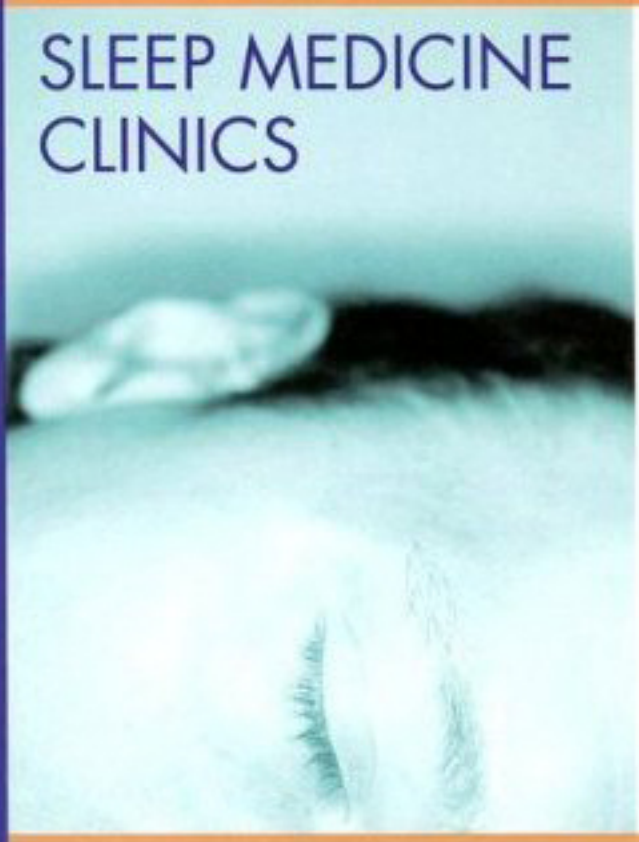
SLEEP MEDICINE CLINICS



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SLEEP MEDICINE CLINICS

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Foreword

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Across the lifespan of women, reproductive cycles can significantly affect sleep. In general, women appear to describe more subjective complaints of unsatisfactory sleep quality, as well as non-restorative sleep, but also tend to report a greater need for sleep compared to men.

During the menstrual cycle, sleep quality is commonly poorer immediately before and during the initial part of menstruation. Duration of nighttime sleep is also longer prior to menses. Many factors potentially contribute to sleep disturbance during this time, including mood changes and physical complaints (eg, breast tenderness, abdominal bloating, cramping, and headaches). The luteal phase of the menstrual cycle is associated with increased subjective sleepiness, as well as decreased sleep efficiency and more prolonged sleep latency. There is also commonly an increase in non-rapid eye movement (NREM) stage 2 sleep, increase in frequency of sleep spindles, and decrease in rapid eye movement (REM) sleep during the luteal phase as compared to the follicular phase. Menstruation itself can be accompanied by an increase in latency to slow-wave sleep.

Specific sleep disturbances can also develop during the menstrual cycle, secondary to dysmenorrhea (painful uterine cramping), endometriosis (presence of endometrial tissue in the pelvis or abdomen), premenstrual syndrome, and premenstrual dysphoric disorder. Dysmenorrhea can result in diminished sleep quality and duration of REM sleep. Sleep can be disturbed by pain from endometriosis. Premenstrual syndrome (PMS) is characterized by bloating, irritability, and fatigue that develop prior to menses during the late luteal phase. PMS can be associated with poor sleep, frequent awakenings, unpleasant dreams, and complaints of insomnia or excessive sleepiness. Considered a more severe form of PMS, premenstrual dysphoric disorder can also be complicated by complaints of insomnia or excessive sleepiness, along with functional impairment and mood changes. Finally, parasomnias, including sleepwalking and sleep terrors, occurring repeatedly during the luteal phase of menstruation have been described.

The use of oral contraceptives can also produce significant changes in NREM stage 2 sleep and decreases in REM sleep latency; however, no

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changes in daytime alertness have been noted with oral contraceptive use.

Sleep quality and duration are profoundly affected by pregnancy. Increase in frequency of awakenings and wake time after sleep onset, as well as decrease in nighttime sleep duration and increase in daytime napping, can occur as early as the first trimester of pregnancy. Sleep tends to improve during the second trimester, only to significantly deteriorate again during the final months of pregnancy. Causes of sleep disturbance during pregnancy vary from one individual to the next but may be due to a combination of any of the following factors: breast tenderness, dyspnea, nausea, urinary frequency, fetal movements, leg cramps, or anxiety. Sleep-related breathing disorders, including snoring and obstructive sleep apnea, and restless legs syndrome may be precipitated or aggravated by pregnancy. Excessive sleepiness may extend into the postpartum period, and mothers may experience significant sleep loss, changes in mood, and frequent napping.

Finally, peri-menopausal and post-menopausal phases with their declining levels of estrogen and progesterone, and irregular menstrual cycles can lead to the development of hot flashes, night sweats, headaches, and urinary frequency; these, in turn, can give rise to excessive sleepiness, sleep fragmentation, and insomnia. In addition to insomnia, obstructive sleep apnea also has a higher prevalence during this period compared to the pre-menopausal period.

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Preface

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This issue of *Sleep Medicine Clinics* highlights the emerging scientific consensus on the importance of female-specific sleep changes through a diverse and high-level set of articles. The authors' unique voices and distinct scientific and clinical perspectives ensure that this issue on sleep and sleep disorders in women fully encompasses a woman's reproductive lifespan, with topics related to menstrual cycles, pregnancy, childrearing, and menopause. Its clinical components cover medical conditions that are either specific to or more prevalent in women, such as insomnia, or that demonstrate sex-based differences, such as obstructive sleep apnea (OSA). Data-driven articles from well-known research groups and reviews by clinical specialists from across the world link the pure science to clinical practice.

The first three articles cover a series of discussions on menstrual cycle. Sleep homeostasis is relatively unaffected by menstrual cycle changes, but many women experience subjectively poorer sleep around menstruation. Driver, Werth, Dijk and Borbély describe their findings that changes in the post-ovulation sleep EEG coincide with a progesterone-mediated increase in nocturnal body temperature and elevated heart rates during sleep. Shechter, James, and Boivin review reproductive and health issues for the approximately 25% of Canadian women in the work force who are shift workers. Shift work causes a misalignment of circadian rhythms resulting in menstrual cycle irregularities, weight gain, increased risk of cardiovascular disease, functional bowel disorders, and breast cancer. Baker, Lamarche, Iacovides and Colrain describe menstrual-related disturbances. They review the influence of dysmenorrhea (pain at menstruation), and the impact of premenstrual syndrome and premenstrual dysphoric disorder on sleep.

A series of papers examines disturbed sleep caused by pain, fatigue, and depression. Women experience pain acutely in predictable recurring cycles, such as dysmenorrhoea, and they also are disproportionately prone to manifest chronically widespread and regional painful, multi-symptom syndromes including fibromyalgia, irritable bowel syndrome, and chronic pelvic pain. Sleep disturbance, with complaints of poor and unrefreshing sleep, in relation to menstrual-related disorders in women who have functional somatic syndromes, as

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outlined by Shaver, appears to be highly prevalent. In addition to the menstrual-related disorders and functional somatic syndromes, breast cancer survivor's fatigue, reviewed by Bardwell and Ancoli-Israel, is linked to pain and sleep disturbance, worse physical health, less physical activity, and depressive symptoms.

Two articles examine the altered hormone profiles of pregnancy and menopause and their effect on sleep. In her article, Sloan summarizes sleep changes during pregnancy and postpartum, emphasizing sleep disruption, insomnia, depression, and restless legs syndrome and their response to various treatment strategies. The gradual withdrawal of estrogen and progesterone around menopause results in an increase in sleep problems. Polo-Kantola considers these changes and therapies, including hormone replacement.

Women are at increased risk for developing insomnia in pivotal periods such as pregnancy, childbirth, and especially menopause. These periods are associated with changing hormone profiles and changes in lifestyle and/or environment. For example, sleep behaviors and practices often are radically altered with the arrival of an infant in the home. Owens discusses how biological determinants of sleep, cultural influences, and lifestyles contribute to sleep practices, particularly during the formative years. Davidson outlines insomnia predisposing, precipitating, and perpetuating factors and therapeutic options. Since persistent insomnia correlates with increased use of healthcare services and the risk of developing depression (as highlighted by Banno and Kryger and by Davidson), appropriate pharmacologic and nonpharmacologic interventions described in this issue should be given serious consideration.

Another set of articles highlight women's unique challenges from sleep disorders. Women with sleep disordered breathing are more likely to present with depression, and complain of fatigue and unrefreshing sleep rather than the more traditionally accepted symptom of excessive daytime sleepiness, as summarized by Banno and Kryger. Women are more likely to have increased upper airway resistance syndrome rather than frank apneas. Edwards and Sullivan review these sex-differences in their discussion of unique changes during pregnancy and the impact on sleep disordered breathing, while Polo-Katola examines the increased incidence of OSA in postmenopausal women. The influence of hormones is particularly relevant during pregnancy when women traditionally have been thought to be "protected" from developing breathing disorders during sleep. However, there is growing concern regarding increased risk for OSA in this population, particularly in women who have preeclampsia and in those who are obese. Tasali, Van Cauter, and Ehrmann conclude that not only do women who have polycystic ovary syndrome have higher levels of androgens, lower levels of progesterone and estrogen, menstrual irregularity, and obesity, but also they are at increased risk for insulin resistance, hypertension, and OSA. The multi-faceted influence of hormones, weight gain, and the possible role of proinflammatory cytokines in developing OSA is also described in the articles on polycystic ovaray syndrome, pregnancy, and menopause.

With this issue of *Sleep Medicine Clinics* the reader is provided with the background to be able to identify and consider treatment options for women who are at high risk for sleep disorders. I thank the authors who have contributed to this issue on women's sleep matters from childbirth to menopause, and I thank the editors and publishers who helped bring it to publication.

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The Menstrual Cycle Effects on Sleep

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- Ovulatory menstrual cycles
- Subjective effects of the menstrual cycle on sleep
- Objective polysomnographic findings across the menstrual cycle
- Menstrual, diurnal, and sleep-associated changes in body temperature
- Sleep-related electroencephalographic spectra, temperature, and heart rate during the mid-follicular and mid-luteal phases

Methods for investigating the temporal evolution of sleep, temperature, and heart rate

Changes in temperature and heart rate across the first four sleep cycles

Changes in sleep across the first four sleep cycles

Are progesterone and/or temperature associated with sleep and heart rate changes?

- Oral contraceptives

Oral contraceptives and body temperature

Effects of oral contraceptives on sleep

- Summary
- References

The physiology of menstrual cycles provides inherent challenges for research, given the variability in cycle length, the presence or absence of ovulation, individual and cycle-to-cycle differences, changes with age, and the interaction with mood, discomfort, and pain around menstruation. Research on young women has been complicated by concerns around the need to select discrete times in the cycle during which to study women, the frequency of data sampling required, and the use of oral contraceptives (OCs). To control for potential confounds across the menstrual cycle, many researchers opt to study women in the follicular phase. With ovulatory cycles, and with the associated changes in estrogen and progesterone in particular, there are changes in body temperature and effects on subjective and objective measures of sleep that have been described in recent reviews [1–4] and are summarized in this article.

The most remarkable effects on the sleep electroencephalograph (EEG) occur in the luteal phase when progesterone predominates compared with the follicular phase when estrogen predominates. The authors have conducted an analysis of changes

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in sleep, the sleep EEG, body temperature, and heart rate across 1 night at the midpoints of the follicular and luteal phases. These data extend the discussion of the influence of progesterone and temperature on sleep and include the changes in temperature and heart rate in rapid-eye-movement (REM) and non-REM sleep during the first four sleep cycles.

Although about 100 million women worldwide use OCs, there has been very little research on their effects on sleep and temperature. These influences may be small, but the relatively undocumented effects have contributed to the exclusion of women taking OC therapy from studies. This article concludes with a summary and suggestions for future research.

Ovulatory menstrual cycles

In an ovulatory menstrual cycle there are cyclical changes in four reproductive hormones, namely the pituitary gonadotropins—luteinizing hormone and follicle-stimulating hormone—and estrogen and progesterone that occur in conjunction with a bi-phasic change in body temperature [5]. The common identification, based on the days of the cycle, starts with the first day of menstruation as day 1 and continues until the start of the next bleeding period. Menstrual cycle length decreases from an average of 28 days for women in their twenties to 26 days for women in their forties [6]; an average cycle lasts 28 days but may range from 25 to 35 days.

On the day menstruation begins, all four key reproductive hormones are low. As follicle-stimulating hormone and estrogen rise, ovarian follicles develop and mature during this follicular or proliferative phase. The follicular phase, which precedes ovulation, may vary in length. Luteinizing hormone peaks about 16 hours before ovulation, and the appearance of luteinizing hormone in urine is a reliable marker of ovulation. At ovulation an oocyte is released from the follicle. Thereafter, the corpus luteum evolves from the ruptured follicle and secretes progesterone and estrogen in the luteal phase (also called the "secretory phase"). If ovulation has occurred, body temperature, when measured at the same time every morning, increases by about 0.4°C [1,7,8]. About 10 days after ovulation, and if fertilization does not occur, the corpus luteum begins to degenerate, and hormone production begins to decline, leading to shedding of the endometrium and the start of a new cycle. The luteal phase usually is constant, lasting 14 days. Most negative menstrual symptoms are experienced during the last 4 to 8 days of the cycle (as estrogen and progesterone concentrations decline) and the first few days of menstruation (when ovarian hormones are low).

Subjective effects of the menstrual cycle on sleep

Subjective sleep quality is reduced both premenstrually and at menstruation [1,9–11]. In a telephone survey of 514 women, approximately 70% reported that their sleep is affected adversely by menstrual symptoms such as bloating, tender breasts, headaches, and cramps, on average 2.5 days every month [12]. Earlier retrospective surveys found that 16% to 32% of women report increased fatigue, difficulty in concentrating, or lethargy in the premenstrual period ([13–14]; for reviews see Refs. [2–4]).

Prospective studies also show that sleep disturbance increases around menstruation [9–11]. A study of 32 women who kept daily diaries across two menstrual cycles found no change in sleep duration, but sleep disturbances increased, with poorer sleep quality, in the late luteal phase as compared with the mid-follicular phase [11]. There was a delay in sleep onset and an increased number of awakenings premenstrually. Laessle and colleagues [10], however, found no change in sleep quality or sleep duration in young women (n = 30) who had normal menstrual cycles. A more recent study by Baker and Driver [9], in which ovulatory cycles were confirmed, found that young women (n = 26) without significant menstrual-associated complaints reported poorer sleep quality 3 to 6 days premenstrually and during the first 4 days of menstruation.

In general, women across a wide age range (18–50 years) report more sleep disturbances, including time to sleep onset and number of awakenings [11,13] and decreased sleep efficiency or quality [9] during the premenstrual week than at other times. As discussed in more detail in the article by Baker and colleagues in this issue, the experience of pain at menstruation and the severity of premenstrual symptoms should be considered. Women who have more severe symptoms have reported more unpleasant dreams and a lower quality of sleep in the luteal phase [14] and increased sleepiness [15] than women who have minimal symptoms. Similarly, women who have dysmenorrhea, who experience extremely painful cramps during menstruation, and women who have endometriosis, who suffer extreme menstrual pain caused by misplaced uterine (endometrial) tissue in the abdominal and pelvic area, report poorer sleep quality and higher anxiety during menstruation than symptom-free women. Baker and colleagues [16] found that dysmenorrheic women had more disturbed sleep and subjective sleepiness than controls.

Given the cyclical, although modest, reduction in sleep quality around menstruation in women who do not have sleep complaints, investigation of insomnia in women who have ovulatory cycles should consider the temporal relationship of sleep complaints and the phase of the menstrual cycle.

Objective polysomnographic findings across the menstrual cycle

Early gender-specific laboratory studies yielded limited information on sleep changes across normal ovulatory cycles. These studies were based on small sample sizes, usually in young women (< 30 years of age) with heterogeneous groups including those who had affective symptoms and those taking OCs, often without verification that ovulation had occurred [1,2,4]. Two controlled studies addressed this issue [7,17]. These studies conducted more frequent recordings across the cycle—3 nights/week [17] and every other night [7], respectively—in nonsymptomatic, good sleepers who had verified ovulatory cycles and included temperature measurements and spectral analysis of the sleep EEG.

Slow-wave sleep (SWS) [7,17,18] or slow-wave activity (SWA) in the power spectrum [7] was not different across the cycle, suggesting that sleep homeostatic mechanisms are not altered by menstrual phase.

REM sleep seems to be influenced slightly by menstrual phase. Some studies have found that REM sleep has an earlier onset in the luteal phase [18]. The percentage of REM sleep tends to be decreased [8,16,19,20] in association with raised body temperature in the luteal phase compared with the follicular phase. The authors found that REM sleep tended to decrease from the early follicular phase (27.4%) to the late luteal phase (22.9%) [7].

A consistent finding was a menstrual cycle–associated variation in stage 2 sleep, which was higher in the luteal phase than in the follicular phase. In the study by Driver and colleagues [7], stage 2 sleep increased from (50%) in the late follicular phase to (55.3%) in the early luteal phase. Selected sleep parameters for a full night during the mid-follicular and mid-luteal phases are provided in Table 1. The only significant difference in visually scored sleep was in the proportion of stage 2 sleep.

Specific effects on the sleep EEG was a prominent variation in sleep spindles in the upper frequency range (14.25–15 Hz), which were lowest in the mid-follicular phase and maximal in the mid-luteal phase [7]. Because the menstrual effect on the spindle frequency region in non-REM sleep coincided with the progesterone-mediated increase in rectal temperature [21], it was proposed that the variation could be a temperature-dependent response [22].

Table 1: **Mean over the whole night for selected sleep measures based on visual scoring body temperature, and heart rate during the first four episodes of non-REM and REM sleep from nine women who had ovulatory menstrual cycles for 1 night in the mid-follicular phase and 1 night in the mid-luteal phase (Age 20–30 years)**

Parameter	Follicular phase (SD)	Luteal phase (SD)
TST (mins)	449.5 (30.6)	455.1 (30.2)
SOL (mins)	14.9 (7.0)	14.3 (10.5)
ROL (mins)	66.1 (10.2)	64.0 (8.8)
Stage 1 (% of TST)	4.8 (1.9)	4.2 (1.5)
Stage 2 (% of TST)[a]	49.6 (3.2)	53.7 (3.2)
Stage 3 (% of TST)	5.3 (2.5)	5.5 (2.4)
Stage 4 (% of TST)	14.5 (3.3)	12.0 (3.4)
SWS (% of TST)	19.8 (4.9)	17.5 (4.2)
REM (% of TST)	25.8 (2.7)	24.6 (3.5)
WASO (% of TST)	3.3 (4.8)	2.5 (3.3)
MT (% of TST)	2.6 (1.2)	2.3 (0.7)
SE (% of TST)	91.7 (3.8)	92.8 (3.6)
$Temp_{sleep}$ (°C)[a]	36.7 (0.2)	37.1 (0.2)
HR_{SO}(bpm)	63.9 (10.1)	65.7 (10.9)
HR_{sleep}(bpm)[a]	59.8 (5.5)	63.5 (7.0)

Abbreviations: TST, total sleep time; SOL, sleep onset latency; ROL, REM sleep onset latency; SWS, slow wave sleep; WASO, wakefulness after sleep onset; MT, movement time; SE, sleep efficiency (TST as percentage of time in bed); % as a percentage of TST; $Temp_{sleep}$, rectal temperature during the first four nonREM and REM sleep episodes; HR_{SO}, heart rate (beats per min (bpm)) during wake preceding sleep onset; HR_{sleep}, overnight heart rate during the first four nonREM and REM sleep episodes.
[a] $P < .05$, paired *t*-test.
Data from Driver HS, Dijk DJ, Werth E, et al. Menstrual cycle effects on sleep EEG in young healthy women. J Clin Endocrinol Metab 1996;81:728–35.

Alternatively, it might be induced by progesterone and other agonistic modulators of γ-aminobutyric $acid_A$ ($GABA_A$) receptors, such as benzodiazepines and non-benzodiazepines [23] and neuroactive metabolites of progesterone, that facilitate $GABA_A$ receptor functioning independent of the temperature response ([24–26]; for review see Ref. [27]).

Menstrual, diurnal, and sleep-associated changes in body temperature

In addition to the menstrual cycle–associated changes in body temperature, there are also diurnal fluctuations. Circadian disruption, such as occurs with shift work or increased nocturnal exposure to light, may lead to an increased risk for breast cancer in women [28], as discussed in more detail in the article by Shechter and colleagues in this issue. The largest difference in body temperature between the follicular and luteal phase occurs during the early

hours of the morning [29–31]. Studies that have reported thermoregulatory effects of the menstrual cycle are those that have taken cognizance of the circadian profile influencing the thermogenic effect of progesterone [32,33]. There is a rapid increase in body temperature in response to progesterone administration [34], and body temperature in women increases about 24 hours after a detectable increase in progesterone plasma concentration [21]. Estrogen, on the other hand, lowers body temperature [35]. Considering that body temperature in women who have ovulatory menstrual cycles has both a menstrual and a circadian profile (for review, see Ref. [28]), compensatory responses to the temperature changes (eg, on the cardiovascular system) may be more evident at night than during the day [36].

Sleep-related electroencephalographic spectra, temperature, and heart rate during the mid-follicular and mid-luteal phases

The most remarkable changes in polysomnographically recorded sleep seem to be from the mid-follicular phase, when nocturnal body temperature is low and estrogen predominates, to the mid-luteal phase, when progesterone and temperature are elevated. This finding is in contrast to a subjective increase in sleep disturbances and reduced sleep quality around menstruation, when endogenous levels of these steroid hormones are low.

Methods for investigating the temporal evolution of sleep, temperature, and heart rate

To investigate the temporal evolution of the changes during sleep through one night in the mid-follicular and mid-luteal phase, the authors examined the sleep EEG, nocturnal body temperature, and heart rate during the first four sleep cycles. These data were from nine healthy young women aged 20 to 30 years, with normal body mass indices (mean ± SD 22.1 ± 2.4 kg/m^2) and documented ovulatory cycles, as previously reported [7]. Recordings of sleep, rectal temperature, and heart rate were made every alternate night over 32 to 36 days for the duration of one menstrual cycle. Estradiol, progesterone, and prolactin hormone concentrations measured 6 to 8 days after ovulation were in the normal range for the luteal phase [7]. Progesterone levels ranged from 22.5 to 44.1 nmol/L (normal luteal-phase levels, 20–90 nmol/L), the estradiol concentrations ranged from 190 to 470 pmol/L (normal luteal-phase levels, 180–1100 pmol/L), and prolactin levels ranged from 7.9 to 21.1 μg/L. For the present analysis, one night in the mid-follicular and one night in the mid-luteal phase were selected for each woman relative to her temperature, ovulation, and the onset of menstruation.

For the temporal evolution of changes through the night, sleep cycles of non-REM and REM sleep were defined according to modified criteria described by Aeschbach and Borbély [37]. A cycle that comprised non-REM and REM sleep began with stage 2 sleep, contained at least 15 minutes of stages 2, 3, and 4 sleep, and ended with an REM sleep episode of at least 5 minutes. For the first cycle, no minimum duration of REM sleep was required.

The power spectra were calculated over the first 7.5 hours for non-REM sleep (stages 2, 3, and 4) and for REM sleep. Individual power density values in the 0.625 to 4.625 Hz band, defined as SWA, and EEG power in the 12.125 to 15.125 Hz region, defined as spindle frequency activity (SFA), were computed. The time course of the changes in sleep power spectra for each woman was analyzed for the wake period between lights-out and sleep onset and for the first four non-REM and REM sleep episodes (sleep cycles). For the period before sleep onset, the individual means were calculated for one time bin. In each of the four sleep cycles, individual non-REM sleep episodes were subdivided into 20 equal parts (percentiles), and REM sleep was divided into four equal parts. For each subdivision in the four cycles, the means for SWA and SFA were calculated then averaged over subjects and plotted with respect to the mean duration of each non-REM and REM sleep episode in **Fig. 1**.

Rectal temperatures were recorded continuously while the women were sleeping in the sleep laboratory (ambient temperature, 19°C–22°C). The data were digitized and stored at 60-second intervals on an ambulatory monitoring system. Heart rate (beats per minute) was calculated based on beat-to-beat intervals, determined as the time between successive R-waves and stored for 20-second epochs as described previously [38]. R-waves were detected by a level-crossing algorithm. Twenty-second intervals containing RR intervals of 20 milliseconds or less were considered as artifact and removed from further analysis.

For the cycle analysis, the relative heart rates and temperatures were calculated in parts of consecutive non-REM and REM sleep episodes for each woman. To align the 60-second temperature data with the 20-second sleep epochs, the same temperature value was taken for three consecutive epochs. As in the analysis of sleep and EEG power density, individual heart rates and temperatures were calculated for one time bin before sleep onset. For non-REM sleep and REM sleep episodes heart rate and temperature data were subdivided into 20 equal parts for non-REM sleep and into four equal parts for REM sleep for each woman. Thereafter the

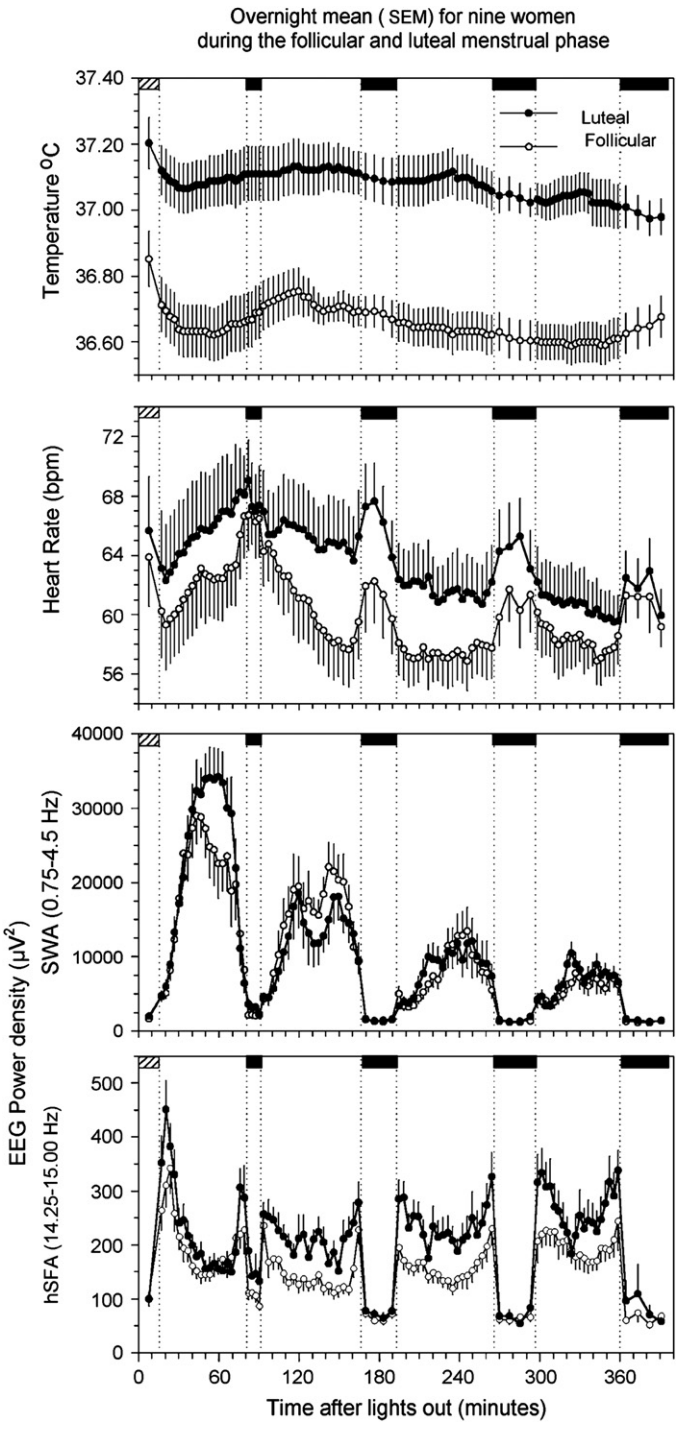

Fig. 1. Overnight mean values (± 1 SEM) for rectal temperature, heart rate, and slow-wave activity power (SWA) in the frequency range from 0.625 to 4.625 Hz and high spindle frequency activity (hSFA: 14.125–15.125 Hz) from nine young women during the mid-follicular (*open symbols*) and mid-luteal (*closed symbols*) menstrual phases. Data were aligned with respect to lights-out at time zero, sleep onset as the first occurrence of stage 2 sleep, and the mean timing of the first four complete non-REM–REM sleep cycles for all nights (n = 18). The first dotted vertical line denotes sleep onset. Dotted lines thereafter mark episodes of REM sleep (indicated by the black bars at the top of the panels). One time bin was allocated to the wake period before the onset of sleep (*hashed bar*). Individual non-REM sleep episodes were subdivided into 20 equal time bins, and REM sleep episodes were divided into four equal timebins. Rectal temperature was significantly higher at all time points in the luteal phase than the follicular phase. (Paired *t*-test based on means per non-REM and REM sleep episode, $P \leq .0125$, for heart rate: non-REM cycles 1–4, REM cycles 2 and 3; SWA: non-REM cycles 1, 2, and 4; hSFA: non-REM cycles 1–4).

means in sleep cycles 1 to 4 were computed for non-REM (20 percentiles) and REM sleep (four percentiles) and averaged across subjects.

Initial comparisons were for the 7.5-hour all-night data, then by cycles 1 through 4, and over the mean for cycles 1 to 4 (390 minutes). Absolute values for the EEG power spectra were log-transformed before statistical analysis. Statistical differences based on repeated measures of ANOVA were followed by paired *t*-test comparisons using a software statistical package (SAS Institute Inc., Cary, North Carolina). Missing values in non-REM sleep were replaced with the mean for the two parts adjacent to the missing value for that subject, and

missing REM sleep values were replaced with the subject mean from that REM period. For two women in the follicular phase, heart rate data were missing from non-REM cycle 2, through to REM cycle 3 for one woman and to the end of the recording for the other woman. Statistical analysis of the heart rate data was performed without replacing data after cycle 1 for these two women. Missing values for temperature and heart rate before sleep onset were replaced with the group mean of the menstrual phase for which data were missing. Significant differences for all-night data were Huynh-Feldt adjusted and set at $P \leq .05$ and at $P \leq .0125$ for the cycle data because of repeated comparisons over the four sleep episodes.

Changes in temperature and heart rate across the first four sleep cycles

Luteal phase overnight body temperature was increased by about 0.4°C compared with the follicular phase (see Table 1 and Fig. 1, top panel). This temperature difference ($F_{1,95}$1949.73; $P = .0001$) was present from before lights-out and over all four non-REM (20 parts per episode) and REM sleep episodes (four parts per episode).

Changes in temperature were correlated with heart rate. Combining the two study nights, the Pearson correlation coefficient for the means of temperature and heart rate during wake preceding sleep onset and during the first four episodes of non-REM and REM sleep was 0.522 ($P = .026$). During the wake period before sleep onset, there was no difference in mean heart rate, as shown in Table 1 (HR_{so}) and Fig. 1 (second graph from the top, first data point). The mean non-REM– and REM sleep–associated heart rate (HR_{sleep}) during the first four sleep cycles differed between the two phases, however. The mean heart rate during the four sleep cycles was higher in the luteal phase ($F_{1,95}$75.44; $P = .0001$) than during the follicular phase. This difference was significant for all non-REM sleep episodes and in the second and third REM sleep episodes. Heart rate initially decreased on going to sleep, then increased gradually during the first non-REM sleep episode, decreased again in the second non-REM sleep episode, and remained low during the third sleep cycle (see Fig. 1). Cyclical changes in heart rate were evident, with lower rates during non-REM sleep and increases during REM sleep episodes.

Changes in sleep across the first four sleep cycles

The length of the sleep cycle and the length of the REM sleep episode were affected by menstrual phase (Table 2). The first sleep cycle and the first REM sleep episode were shorter in the luteal phase than in the follicular phase. In addition, REM sleep episodes showed a significant interaction (see Table 2), indicating a different evolution in the course of the night during the two phases of the menstrual cycle. During the follicular phase, REM sleep episodes increased progressively in duration across the first four episodes, whereas in the luteal phase the duration of the REM sleep episode increased from the first to the second episode and then remained on a similar level for the second, third, and fourth cycles. Thus, over the first four non-REM–REM sleep cycles, there was a menstrual-phase effect on the time spent in REM sleep ($F_{1,71}$5.18; $P = .026$) that was not evident over the whole night (see Table 1). In the luteal phase compared with the follicular phase, there was less REM sleep in the first and fourth sleep cycles whereas during the second sleep cycle there was more stage 2 sleep (menstrual phase× sleep cycle: $F_{3,71}$2.89; $P = .042$), and less SWS (menstrual phase×sleep cycle: $F_{3,71}$4.00; $P = .011$; stage 4 sleep $F_{3,71}$3.83; $P = .014$).

Relative power density in the luteal phase expressed relative to the follicular phase revealed a significant effect of frequency ($F_{99,792} = 5.59$; $P < .0001$; 1-way rANOVA on log-transformed relative values; factor 'frequency') for the all-night non-REM sleep spectrum and no effect for the REM sleep spectrum. In the first non-REM sleep cycle, menstrual-phase differences were noted in the lower frequency range corresponding to SWA (0.75–4.5 Hz) that were less evident in the second cycle and absent in the third cycle. The menstrual-phase effect on frequency in non-REM sleep was in the range of sleep spindles, from 14 to 16 Hz. The luteal-phase increase in power in the frequency region of sleep spindles was evident in the high range of spindle frequency activity (hSFA) at 14.25 to 15.00 Hz in all non-REM sleep episodes and was particularly noticeable after the first episode.

The temporal evolution of the two frequency ranges with a menstrual-phase effect is illustrated in Fig. 1. The bottom two graphs depict SWA and hSFA. Significant menstrual differences in SWA were present in non-REM sleep episodes 1, 2, and 4—higher in the luteal-phase first cycle and lower in the second cycle than in the mid-follicular phase ($F_{1,95}$10.3; $P = .0015$). EEG activity in the hSFA range ($F_{1,95}$162.87; $P = .0001$) also was higher in the luteal phase than in the follicular phase (see Fig. 1, bottom panel).

Are progesterone and/or temperature associated with sleep and heart rate changes?

The relative absence of progesterone in the follicular phase suggest that it plays a major role in orchestrating the changes in the sleep EEG noted in the

Table 2: **Mean duration of non-REM–REM sleep cycles (CYC-1 to CYC-4) and non-REM (non-REM-1 to non-REM-4) and REM sleep (REM-1 to REM-4) episodes for nine young women during 1 night in the follicular phase and 1 night in the luteal phase**

Cycle or episode	Follicular phase in minutes (SD)	Luteal phase in minutes (SD)	Statistics[a]		
CYC-1	82.0 (11.5)	70.7 (7.3)	Menstrual phase	Cycle or episode	Interaction
Non-REM-1	66.1 (10.2)	64.0 (8.8)	P ($F_{1,8}$)	P ($F_{3,24}$)	P ($F_{3,24}$)
REM-1[a]	15.2 (9.2)	6.5 (4.1)			
CYC-2	103.3 (15.2)	100.4 (20.4)		Cycle duration	
Non-REM-2	77.1 (13.0)	72.6 (13.9)	0.032 (6.68)	0.0004 (10.71)	Not significant
REM-2	25.5 (9.0)	27.6 (9.4)			
CYC-3	107.9 (22.6)	101.6 (25.4)		Non-REM episodes	
Non-REM-3	73.7 (14.0)	72.6 (13.2)	Not significant	0.071 (2.66)	Not significant
REM-3	32.9 (15.0)	28.1 (14.6)			
CYC-4	106.9 (13.1)	96.4 (16.4)		REM episodes	
Non-REM-4	65.8 (12.8)	61.1 (5.8)	0.007 (12.92)	0.0004 (14.47)	0.035 (3.61)
REM-4	39.8 (12.2)	30.6 (10.8)			

Statistical details: P (F value) based on a two-way ANOVA for repeated measures on log-transformed values (factors: menstrual phase, cycle or episode, and their interaction).
[a] $P < .05$, paired t-test (performed if ANOVA revealed significant effect of 'menstrual phase' or a significant interaction).

luteal phase, and its effect may be in addition to, or in association with, other effects such as elevating body temperature. From the mid-follicular to the mid-luteal menstrual phase an increase in body temperature was associated with more stage 2 sleep, higher SFA, and elevated heart rates during sleep. The trend for a reduction in REM sleep when body temperature was higher that the authors have reported [7] is small and has not has been a consistent finding in other studies (reviewed in [1,28]). In the present analysis, the difference in REM sleep proportion was found over the first four sleep cycles but not for the whole night, suggesting an effect of sleep duration.

Although the higher luteal temperatures were sustained during the night, the SWA effect was transient (see Fig. 1), being elevated in the first cycle of the luteal phase and reduced in the second cycle when differences in SFA with the follicular phase became more pronounced. The time course of the overall decline in SWA during the first four sleep cycles with a decrease in temperature from sleep onset showed the overall monotonic slope as for a normal night [37] rather than the modification seen with sleep deprivation [39] or napping [40]. The suggestion that the higher luteal-phase temperatures during sleep may be caused by poorer sleep [30] is not supported by the present and other recent studies [1,28]. Rather, sleep in the early part of the night may be improved in the mid-luteal phase. Mid-luteal sleep did not seem to be disturbed, and reported detriments in subjective sleep occur from the late luteal phase, when the levels of the steroid hormones estrogen and progesterone are decreasing, and during menstruation [11,12]. The higher SWA in the first cycle of the luteal phase may be attributed to the higher temperature, because studies in the rat have shown SWA to be increased with elevated body temperature [41].

The difference in temperature also could explain the SFA effects, in part [22]. Studies have shown that administration of progesterone raises body temperature in rats [42] and in human males [43] and females [21]. Compared with single doses of exogenous steroids, secretory hormone profiles during the menstrual cycle and the additional priming or interactions of progesterone with estrogen influencing the central nervous system need to be considered also. Thus, the effects may not be entirely temperature dependent, because progesterone administration induced changes in sleep in male rats without affecting body temperature [25].

There may be an interplay between progesterone and its metabolites and their effects on the sleep EEG. Progesterone has been found to induce changes in sleep in young men and in rats [24,25]. In young men, administration of progesterone at 21:30 resulted in marked increases in plasma levels of progesterone and the metabolites, allopregnanolone and pregnanolone, and led to increased stage 2 sleep and a tendency to reduced REM and stage 4 sleep [24]. There was a slight reduction in SWA and enhanced activity in the higher spindle frequency range (> 15 Hz), particularly in the first hours after progesterone administration. In contrast, elevated SWS and depressed EEG sigma power (10.26–14.1 Hz) has been reported with

pregnanolone in young men [44]. Elevated SWA has been found in rats given pregnanolone [45] and with a selective $GABA_A$ agonist [46].

Sleep spindles, reflected by SFA, have been considered to indicate inhibitory activity in the central nervous system and are modulated by the circadian pacemaker [47] and the menstrual rhythm [7]. The hormonal milieu with progesterone and its metabolites, as well as estrogen, which has been shown to decrease binding to $GABA_A$ receptors [1,27], influences the balance between neural excitation and inhibition across the menstrual cycle. Even though inhibitory processes with higher SFA may be amplified in the mid-luteal phase, an increase in sleep intensity (SWA) was accommodated early in the night during normal menstrual cycles.

With the elevated body temperature in the luteal phase, the authors found that nocturnal heart rates were higher (by 3%–5%) than during the follicular phase. This finding is in contrast with studies of the effects of menstrual cycle on autonomic activity, measuring heart rate variability during the daytime, which found that heart rate was not different between the two phases [48,49]. These studies, however, did find an influence of the menstrual cycle on heart rate variability, with increased sympathetic activity at rest in the luteal versus the follicular phase, [48,49]. The largest progesterone-induced temperature effects are timed to occur during sleep, even though they seem to be independent of this state [50], possibly explaining why these studies found that the menstrual cycle had no effect on heart rate, whereas the authors' study did.

During sleep itself there are variations in heart rate as well as in blood pressure and cardiac output [51]. As reported in studies on men [51], there was a graded decrease in heart rate during non-REM sleep, followed by increases during REM sleep and wake periods. These effects result from central sympathetic nervous system activation, with depression of this system in non-REM sleep [38,52]. A gender difference in heart rate has been reported, tending to be lower in healthy men between 20 and 69 years of age than in women [53]. Along with the elevated temperature and metabolic rate in the luteal phase, heart rate and arm blood flow have been found to increased by 5% at thermoneutral conditions [32]. Possibly, with the relative lowering of the heart rate during sleep, any potential stress on the cardiovascular system with hormone- and/or temperature-associated elevations in heart rates would be reduced. Because young, healthy women have the lowest cardiovascular risk among adults [36], the small but predictable changes in heart rate may contribute to affording them more cardiovascular plasticity and protection from cardiovascular disease than men. Whether this effect on heart rate, nocturnal temperature and sleep is present with OCs, which carry a concern for cardiovascular risk, should be investigated.

Oral contraceptives

Remarkably few studies have examined the effects of OCs on sleep. Studies are also complicated by the different levels of synthetic estrogen and progestin within the various monophasic and triphasic pills. OCs contain synthetic estrogen and/or progestin, with 21 days of active hormone and the last 7 days inactive. Monophasic pills provide the same dosage of hormones through the entire active cycle; triphasic pills give different dosage levels during each week of the month, more closely duplicating the natural hormonal pattern. These "combined" pills contain estrogen and progesterone, whereas "minipills" contain only progestin. Oral contraceptives prevent ovulation by suppressing endogenous reproductive hormones so that women taking these preparations do not have normal cycles. The progestin is responsible for the contraceptive effects, and the estrogen component is included for cycle control; ethinyl estradiol (EE) is a potent suppressor of pituitary gonadotropins.

During the 40-plus years since the introduction of OCs in the 1960s, there has been a trend to lowering the dose of EE and, more recently, extending the use of EE over 84 days and 7 days of placebo. This trend developed because of a concern about the cardiovascular risks, particularly venous thromboembolism, and the side effects commonly associated with OCs, such as weight gain, nausea, breast tenderness, and bleeding, as well as greater acceptance and understanding of the OCs [54,55]. Effects of OCs on sleep may vary, depending on hormonal concentrations and combinations. Although disturbed sleep is not one of the reported symptoms in studies investigating side effects and contraceptive tolerance [56], OCs have been found to alter temperature and sleep architecture.

Oral contraceptives and body temperature

Progestins contained in the contraceptive pill seem to have the same thermogenic effect as endogenous progesterone, in that the 24-hour body temperature profiles in women taking OCs are similar to those of women in the luteal phase of ovulatory cycles. The temperature nadir occurs at a similar time [30,57] or slightly later [58]. In contrast to the rapid decrease in body temperature with the withdrawal of endogenous progesterone before menstruation [59], body temperatures in women taking OCs remain elevated at least 3 days after they have taken the final active contraceptive pill [58]. Thus synthetic steroid hormones have a more prolonged

Table 3: Changes in temperature and sleep as a function of menstrual cycle phase and oral contraceptive use and the main effects of shift-work on reproductive function in women

Condition and parameter	Effect/consequence
Women who have normal menstrual cycles	
Body temperature	LP versus FP: ↑ mean temperature, ↓ amplitude
Sleep	LP versus FP: ↑ SFA (high frequency 14.25–15.00 Hz), ↓ REM sleep (first four sleep cycles), No change in night-time SWS/SWA, ↑ daytime SWS (naps)
Heart rate during sleep	LP versus FP: ↑
Women taking oral contraceptives	
Body temperature	OC versus FP: ↑ mean temperature, ↓ amplitude OC versus LP: Similar temperature rhythm
Sleep	OC versus LP: ↓ SWS OC versus FP, LP, and placebo: ↑ Stage 2 sleep
Shift-work	
Menstrual cycle	↑ irregularities and painful menses ↑ fertility problems
Breast cancer	↑ incidence in shift-workers

Abbreviations: FP, follicular phase; LP, luteal phase; OC, oral contraceptive; SFA, spindle frequency activity; SWA, slow wave activity; SWS, slow wave sleep.
Data from Baker F, Driver HS. Circadian rhythms, sleep and the menstrual cycle. Sleep Medicine 2007;8:613–22.

effect on body temperature rhythms than does the endogenous hormone.

Effects of oral contraceptives on sleep

In an archival analysis that compared women diagnosed as having major depressive disorder and healthy controls, but in which menstrual phase or type of contraceptive was not controlled [60], a reduction in SWS was found to be associated with OC use. OC use, however, does not seem to affect sleep efficiency [58,60] or subjective sleep quality. Reduced REM latency has been reported in healthy women taking OCs [60].

In the active phase of the OC, the proportion of stage 2 sleep was increased compared with placebo [58]. Women taking OCs also had more stage 2 sleep than the naturally cycling women in both menstrual cycle phases but had less SWS than naturally cycling women in the luteal phase. On balance, because the effects of OCs on sleep seem modest, the use of OCs to attenuate pain and mood symptoms may improve sleep in women who have premenstrual and menstrual symptoms.

Summary

In the presence of progesterone, the mid-luteal phase has an increase in body temperature that is associated with more stage 2 sleep, higher SFA, reduced REM sleep, higher SWA in the first cycle, and elevated heart rates during sleep than occur in the mid-follicular phase. A summary of changes in sleep, body temperature, and heart rate is provided in Table 3. The relative stability in all-night sleep processes may be an important factor in affording women the flexibility to adapt to the thermoregulatory and cardiovascular challenges of the menstrual cycle. Most of the studies have been conducted in young women in their early twenties. For women in their forties, waning ovarian function leads to decreased ovulation and increased cycle irregularity, which in turn may negatively influence their sleep. Changes in sleep with OCs seem small (ie, increasing stage 2 sleep), but the effects of OCs and fertility treatments on the sleep EEG and nocturnal heart rate have not been investigated.

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Circadian Rhythms and Shift Working Women

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- The central circadian clock
- Circadian and sleep/wake disorganization in shift work
- Health effects of shift work in women: menstrual cycle, fertility/reproduction, and breast cancer
  - *Menstrual cycle effects*
  - *Fertility, pregnancy, and fetal development*
  - *Breast cancer, light at night, and melatonin*
- Clock genes, peripheral circadian clocks, cancer development, and shift work
- More health effects of shift work in women: nutrition, cardiovascular, and gastrointestinal disorders
  - *Nutrition, eating, and weight*
  - *Cardiovascular disease and smoking*
  - *Gastrointestinal disease*
- Psychosocial and behavioral
  - *Domestic and family life*
  - *Psychological effects*
- Countermeasures
- Summary
- References

Shift work, defined as working on schedules that are outside of the typical nine-to-five workday, is a necessity in and a product of the 24/7, "around-the-clock" society. As recently as 2001, 30% of employed Canadian men between ages 18 and 54 years worked on nonstandard shifts [1]. Over the past few decades, the number of employed women has increased, with many working shifts. Almost 75% of women who have children younger than 16 years participate in the workforce [2], and in Canada 26% of employed women between ages 18 and 54 years are involved in shift work [1]. Shift work can result in a severe disruption of the temporal harmony between various physiologic and

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psychological rhythms, contributing to several medical and psychosocial health problems.

Women have more difficulty adapting to shift work than men [3]; they are especially at risk for several female-specific disorders, including menstrual cycle disruption, problems with fertility and reproduction, and breast cancer. The recent identification of functional clocks in tissues outside the brain suggests that circadian desynchronization experienced by shift workers is complex [4]. For women, the finding that neurons in the central 24-hour or circadian clock, the suprachiasmatic nucleus (SCN), contain receptors for estrogen and progesterone [5] indicates a functional interaction between the circadian system and the menstrual cycle that adds another level of complexity to perturbations in their circadian rhythm and sleep/wake schedule. This article explores concerns for the female shift worker, from physiologic to personal and family life, and addresses the relationship between an altered sleep/wake cycle and the circadian system as a consequence of shift work, and various associated health and psychosocial disorders.

The central circadian clock

Twenty four–hour rhythmicity is observed in many aspects of human physiology and behavior, including levels of hormone secretion [6], sleep propensity and architecture [7,8], and subjective and electroencephalographic-estimated alertness [9,10] throughout the day. Experiments identifying an intrinsic 24-hour mean activity in the neurons of the SCN together with studies showing that ablation of the SCN abrogates rhythmic behavior confirm that the SCN is the location of the central circadian clock [11]. Lesion of the SCN in nocturnal and diurnal mammals results in a loss of sleep/wake rhythmicity [12].

In humans, just as in many other organisms, the most powerful synchronizer of the central circadian clock is light [13,14]. Nonphotic synchronizers, such as exercise and melatonin, also have demonstrable effects on circadian phase, although the efficacy of these measures is less well characterized than light stimuli [15,16]. The synchronizing effect of light permits the central circadian clock to predictably coordinate internal physiology with the external environment.

The pattern of light exposure can be planned to rapidly reset the central circadian pacemaker to earlier or later phases [14]. The central circadian clock is especially sensitive to light in the 440 to 480 nm range [17,18], and therefore shorter wavelength light (eg, in the blue visible light range) can more efficiently induce significantly larger phase shifts in the temperature and melatonin rhythms than light of longer wavelengths [19,20]. The central circadian clock is also sensitive to low intensities of light, including ordinary indoor room light [14,21], and integrates light information so that the effect of light exposure is sustained even when light is intermittently interrupted by darkness [22].

The consolidation of human sleep is the result of a complex interaction, including homeostatic and circadian components [7,8]. The circadian phase at which sleep is initiated and the time passed since a previous sleep episode interact to regulate the length of sleep [7,13]. Sleep parameters measurable with polysomnography, such as sleep propensity, sleep latency, sleep efficiency, the proportion of rapid eye movement (REM) sleep, REM sleep latency, and the fraction of sigma activity (12–15 Hz) (ie, sleep spindles) in non-REM sleep, co-vary with circadian rhythms of core body temperature (CBT) and plasma melatonin concentration [7,13,23]. Under normally entrained conditions, sleep is initiated on the falling limb of the CBT rhythm, approximately 6 hours before the temperature minimum, resulting in sleep durations approximating 8 hours [24].

Circadian and sleep/wake disorganization in shift work

A misalignment between the endogenous circadian system and the timing of sleep contributes to sleep disruption and impaired vigilance. Initiating sleep close to the temperature nadir, as is the case for many shift workers, results in abbreviated sleep length with an increase in the amount of wakefulness in the later part of the displaced sleep episode [7,13,25]. Night shift work in particular is associated with the most sleep disruption. In one study, almost one third of night shift workers reported symptoms of insomnia or excessive sleepiness, whereas these symptoms were reported in only 18% of day workers from the same sample population [26]. Data from actigraphy [27], sleep diary [26,28], and polysomnography-based studies [10,29,30] indicate a disruption in sleep associated with the night shift in particular, so that the duration of daytime sleep in night shift workers typically ranges from 4 to 7 hours.

The central circadian pacemaker does not adapt to rapid reorientations in the shift worker's sleep/wake schedule. In most individuals, circadian adjustment of cortisol and melatonin rhythms to the shifted sleep/wake schedule remains incomplete and may persist despite consecutive shifts worked [31]. Slow-rotating shift arrangements could favor some circadian realignment to the work schedule, because consecutive sleep episodes on the same schedule may lead to larger phase shifts of temperature, melatonin, and cortisol rhythms [32,33].

Sleep duration is also influenced by the length and timing of shifts (eg, longer periods between shifts may foster longer sleep times) [34].

Shift work sleep disorder, as described by the International Classification of Sleep Disorders, is characterized by excessive sleepiness or insomnia [35]. Shift work–related sleep disruptions, sleep deprivation, and especially working during night hours can result in lapses in vigilance and attention, decrement in performance, and reduced cognitive throughput [10]. Recent work has used waking electroencephalographic and imaging techniques (positron emission tomography and functional MRI) to more objectively explore the effects of sleep loss on neurocognitive function [36]. In addition to the effects on workplace productivity and the safety of others, decreased vigilance and attention after a night or extended shift was shown to be associated with increased risk for motor vehicle crashes and accidents [10,37].

Health effects of shift work in women: menstrual cycle, fertility/reproduction, and breast cancer

In women who work shifts, the disruption of the circadian clock and its immediate effect on hormonal production, sleep, and clock gene expression form the background on which sex-specific issues may present themselves.

Menstrual cycle effects

Circadian rhythms, most notably the circadian curve of CBT, vary as a function of the changing hormone profile across the menstrual cycle [38], which may have implications on sleep quality [39–41]. Recently, neurons in the SCN were found to contain receptors for both estrogen and progesterone, the two main steroid hormones associated with the menstrual cycle [5], which further suggests a functional interaction between the circadian system and the menstrual cycle.

Female shift workers, who experience atypical sleep/wake schedules and a desynchronization of their daily rhythms, experience several menstrual cycle irregularities. An early study by Tasto and colleagues [42] investigated, among other health consequences, the effects of shift-working on menstrual function in a large group of nurses. The results showed that nurses on a rotating schedule experience the most disruption. Compared with all other fixed schedules (including night only), rotating nurses reported lengthened menstrual cycles, visited the clinic more often with menstrual-associated complaints, and experienced more "tension, nervousness, weakness, and sickness at menstruation." Another survey of 2264 shift-working women found an increased occurrence of menstrual irregularity and dysmenorrhea (painful menstruation) in night-shift workers [43]. Although some investigators have found no evidence of altered menstrual cycle length or other irregularities in shift workers [44], a recent report showed that 60% of night-shift nurses who had regularly occurring cycles experienced cycles of fewer than 25 days [45]. In another study, 53% of shift-working nurses experienced altered menstrual function, with symptoms including dysmenorrhea, changes in menstrual flow and length, and duration of bleeding [46].

Hormonal changes (specifically, increased amounts of circulating progesterone) associated with the luteal, or postovulatory, phase of the menstrual cycle influence mood, circadian rhythms, and sleep, and the possibility exists that these factors may contribute to and influence shift-work maladaptation. An interaction between shift work and menstrual phase has been observed, with decreased subjective sleep quality in evening shift workers and increased irritability and decreased alertness in night-shift workers during the premenstrual (late luteal) phase compared with the follicular phase [47]. Therefore, in addition to social and familial conditions that are unique to women, the physiology of the menstrual cycle should be considered when discussing problems with shift work.

Fertility, pregnancy, and fetal development

As a consequence of alterations in their menstrual cycle, a decline in the reproductive health of night and rotating shift workers is likely. A series of studies, although not unequivocal [48], indicate that exposure to shift work [44,49], rotating shifts [50], and evening/night shifts [51] resulted in subfecundity (longer time to pregnancy). However, a meta-analysis of the literature published between 1966 and 2005 investigating the occurrence of preterm delivery, low–birth weight, and preeclampsia as a result of various unusual working conditions concluded that shift work poses only a minimal risk to the reproductive system [52]. Nevertheless, evidence suggests that shift work during pregnancy has consequences for fetal development. Fixed night work was associated with increased incidence of fetal loss [53–55], especially during the first trimester, which resulted in a 60% increased risk for miscarriage compared with workers on a day schedule [56]. Compared with day workers, young women working rotating shifts showed significant reductions in gestational age and birth weight in live births [57], although no increased risk for fetal loss was seen [54–56].

Breast cancer, light at night, and melatonin

Breast cancer, a sex hormone–dependent malignancy with a possible estrogen-related origin, is the second leading cause of death and the most frequently reported cancer in women [58]. Several epidemiologic studies, although not all [59], have found a disproportionate incidence of breast cancer in shift-working women, including those on rotating shifts [60–62] and fixed-night schedules [63–65], and in radio/telegraph operators at sea [66] and flight attendants [67]. Exposure to artificial light at night and subsequent melatonin suppression may increase the risk for breast cancer [68].

The melatonin hypothesis proposed by Stevens [69] suggests that factors (eg, magnetic fields, light at night) that decrease nocturnal melatonin levels can influence breast cancer development. Melatonin secretion is suppressed by light [70] of intensities as low as 200 lux [71]. This hypothesis is supported by evidence of melatonin's oncostatic properties. Ablation of the pineal gland (eliminating all melatonin secretion) in 20-day-old rats [72], and "functionally pinealectomizing" rats by keeping them in constant light from birth [73], significantly increased the incidence of 7,12-dimethylbenz(α)anthracene (DMBA)–induced mammary tumors. Cancer development was reduced from 95% (in DMBA + vehicle treated rats) to 25% (in DMBA + melatonin treated rats) after a 500 μg/d melatonin administration [73]. Furthermore, addition of 10^{-9} to 10^{-11} M concentrations of melatonin (ie, physiological nocturnal concentrations) significantly reduced tumor proliferation in human breast cancer cells in vitro, with a loss of this inhibition with melatonin-free medium [74]. These results were recently reinforced by Blask and colleagues [75], who first implanted human breast cancer xenografts or rat hepatomas in rats, and then perfused them with blood samples from premenopausal women. Increased cell proliferation was found in tumors perfused with melatonin-deficient blood (collected either during the day or at night after suppression by bright white light) compared with those perfused with melatonin-rich blood (collected during night time in darkness). Finally, blind women, who are less sensitive to light and therefore melatonin suppression from light exposure at night, show a reduced risk for developing breast cancer [76–78].

In shift workers, exposure to light at night was proposed as the means through which nocturnal levels of melatonin are blunted, which in turn reduces melatonin's oncostatic function in night-shift workers [79]. In a nested case-control study, almost twice as many cases of breast cancer were identified in nurses who provided a morning urine sample within the lower quartile of urinary 6-sulfatoxymelatonin concentrations compared with nurses who provided samples within the highest quartile of urinary 6-sulfatoxymelatonin concentration [80]. However, this particular study included no control for the light intensities at sampling, the number of night shifts worked before the sample, or the shape of the melatonin rhythm. A separate investigation could identify no association between 24-hour urinary 6-sulfatoxymelatonin concentration and breast cancer risk [81].

Clock genes, peripheral circadian clocks, cancer development, and shift work

Recent studies elucidating the mechanisms that underlie circadian rhythmicity bring an added dimension to our understanding of the physiological consequences of shift work. The intrinsic function of SCN neurons depends on a regulated loop of clock genes that includes *Clock* and *Bmal1*, three Period genes (*Per 1, 2, 3*), and two cryptochrome genes (*Cry 1, 2*) [4,82]. The autoregulatory loops are organized so that protein complexes of transcription factors CLOCK and BMAL1, or alternatively NPAS2 and BMAL1, promote the expression of the *Per* and *Cry* genes and clock-controlled genes that are the output of the pacemaker [82]. The PER and CRY proteins in turn heterodimerize in the cytoplasm and repress their own transcription in the nucleus. The CLOCK:BMAL1 protein dimer is also believed to promote the transcription of orphan nuclear receptors *Rev-erb* (α and β) and *Ror* (α and β), which in turn promote or repress *Bmal1* transcription [83]. The result of this organization is that a circadian rhythm in the levels of clock gene RNA and protein products can be discerned within the SCN. Rhythmicity in the expression of a modified clock protein also exists outside the SCN [84]. *Per* and *Bmal1* RNA levels peak in antiphase to each other in peripheral tissues just as in the SCN, suggesting that the molecular organization of these clocks is similar [4]. The central circadian clock of the SCN is considered dominant because it is required for coordination of clock gene expression [85,86].

Peripheral clocks have also been sampled in humans in vivo under entrainment [87–89] and constant conditions [89–91]. In human peripheral blood mononuclear cells (PBMCs) and polymorphonuclear white blood cells, *HPER1* expression peaks near the habitual time of awakening and after the peak of plasma melatonin concentration [89–91]. *HPER2* levels are also higher in the morning, near the time of habitual awakening [89,91,92]. In humans, as in animals, clock gene expression can become aligned to a shifted light/dark