Relationship of Day-to-day Reproductive Hormone Levels to Sleep in Midlife Women

Howard M. Kravitz, DO, MPH; Imke Janssen, PhD; Nanette Santoro, MD; Joyce T. Bromberger, PhD; Miriam Schocken, PhD, MPH; Susan A. Everson-Rose, PhD, MPH; Kelly Karavolos, MA; Lynda H. Powell, PhD

Background: We analyzed data from a single menstrual cycle from 630 women, aged 43 to 53 years, in the Daily Hormone Study component of the Study of Women’s Health Across the Nation to determine whether hormone levels are associated with trouble sleeping as women enter the menopausal transition.

Methods: Women recorded whether they had trouble sleeping the previous night. Morning urine specimens were obtained for daily determinations of levels of luteinizing hormone, follicle-stimulating hormone, estradiol metabolites (ie, estrone conjugates), and the progesterone metabolite (pregnanediol glucuronide). Women were categorized as premenopausal or early perimenopausal by bleeding patterns.

Results: Average adjusted odds of reporting trouble sleeping were 29% higher in perimenopausal than in premenopausal women. The highest percentages of women in both menopausal groups reported trouble sleeping in the beginning or at the end of their cycle. After controlling for covariates, pregnanediol glucuronide level was associated with increased trouble sleeping in perimenopausal women and follicle-stimulating hormone level was associated with increased trouble sleeping in premenopausal women. Mood and vasomotor symptoms were the strongest and most consistent cocontributors to trouble sleeping.

Conclusion: In this community-based sample of middle-aged women, the most trouble sleeping was observed at the beginning and end of the menstrual cycle.

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Methods

SWAN is a multiethnic, community-based cohort study of 3302 women enrolled at the following 7 sites: Boston, Mass; Chicago, Ill; Detroit, Mich; Los Angeles, Calif; Oakland, Calif; Newark, NJ; and Pittsburgh, Pa. The design of the main cohort study has been reported. Women of white, African American, Chinese, Japanese, and Hispanic ethnic origins aged 42 to 52 years were included.

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In the Daily Hormone Study (DHS), a subset of women (n=848), aged 43 to 53 years and representing all SWAN ethnic groups, collected their first morning urine specimen and completed a bedtime diary daily for a single menstrual cycle (from the first day of bleeding until the first day of bleeding of the next cycle or 50 days, whichever came first) annually. Inclusion criteria for the DHS were (1) an intact uterus and at least 1 ovary, (2) at least 1 menstrual period in the previous 3 months, (3) no sex steroid hormone use in the previous 3 months, and (4) not pregnant. Details on specimen collection and the principal findings from the baseline DHS collection in early-transitioning women with evidence of luteal activity have been published.

There were 680 (80.2%) women with evidence of luteal activity, ie, women presumed to have ovulatory cycles (determined by an increment in pregnanediol glucuronide [PdG] excretion). Eligible participants provided at least 80% of the required specimens for determinations of levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol metabolites (ie, estrone conjugates [E1c]), and the progesterone metabolite (PdG). The DHS participants also completed a diary nightly that contained 1 question regarding sleep quality. Eligible participants had to complete the sleep question on at least 70% of the nights of the collection cycle.

Data for this study were provided by 630 (92.6%) of the 680 women with evidence of luteal activity. Fifty women were disqualified. Seven had no menstrual bleeding within a 4-month enrollment period, 4 were missing information on menstrual status, 1 was pregnant, 13 began hormone therapy, and 25 did not satisfy the diary completion requirement. Of the 630 women, 62% completed the sleep item nightly, and 92% completed it for at least 90% of their cycle.

We report findings from the first DHS collection obtained in the year between the SWAN second and third (n=626) or SWAN third and fourth (n=4) annual assessments. Each site’s institutional review board approved the study, and all women gave written informed consent to participate.

PROCEDURES AND MEASURES

DHS Diary

At bedtime, participants completed an 18-item questionnaire covering the past 24 hours that asked about mood, physical and vasomotor symptoms, and trouble sleeping (0 indicates no; 1, yes). Specifically, participants were asked to “Think back over the last 24 hours and indicate whether or not you had trouble sleeping.” As Figure 1 illustrates, this sleep item pertained to the previous night’s sleep, and the finding was matched with results of the hormone assays from the morning urine collection covering the same overnight interval.

Hormone Assays

Levels of excreted hormones (LH, FSH, E1c, and PdG) were measured using newly adapted chemiluminescent assays.

Covariates

Variables selected have been related to trouble sleeping or have mediated the association between reproductive hormone levels and trouble sleeping in previous research.

Menopausal Status. Transition status was determined using bleeding criteria. Women reporting no menstrual irregularity in the past 12 months were categorized as premenopausal, and those reporting irregularity were categorized as early perimenopausal. Only premenopausal and early perimenopausal women were recruited.

Body Mass Index. Body mass index (calculated as weight in kilograms divided by the height in meters squared) was classified as underweight (<18.5); normal (18.5 to <25.0); overweight (25.0 to <30.0); and obese (≥30.0). For 18 participants, the average of the first and third annual visit was used because body mass index information was missing at the second annual visit.

Sociodemographics. Ethnicity was determined by self-identification as African American, white, Chinese, Japanese, or Hispanic. Other sociodemographic variables included age, marital status (single/never married, married or living as married, or separated/widowed/divorced), educational level (high school graduate or less, some college, college graduate, or graduate studies), currently employed (yes or no), and annual income (<$20,000, $20,000-$34,999, $35,000-$49,999, $50,000-$74,999, or ≥$75,000).

Mood. The diary included 9 mood symptoms rated from 1 (not at all) to 4 (a lot), indicating intensity of the symptoms, and a daily average mood score was computed.

Month of Collection. Month of collection (or the month in which most collections occurred) was included to control for possible seasonal variation in trouble sleeping associated with photoperiod length. November, December, and January were selected as the reference for the darkest months of the year (winter), and the successive 3-month periods were grouped.

Social Support and Perceived Health. Measures of social support (4-item sum; 0-11 indicates low; 12-16, high) and health (excellent, very good, good, fair, or poor) were self-rated.

Health Behaviors. Alcohol consumption, measured at the first annual visit, was coded as none, 1 to 2 drinks/wk, or 3 or more drinks/wk. Current cigarette smoking was categorized as yes or no.

Concurrent Medical Conditions. Women reported whether they had been told by a health care provider in the past year that they had or whether they had been treated for anemia, diabetes, high blood pressure, hypercholesterolemia, migraines, stroke, arthritis, thyroid disease, heart attack, angina, osteoporosis, fibroids, cancer (other than skin), and back pain. This variable was coded as 0, 1, or 2 or more.
Thus, we created an average estimate for the sleep when inferences about the population average are the fo-
sassumptions about time dependence and are appropriate
sistent regression coefficient estimates with minimal as-
tions within each subject. They provide robust and con-
deal efficiently with longitudinal, binary outcomes while
correlation structure. Generalized estimating equations
was centered at the day of luteal transition (DLT), ie, the
formed to natural logs to normalize their distribution.
All hormones showed a skewed distribution and were trans-
formed to natural logs to normalize their distribution.
Cycle length ranged from 15 to 49 days. Each cycle
was centered at the day of luteal transition (DLT), ie, the
presumed date of ovulation, or midcycle.41 Owing to di-
iminishing sample sizes leading to unstable estimates be-
yond 15 days before or after the DLT, analyses were lim-
ited to these 31 days.
We used logistic regression (PROC GENMOD24) with
day of cycle as the time variable to test and estimate as-
sociations between hormone levels and trouble sleep-
ing. Each logistic regression model was fitted using gen-
eralized estimating equations,25,26 with an exchangeable
sociation terms of menopausal status with cycle day and cycle
day squared were added to assess whether differences be-
tween premenopausal and perimenopausal women var-
ied by cycle day. Because this interaction was signifi-
cant, we performed further analyses separately for each
menopausal status group. The second set of analyses added
each hormone separately to the model from the first set
of analyses (4 models in each group) to examine inde-
pendent effects of each hormone. Each estimate for the
hormone coefficient is an across-cycle average. The third
set of analyses added mood and vasomotor symptoms
(both varying from day to day). Finally, we added all other
covariates (all constant over the cycle), including sea-
son, education, body mass index, income, employment
status, smoking, alcohol, marital status, pain and tran-
quilizer medication, health, number of medical condi-
tions, and social support. Odds ratios (ORs) and/or re-
gression coefficients (β) with 95% confidence intervals
(CIs) are presented.

### RESULTS

**PARTICIPANT CHARACTERISTICS**

The mean age of the cohort was 47.0 years (SD, 2.4 years).
Racial/ethnic distribution in our sample was 32.4% white,
19.8% African American, 21.6% Japanese, 18.3% Chi-
nese, and 7.9% Hispanic. Based on bleeding criteria, 434
(68.9%) of the sample were perimenopausal and 196
(31.1%) were premenopausal. Most were married (69.8%)
vs 18.1% divorced/separated/widowed and 12.1% single).
College degrees were reported by 46.4% of the women,
27.9% had completed some college, and 24.3% had a high
school diploma or less (1.4% had no information).

**SLEEP ACROSS THE CYCLE**

Four hundred sixty-seven women (74.1%) reported trouble
sleeping on at least 1 night. One hundred twenty-one
(19.2%) reported trouble sleeping on at least 40% of diary-
recorded nights. On average, these women had trouble
sleeping almost 3 nights/wk, consistent with criteria for in-
somnia in epidemiological studies.28 Fifteen women (2.4%)
reported trouble sleeping on all recorded nights.

**Figure 2** shows the cycle pattern and percentage of
women with trouble sleeping by cycle day and meno-
pausal status. After adjusting for age, ethnicity, and meno-
pausal status, this U-shaped pattern is highly significant
(cycle day squared β, 0.002; 95% CI, 0.001-0.003; 
P<.001). Across these 31 days, the average odds of re-
porting trouble sleeping, adjusted for age, ethnicity, cycle
day, and cycle day squared, was 29% higher in the peri-
menopausal than in the premenopausal group (OR, 1.287;
95% CI, 1.003-1.653; P = .048). Although at least 20% of
the premenopausal women reported trouble sleeping each
cycle day, at most 20% of the premenopausal women
reported trouble sleeping during the middle half of their
cycle. Significantly higher percentages in both groups re-
ported trouble sleeping on days farther from the DLT,
during the early follicular and late luteal phases.
We limited multivariate analyses to PdG and FSH levels, which were significantly related to trouble sleeping. Owing to missing covariate data, 10 women were excluded from these analyses, leaving 195 premenopausal and 425 perimenopausal women. Table 2 shows that after covariate adjustment, PdG level was significantly related to trouble sleeping in both groups. In the perimenopausal group, PdG level also was significantly associated with trouble sleeping. Levels of E1c and LH had no significant associations with trouble sleeping.

### TROUBLE SLEEPING, REPRODUCTIVE HORMONE LEVELS, AND NONHORMONAL FACTORS

We found that, compared with premenopausal women, a higher percentage of women beginning the menopausal transition (ie, perimenopausal group) reported difficulty sleeping, and that trouble sleeping varied with cycle phase and was maximal at the cycle’s beginning and end. Levels of FSH and PdG were associated with reduced sleep quality, but these relationships varied according to stage of the menopausal transition. Nonhormonal factors, particularly mood and vasomotor symptoms, contributed to trouble sleeping, but even after all these covariates were taken into account, increasing levels of FSH and PdG were consistently and strongly associated with trouble sleeping.

Table 1. Reproductive Hormone Levels and Trouble Sleeping in Premenopausal and Early Perimenopausal Women

<table>
<thead>
<tr>
<th>Hormone Level</th>
<th>Reproductive Hormone, OR (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log PdG</td>
<td>1.069 (1.021-1.116)</td>
<td>.009</td>
</tr>
<tr>
<td>Log E1c</td>
<td>1.017 (0.905-1.141)</td>
<td>.78</td>
</tr>
<tr>
<td>Log FSH</td>
<td>1.058 (1.003-1.117)</td>
<td>.04</td>
</tr>
<tr>
<td>Log LH</td>
<td>1.032 (0.994-1.072)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Table 2. Multivariate Generalized Estimating Equation Models for Trouble Sleeping for FSH and PdG Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>FSH in Premenopausal Women (n = 195)</th>
<th>PdG in Perimenopausal Women (n = 425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>0.400 (0.217-0.741)</td>
<td>0.719 (0.465-1.113)</td>
</tr>
<tr>
<td>Some college</td>
<td>0.745 (0.409-1.358)</td>
<td>0.719 (0.452-1.142)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>0.643 (0.336-1.230)</td>
<td>0.537 (0.322-0.894)</td>
</tr>
<tr>
<td>Missing</td>
<td>0.561 (0.138-2.283)</td>
<td>1.932 (0.393-9.509)</td>
</tr>
<tr>
<td>No. of medical conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>1</td>
<td>0.805 (0.495-1.310)</td>
<td>0.817 (0.573-1.616)</td>
</tr>
<tr>
<td>2</td>
<td>1.843 (1.115-3.046)</td>
<td>0.880 (0.589-1.315)</td>
</tr>
<tr>
<td>Medication for pain</td>
<td>0.386 (0.238-0.625)</td>
<td>0.860 (0.599-1.235)</td>
</tr>
<tr>
<td>Perceived health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Very good</td>
<td>0.764 (0.426-1.368)</td>
<td>1.201 (0.768-1.877)</td>
</tr>
<tr>
<td>Good</td>
<td>0.462 (0.240-0.969)</td>
<td>1.447 (0.891-2.349)</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>1.033 (0.478-2.232)</td>
<td>1.921 (1.107-3.334)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E1c, estradiol metabolites (ie, estrone conjugates); FSH, follicle-stimulating hormone; LH, luteinizing hormone; OR, odds ratio; PdG, progesterone metabolite (ie, pregnanediol glucuronide).

*Estimates for each hormone were adjusted for age, ethnicity, cycle day, and cycle day squared.

Because the basic model demonstrated differences in trouble sleeping between premenopausal and perimenopausal groups, subsequent analyses were stratified by menopausal status. Table 1 shows that after controlling for age, ethnicity, cycle day, and cycle day squared, FSH level was significantly related to trouble sleeping in both groups. In the perimenopausal group, PdG level also was significantly associated with trouble sleeping. Levels of E1c and LH had no significant associations with trouble sleeping.

### RELATIONSHIP OF TROUBLE SLEEPING TO CONCURRENT HORMONE LEVELS

We found that, compared with premenopausal women, a higher percentage of women beginning the menopausal transition (ie, perimenopausal group) reported difficulty sleeping, and that trouble sleeping varied with cycle phase and was maximal at the cycle’s beginning and end. Levels of FSH and PdG were associated with reduced sleep quality, but these relationships varied according to stage of the menopausal transition. Nonhormonal factors, particularly mood and vasomotor symptoms, contributed to trouble sleeping, but even after all these covariates were taken into account, increasing levels of FSH and PdG were consistently and strongly associated with trouble sleeping.

### COMMENT

We found that, compared with premenopausal women, a higher percentage of women beginning the menopausal transition (ie, perimenopausal group) reported difficulty sleeping, and that trouble sleeping varied with cycle phase and was maximal at the cycle’s beginning and end. Levels of FSH and PdG were associated with reduced sleep quality, but these relationships varied according to stage of the menopausal transition. Nonhormonal factors, particularly mood and vasomotor symptoms, contributed to trouble sleeping, but even after all these covariates were taken into account, increasing levels of FSH and PdG were consistently and strongly associated with trouble sleeping.
related to increases in trouble sleeping in premenopausal and perimenopausal women, respectively. Reanalyses that excluded mood and vasomotor symptoms showed that the estimates for the coefficients of log FSH level in the premenopausal women and log PdG level in the perimenopausal women were only slightly attenuated and \( P \) values slightly different. Thus, the conclusions are the same, despite the apparent large contributions of mood and vasomotor symptoms.

In cycles with clear increases in PdG excretion compatible with ovulation, both premenopausal and perimenopausal women reported that sleep was best at midcycle and worst at the extremes of the cycle (ie, the early follicular and late luteal phases).

Figure 3. Unadjusted hormone-sleep relationships plotted across a single menstrual cycle for follicle-stimulating hormone (FSH) levels in premenopausal women (A) and pregnanediol glucuronide (PdG) levels in early perimenopausal women (B). A. The relationship between percentages of nights with trouble sleeping and mean urine log FSH levels by cycle day of urine specimen collection. B. The relationship between percentages of nights with trouble sleeping and mean urine log PdG levels by cycle day of urine specimen collection.

This association between increased PdG excretion and trouble sleeping contrasts with other data suggesting that progesterone facilitates sleep.\(^{20}\) Progesterone is a central nervous system depressant,\(^{20}\) believed to act as a \( \gamma \)-aminobutyric acid \( \text{A} \) receptor agonist,\(^{31-33} \) and is used to stimulate breathing in hypercapnia syndromes, particularly sleep apnea.\(^{31,34,35} \) Lower levels of progesterone are found in women with sleep apnea.\(^{36} \) Thus, we expected the PdG level to be associated with better sleep. However, our observations indicate the opposite effect in the perimenopausal group, despite similar PdG excretion patterns in both groups.

There are several possible explanations for our findings. Trouble sleeping was reported in our study as a binary variable, and the proportion of women reporting trouble sleeping demonstrated an approximately U-shaped curve across the menstrual cycle. This relationship was visualized most clearly when cycle days were centered around the DLT. Estradiol and progesterone levels both fluctuate dramatically, across a 10-fold range of concentrations during the cycle. Because of these dramatic fluctuations of both hormone levels and sleep across the cycle, it is possible that the relationship is simply coincidental yet highly statistically significant owing to the concurrent timing of changes in sleep and PdG level. However, we examined both variables (proportion of women with trouble sleeping and urinary hormone levels) in the following 2 ways: by examining change during the first 30 days of collection, and by centering hormone levels and sleep data on the DLT, a physiological marker that indicates the shift in hormone levels associated with ovulation. Centering maps cycles in a manner that preserves important aspects of the hormonal milieu across cycles of different lengths and displays the pattern over time more clearly for both of our variables (proportion of women with trouble sleeping and urinary hormone levels). The relationships of PdG level to trouble sleeping in perimenopausal women and of FSH level to trouble sleeping in premenopausal women were the same whether we used time of collection or time centered on the DLT. It therefore seems unlikely that the relationships between sleep and both progesterone and FSH levels are coincidental.

It is possible that the central nervous system response to progesterone level is altered in perimenopausal women, such that the \( \gamma \)-aminobutyric acid \( \text{A} \) receptor agonist effect of progesterone is impaired compared with its effect in men or in premenopausal or postmenopausal women. Pregnenolone, the progesterone precursor, produces sleep electroencephalographic changes opposite of those induced by \( \gamma \)-aminobutyric acid \( \text{A} \) receptor agonists.\(^{37} \) There may be age-related alterations in the metabolic pathways of progesterone production or metabolism in women. Finally, since progesterone is released in a pulsatile fashion in the luteal phase of the menstrual cycle,\(^{38} \) there may be circadian or ultradian changes in its secretion concurrent with the menopausal transition that relate to the increased symptoms. The pulsatile pattern of progesterone excretion by the corpus luteum has not, to our knowledge, been studied as a function of age. The relationship between PdG level and trouble sleeping observed in this study is novel and largely unexplained by the available data.

Increased FSH level was significantly related to trouble sleeping in perimenopausal but not in perimenopausal...
women after controlling for covariates. This contrasts with previous findings in women aged 35 to 47 years with regular menstrual cycles, for whom low follicular-phase plasma estradiol level but not FSH level was associated with poor sleep. However, the FSH level was obtained at baseline and 8-month intervals for 2 years, which is quite different from measuring changes across a menstrual cycle. In another study, neither menopausal status nor serum FSH level was related to sleep disturbances in women aged 40 to 54 years. One FSH sample was obtained, and sleep was self-rated for 7 nights. Taken together, our data suggest that FSH level is most predictive of trouble sleeping when it is not expected to be elevated and when trouble sleeping is relatively infrequent, as was observed in our group of premenopausal women.

We confirmed previous findings from our group that vasomotor and mood symptoms were strongly associated with trouble sleeping in premenopausal and perimenopausal women, which is consistent with the finding by Young et al of increasing sleep dissatisfaction in transitioning women. Odds of trouble sleeping were increased with 2 or more medical conditions and decreased with use of pain medications. The latter could be due to sedation; analgesics and a sedative-analgesic combination may improve sleep in patients with pain. Lack of polysomnographic sleep evaluation may be a limitation of this study. However, discrepancies between subjective and objective sleep quality have been observed in studies of menopausal women. Because we were able to collect data during a full menstrual cycle for more than 90% of our women, we provide a longitudinal dimension for this symptom. Moreover, plots of standard deviation of sleep vs day of collection and DLT show no evidence of response bias. In a community-based sample, self-selection bias for reporting trouble sleeping is minimized.

We did not monitor body temperature. Increases in core body temperature during the luteal phase due to progesterone production have been associated with sleep spindle increase and may contribute to the phase differences and PdG effect that we observed. We also lack information on caffeine intake.

In summary, we have found that trouble sleeping is a relatively prevalent complaint in the early stages of the menopausal transition. An association of FSH and PdG levels with poor sleep was noted in cycles with luteal activity, indicating that these hormones have a negative effect on sleep quality, at least in midlife women. On the basis of our cross-sectional analyses, we anticipate that progress through the menopausal transition will be associated with increasing trouble sleeping.

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Correspondence: Howard M. Kravitz, DO, MPH, Department of Psychiatry, Rush University Medical Center, Marshall Field IV Bldg, 1720 W Polk St, Chicago, IL 60612 (hkravitz@rush.edu).
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