High nocturnal body temperatures and disturbed sleep in women with primary dysmenorrhea

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Baker, Fiona C., Helen S. Driver, Geoffrey G. Rogers, Janice Paiker, and Duncan Mitchell. High nocturnal body temperatures and disturbed sleep in women with primary dysmenorrhea. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E1013–E1021, 1999.—Primary dysmenorrhea is characterized by painful uterine cramps, near and during menstruation, that have an impact on personal life and productivity. The effect on sleep of this recurring pain has not been established. We compared sleep, nocturnal body temperatures, and hormone profiles during the menstrual cycle of 10 young women who suffered from primary dysmenorrhea, without any menstrual-associated mood disturbances, and 8 women who had normal menstrual cycles. Dysmenorrheic pain significantly decreased subjective sleep quality, sleep efficiency, and rapid eye movement (REM) sleep but not slow wave sleep (SWS), compared with pain-free phases of the menstrual cycle and compared with the controls. Even before menstruation, in the absence of pain, the women with dysmenorrhea had different sleep patterns, nocturnal body temperatures, and hormone levels compared with the controls. In the mid-follicular, mid-luteal, and menstrual phases, the dysmenorrheics had elevated morning estrogen concentrations, higher mean in-bed temperatures, and less REM sleep compared with the controls, as well as higher luteal phase prolactin levels. Both groups of women had less REM sleep when their body temperatures were high during the luteal and menstrual phases, implying that REM sleep is sensitive to elevated body temperatures. We have shown that dysmenorrhea is not only a disorder of menstruation but is manifest throughout the menstrual cycle. Furthermore, dysmenorrheic pain disturbs sleep, which may exacerbate the effect of the pain on daytime functioning.

Women who suffer from primary dysmenorrhea experience painful, spasmodic uterine cramps that may be so severe as to incapacitate them, just before and during menstruation every month, for the duration of their reproductive lives (1). The pain occurs in the absence of any macroscopically identifiable pelvic pathology and is not attributable to psychological factors (7). Prostaglandins (PG) are central to the pathogenesis of dysmenorrhea; women with dysmenorrhea have higher circulating levels of PGF2α and PGE2 during menstruation, compared with asymptomatic women (7). Dysmenorrhea occurs only in ovulatory cycles because exposure of the endometrium to luteal phase progesterone is necessary to enhance the production of uterine PG (7). Excessive release of PG by the endometrium during menstruation causes hypercontractility of the uterus, leading to uterine muscle ischemia and hypoxia, which is primarily responsible for the pain (7). There also is evidence that increased serum arginine vasopressin (AVP), during menstruation, causes dysrhythmic uterine contractions, contributing to the pain (7, 12).

Pain disrupts sleep (27). Postoperative patients, who suffer from acute pain, have disturbed, fragmented sleep, with increased wake time and reduced slow wave sleep (SWS) and rapid eye movement (REM) sleep (20, 39). Patients with chronic pain-associated diseases, such as lower back pain, fibromyalgia syndrome, and rheumatoid arthritis, take longer to fall asleep and have increased amounts of wakefulness, stage 1 sleep, and electroencephalographic-α activity during non-REM sleep (9, 28, 39). Primary dysmenorrhea exhibits characteristics of both chronic and acute pain syndromes, as it is a recurring pain with a regular and predictable onset but is of short duration with a severity that temporarily debilitates the sufferer. Women with dysmenorrhea commonly report fatigue as a symptom accompanying the uterine cramps (7), but the extent to which their pain disrupts sleep, and whether this disruption may contribute to their fatigue, has not been investigated previously.

Sleep may be affected not only by physical pain in women with dysmenorrhea but also directly by the increase in PG during menstruation; PGD2 induces sleep, and PGE2 induces wakefulness in rats (16). Furthermore, women with dysmenorrhea potentially have a modified cytokine status during menstruation (24), and interleukin (IL)-1β and tumor necrosis factor (TNF) enhance the duration and intensity of SWS (5). However, cytokine levels in women with dysmenorrhea have not yet been established.

Although cytokine status has not been measured, hormone status has been. There are reports of higher luteal phase estrogen (40) and either higher (22) or lower (40) plasma prolactin (PRL) concentrations, compared with controls. Nevertheless, women with primary dysmenorrhea apparently have normal menstrual cycles before the onset of menstrual pain. However, the hormonal variations even of normal menstrual cycles influence sleep (see Ref. 10 for review), with some women reporting a longer sleep onset latency (SOL) and poor sleep quality during the late luteal phase (10). Driver et al. (11) found that REM...
sleep varies across the menstrual cycle, being lowest during the luteal phase, which may be associated with the progesterone-mediated increase in body temperature of \(-0.4^\circ\text{C}\). Also, there is a significant increase in stage 2 sleep and increased activity in the upper spindle frequency band in the luteal compared with the follicular phase, events that may be mediated by progesterone (11) or by the temperature change (8). Therefore, if women with primary dysmenorrhea have disturbed hormonal status, they may well have disturbed sleep even when not in pain.

Another menstrual-associated disorder, late luteal phase dysphoric disorder (LLPDD) or premenstrual syndrome (PMS), influences body temperature and sleep. Blunted luteal phase melatonin rhythms, a phase advance of the circadian temperature rhythm, and higher nocturnal temperatures have been reported in women with LLPDD compared with women without any severe mood symptoms (29). Patients with LLPDD also have more frequent awakenings and movements and more daytime sleepiness, during the luteal phase, when they experience the mood disturbances characteristic of this disorder (10).

We investigated sleep, nocturnal temperatures, and pain over the menstrual cycle in women with primary dysmenorrhea who did not report any premenstrual mood disturbances and compared them with women who had normal menstrual cycles.

**MATERIALS AND METHODS**

Subjects. Twelve healthy, young women without any menstrual-associated disorders and 13 healthy, young women who suffered from primary dysmenorrhea volunteered to participate in our study and gave their written informed consent. Ethical clearance was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (clearance no. M960401), which adheres to the principles of the Declaration of Helsinki. All the women were interviewed and completed questionnaires to ensure that they had regular sleep-wake schedules and menstrual cycles. In their interview, the women were specifically asked to describe any mood changes that occurred during the course of their menstrual cycles and were excluded if the investigators suspected the presence of PMS. The General Health Questionnaire (GHQ; General Practice Research Unit 1972) was used for psychological screening and only women scoring less than 12 of 30 were included in the study. None of the women showed any indication of PMS, depression, or insomnia. The women were nonsmokers and nulliparous and had not taken any contraceptives or other chronic medication for at least 3 mo before the study. All the women assessed their pain ratings, the women in the control group were nondysmenorrheic and the dysmenorrheic women were classified as having mild-to-moderate dysmenorrhea (1). In the dysmenorrheic women, the effect of the dysmenorrhea on daily activity, the presence of associated symptoms, and analgesic requirements also were evaluated. All the dysmenorrheic women had a history of primary dysmenorrhea, starting shortly after menarche. The absence of any pathology was confirmed by a gynecological examination.

Screening phase. During a month-long screening period and for the duration of the study, the women kept a daily sleep log and were requested to maintain a regular sleep-wake schedule. Every morning, the women assessed the preceding night’s sleep quality on a VAS with anchor points of worst possible and best ever, and morning vigilance on a VAS with anchor points of feeling awfully sleepy and lack luster and feeling marvelously alert and energetic. The women also recorded their menses and measured their rectal temperature every morning before getting out of bed, with a digital thermometer (Soar M.E., Nagoya, Japan). The women were given a commercially available self-test kit (ClearPlan One Step, Unipath, Bedford, England) to confirm ovulation. On the first 2 days of menstruation, all the women assessed morning pain severity, before taking any medication, on a 100-mm VAS as previously described and with the McGill Pain Questionnaire (25), which has been used extensively to describe different pain types, including dysmenorrhea. From the questionnaire, a pain-rating index (PRI) was calculated, and in another component of the questionnaire, the women compared their present pain to other painful experiences, based on a 0–10 intensity scale, from which an index of present pain intensity could be calculated.

Only women who had predictable and ovulatory menstrual cycles, as assessed by a biphasic temperature rhythm and the mid-cycle presence of luteinizing hormone (LH), were accepted for the recording phase of the study. Ten women without any menstrual-related disorders and all 13 dysmenorrheic women fulfilled these criteria and participated in the study during the spring and summer months.

Recording phase. The women came to our sleep laboratory on three occasions during one menstrual cycle: 1 night during the mid-follicular phase (between 7 and 10 days after the onset of menstrual flow); 1 night during the mid-luteal phase; and between 2 and 4 nights beginning just before the expected menstrual period to capture the first night of menses. Because the women had regular cycles that had been monitored over 2 mo, we were correct in our prediction of the first day of menses in 13 of 18 women. The first night of actual menstruation (day 1) was compared with the mid-follicular and luteal nights. The luteal phase night was either the fifth or sixth night after the LH surge, as established with the ovulation prediction kit. The women were admitted to the recording phase of the study at different points of their menstrual cycle to avoid bias resulting from sequencing and acclimation effects. On their first visit, they spent an adaptation night in the controlled environment of our laboratory before the recording night. Three of the women had to return to the sleep laboratory for a repeat recording of one of their phases in the following month, owing either to incomplete data collection or delays in the onset of menstruation. The women refrained from caffeinated or alcoholic beverages and from participating in any physical exercise to which they were unaccustomed for 8 h before the start of the sleep recordings. Lights were turned out at each woman’s habitual bedtime, which ranged from 2200 to 2400. Subjects maintained their customary sleep periods for the duration of the study. The recording periods were close to 7 h for six of the controls and seven of the dysmenorrheics and close to 8 h for the remaining women in each group.

Data acquisition and analysis. Sleep recordings, comprising standard polysomnographic electroencephalographic, electro-oculographic, and electromyographic recordings, were made on a computerized electroencephalograph (Medelec DG 20, Vickers Medical, Surrey, England) at a nominal recording speed of 15 mm/s. Twenty-second epochs were scored according to standard criteria (31) by one of us (F.C.B.) who was...
blind to the identity of the subject and the menstrual phase. SOL was taken as the time from lights-out to the first appearance of at least three consecutive epochs of stage 2 sleep. The time between sleep onset and the first indication of any REM sleep was the REM sleep onset latency (ROL). The latency-to-stage 3 sleep was the time from sleep onset to the appearance of at least three consecutive epochs of stage 3 sleep.

Rectal temperatures were recorded every 10 min with 26-gauge copper-constantan thermocouples connected to a data logger (MC Systems, Cape Town, South Africa). The thermocouples were encased in a polythene sheath and inserted into the rectum to a depth of ~120 mm. Ambient dry-bulb temperature was recorded by a thermocouple array every 30 min and was maintained between 21 and 23°C. All thermocouples were calibrated, by water immersion against a quartz thermometer (Quat 100, Heraeus, Hanau, Germany), to an accuracy of 0.1°C.

On the adaptation night, each woman again completed a GHQ. In the evening of every recording night, the women completed a questionnaire describing the events of that day and indicated their evening mood on a VAS, with anchors of terrible agitation and utterly calm and peaceful. After each recording night, subjective sleep quality and morning vigilance were assessed by VAS. During menstruation, all the women rated their evening and morning pain severity with the McGill Pain Questionnaire and VAS. The women who suffered from dysmenorrhea were requested not to take any medication for their pain, but we could not withhold medication from four of the women who required a standard cyclooxygenase inhibitor (250 mg mefenamic acid) to alleviate their pain in the evening or during the recording night. The women rated their pain severity before taking any medication. A 30-ml blood sample was taken after each recording night, at between 0645 and 0800, and the serum was frozen for later analysis. Plasma estradiol, progesterone, LH, PRL, and corticotropin concentrations were measured with automated chemiluminescent immunoassays (estradiol-6; progesterone; LH; prolanctin; and cortisol, Chiron Diagnostics, East Walpole, MA). IL-1β, IL-6, and TNF-α plasma concentrations were determined with immunonassays (Quantikine, R&D systems, Minneapolis). Plasma ANG II and AVP concentrations were measured by radioimmunoassay as described elsewhere (15, 34). All of the samples for each hormone determination were included in the same assay batch. The mean within-assay variation was 2.8% in the PRL assay, 5.0% in the LH assay, 4.5% in the cortisol assay, 7.2% in the estradiol assay, 6.6% in the progesterone assay, 8.5% in the cytokine assays, 7.6% in the ANG II assay, and 7.1% in the AVP assay. The follicular phase blood sample from one of the dysmenorrheics was unsuitable for PRL analysis.

We excluded one of the control subjects from analysis because she did not show an increase in plasma progesterone or body temperature during the luteal phase, and one of the dysmenorrheics did not complete all of her recording nights. During the recording phase of the study, the menstrual cycles of one of the control women and one of the dysmenorrheics unexpectedly became longer than 40 days so that we were unable to complete their recordings. One woman who suffered from dysmenorrhea was excluded from analysis because her polysomnogram showed a ROL of <50 min and increased REM sleep (28%), suggesting depressed affect (4), even though her GHQ was in the normal range.

We used the recordings from 8 controls (age: 20 ± 1 yr; mass: 61.3 ± 3.0 kg; height: 1.67 ± 0.05 m; body mass index: 22.1 ± 1.7 kg/m²; menstrual cycle length: 32 ± 6 days; all means ± SD) and 10 dysmenorrheics (age: 23 ± 5 yr; mass: 60.1 ± 9.3 kg; height: 1.63 ± 0.08 m; body mass index: 22.5 ± 2.5 kg/m²; menstrual cycle length: 29 ± 6 days) in the final analysis.

Statistical analysis. We evaluated rectal temperature and sleep over the first 7 h of the recording nights. Temperature responses were assessed by determining the lights-out, nocturnal-minimum, and mean in-bed body temperatures. VAS measurements were normalized before statistical analysis through the arc sine square root transform. Temperature, subjective and objective sleep measures, and mood assessments were analyzed by means of a repeated-measures two-way ANOVA at a 95% confidence interval, according to menstrual phase or study group (Statistica, Statsoft, Tulsa, OK). When appropriate, the Student-Newman-Keuls (SNK) test was used to identify the origins of any differences. Pain indexes at menstruation were analyzed with a repeated-measures two-way ANOVA, according to study group or time. Results are expressed as means ± SD.

RESULTS

Subjective assessments. During menstruation, the VAS pain ratings of the dysmenorrheic women in the evening (PM: 81 ± 16 mm, mean ± SD) and the morning (AM: 62 ± 18 mm) were significantly greater than those of the controls (PM: 9 ± 8 mm; AM: 2 ± 3 mm) during menstruation [group effect: F(1,16) = 81.0, P < 0.0001]. The dysmenorrheic pain could be classified as “severe” because the VAS ratings were >54 mm for all of the women (6). The women with dysmenorrhea had a significantly higher PRI derived from the McGill Pain Questionnaire (PM: 29 ± 12; AM: 19 ± 13) than the controls (PM: 4 ± 8; AM: 1 ± 2) during menstruation [group effect: F(1,16) = 27.8, P = 0.00008]. Similarly, the present pain intensity of the dysmenorrheics (PM: 3.1 ± 0.9; AM: 2.8 ± 1.0) was significantly higher than that of the controls (PM: 0.6 ± 1.0; AM: 0.3 ± 0.5; group effect: F(1,15) = 36.8, P = 0.00002). Both the women with dysmenorrhea and the control women rated their pain as being significantly less on the morning of the second day of menstruation than on the evening of the first day [VAS ratings time effect: F(1,16) = 15.4, P = 0.001; PRI time effect: F(1,16) = 5.8, P = 0.03]. The words from the McGill Pain Questionnaire selected most commonly by the women with dysmenorrhea to describe their pain at menstruation were “throbbing,” “stabbing,” “cramping,” “pulling,” “shooting,” “nagging,” and “tiring” or “exhausting.”

Evening mood differed between menstrual cycle phases in the dysmenorrheics and between the two study groups [group-phase interaction: F(2,32) = 6.0, P = 0.006]. The dysmenorrheics were significantly more agitated (36 ± 26 mm) during menstruation than during their follicular phase (74 ± 16 mm; SNK: P = 0.005) and almost significantly more agitated than during their luteal phase (61 ± 29 mm; SNK: P = 0.08). During their follicular phase, however, the women with dysmenorrhea had significantly better evening mood states than did the controls (46 ± 34 mm) during their follicular phase (SNK: P = 0.04).

The dysmenorrheic women rated their sleep quality (48 ± 24 mm) as significantly worse than the controls did (65 ± 21 mm) during menstruation (SNK: P = 0.04)
The morning plasma PRL concentrations revealed a significant phase effect \( F(2,30) = 5, P = 0.01 \) and phase group effect \( F(2,30) = 5, P = 0.01 \). The dysmenorrheics had significantly higher PRL concentrations during their luteal phase than during their follicular (SNK: \( P = 0.004 \)) and menstrual (SNK: \( P = 0.05 \)) phases and higher than that of the controls during their luteal phase (SNK: \( P = 0.002 \)). The mean luteal phase plasma PRL concentration in the women with dysmenorrhea was above the normal range for premenopausal women (<20 ng/ml; Ref. 3). PRL concentrations in the controls did not vary significantly between phases.

Plasma ANG II, AVP, and cortisol did not vary significantly across the menstrual cycle and did not differ between the two groups of women. The plasma concentrations of IL-6, IL-1β, and TNF-α all were within the normal range, did not change significantly during the three phases of the menstrual cycle, and were not different between the controls and dysmenorrheics.

**Body temperature.** Rectal temperatures over the first 7 h of the night during three menstrual phases are shown in Fig. 2. Both groups of women showed the expected increase in body temperature during the luteal phase, compared with their other two phases. The women who had higher body temperatures at lights-out, higher mean in-bed temperatures, and higher nadir temperatures in the luteal phase compared with the follicular and menstrual phases (Table 1). Unexpectedly, the women with dysmenorrhea had higher nocturnal body temperatures than the controls (Fig. 2); indeed, although the rectal temperatures of the women at lights-out were similar, the dysmenorrheics had higher mean in-bed temperatures and higher nadir temperatures than did the controls throughout the menstrual cycle (Table 1).

Sleep variables derived from polysomnograms. Figure 3, which amplifies Table 1, depicts the combined time spent awake, moving, and in stage 1 sleep and the time spent in SWS and REM sleep for the control and dysmenorrheic women, during the first 7 h of the night, at three phases of the menstrual cycle.

The men with dysmenorrhea had a significantly lower sleep efficiency (Table 1), attributable to more time spent awake, moving, and in stage 1 sleep during menstruation, than during their follicular (SNK: \( P = 0.003 \)) and luteal (SNK: \( P = 0.004 \)) phases and compared with the controls during menstruation (SNK: \( P = 0.002 \)). There were no significant differences in SOL, but there was a menstrual-phase effect on the latency to SWS (latency-to-stage 3 sleep), which was
longer in both study groups during menstruation than during the luteal phase (SNK: \( P = 0.04 \)). The time spent in SWS and stage 2 sleep was similar during the three menstrual cycle periods and in the two groups of women (Table 1). For REM sleep, however, there was a significant menstrual phase and group effect. The controls and dysmenorrheics had less REM sleep during the luteal phase (SNK: \( P = 0.01 \)) and at menstruation (SNK: \( P = 0.001 \)) than during the follicular phase. Also, the dysmenorrheics had less REM sleep than did

Table 1. Sleep variables and rectal temperatures for 8 control women and 10 women with primary dysmenorrhea during 7 h of sleep in their mid-follicular, mid-luteal, and menstrual phases of their menstrual cycles

<table>
<thead>
<tr>
<th>Phase</th>
<th>Follicular</th>
<th>Luteal</th>
<th>Menstrual</th>
<th>2-Way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>10 ± 7</td>
<td>11 ± 9</td>
<td>11 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>12 ± 9</td>
<td>11 ± 10</td>
<td>18 ± 16</td>
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<tr>
<td>Latency to stage 3 sleep, min</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11 ± 5</td>
<td>9 ± 7</td>
<td>11 ± 8*</td>
<td>group effect, NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>10 ± 7</td>
<td>8 ± 5</td>
<td>12 ± 8*</td>
<td>phase effect, ( F(2, 32) = 3.5, P = 0.04 )</td>
</tr>
<tr>
<td>REM sleep onset latency, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>71 ± 11</td>
<td>72 ± 26</td>
<td>84 ± 41</td>
<td>NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>71 ± 17</td>
<td>72 ± 13</td>
<td>69 ± 13</td>
<td></td>
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<tr>
<td>Sleep efficiency, %</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>96 ± 2</td>
<td>95 ± 3</td>
<td>95 ± 2</td>
<td>group effect, NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>96 ± 2</td>
<td>96 ± 2</td>
<td>88 ± 11†</td>
<td>phase effect, ( F(2, 32) = 5.4, P = 0.009 )</td>
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<tr>
<td>Stage 2 sleep, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>163 ± 35</td>
<td>166 ± 37</td>
<td>174 ± 30</td>
<td>NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>193 ± 16</td>
<td>189 ± 41</td>
<td>167 ± 30</td>
<td></td>
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<tr>
<td>Slow wave sleep, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>127 ± 35</td>
<td>131 ± 38</td>
<td>129 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>105 ± 19</td>
<td>124 ± 42</td>
<td>107 ± 31</td>
<td></td>
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<tr>
<td>REM sleep, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95 ± 13</td>
<td>84 ± 12†</td>
<td>79 ± 17†</td>
<td>group effect, ( F(1, 16) = 5.6, P = 0.03 )</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>88 ± 12</td>
<td>73 ± 13†</td>
<td>65 ± 22†</td>
<td>phase effect, ( F(2, 32) = 8.3, P = 0.001 )</td>
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<tr>
<td>Awake, movement, and stage 1, min</td>
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<tr>
<td>Control</td>
<td>22 ± 8</td>
<td>28 ± 16</td>
<td>29 ± 12</td>
<td>group effect, NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>23 ± 5</td>
<td>23 ± 8</td>
<td>66 ± 53†</td>
<td>phase effect, ( F(2, 32) = 6.2, P = 0.005 )</td>
</tr>
<tr>
<td>Lights-out temperature, °C</td>
<td></td>
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<tr>
<td>Control</td>
<td>37.1 ± 0.2*</td>
<td>37.4 ± 0.2</td>
<td>37.1 ± 0.3*</td>
<td>group effect, NS</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>37.0 ± 0.2*</td>
<td>37.5 ± 0.2</td>
<td>37.3 ± 0.2*</td>
<td>phase effect, ( F(2, 32) = 19.3, P = 0.000003 )</td>
</tr>
<tr>
<td>Temperature nadir, °C</td>
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<tr>
<td>Control</td>
<td>36.4 ± 0.1*</td>
<td>36.7 ± 0.2</td>
<td>36.7 ± 0.2*</td>
<td>group effect, ( F(1, 16) = 11.2, P = 0.004 )</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>36.5 ± 0.1*</td>
<td>37.0 ± 0.1</td>
<td>36.8 ± 0.2*</td>
<td>phase effect, ( F(2, 32) = 26.0, P = 0.00000 )</td>
</tr>
<tr>
<td>Mean 7-h in-bed temperature, °C</td>
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<td></td>
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<tr>
<td>Control</td>
<td>36.7 ± 0.1*</td>
<td>37.1 ± 0.1</td>
<td>36.9 ± 0.2*</td>
<td>group effect, ( F(1, 16) = 10.6, P = 0.005 )</td>
</tr>
<tr>
<td>Dysmenorrheic</td>
<td>36.8 ± 0.1*</td>
<td>37.2 ± 0.1</td>
<td>37.0 ± 0.1*</td>
<td>phase effect, ( F(2, 32) = 67.5, P = 0.00000 )</td>
</tr>
</tbody>
</table>

Values are means ± SD. REM, rapid eye movement; SNK, Student-Newman-Keuls; NS, nonsignificant. *Significantly different from luteal phase; †significantly different from follicular and luteal phases; ‡significantly different from follicular phase (SNK, \( P < 0.05 \)).
The women with dysmenorrhea had a more disturbed sleep and a poorer sleep quality when they were suffering from uterine pain than did asymptomatic women and compared with other times during the menstrual cycle when they did not suffer from any pain. Interestingly, we found signs of homeostatic and hormonal imbalance in women with primary dysmenorrhea even when they were not experiencing menstrual pain, in that their nocturnal body temperatures were higher and REM sleep was shorter than those of asymptomatic women in the mid-follicular and mid-luteal phases. Also, the women with dysmenorrhea had higher PRL concentrations than did the control group during the luteal phase. Although plasma estrogen levels were within the normal range, the women with dysmenorrhea also consistently had higher estrogen levels than the controls both in the mid-follicular and mid-luteal phases. Primary dysmenorrhea therefore cannot be considered only as a disorder of menstruation. Finally, REM sleep, but not SWS, varied with the hormonal and temperature changes during the menstrual cycle; both the women with normal menstrual cycles and those suffering from dysmenorrhea had less REM sleep during their luteal and menstrual phases, when their body temperatures were higher, than they did during their follicular phases. Previous studies (10) of the menstrual cycle have reported changes in stage 2 sleep and SWS during the menstrual cycle, which we did not find. Small variations that occur as a function of the continuous nature of the menstrual cycle may not have been detected in the three discreet recordings we made.

Pain is difficult to quantify, and its assessment usually is reliant on subjective assessments. Furthermore, dysmenorrheic pain is very variable, both between sufferers and between cycles in the same woman. We reduced the potential variability in pain responses by including in our study only women who suffered from dysmenorrhea without any underlying pelvic pathology. We also used several established pain assessment scales to quantify the pain of each woman. During menstruation, the women with dysmenorrhea recorded VAS scores that were almost as severe as their most painful experience ever and that corresponded to the pain intensity reported by patients with severe postoperative pain (6). The dysmenorrheic pain negatively affected evening mood, and it was presumably the pain that disrupted the sleep, just as sleep is disrupted by acute postoperative pain (20, 39). Although the subjective pain ratings of postoperative patients and women with dysmenorrhea are similar, SWS and REM sleep are almost entirely absent in postoperative patients (20), whereas SWS was not disturbed by the dysmenorrheic pain. But anesthesia, medications, analgesic use, patient age, and disturbances by routine hospital procedures confound measurements of sleep in postoperative patients (20). Furthermore, dysmenorrhea differs from postoperative pain in that it recurs regularly and is well known to each woman and, therefore, is not associated with the fear and anxiety of postoperative pain (17), which also could influence sleep. The women
in our study had significantly less REM sleep when experiencing pain than they did when they were free of pain. Uterine activity increases during REM sleep (18), and uterine contractility is significantly higher during the night in women with dysmenorrhea than in asymptomatic women (23), so uterine cramps might be most painful and disturbing during REM sleep, hence reducing the total amount of REM sleep compared with when the women were free of pain.

Our finding of more wakefulness, movement, and stage 1 sleep and poorer subjective sleep quality in women with dysmenorrhea pain than in pain-free controls also concurs with the observations of others who have investigated the effect on sleep of chronic pain (9, 28). As was the case in our women, SWS was unaffected by pain in patients with rheumatoid arthritis (9). The pain threshold may be higher during SWS, which is the deepest stage of sleep. Chronic pain patients also have a longer SOL compared with controls (39), a phenomenon we did not observe in dysmenorrheic women. Dysmenorrhea pain therefore does not affect sleep in exactly the same way as other acute or chronic pain; homeostatic sleep regulatory mechanisms as indicated by SWS and SOL are unaffected, but sleep is disrupted by the pain, worsening both objective measures of sleep quality and subjective perception of sleep. Poor sleep and the subsequent daytime fatigue also would likely exacerbate the effects of the pain on daytime functioning and mood (27).

Although dysmenorrhea traditionally is considered to be a disorder of menstruation only, we found evidence of homeostatic imbalance before the onset of menstruation. Our finding of higher estrogen, but normal progesterone levels, in dysmenorrheic women has been reported by others (40, 41). There is a positive correlation between endometrial PGF levels and uterine venous estrogen levels, and endometrial PG production is increased after estradiol treatment (40). Elevated estrogen levels, throughout the menstrual cycle, therefore, may be central in the etiology of primary dysmenorrhea, stimulating the excessive production of certain uterine PGs, and, hence, the uterine ischemia and hypoxia characteristic of dysmenorrheic pain (40, 41).

The high estrogen levels in the women with dysmenorrhea, particularly in the luteal phase, also may have stimulated PRL secretion; estrogen is thought to be a releasing factor for PRL (19). Hyperprolactinemia has been reported previously in dysmenorrheic women (22). However, so has hypoprolactinemia (40), but it is not clear at what time the blood was sampled. The time of blood sampling is important because PRL secretion shows a clear circadian rhythm characterized by a nocturnal increase and a rapid fall after waking (37); we took blood samples once in the morning after falling asleep. Apart from being implicated in dysmenorrhea, PRL has been implicated in endometriosis (30) and in menstrual-associated hypersomnia (3). PRL secretion is dependent on sleep (21); therefore, a more detailed investigation is needed of nocturnal PRL secretion, particularly in the luteal phase, in women with dysmenorrhea.

We did not find the menstrual-phase increase in AVP in the dysmenorrheic women that has been reported in some other studies (12). Also, we thought we might find an increase in cortisol or cytokine levels associated with the dysmenorrheic pain but did not do so. Again, the single morning blood sample taken from the women in our study may not have been sufficient to detect differences in the two groups of women or between different menstrual phases.

To our knowledge, the nocturnal body temperatures of women with dysmenorrhea have not been investigated previously, and we therefore are the first to discover the higher nocturnal temperatures in women with primary dysmenorrhea. Disturbances in body temperature have been reported in association with mood disorders such as in depression and LLPDD. Depressed patients have higher nocturnal temperatures and reduced temperature rhythm amplitudes compared with those of healthy controls (35), whereas women with LLPDD have higher mean in-bed temperatures and higher nocturnal minimum temperatures compared with controls, across the entire menstrual cycle (33). Furthermore, women with LLPDD have decreased temperature rhythm amplitudes in the luteal phase compared with the follicular phase (29), and they tend to have higher nocturnal temperatures and temperature maxima and mesors compared with controls (29). Parry et al. (29) postulated that the temperature rhythm disturbances in women with LLPDD might reflect alterations in the underlying pacemaker regulating the amplitude of the temperature rhythm. However, our dysmenorrheic women neither were depressed nor had any premenstrual mood disturbance, so a different mechanism may be responsible for the temperature effects we saw.

We believe that a more feasible explanation for the high nocturnal body temperatures in dysmenorrhea is elevation of PG concentration. Although we were unable to measure PG concentrations in our study, PGs have been implicated clearly in the etiology of dysmenorrhea (7) and some research indicates that PGE2 and PGF2α are high in the endometrium not only during menstruation, but also throughout the menstrual cycle of dysmenorrheics (38). PGs of the E series are primary mediators of fever (26), and they also are primary mediators of the increase in pain sensitivity associated with peripheral ischemia (13). If PGE levels were elevated, they were elevated independently of circulating concentrations of the cytokines IL-6, IL-1β, and TNF-α, which did not differ between the two groups of women nor during the menstrual cycle. However, the relevant cytokine concentrations are more likely to be the concentrations in the central nervous system rather than those in the periphery (32).

When body temperatures were higher, both during the luteal phase compared with other menstrual phases and in the women with dysmenorrhea compared with asymptomatic women, REM sleep was reduced. A reduction in REM sleep during the luteal phase, compared
with the follicular phase, has been reported previously (11) and may be related to the processes that regulate body temperature. During REM sleep, thermoregulatory responses are inhibited so REM sleep cannot occur simultaneously with competent thermoregulation (for review see Ref. 14). It would appear that if the thermoregulatory system is challenged at night, some REM sleep is sacrificed; women taking oral contraceptives and less efficient sleep during menstruation compared with controls and with when they are free of pain. Also, dysmenorrhea is not only a disorder of menstruation, and the pain of primary dysmenorrhea have more disturbed sleep concomitant with the elevated core body temperature (14), and if our women had elevated PG concentrations, their status mimicked that of a low-grade fever.

In conclusion, we have shown that women with the pain of primary dysmenorrhea have more disturbed and less efficient sleep during menstruation compared with controls and with when they are free of pain. Also, dysmenorrhea is not only a disorder of menstruation, but a disorder of the menstrual cycle, throughout which estrogen levels and body temperatures are elevated and REM sleep is reduced compared with nonsymptomatic menstrual cycles.

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