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Depressive symptoms and their relationship with endogenous reproductive hormones and sporadic anovulation in premenopausal women

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Abstract

Purpose—To determine whether depressive symptoms are associated with ovulation or reproductive hormone concentrations in eumenorrheic women without a reported diagnosis of clinical depression.

Methods—A prospective cohort of 248 regularly-menstruating women, aged 18–44 years (27.3± 8.2) were evaluated for depressive symptoms at baseline using the 20-item Center for Epidemiological Studies Depression (CES-D) scale and categorized dichotomously (< 16, no depressive symptoms [92%] vs. ≥16, depressive symptoms [8%]). Serum concentrations of estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone were measured up to 8 times/cycle for up to two menstrual cycles. Linear mixed models estimated associations between depressive symptoms and hormone concentrations while generalized linear mixed models assessed their relationship with sporadic anovulation.

Results—No significant associations were identified between depressive symptoms and reproductive hormone levels (all $P > 0.05$) or the odds of sporadic anovulation (adjusted OR: 1.1, 95% confidence interval [0.02, 5.0]), after adjusting for age, race, body mass index, perceived stress level, and alcohol consumption.

Conclusions—Despite reported associations between mental health and menstrual cycle dysfunction, depressive symptoms were not associated with reproductive hormone concentrations or sporadic anovulation in this cohort of regularly-menstruating women with no recent (within one year) self-reported history of clinical depression.

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Keywords

depression; depressive symptoms; menstrual cycle; ovulation; reproductive hormones; mental health; women's health

INTRODUCTION

Depression is an often overlooked but pervasive disorder having a lifetime prevalence of 16% among the U.S. population (1) with women twice as likely to be affected as men (2). In women, depression has been studied in relation to polycystic ovarian syndrome (3), *in vitro* fertilization treatment success (4;5), and premenstrual dysphoric disorder (6). In addition, women with mental disorders, including clinical depression, are more likely to report menstrual cycle disturbances (7–11). Furthermore, hormonal changes across the menstrual cycle are reported to modify symptoms of other mental disorders such as anxiety, bipolar, and psychotic and eating disorders (12).

Although several studies relate depression to certain reproductive disorders, it remains to be determined how depressive symptoms may be associated with reproductive hormone concentrations and ovulatory function, relationships which may underlie these previously reported observations, in regularly-menstruating, healthy women without clinical depression. Therefore, our objective was to evaluate the association between depressive symptoms and reproductive hormone concentrations and sporadic anovulation, as well as characterize menstrual cycle-related mood symptoms across the cycle, in a cohort of healthy, premenopausal women without a diagnosis or treatment of clinical depression within the past year.

MATERIALS AND METHODS

Study description

The BioCycle Study (2005–2007) was a prospective cohort study of 259 healthy, regularly menstruating women aged 18 to 44 years followed for one (n=9) or two (n=250) menstrual cycles. Study population, materials and methods details have been described (13). Exclusion criteria included psychiatric conditions requiring medical therapy in the last year, including premenstrual dysphoric disorder; alcohol abuse and/or any other substance abuse within the past 30 days; current use of oral contraceptives, vitamin and mineral supplements, or certain prescription medications including medications for treatment of depression; pregnancy or breastfeeding within the past 6 months; currently trying to conceive; and diagnosis of chronic conditions, including menstrual or ovulatory disorders. Additionally, women with a self-reported body mass index (BMI) of <18 or >35 kg/m^2 were excluded.

Hormone measurement and sporadic anovulation

Fasting blood samples were collected five to eight times per cycle during the following expected menstrual cycle phases: menses, early follicular, late follicular, luteinizing hormone (LH) surge, ovulation, and early, mid, and late luteal phases. Midcycle visit timing was facilitated by the use of home fertility monitors (Clearblue Easy Fertility Monitor ®;

Inverness Medical, Waltham, Massachusetts) (14). Nearly all women (94%) completed at least seven clinic visits per cycle.

Biospecimen collection and handling protocols were designed to minimize variability (13). Samples were collected in the morning after an overnight fast, then processed and serum frozen at −80°C within 90 minutes of phlebotomy. Analytes were measured serially in participant-specific batches within a single run to limit analytical variability. Estradiol, LH, follicle stimulating hormone (FSH), and progesterone were measured using solid-phase competitive chemiluminescent enzymatic immunoassays (DPC Immulite 2000 analyzer, Siemens Medical Solutions Diagnostics, Deerfield, IL) at the Kaleida Health Center for Laboratory Medicine (Buffalo, NY). Total serum testosterone was measured by liquid chromatography/tandem mass spectrometry (Shimadzu Prominence Liquid Chromatogram with an ABSceix 5500 tandem mass spectrometer) by the Advanced Research and Diagnostic Laboratory (Minneapolis, MN). Across the study period the coefficients of variation (CV) were ≤10% for estradiol, ≤5% for LH and FSH, ≤14% for progesterone, and ≤7% for testosterone.

Anovulatory cycles were defined as cycles with peak serum progesterone concentrations ≤5 ng/mL with no observed serum LH peak during the mid or late luteal phase visit (15).

Depressive symptoms and covariate assessment

Depressive symptoms were assessed using the 20-item Center for Epidemiological Studies Depression (CES-D) scale administered at baseline (corresponding to first menses visit) (16). Participants were asked to measure their frequency of 20 depressive feelings and behaviors in the past week, with responses ranging from “Rarely or none of the time” (0 points) to “Most or all of the time” (3 points). Each participant was then given an overall score (range 0 to 60 points), with a score of 16 or greater considered indicative of depressive symptoms (17).

Participant socio-demographic characteristics including race, age, history of sexual activity, smoking status and history of contraceptive use were assessed via a baseline questionnaire. In addition, perceived stress level was assessed using the 14-item Cohen Perceived Stress Scale (PSS) (18), with stress levels subsequently categorized into tertiles (low [≤17], moderate [18 to 23], or high [≥24]), and physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) long form with high, moderate, and low physical activity categories determined using standard IPAQ cutoffs (19). Daily sexual activity (yes/no) and alcohol intake (drinks per day) were prospectively captured via daily diaries and averaged across each menstrual cycle. Average alcohol intake was categorized as low (< 0.5 drinks/day), moderate (0.5 to 1 drink/day), and high (≥ 1 drinks/day).

Additionally, at four clinic visits per cycle, participants completed a questionnaire designed to assess the presence and severity of a menstrual symptoms, including a total of 20 items, during the previous week (20;21) and a 4-item perceived stress level (PSS-4). Therefore, to provide an additional measure of mood-related symptoms that were assessed across the cycle, a ‘mood-related menstrual cycle symptoms score’ was calculated based on responses to five mood-related items from the menstrual symptoms questionnaire (depression or

sadness; tension or irritability; anxiety or nervousness; anger, aggression, or short temper; and crying spells) and responses to items from the PSS-4 (control of important things in life, confidence to handle personal problems, felt things were going your way, felt unable to overcome difficulties). A mood-related menstrual cycle symptoms score, for which a higher score meant a stronger occurrence of negative symptoms, was calculated for each clinic visit, and an average of those visit scores was used to describe mood-related symptoms for each woman in each cycle.

Statistical Analysis

Baseline characteristics were compared between women with depressive symptoms (CES-D score ≥16) versus without depressive symptoms (CES-D score <16). All hormones were log-transformed for normality, and Fisher's exact and Chi-Square tests were used to assess differences in categorical variables, and analysis of variance was used for continuous variables.

Linear mixed models were used to estimate the association between depressive versus no depressive symptoms and reproductive hormone concentrations across the menstrual cycle, and also to determine differences in mood-related menstrual cycle symptoms score across cycle phases overall and between women with versus without depressive symptoms, while accounting for repeated measurements within each woman. Random intercepts were applied to account for differences in baseline hormone levels between women. Generalized linear mixed models were used to estimate the association of depressive symptoms with the odds of sporadic anovulation while accounting for multiple cycles per woman. Depressive symptoms were analyzed both as a dichotomous measure (described above) and as a continuous CES-D score. All models were adjusted for factors associated with depressive symptoms and reproductive function, including age (continuous), race (white, black, other), BMI (continuous), perceived stress level (continuous), and alcohol intake (continuous).

RESULTS

The CES-D was completed by 248 women at baseline, contributing a total of 488 cycles. Participants were 27.3 ± 8.2 [mean ± SD] years of age (Range: 18, 44 years) with a BMI of 24.1 ± 3.9 (16, 34 kg/m^2) (Table 1). Almost all (96%) were nonsmokers. Approximately 8% (n=19) of women exhibited depressive symptoms, and were more likely to report high perceived stress levels (79% versus 31%, $P<0.001$) and more likely to be black (47% versus 17%, $P<0.001$) compared to women without depressive symptoms. There were no other significant differences in demographic/lifestyle characteristics between groups, although women with depressive symptoms were marginally more likely to report high physical activity level (79% versus 53%, $P=0.09$).

The mood-related menstrual cycle symptoms score exhibited a range of 9 to 39 overall, with a Cronbach's alpha of 0.84 indicating good internal consistency. Scores were highest during the menstrual phase (mean ± SEM, 17.4 ± 0.2) compared to each of the other three phases ($P<0.001$, all comparisons), followed by the mid-follicular phase (16.3 ± 0.2, $P<0.01$ compared to ovulatory and luteal phases), and were lowest in the ovulatory (15.6 ± 0.2) and luteal phases (15.6 ± 0.2). Women with depressive symptoms at baseline reported 30%

higher mood-related menstrual cycle symptoms scores overall (20.7 ± 0.4 vs. 15.9 ± 0.1; $P<0.001$), a difference which was not dependent on cycle phase.

Estradiol concentrations were marginally elevated among women with versus without depressive symptoms before adjustment for covariates (% difference = 26.6, 95% confidence interval [CI]: 8.1, 48.3) but not after adjustment (% difference = 11.7, 95% CI: −6.0, 32.7) (Table 2). There were no significant differences in LH, FSH, testosterone or progesterone concentrations among women with versus without depressive symptoms before and after adjustment for covariates. Similarly, there were no associations between continuous depression score and reproductive hormones, except for estradiol before adjustment for covariates (% change per unit increase in depression score = 0.8, 95% CI: 0.2, 1.4). Though potential effects of cycle phase were explored, findings for the relationships between depressive symptoms and hormone concentrations did not vary by cycle phase.

Anovulation was identified in 8.6% of cycles, but the percentage of anovulatory cycles was similar between women with (4/38 cycles, 10.5%) versus without (38/450 cycles, 8.4%) depressive symptoms (Table 3). Likewise, there was no significant difference in the odds of sporadic anovulation in those with versus without depressive symptoms before or after adjustment for baseline confounders (adjusted OR: 1.1; 95% CI: 0.2, 5.0) (Table 3). Depressive symptoms assessed as a continuous score also resulted in null findings.

DISCUSSION

Depressive symptoms were not associated with changes in reproductive hormones or odds of sporadic anovulation in this population of healthy, premenopausal women without a recent history of clinical depression. Moreover, we observed that women with depressive symptoms reported higher levels of mood-related menstrual symptoms across all phases of the menstrual cycle, and that overall the greatest mood-related menstrual symptoms were reported during the week prior to menses.

Researchers have pointed to three critical time periods when depression affects women most: premenstrual, post-partum, and menopause (22). It is thought that changes in estrogen levels during these critical periods could contribute to depression. However, other changes associated with lifestyle (job, family, etc.) during post-partum and menopause periods could also contribute to depression (2). Although the mechanism of estrogen's relationship to depressive symptoms is debated and hormone therapy is no longer standard treatment for menopause symptoms, some studies report reduced depressive symptoms with hormone therapy in post-menopausal women (23). In addition to estrogen, studies report conflicting evidence of the potential relationship between androgens and mood, for example, illustrating a negative relationship between mood and free testosterone in the context of women with polycystic ovary syndrome compared to controls (24), but a positive association between mood and hormone replacement therapy including androgen in women following surgical removal of the ovaries (25). Such studies provide a biological framework for our hypothesis that total and free testosterone may relate to depressive symptomatology in premenopausal women, while most previous research is estrogen-centric, but the former example is

complicated by a complex and chronic disease process and the latter by supraphysiologic androgen levels induced in women acutely void of gonadal steroid production, thereby limiting their applicability to interpreting the present results. Findings here provide little additional evidence that estrogen or testosterone may relate to depressive symptoms in healthy premenopausal women, as we found a small significant positive association between estrogen and depressive symptoms which was eliminated upon confounder adjustment. Also, the directionality of the association we observed is unclear, as it is unknown whether steroid hormone levels are secondary to depressive symptoms, or vice versa.

We also observed that mood-related menstrual symptoms were highest during the week preceding menses overall. Further, women with depressive symptoms showed higher levels of these symptoms throughout the menstrual cycle compared to women without depressive symptoms, in agreement with others' observations that women with psychiatric disorders report higher prevalence of menstrual disturbances (7–11). These data support that screening for clinical depression in patients who report severe mood-related menstrual cycle symptoms may be advisable.

As a prospective cohort study that included multiple measurements of reproductive hormones throughout the cycle, we were able to thoroughly assess and compare reproductive function among women with and without self-reported depressive symptoms. Unlike other studies, our population included women who were not clinically diagnosed with depression nor had taken or were currently on any medications prescribed for treating depression which may influence hormone concentrations. Also, we used the CES-D to assess depressive symptoms, which is a validated and commonly used questionnaire. However, participants completed the CES-D only at baseline, preventing the prospective measurement of depressive symptoms and, therefore, the estimation of acute relationships between depressive symptoms and hormone concentrations across the cycle. Furthermore, our study may be underpowered to detect associations between depressive symptoms and the reproductive outcomes evaluated here given, first, that none of the women were clinically diagnosed with depression, and thus exhibited relatively low depressive symptomatology (8% meeting criteria for depressive symptoms), and second, that the occurrence of anovulation was also low (8.6% of all cycles) further limiting our analysis focused on sporadic anovulation. In addition, as our study was conducted among healthy women with no recent diagnosis of depression, history of menstrual cycle disorders, other chronic diseases, or use of most chronic medications, the generalizability of our results is limited.

Overall, among healthy women with normal menstrual cycles and without a recent history of clinical depression, we observed no significant relationship between depressive symptoms, reproductive hormones, or sporadic anovulation. This evidence indicates that previously observed links between mental health and menstrual cycle dysfunction in women are not evident across the subclinical spectrum.

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List of Abbreviations

BMI	body mass index
CES-D	Center for Epidemiological Studies Depression Scale
E2	estradiol
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
LH	luteinizing hormone
OR	odds ratio
PSS	Perceived Stress Scale
SD	standard deviation

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Table 1

Selected baseline characteristics of study participants according to presence of depressive symptoms (CES-D scale) at baseline.

	Total Cohort	No Depressive Symptoms	Depressive Symptoms[a]	*P*-value[b]
Number of women (%)	248	229 (92)	19 (8)	----
Demographics				
Mean ± SD				
Age, yrs	27.3 ± 8.2	27.3 ± 8.2	26.9 ± 8.5	0.85
BMI, kg/m^2	24.1 ± 3.9	24.1 ± 3.9	24.2 ± 3.6	0.80
n (%):				
Race:				
White	150 (60)	146 (64)	4 (21)	
Black	48 (19)	39 (17)	9 (47)	<0.001
Other	50 (20)	44 (19)	6 (32)	
Education				
≤ High school	29 (12)	26 (11)	3 (16)	0.47
Marital Status				
Married	65 (26)	61 (27)	4 (21)	1.00
Parity				
Nulliparous	180 (74)	165 (72)	15 (79)	0.63
Smoking				
Current smoker	9 (4)	9 (4)	0 (0)	1.00
Physical Activity:				
Low	23 (9)	22 (10)	1 (5)	
Moderate	89 (36)	86 (38)	3 (16)	0.09
High	136 (55)	121 (53)	15 (79)	
Currently sexually active	132 (53)	120 (52)	12 (63)	0.37
Ever sexually active	192 (78)	177 (77)	15 (79)	0.87
Alcohol consumption[c]				
Low	214 (86)	198 (86)	15 (79)	
Moderate	20 (8)	17 (7)	3 (16)	0.25
High	14 (6)	14 (6)	0 (0)	
Stress (PSS scale)[d*]				
Low	74 (30)	73 (32)	1 (5)	
Moderate	88 (35)	85 (37)	3 (16)	<0.001
High	86 (35)	71 (31)	15 (79)	

SD, standard deviation; BMI, Body mass index; PSS, perceived stress scale

[a] Depressive symptoms categorized using the CES-D scale with scores ranging from 0–60. No depressive symptoms (CES-D score <16) and depressive symptoms (CES-D score ≥16).

[b] *P*-values calculated using Fisher's exact test, Chi-square test or ANOVA where appropriate

[c] Alcohol levels: low (≤ 0.5 drinks/day), moderate (0.5 to 1 drinks/day), high (≥ 1 drinks/day)

[d] Perceived Stress Scale categorized into tertiles: low (≤17), moderate (18 to 23), or high (≥24)

[*] Missing values (N): nulliparous (6), stress (1)

Table 2

Estimated association of reproductive hormone concentrations in women with depressive symptoms compared to no depressive symptoms

		Categorical		Continuous
Log Hormones		**No Depressive Symptoms[a]**	**Depressive Symptoms[a] % difference (95% CI)**	**Depression Score % difference (95% CI)**
E2 (pg/mL)	Unadjusted	Reference	26.6 (8.1, 48.3)	0.8 (0.2, 1.4)
	Adjusted[b]	Reference	11.7 (−6.0, 32.7)	0.5 (−0.2, 1.2)
Free E2	Unadjusted	Reference	24.9 (6.8, 46.0)	0.8 (0.2, 1.4)
	Adjusted[b]	Reference	14.1 (−4.3, 36.0)	0.4 (−0.3, 1.2)
Testosterone (ng/dL)	Unadjusted	Reference	12.4 (−4.5, 32.3)	0.3 (−0.3, 0.9)
	Adjusted[b]	Reference	12.7 (−3.7, 31.9)	0.1 (−0.6, 0.8)
Free Testosterone (ng/dL)	Unadjusted	Reference	10.2 (−6.1, 29.3)	0.4 (−0.3, 1.0)
	Adjusted[b]	Reference	13.9 (−1.7, 31.8)	0.2 (−0.5, 0.8)
Progesterone (ng/mL)	Unadjusted	Reference	12.1 (−20.8, 58.8)	0.2 (−1.1, 1.6)
	Adjusted[b]	Reference	7.9 (−27.4, 60.4)	0.3 (−1.4, 2.0)
LH (ng/mL)	Unadjusted	Reference	−11.4 (−24.3, 3.7)	−0.4 (−1.0, 0.2)
	Adjusted[b]	Reference	−2.4 (−18.0, 16.2)	0.0 (−0.7, 0.8)
FSH (mIU/mL)	Unadjusted	Reference	−7.6 (−20.0, 6.6)	−0.2 (−0.8, 0.3)
	Adjusted[b]	Reference	−7.6 (−20.3, 7.0)	−0.1 (−0.7, 0.6)

Data are % differences in log hormone concentrations between groups (for categorical analysis) or per 1-unit change in depression score (for continuous analysis).

E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone

[a] Depressive symptoms categorized using the CES-D scale with scores ranging from 0–60. No depressive symptoms (CES-D score <16) and depressive symptoms (CES-D score ≥16).

[b] Adjusted for age, race, body mass index, perceived stress level, and alcohol intake.

Table 3

Menstrual cycles classified as anovulatory (n=38) and estimated associations (OR) of depressive symptoms with sporadic anovulation in healthy, premenopausal women

	Categorical		Continuous
	No Depressive Symptoms	**Depressive Symptoms**	**Depression Score**
Anovulation/total cycles (%)	38/450 (8.4)	4/38 (10.5)	
OR	Reference	1.1 (0.4, 4.3)	1.0 (0.9, 1.0)
aOR[b]	Reference	1.1 (0.2, 5.0)	1.0 (0.9, 1.0)

[a] Depressive symptoms categorized using the CES-D scale with scores ranging from 0–60. No depressive symptoms (CES-D score <16) and depressive symptoms (CES-D score ≥16).

[b] Adjusted for age, race, body mass index, perceived stress level, alcohol intake