased variability around her own levels of estradiol (*P*=.03), FSH (*P*<.001), and LH (*P*=.005) than she did before the high CES-D scores (**Table 6**). On average, the women were 4.58 times more likely to have higher FSH levels (*P*<.001), 3 times more likely to have higher LH levels (*P*=.002), and 63% more likely to have lower inhibin B levels (*P*<.001) at the time of high CES-D scores compared with the time before the high CES-D scores.

Table 7 shows the associations of the hormone measures with diagnosed depressive disorders. At the time of diagnosis, a woman was more likely to have an increased variability around her own levels of estradiol (*P*<.001) and FSH (*P*=.006) than before the diagnosis.

On average, the women were 9.33 times more likely to have higher FSH levels ($P<.001$) and 4.47 times more likely to have higher LH levels ($P=.002$) than before the diagnosis of depressive disorder.

COMMENT

These findings provide evidence that new onset of depressive symptoms and new onset of a diagnosed depressive disorder were significantly more likely to occur when a woman was in menopausal transition than when she was premenopausal. Within-woman increases in the levels of FSH and LH, decreased levels of inhibin B, and greater variability of estradiol and FSH levels were identified when these outcomes occurred compared with the preceding periods when these outcomes did not occur. The findings support the possibility that destabilizing effects of the cyclic fluctuations of estradiol, which can increase with ovarian aging, particularly in the transition to menopause, are an important factor both for depressive symptoms and for diagnosis of depressive disorders.[14-16]

These results add support to the findings of Schmidt et al,[12] who reported a similar frequency of new onset of major or minor depression in the menopausal transition (21% vs 26% in the present study in which the women were followed up 3 years longer) and to the growing epidemiologic evidence that depressive symptoms and other psychologic distress increase in the early transition to menopause.[4,9-11,13,29,34] The results also support treatment studies such as the effectiveness of hormone therapy in perimenopausal women with diagnosed major or minor depression[35-38] and the effectiveness of estrogen augmentation of antidepressants in perimenopausal depression[39] that suggest hormonal involvement in the menopausal transition.

The results indicate that other health and demographic factors, including hot flashes, BMI, smoking status, PMS, employment, and marital status, are significant risk factors for high CES-D scores, confirming and substantiating the multifactorial nature of depressive symptoms. Although only BMI among the health and demographic factors was significantly associated with diagnosed depressive disorders, we believe that the smaller sample size in the group having diagnosed depression is the most likely reason for results that differed from the CES-D model.

Although other reports have not found that menopausal status is associated with high CES-D scores,[5-8] it is important to note differences in these studies. We examined only new-onset depression in women with no history of depression and conducted a within-woman analysis of risk factors that did not address the between-group comparisons that have been previously reported. Although we found that increased within-woman variability in estradiol and other hormone levels was related to the measures of depressed mood, we did not find that mean estradiol levels were significantly associated with these measures, consistent with previous findings.[2]

Other results of this study indicated that PMS was a significant predictor of high CES-D scores, although a woman was less likely to report severe PMS at the time of high CES-D scores than during the preceding years. These results indicated that PMS decreased as ovarian production declined in the years leading to menopause but was a strong within-woman predictor of depressive symptoms that subsequently occurred in the menopausal transition. The findings are consistent with our previous study of the full cohort, in which PMS declined in menopausal transition but was a strong predictor of subsequent menopausal symptoms.[18]

The women in the high CES-D group were significantly more likely to smoke at baseline, as previous studies have found,[29] although the present results showed that smokers at the time of high CES-D scores were not smoking at the baseline assessment. We examined these data and found that these women were chronic smokers who reported smoking at some assessments but not others. We observed the same pattern of sporadic reports of smoking in the group having diagnosed depression, although only 5 women in this group reported a change in smoking, and the association with diagnosed depressive disorder was not significant. The number of smokers in the group having diagnosed depression was too small for reliable analysis and is the most likely reason that results differ from those of the CES-D model. Hot flashes were another risk factor that was not significantly associated with diagnosed depressive disorders, although hot flashes were a strong risk factor for high CES-D scores, consistent with other reports.[2,3,40]

Finally, the observation that new onset of depressive symptoms and diagnosed depression were predominant in the earlier years of the study raises the question of whether these women entered the menopausal transition at an earlier age. Harlow et al[11] found that a history of major depression may be associated with an earlier decline in ovarian function. This study did not find that the women with depressed mood entered the transition sooner or transitioned more rapidly, but we emphasize that the study was designed to examine all women starting at a similar premenopausal baseline. Women who already had irregular cycles (an indication of transition to menopause) were excluded from enrollment in the cohort, as were those who were being treated for depression. Consequently, age was also not a significant predictor, in part because the cohort was balanced for age, observation time was constant, and the women were equally likely to have onset of depressed mood at any time. We identified the age of each woman when she was first classified in the menopausal transition and found no significant difference in age at first transition to menopause (mean±SD high CES-D scores group, 44.3±4.0 years; diagnosed depression group, 43.8±4.0 years); and no depression group, 44.3±4.0 years).

Major strengths of this study are the longitudinal assessment of depressed mood in women with no history of depression, the unique focus on within-woman risk factors for depressed mood in the menopausal transition, and longitudinal hormone measures that were initiated at a clearly defined premenopausal baseline. However, the study does not address other important questions, such as differences between groups of subjects. Although it would be informative, multiple hormone levels could not be examined simultaneously in these models because the multicollinearity of their measures made the results uninterpretable. Other considerations due to the study design are the fixed intervals of the follow-up assessments, which may lack precision, and the within-

woman differences in the cycle day of the hormone measures, which could increase the variability of the hormones. However, these data overall showed that the hormone measures were nondifferential with respect to cycle day, and we believe the results are conservative and biased toward the null hypothesis. It is possible that a history of depression was not identified in the medical history interview and that some women had an undetected history of depression, although the analysis compares the women with their own baseline and undetected depression would bias the results toward the null hypothesis. The study results may not be generalized to women not represented in this cohort.

In summary, our data indicate that transition to menopause and its changing hormonal milieu are strongly associated with both new onset of high depressive symptoms and new onset of diagnosed depressive disorders in women with no history of depression. Further follow-up study is needed to determine the extent to which these reports of depressed mood are limited to the perimenopausal period and to determine whether the identified risk factors are associated with more persistent depression.

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