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Brief communication

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 to 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 eight times per cycle for up to two menstrual cycles. Linear mixed models estimated associations between depressive symptoms and hormone concentrations, whereas generalized linear mixed models assessed their relationship with sporadic anovulation.
Results: No significant associations were identified between depressive symptoms and reproductive hormone levels (all $P > .05$) or the odds of sporadic anovulation (adjusted odds ratio, 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 1 year) self-reported history of clinical depression.

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Introduction

Depression is an often overlooked but pervasive disorder having a lifetime prevalence of 16% among the US 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.

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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) at screening of less than 18 or greater than 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, MA) [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 were 10% or less for estradiol, 5% or less for LH and FSH, 14% or less for progesterone, and 7% or less for testosterone.

Anovulatory cycles were defined as cycles with peak serum progesterone concentrations of 5 ng/mL or less 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 the time" (3 points). Each participant was then given an overall score (range 0–60 points), with a score of 16 or greater considered indicative of depressive symptoms [17].

Participant sociodemographic 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 [18–23], or high [≥24]), and physical activity was assessed using the International Physical Activity Questionnaire long form with high, moderate, and low physical activity categories determined using standard International Physical Activity Questionnaire cutoffs [19]. Daily sexual activity (yes or 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 (0.5–1 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 menstrual symptoms, including a total of 20 items, during the previous week [20,21] and a four-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 χ^2 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 previously) 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, and 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% of women ($n = 19$) exhibited depressive symptoms and were more likely to report high perceived stress levels (79% vs. 31%, $P < .001$) and more likely to be black (47% vs. 17%, $P < .001$) compared with women without depressive symptoms. There

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