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Original Article

Objective sleep interruption and reproductive hormone dynamics in the menstrual cycle

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ABSTRACT

Objectives: Women report greater sleep disturbance during the premenstrual phase of the menstrual cycle and during menses. However, the putative hormonal basis of perceived menstrual cycle-related sleep disturbance has not been investigated directly. We examined associations of objective measures of sleep fragmentation with reproductive hormone levels in healthy, premenopausal women.
Methods: Twenty-seven women with monthly menses had hormone levels measured at two time points during a single menstrual cycle: the follicular phase and the peri-ovulatory to mid-luteal phase. A single night of home polysomnography (PSG) was recorded on the day of the peri-ovulatory/mid-luteal-phase blood draw. Serum progesterone, estradiol, and estrone levels concurrent with PSG and rate of change in progesterone (PROGslope) from the follicular blood draw to PSG were correlated with log-transformed wake after sleep onset (lnWASO%) and number of wakes/hour of sleep (lnWake-Index) using linear regression.
Results: Sleep was more fragmented in association with a steeper PROGslope (lnWASO% $p = 0.016$; lnWake-Index $p = 0.08$) and higher concurrent estrone level (lnWASO% $p = 0.03$; lnWake-Index $p = 0.01$), but the effect of estrone on WASO was lost after accounting for PROGslope. WASO% and Wake-Index were not associated with concomitant progesterone or estradiol levels.
Conclusions: A steeper rate of rise in progesterone levels from the follicular phase through the mid-luteal phase was associated with significantly greater WASO, establishing a link between reproductive hormone dynamics and sleep fragmentation in the luteal phase of the menstrual cycle.

1. Introduction

Studies in premenopausal women have documented more subjective sleep disruption during the week preceding menses [2], and during menses [2], coinciding with fluctuating levels of progesterone and estrogens. Sleep complaints include longer sleep-onset latency, lower sleep efficiency, and worse sleep quality during the mid-luteal through late luteal phase compared with the mid-follicular phase [1] and lower subjective sleep quality [1,2] during the late luteal phase and menses compared with the mid-follicular, ovulatory, and early/mid-luteal phases. In general, the few polysomnographic studies that have examined sleep at different phases of the menstrual cycle in young, healthy women with no sleep complaints have found that sleep efficiency remains high and relatively stable across the menstrual cycle [3–6], although at least one small study detected higher arousal indices and more wake after sleep onset in a sample of 12 healthy young women studied during the mid-luteal through late luteal phase [7].

While these studies have linked sleep disturbance and changes in sleep architecture to the mid-luteal through late luteal phase, fluctuations in reproductive hormones, including declining levels of estradiol and progesterone prior to menses, were assumed but not measured. Sleep quality has not been examined specifically in relation to reproductive hormone levels or their trajectories. The subjective and objective observations of reduced sleep quality during the mid-luteal through late luteal phase suggest that progesterone plays a critical role, but levels of estrogens also rise and fall in the luteal phase, raising the possibility that both of these reproductive hormones may adversely affect luteal-phase sleep quality. As a result, it is not clear how mid-luteal-phase through late luteal-phase worsening of sleep quality relates to specific hormone levels

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or the rate of change in reproductive hormone levels across the menstrual cycle.

During an ovulatory menstrual cycle, progesterone is monotonic, produced only by the corpus luteum after ovulation and rising during the luteal phase until levels peak mid-luteally, and then decline during the late luteal phase [8]. Progesterone is responsible for the luteal-phase increase in core body temperature of 0.3–0.6 °C [9], a level of elevation in core body temperature that has been shown to fragment sleep [10]. Therefore, the effect of progesterone on body temperature is a putative mechanism by which progesterone could disturb sleep. Progesterone is also a $GABA_A$ receptor agonist [11] that has been shown to increase non-rapid eye movement (NREM) sleep [12,13]. Indeed, observations of increased sleep disturbance in the mid-luteal through late luteal phase have been attributed to changing levels of progesterone [14], although the relationship has not been studied empirically.

In contrast to progesterone, estradiol rises and falls twice during the menstrual cycle: first, during the late follicular phase prior to ovulation and then, again, during the luteal phase [8]. Estrone is a weaker estrogen produced and stored in the adipose tissue [15], rather than the ovary, that mirrors the biphasic dynamics of estradiol, the most potent estrogen. Unlike progesterone, estrogens decrease core body temperature in the absence of progesterone [16], which may protect against sleep disruption. However, data bearing on the effect of estrogens on sleep quality are mixed with estrogen therapy shown to improve sleep quality in postmenopausal women with hot flashes [13,17–21] but also to disrupt sleep by decreasing rapid eye movement (REM) and NREM sleep in ovariectomized rodents [22].

The primary aim of this study was to examine the association of objective measures of sleep fragmentation during the luteal phase in healthy premenopausal women in relation to concurrent levels of progesterone and the rate of change in progesterone from the follicular to mid-luteal phase. We hypothesized that higher progesterone levels as well as a steeper increase in progesterone would be associated with more sleep fragmentation. Our second, exploratory aim was to examine associations of sleep measures with concurrent levels of estrogens (estradiol and estrone), given the inconsistencies in the literature on estrogens' effects on sleep and the gap of knowledge about the impact of physiologic levels of estradiol and estrone on sleep in premenopausal women.

2. Methods

2.1. Participants

Healthy premenopausal women aged 18–45 with monthly menstrual cycles (defined as every 23–35 days for the past 6 months) were recruited from the community to an experimental study where leuprolide was used to induce hot flashes and to study changes in sleep and mood occurring secondary to hot flashes (Clinicaltrials.gov Identifier: NCT00455689 [23]). The current analysis is based on the PSG and serum hormone data obtained at baseline before leuprolide was administered.

Women were excluded if they were pregnant, had a sleep disorder diagnosis confirmed with in-laboratory screening PSG ($n = 1$ excluded for obstructive sleep apnea, $n = 1$ for periodic limb movement disorder), worked a night-shift job, reported experiencing hot flashes, had a current or prior history of psychiatric illness or substance-use disorders confirmed on structured psychiatric assessment, had abnormal screening blood tests (hemoglobin, thyroid-stimulating hormone, prolactin, renal or liver function), or had body mass index (BMI) >35 kg/m^2. A Montgomery–Åsberg Depression Rating Scale (MADRS) score <10 was required to exclude those with depressive symptoms. Women taking or recently using prescription or over-the-counter centrally active medications (antidepressants, anxiolytics, hypnotics, or the anticonvulsant gabapentin) or systemic hormone medications (e.g., birth control pills) were excluded. All participants provided written informed consent and this study was approved by the Partners HealthCare Institutional Review Boards.

2.2. Sleep measures

Prior to mid-luteal administration of leuprolide, participants completed two nights of home PSG scheduled between the peri-ovulatory and mid-luteal phase of the menstrual cycle. Data from the second home PSG were used in the present analyses because hormone levels were obtained concurrent with the second PSG. PSG studies were not obtained during the follicular phase.

PSGs were conducted with the Compumedics Safiro (Charlotte, NC, USA) using standard procedures to define sleep staging, including electroencephalogram (EEG), bilateral electro-oculogram, and bilateral submentalis electromyogram [24]. Respiratory and electrocardiography (ECG) signals were not measured. Concurrent with PSG, participants wore a time-synched actigraph with an event marker to record lights-out and lights-on time.

All records were visually scored in 30-s epochs by the Harvard Polysomnography Core using American Academy of Sleep Medicine (AASM) criteria [24]. The primary measures of sleep fragmentation were: (1) WASO as a percent of sleep period time and (2) the number of awakenings per hour of sleep. Awakenings were defined as alpha EEG activity comprising >15 s of a 30-s epoch. Stage N1 percent, Stage N2 percent, Stage N3 percent, REM percent, and sleep efficiency were also obtained.

2.3. Hormone measurements

Participants were followed closely across one menstrual cycle, from the first day of menstrual bleeding until the mid-luteal phase. Leuprolide was administered approximately 7 days after ovulation, which was determined by an increase in basal body temperature and urinary luteinizing hormone. Blood was drawn first in the follicular phase ("follicular") and then concurrent with the PSG ("concurrent"), which was obtained between the peri-ovulatory and mid-luteal phase before the leuprolide injection based on logistic considerations. As a result, the interval between the blood draw at the PSG and the preceding follicular-phase draw varied.

Blood samples were assayed for serum progesterone (PROG), estradiol (E2), and estrone (E1) at both time points. We calculated the rate of change in progesterone between the two blood draws over the intervening time interval (PROGslope) to determine the rate of increase in progesterone leading up to the PSG. Slope was not calculated for E2 or E1 because estrogens are biphasic between the two time points that were measured.

2.4. Hormone assays

Serum progesterone was measured by automated immunoassay (ARCHITECT®, Abbott Diagnostics, Chicago, IL, USA) [25]. The minimum reportable concentration of this test is 0.1 ng/mL. The inter-assay coefficients of variation (CVs) are 5.2%, 3.8%, and 3.5% for quality-control sera containing 0.7, 6.9, and 16.7 ng/mL, respectively. The reference ranges for women with regular menstrual cycles are follicular phase <0.1–0.3 ng/mL and luteal phase 1.2–15.9 ng/mL.

Estradiol and estrone were measured using liquid chromatography, tandem mass spectrometry (Mayo Clinic, Rochester, NY, USA) [26,27]. The inter-assay CV ranges for estradiol and estrone in the low range studied were 8.6% and 8.7%, respectively [26].