ERRATA

The original publication had errors in the numbering of references. The correct reference list follows.

SLEEP regrets this error

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In addition, the following corrections apply to the body of the manuscript.

The first reference numbered 86 should be #86a.
The last refernce in the section entitled "Subjective sleep data" should be 110.
Reference number 157 on Page 549 refers to the Stanford Sleep Disorder Center.
The first sentence on page 547 should say infradian rhythm, not ultradian rhythm.
Four of the references are labeled by (A, B, C, D) in the text and in the reference list.

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Sex, Steroids, and Sleep: A Review

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Summary: The present article reviews direct and indirect evidence of the effects of sex steroids on different aspects of sleep. It begins with a review of what is known about the effects of steroid hormones on sleep and on central nervous system processes related to sleep, such as the GABA-ergic system, in animals. It continues with a review of the effects of exogenous hormones on human sleep and a review of studies comparing sleep during hypogonadal states secondary to surgical or natural menopause. The article proceeds to review the data on the effects of the menstrual cycle on both subjective and objective aspects of sleep and circadian temperature and melatonin rhythms in samples of healthy women, women with premenstrual dysphoric disorder, and women with primary insomnia. Then, the article reviews gender differences in sleep during depression and raises the possibility that sex steroids moderate these differences. Finally, the article concludes with a discussion of the implications of the data reviewed for basic clinical, and methodological aspects of sleep research.

INTRODUCTION

THE REPORT OF THE NATIONAL COMMISSION ON SLEEP DISORDERS RESEARCH1 states that "...most of what is known about sleep — its physiology, normative values, and consequences of sleep disruption — has been obtained only for males." The scarcity of research on sleep in women should be of concern to the sleep research community because inattention to factors unique to women, such as the phase of the menstrual cycle during which participants are studied, can and has led to inconsistent findings and false conclusions. For example, early studies of gender differences in circadian temperature rhythm reported lower mean levels and larger circadian temperature amplitude in men than women.2,3 Recent attention to menstrual phase revealed that gender differences in temperature rhythm are present primarily during the luteal phase, and that during the follicular phase there are no significant differences between the circadian temperature rhythm of women and men.4

Sleep patterns are sexually dimorphic in several species. Although limited in number, studies have also shown some sex differences in humans. Women have twice as many sleep spindles,5 more slow-wave sleep,6 a differential time course in delta activity,7 and a slower age-related decline in delta8 compared to men. Others have suggested that sex differences in humans are reasonably subtle under baseline "normal" sleep conditions but increase in magnitude under biological and chronobiological challenges such as drug administration, sleep deprivation, shift work and travel across multiple time zones.9

There is substantially more work on sex differences in other species. Sex differences in age-related changes in slow-wave activity are present in cats, with faster age declines in delta in males.10 Male rats have more REM sleep than females throughout the light/dark cycle.11 Mice may also show sex differences in the amount of REM sleep, but it depends on phase of the light/dark cycle.12 Moreover, there is sexual dimorphism in sleep architecture following caffeine administration in mice, with increases in slow-wave sleep in males and in REM in females.13

These, and more data reviewed here, suggest that sex hormones influence sleep, its physiology, and its pathology in a number of different species including humans. The present article will review direct and indirect evidence of the effects of sex steroids on different aspects of sleep. It begins with a review of what is known about the effects of steroid hormones on sleep and on central nervous system processes related to sleep, such as the g-Aminobutyric acid (GABA) system, in animals. It continues with a review of the effects of exogenous hormones on human sleep and a review of studies comparing sleep during hypogonadal states secondary to surgical or natural menopause. The article proceeds to review the data on the effects of the menstrual cycle on both subjective and objective aspects of sleep and circadian temperature and melatonin rhythms in samples of healthy women, women with premenstrual dysphoric disorder, and women with primary insomnia. Then,
the article reviews gender differences in sleep during depression and raises the possibility that sex steroids moderate these differences. Finally, the article concludes with a discussion of the implications of the data reviewed for basic, clinical, and methodological aspects of sleep research.

**Neuroendocrine influences on sleep in animals**

Receptors for sex steroids including estrogens, progestins and androgens have been identified in the brain of several species including fish, birds, reptiles, and mammals (rodents, carnivores, and the rhesus monkey). For example, estrogen receptors have been located in the medial preoptic nuclei, the medial cell groups in the hypothalamus, medial limbic forebrain structures such as the medial amygdala and the lateral septum and the hippocampus. Estrogen and progesterone act on the CNS both through interaction with intracellular receptors that trigger genomically directed interactions in protein synthesis and through a more rapid nongenomic alteration of neuronal excitability through binding sites on neurotransmitter-gated ion channels such as the GABA$_A$ receptor complex.

**Progesterone.** There is evidence demonstrating the hypnotic anesthetic, anxiolitic anxiolytic, and anticonvulsant properties of progesterone. Intrapertitoneal administration of progesterone has dose-dependent hypnotic effects. The picture that emerges from recent studies of the mechanism by which progesterone might exert its sedating effects is complex. It is believed that progesterone might exert its sedating effect through the nongenomic direct action of select progesterone metabolites (particularly 5α-pregnanolone and 5β-pregnanolone) on the GABA$_A$ receptor rather than through activation of intracellular progesterone receptors. Progesterone derivatives were shown to increase the frequency and duration of chloride channel openings, leading to hyperpolarization and decrease in neuronal excitability. Their potencies in biochemical and electrophysiological assays were shown to correlate with their sedative effects in vivo. In fact, it has been suggested that the potency of progestin actions on GABA$_A$ receptors, even at naturally occurring levels, is at least as large as that of pharmacological agonistic modulator of the GABA$_A$ receptor, such as the benzodiazepines, whose effects on sleep are well documented.

Despite the indications that progesterone and its metabolites are sedating and have similar agonistic interactions with the GABA$_A$ receptors, attention to the effects of progesterone and its metabolite and precursors on sleep EEG has begun only recently. With respect to NREM sleep, progesterone decreased wakefulness and shortened latency to NREM in a dose-dependent manner. Moreover, like benzodiazepines, progesterone reduced EEG activity in the low frequency range (≤7Hz) and increased EEG activity in higher frequency ranges (≥10Hz) during NREM. With respect to REM sleep, progesterone, like benzodiazepines and most antidepressants, has a suppressing effect. In addition to lengthening latency to REM, and reducing the amount of REM in a dose-dependent manner, progesterone administration increases activity in the high frequency range (≥11Hz) during REM. These effects were noted between one and four hours after progesterone administration. Like progesterone, allopregnanolone, a neuroactive metabolite of progesterone, reduces the latency to NREM sleep and in a dose-dependent manner influenced EEG activity both during NREM sleep and during REM sleep. During NREM sleep, EEG activity was reduced in the lower frequencies (≤7Hz) and enhanced in the higher frequencies (≥13Hz). During REM sleep, allopregnanolone increased high-frequency EEG activity (≥17Hz). These effects were most pronounced during the first post-injection hours and gradually diminished thereafter. Similarly, pregnanolone, another neuroactive metabolite of progesterone, produces dose-dependent decreases in wakefulness and increases in NREM sleep with little influence on REM. Even though the evidence reviewed here indicates that, like benzodiazepines, progesterone and its metabolites act as GABA$_A$ receptor agonists an attempt to use micronized progesterone as an adjunct treatment of benzodiazepine withdrawal after long-term drug use did not prove effective. It is possible that the modulatory action of progesterone and its metabolites are mediated either by a unique binding site different from that of benzodiazepines or by indirect mechanisms.

In contrast with the action of progesterone metabolites, such as pregnanolone and allopregnanolone as GABA$_A$ receptor agonists, in vitro experiments demonstrate that pregnenolone, a precursor of progesterone, acts as a GABA$_A$ receptor antagonist. Consistent with the in vivo studies, a recent in-vivo study demonstrated that pregnenolone enhances delta EEG activity in NREM sleep, an effect that is opposite to that observed with either progesterone or benzodiazepines. It was hypothesized that the steady state concentrations of progesterone agonists and antagonists determines the net GABA-ergic response and its effect on sleep.

All of the studies we cited in this section used male rats as subjects so as to avoid the confounding effects of endogenous hormones produced during the estrus cycle of female rats. It is not clear to what extent these findings will generalize to female rats for two reasons. First, exogenous progesterones are usually synthetic and are given at higher doses than levels of circulating hormones making it difficult to generalize the results across gender. Second, given the clear sexual dimorphism in inducing progesterone receptors synaptogenesis and given the active role of progesterone in synaptic downregulation during the estrus cycle it is possible that the influence of endogenous pro-
gesterone, its precursors, and its metabolites on sleep in females would differ from the influence of exogenous progesterone observed in male rats. Similarly, it is not clear to what degree the reported effects of estrogen on sleep are species specific. These studies do, however, indirectly suggest that naturally occurring steroids might also play a physiologic role in modulating GABA-mediated synaptic inhibition in a state of altered central nervous excitability such as sleep.

**Estrogen.** Estrogen increases the turnover of norepinephrine in a number of brain regions, effects that would be expected to decrease REM sleep. Indeed, REM sleep is dramatically decreased during proestrus (behavioral estrus), when plasma concentrations of β-estradiol (E2) levels are peaking, but this effect appears to be pronounced only in the dark cycle. Moreover, REM sleep is enhanced in adult females with ovariectomy and suppressed by subsequent exposure to estradiol. Here again, ovariectomized rats showed a selective increase in REM relative to normal cycling females only during the dark phase.

The fact that daytime sleep in rats does not appear to be influenced by estrogen, progesterone alone, or progesterone delivered after estrogen priming indicates that the effects of estrogen depend, to some degree, on the phase of circadian and/or ultradian rhythms. Ovariectomy enhances the relationship between core body temperature and sleep with a strong negative correlation between temperature and both REM and slow-wave sleep and a strong positive correlation between temperature and wakefulness. In intact female rats, the correlation between body temperature and both REM and slow-wave sleep was of significantly smaller magnitude than that observed in ovariectomized rats. In addition, the temperature acrophase was advanced in the ovariectomized rats whereas the acrophase was delayed during estrus and proestrus in intact females. Moreover, the most dramatic changes in sleep in intact animals also occurred during the days of estrus and proestrus when estrogen and progesterone levels were highest. These findings suggest that ovarian sex steroids, particularly estrogen, weaken the coupling of body temperature and the sleep/wake cycle. Some researchers have suggested that the activation of estrogen receptors in the suprachiasmatic nucleus and dorsal raphe are likely to alter or modulate circadian rhythms. By inference, the uncoupling of temperature and sleep rhythms may be primarily due to estrogens (see also p. 19–21).

The mechanism by which estrogen selectively influences REM sleep is not fully understood. Both genomic and nongenomic mechanisms have been investigated. The expression of c-fos protein in A2 adrenergic neurons is increased during proestrus, decreased by ovariectomy, and reversed by estradiol. The expression of c-fos protein is also involved in the secretion of luteinizing hormone. Further, like progesterone, estrogen alters neuronal excitability through interactions with gamma-aminobutyric acid receptor and 5-HT receptors, two neurotransmitter systems that are involved in sleep regulation. Estrogen increases the turnover of norepinephrine in the brainstem, the hypothalamus, locus coeruleus and nucleus accumbens. These effects would be expected to decrease REM sleep given that noradrenergic neurons are involved in REM sleep suppression and given that these neurons concentrate both androgen and estrogen. Alternatively, choline acetyltransferase activity also appears suppressed during proestrus and thus may also contribute to the REM sleep suppressing effects of estrogen. Moreover, female rats have more locus coeruleus neurons than males which may result in stronger inhibitory influences on REM sleep in females.

**Testosterone.** Gender differences in REM sleep appear to be strongly influenced by androgens. Exposure to prenatal stress alters the perinatal release of testosterone and has dramatic influence on sleep in male mice, resulting in increased REM sleep, eliminating the usual sex differences. Neonatal castration also selectively increases REM sleep in mice, an effect that is reversible by neonatal administration of testosterone. Testosterone also decreases REM sleep in female neonatal mice. Mutant male mice with androgen receptor deficiency show sleep patterns that more closely resemble normal females. Administration of gonadal hormones to adult animals has minimal effect on sleep or on sex differences in sleep. This indicates that there might be a critical period in brain development in which androgens have their strongest influence on sleep.

**Melatonin.** The pineal gland has been used extensively as a model for sex steroid effects on neurons, particularly with regard to circadian rhythms. Nocturnal pineal noradrenergic transmission causes a rise in melatonin production triggered by norepinephrine release in the superior cervical ganglia. Progesterone and estrogen cytosol receptors exist in the pineal gland of the rat and the bovine. Gonadal and adrenal hormones may act on different sites in the pineal and thus may affect melatonin through different routes. In female rats, melatonin synthesis and secretion is reduced during proestrus, when estradiol and progesterone levels are elevated. Antiestrogens, such as Tamoxifen, reduce the nocturnal melatonin peak, whereas antiprogestagens increase it. In male rats, circulating testosterone appears to be necessary to maintain the amplitude of melatonin rhythms. In vivo, gonadal steroids in both male and female rats regulate the response of pineal cells to adrenergic stimulation. Exposure to estradiol and testosterone potentiate pinealocyte response to adrenergic activation in gonadectomized female and male rats, respectively.
Thus, gonadal hormones influence neuroendocrine function at both pre- and post-synaptic sites.  

**Neuroendocrine influences on sleep in humans**

Animal studies reviewed above indicate that gonadal hormone receptors do exist in the central nervous system and that these hormones affect sleep. We first review what is known about the effects of exogenous hormones on sleep and then review the little that is known about the relationship between endogenous levels of hormones and sleep.

**Exogenous hormones.** Most of what we know about the effects of gonadal hormones on sleep in humans comes from the study of the effects of exogenous hormones. It is difficult to generalize from studies of the effects of exogenous hormones on sleep to the effects of these hormones in natural cycles. The main difficulties are that (a) these hormones are usually synthetic compounds; (b) these hormones are usually administered at levels that exceed the naturally occurring levels; and (c) the overall hormonal environment cannot be duplicated.

**Progesterone.** Exogenous administration of high levels of progesterone have marked sedative effect on humans. This effect was first reported by Hans Selye and confirmed by subsequent research both in animals (see above) and in humans. For example, high intravenous doses of progestrogen produced high levels of sedation in four women with carcinoma of the cervix who received 1000 ml over one hour and in pregnant women who received 350 ml over 10 minutes. Drowsiness was also produced when progestogens were orally administered as an anxiolytic or as treatment for aggression. The sedative effects of progesterone and its metabolite pregnanolone were also observed in males. Three of the four studies were not placebo controlled. Of the three open label studies, two reported sedation during the time of active administration and one reported the largest increase in fatigue not during the active administration of progesterone but rather on the two days proceeding its discontinuation. The most recent of the four studies was a double-blind placebo-controlled crossover study of nine healthy males. It revealed that evening administration of progesterone induced a significant increase in NREM sleep. During NREM there was a significant decrease in the slow frequency range (0.4-4.3 Hz) and an increase in the higher frequency range (> 15 Hz). These findings are consistent with the results of a recent study of sleep following the administration of progesterone in male rats. Also consistent with the animal literature is the finding that pregnenolone, a precursor of progesterone that acts as a GABA<sub>A</sub> receptor antagonist, enhances slow-wave sleep and reduces EEG activity in higher frequency bands in men just like it does in male rats.

In addition to the complex nongenomic actions of progesterone, its metabolites, and its precursors on sleep, attention has also recently turned to the possible genomic action of progestrogen and its effect on sleep. For example, administration of mifepristone (RU-486) to nine healthy men produced an increase in time awake, a delay in sleep onset, a decrease in slow-wave sleep during the first sleep cycle, and an overall reduction in REM sleep.

**Estrogen.** Placebo-controlled studies of hypogonadal and perimenopausal women pre- and post-estrogen therapy report decreased latency to sleep onset, decreased wakefulness after sleep onset, increased total sleep time, and decreased rate of cyclic alternating patterns after the initiation of estrogen replacement therapy. Greater insomnia at baseline appears to be associated with greater improvement in sleep quality with HRT. Two recent studies comparing placebo with a more contemporary HRT regimen consisting of a combination of estrogen and progesterone show some increase in sleep continuity with both placebo and treatment but no differential effects. Purdie and colleagues suggest that their failure to find a significant difference between HRT and placebo might be an artifact of their sample which included women who reported lower sleep disturbances at baseline than women in other samples. A naturalistic study indicated that women who chose hormone replacement therapy report greater prevalence of sleep disturbance before treatment initiation than women who did not choose HRT (7% versus 13%) and continue to report higher prevalence of disturbed sleep even a year after the initiation of treatment.

Both within-subject comparisons and between-subjects comparisons indicate that estrogen administration in humans, like in animals, affects REM sleep but does not affect NREM sleep. However, unlike the suppressing effect of estrogen on REM sleep in rats, estrogen has an enhancing effect on REM sleep in humans, with increased time spent in REM sleep and decreased latency to REM sleep.

**Endogenous hormones.** The peri-menopausal period is associated with hyperestrogenism, hypergonadotropism, and decreased luteal phase progesterone excretion. During the menopausal and post-menopausal periods estrogen and progesterone levels decrease. Epidemiological and survey studies report an increase in the incidence of insomnia complaints from pre- to post-menopause. Compared with pre-menopausal women, post-menopausal women have longer latencies to sleep onset, more sleep maintenance insomnia, and a greater incidence of hypnotic use that is more prevalent among women with low body mass index. However, not all studies of sleep in middle-aged women found a significant effect of the menopausal status. A closer look at two potentially confounding factors, aging and hot flashes, revealed that women with hot flashes have more disturbed sleep (a significantly greater number of intermittent awak-
enings, a significantly greater number of stage shifts, and significantly lower sleep efficiencies) and that these findings held even after controlling for the effect of age. This indicates that the hormonal milieu in this age group might have an effect on sleep. It is not clear, however, whether this effect is mediated by hot flashes, or is a direct result of the unstable hormonal milieu that effects both hot flashes and sleep at the same time.

**Menstrual cycle effects on sleep in healthy women**

Early on in the history of sleep research, when norms for sleep parameters were established, concerns about the potential effects of the menstrual cycle on women's sleep architecture were taken into account and the norms for women were obtained during the follicular phase (pre-ovulatory). However, since then, the potential confounding effect of the menstrual cycle has been ignored and very little attention has been paid to the phase of the menstrual cycle of female participants in sleep research. In a survey of the literature published in 1983 and 1984 in *Sleep*, the journal of the American Academy of Sleep Medicine and the Sleep Research Society, Lee and Shaver concluded that "sleep research often excluded women as participants" and that "when female participants are used, menstrual cycle phase as a confounding variable is not considered." In the decade that followed a few researchers began to study the relationship between the phase of the menstrual cycle and sleep, daytime sleepiness, circadian rhythms, and respiratory indices. In reviewing this literature, one is struck by the enormous methodological challenges that the study of women's sleep in relation to the menstrual cycle presents.

**Methodological issues.** To understand these challenges one needs to understand the pattern of change in ovarian steroids across the menstrual cycle. It is customary to identify day one of the menstrual cycle as the first day of menses. As women ovulate and menstruate, gonadal hormones rise and fall. Following ovulation, the levels of estrogen and progesterone rise for the first seven days and begin decreasing thereafter with a sharp drop just preceding the onset of menses. Progesterone remains at low levels until ovulation occurs during the next cycle. Estrogen remains low during the first half of the follicular phase but begins to rise as part of a complex process stimulating the secretion of FSH and LH leading to ovulation. These changes are depicted in Figure 1.

The exact timing of the LH surge, ovulation, peak progesterone and estrogen, and menstruation vary from cycle to cycle within and across individuals. This complicates the task of scheduling sleep studies, aligning the data from different cycles, and comparing results across studies. A few existing studies have begun to address some of the methodological difficulties. These three studies have controlled for potential confounding effects of abnormalities in the menstrual cycle, use of exogenous hormones, health, and presence of sleep disorders. These studies have also confirmed ovulation with hormonal assays and discarded data from anovulatory cycles. All three studies counter-balanced the menstrual-phase during the first night in the sleep laboratory so that an interaction between the first night effect and the phase of the menstrual cycle would not confound the result. Finally, because the number of anovulatory menstrual cycles and the irregularity in the length of the cycles both increase with age, some studies
focus on women who were younger than 35 years. To further minimize scheduling problems that are caused by menstrual cycle factors, some studies\(^9^6\) enroll participants in a long screening phase that monitors the timing of ovulation during pre-study cycles either by using hormonal assays or by performing ultrasound of the ovaries to identify enlarged follicles.

Two important methodological issues that vary from one study to the next are 1) the variability in the timing of sleep measurements relative to the menstrual cycle and 2) the number of intervals into which the cycle is subdivided. For example, whereas Lee and her colleagues\(^9^7\) have subdivided the cycle into follicular and luteal phases and contrasted sleep during follicular days 3 to 10 with sleep during luteal days -12 to -3, Parry and her colleagues\(^9^8\) subdivided the menstrual cycle into four intervals (early follicular, late follicular, early luteal, and late luteal phases) and compared sleep across these four intervals. An even finer subdivision of the cycle was carried by Driver and her colleagues.\(^9^6\) These investigators divided the menstrual cycle into eight intervals consisting of menses, early follicular, mid follicular, late follicular, ovulation, early luteal, mid-luteal, and late luteal. Given the profound differences in the hormonal milieu during different portions of the cycle it is difficult to compare results across studies. When the subdivision of the menstrual cycle is too coarse, the time interval is not homogenous with respect to hormone levels. This makes it difficult to quantify the precise contribution of hormones to the sleep findings. The finer the subdivision of the menstrual cycle, the larger the sample size that is necessary for a meaningful comparison across the intervals. Even with a fine division of the menstrual cycle it is important to first align menstrual cycles of different lengths, both within subjects and between subjects in a meaningful way. That is, once aligned, the important aspects of the hormonal milieu (such as relative hormonal levels and their direction of change) are similar for a given menstrual day across different cycles. Taking advantage of the fact that the length of the luteal phase of ovulatory cycles is relatively constant (14 days) it is possible to map all cycles into 28 days in a manner that preserves important aspects of the hormonal milieu across aligned days. Such a transformation was recently done by Driver and her colleagues\(^9^6\) but not by earlier studies.

Given the inherent difficulty in predicting significant events in the menstrual cycle combined with the expense of polysomnographic sleep EEG studies, it is easy to understand why such studies were based on very small sample sizes (nine participants or less). When small sample sizes are combined with differential timing of sleep measurement relative to the menstrual cycle and with large individual differences in the physiology of the menstrual cycle, it is not surprising that the few existing studies of sleep in relation to the menstrual cycle, though reporting significant menstrual phase effects on sleep architecture, have not converged into a clear and consistent picture.

**Sleep continuity.** A significant main effect for the menstrual phase was found for number of awakenings after sleep onset.\(^9^8,9^9\) The largest number of awakenings was observed during the late luteal phase during which both estrogen and progesterone levels are declining, and the smallest number was observed during the early luteal phase, when both hormone levels are rising. However, the Bonferroni corrected paired t-tests for intermittent awakenings were not significant. These researchers found that higher levels of LH were associated with a larger number of intermittent awakenings. Driver et al.\(^9^6\) reported an almost two-fold increase in percentage awake after sleep onset during the late luteal phase (3.2%) compared to the early follicular phase (1.8%) with an even larger increase during the ovulatory period (4.8%). However, the main effect for menstrual phase interval (eight levels, nine participants) was not significant in this younger sample.

**NREM sleep.** The luteal phase is associated with significantly greater percentage NREM sleep compared to the follicular phase,\(^9^6\) primarily due to the percentage of stage 2 that was highest during the early luteal phase and lowest during the late follicular phase. Consistent with these findings, these researchers also report significant phase effect on EEG activity in the spindle frequency range (sigma, 12–14 Hz) during NREM. In addition, they report that sigma activity varied in parallel with core body temperature such that high body temperature was associated with greater activity in the spindle frequency range. Ishizuka and colleagues\(^1^0^0,1^0^1\) were the first to report changes in spindle frequency associated with the menstrual cycle. They, like Driver et al.\(^9^6\) found lowest spindle activity in the days preceding ovulation (18 days before menstruation) and highest activity during the late luteal phase (3 days before menstruation).

Two studies report a significant premenstrual decrease in slow-wave sleep.\(^9^8,1^0^2\) Parry and colleagues also found a relationship between progesterone levels and stage 3 sleep such that the highest levels of progesterone (usually during the mid-luteal phase) were associated with the longest time spent in stage 3. Other studies did not find significant menstrual phase effects on measures of slow-wave sleep or delta activity.\(^9^6,9^7\)

**REM sleep.** Among the different REM parameters, significant menstrual phase effects were found only in latency to REM sleep, with shorter REM latencies during the luteal phase than during the follicular phase.\(^9^7\) Armitage and Yonkers\(^1^0^3\) report a case of a 28-year old woman with a large decrease in REM latency from 62.5 minutes during the follicular phase to 4.0 minutes during the luteal phase. This woman also had an increase in percentage REM from 19.8% during the follicular days to 27.6% during the luteal days, consistent with an increased REM pressure.
Driver and colleagues\textsuperscript{96} also found a trend for reduced percentage of REM during the late luteal phase (22.9\%) compared with the early follicular phase (27.4\%).

**Subjective sleep data.** Prospective diary-based sleep data indicated an increase in subjective sleep disturbance in the late-luteal phase.\textsuperscript{104,105} Manber and Bootzin\textsuperscript{104} studied 34 regularly menstruating healthy women using daily sleep logs for two menstrual cycles and found increased sleep latency, decreased sleep efficiency, and decreased sleep quality in the late luteal phase compared with the mid-follicular phase. Patkai, et al.\textsuperscript{105} also found that the six healthy women they studied had slept on the average approximately one hour more during the five days preceding menstruation compared with the five days around the time of ovulation (days 12 to 16 premenstrually). One possible factor that might mediate the menstrual phase effect on sleep continuity might be metabolic rates during sleep, which are higher during the late luteal phase\textsuperscript{106} compared with the follicular phase. Moreover, metabolic rates during sleep are significantly correlated with the rate of decrease in the ratio between oestrone-3-glucuronide and pregnanediol-3a-glucuronide,\textsuperscript{106} suggesting that changes in metabolic rates during sleep may be related to changes in the hormones.

Both diary-based data and laboratory-based data indicate a premenstrual increase in disturbed sleep. However, there appear to be large individual differences in the degree to which the physiology of the menstrual cycle affects sleep. Some women experience marked changes in their sleep post-ovulation, whereas others do not. For example, about 31\% of the sample studied by Manber and Bootzin\textsuperscript{104} had a decrease in sleep efficiency of at least a 5\% during the luteal phase. On the other hand, there were four subjects (11\% of the sample) who experienced 5\% or more increase in sleep efficiencies in the luteal phase during at least one of the two cycles during which they were studied. Similar levels of individual variability are present in other samples studied by these authors.\textsuperscript{107,108} It is not clear what influences the observed individual differences in the degree to which the menstrual cycle effects sleep. One possible influence may be the individual differences in levels, rates of change, and rates of metabolism of sex steroid. Indeed, there are individual differences in peak and nadir levels of progesterone in the late luteal phase and in the rate of their decline.\textsuperscript{109} These individual differences might explain why not all women report premenstrual decline in sleep continuity and why some might experience more severe premenstrual sleep disruptions than others. It has been demonstrated that individual differences in the time course to peak allopregnanolone (a progesterone metabolite) following administration of progesterone do exist and are related to the effect of progesterone administration on EEG spectral power. For example, Friess and colleagues\textsuperscript{71} subdivided their sample into participants with early peak of allopregnanolone following progesterone administration and those showing smaller and later peak. They found that early increases in EEG activity in the spindle and alpha frequencies were observed almost exclusively among participants with early peak of allopregnanolone whereas reductions in the slow-wave frequencies were observed mainly among the group with a late peak of allopregnanolone. If rate of metabolism of exogenous progesterone explains differential effects on sleep, it is also possible that differential rates of drop in progesterone during the late luteal phase might differentially effect sleep premenstrually. The sedating effects of progesterone and its metabolites and the fact that these substances have central effects at the same receptors as the benzodiazepine drugs support the notion that a sharper drop in progesterone might lead to rebound sleep disruption. Another possibility is that there are individual differences in the sensitivity to changes in progesterone levels and that individual differences in the ability of the CNS to adjust to changes in progesterone, even in women with similar rates of change, might explain why some women experience a premenstrual change in sleep and others do not.\textsuperscript{110} Neither of the two hypotheses have been tested. A pilot study provides initial support for the first hypothesis. In this pilot study Manber and her colleagues\textsuperscript{107} report that three out of four regularly menstruating healthy women had less consolidated sleep on a late luteal day compared to a follicular day. For these participants, progesterone levels on the late luteal day of polysomnographic recording were already very low and close to the progesterone levels on the follicular day of polysomnographic recording, suggesting that the degree of sleep disturbance is not likely to be related to absolute levels of progesterone and might instead be related to the direction and gradient of change in progesterone levels. A fifth woman, in surgical menopause, was studied on estrogen alone, on estrogen and micronized progesterone, and during withdrawal from progesterone. Consistent with the proposed theory the night of withdrawal from progesterone was associated with the smallest sleep efficiency and the largest number of intermittent arousals and awakenings.

**Daytime sleepiness.** Menstrual phase effects on daytime sleepiness received little attention in the literature. There are two case reports of menstruation-linked periodic hypersomnia in adolescent girls.\textsuperscript{111,112} In addition, daytime sleepiness is more prevalent than difficulty sleeping among women with other premenstrual symptoms.\textsuperscript{113} Finally, Manber and Bootzin\textsuperscript{104} found that self-reported levels of daytime sleepiness were significantly and positively correlated with a premenstrual index (an index of overall severity of premenstrual symptoms) in a sample of healthy women who did not meet criteria for Premenstrual Dysphoria. It appears that the premenstrual increase in daytime sleepiness in healthy women is not simply a consequence of decreased sleep continuity because the latter was not significantly correlated with premenstrual index.
**Body temperature.** The interaction between the menstrual cycle, an ultradian rhythm, and body temperature, a circadian rhythm, has provided women a simple method of confirming ovulation. Body temperature decreases in the pre-ovulatory phase, along with the elevation in E2 level, and increases in the luteal phase, along with the post-ovulatory increase in progesterone level. The body temperature then remains elevated throughout the luteal phase. Taking advantage of the temperature change associated with ovulation, measurements of body temperature upon awakening every morning has allowed women to detect ovulation.\(^{114}\) Research in the past ten years has examined the effect of the menstrual cycle in healthy women on two other aspects of the temperature rhythm, phase and amplitude. Most studies of the temperature rhythm across the menstrual cycle indicate that whereas the phase of the daily temperature rhythm is not affected by the menstrual cycle, its amplitude is.\(^{98,115-118}\) The amplitude of the body temperature rhythm is significantly dampened during the luteal phase compared with the follicular phase.\(^{96,115-121}\) This dampening results primarily from differential temperatures during sleep in the two phases of the cycle. Whereas body temperatures during the day are comparable across the phases of the cycle, mean body temperature during sleep and the temperature minimum are lower during the follicular phase than during the luteal phase.\(^4,122\) Recently, Cagnacci and colleagues\(^{119}\) compared the variations in the amplitude of the circadian rhythm across the menstrual cycle in normal ovulatory cycles and in cycles in which multiple follicular development was induced by administration of FSH injections. During cycles with multiple follicular development the amplitude of the temperature rhythm did not vary significantly with cycle phase yet the average daily temperature did exhibit the normal pre-ovulatory decrease and post-ovulatory increase.

It is not clear why the amplitude of the temperature rhythm is lower during the luteal phase and why it is lower during sleep. Both estrogen and progesterone have thermoregulatory effects. Progesterone raises body temperature\(^{123}\) and the set point for thermoregulatory response\(^{124,125}\) whereas estrogen lowers the body temperature but does not block the effects of progesterone.\(^{126}\) Rogacz and colleagues\(^{116}\) have suggested that progesterone might act directly on the circadian pace maker to reduce amplitude. Certainly there is evidence that estrogen and progesterone have opposite effects on other circadian rhythms in rodents. For example, estradiol shortens the period length of locomotor rhythms, whereas progesterone results in phase delay and dampened amplitude (A B C D). Rogacz and colleagues\(^{116}\) have also suggested that temperature levels might be limited by a physiologic ceiling that prevents the already high daytime temperatures from increasing past a certain point and that consequently progesterone–induced temperature elevations are greater during sleep. Kattapong and her colleagues\(^4\) suggested that progesterone might have differential effects depending on circadian phase of temperature rhythm. The animal data reviewed earlier supports this view. It is also possible that this is the complex interaction between both estrogen and progesterone might be responsible for the observed dampening of the amplitude of the temperature rhythm during the luteal phase is impacted by the complex interaction between estrogen and progesterone. A recent study that examined the relationship between the temperature rhythm and the ratio of progesterone to estrogen supports the latter hypothesis.\(^{119}\) These researchers found that the amplitude of the temperature rhythm was inversely related to the progesterone to estradiol ratio and that this ratio decreased significantly from early follicular to the pre-ovulatory period and was significantly increased premenstrually.

The possibility that higher temperatures during sleep might be caused by or cause intermittent awakening has not been directly tested. Activity monitoring was included in several studies that examined sleep and body temperature in relation with the menstrual cycle. Only one of these studies\(^{118}\) reported the average hourly activity count during the "in bed" portion of the ambulatory monitoring. This study found no significant differences in activity across the four weeks of the cycle in their subsample of six healthy women. These researchers have also found no significant relationship between mean hourly nocturnal activity and mean temperature for their whole sample, that included women with late-luteal dysphoric disorder (the DSM-III-R equivalent of the DSM-IV research diagnosis of Premenstrual Dysphoric Disorder), and concluded that the menstrual phase-related changes in the temperature rhythm they observed are unrelated to sleep disturbances. At present, it is not clear what the implications of the dampening of the temperature rhythm are, if any. Dampered temperature rhythms were observed in special populations including shift workers who tolerate night shift poorly,\(^{127}\) the jet-lagged,\(^{128}\) elderly males,\(^{129}\) and depressed patients.\(^{130}\) In contrast, compared with the average levels of fitness, extremely high levels of physical fitness are associated with significantly greater amplitude in the temperature rhythm.\(^{131,132}\) It is not clear if the dampened temperature rhythm during the luteal phase indicates a "less stable" rhythm,\(^{133}\) as one might find with the jet-lagged\(^{128}\) and with poor adaptation to shift-work.\(^{127}\) Similarly, it is not known whether the phase of the menstrual cycle might be a factor in women's adaptation to shift-work or jet-lag. It is also not clear what is the clinical significance of dampened amplitudes of the temperature rhythm is during the luteal phase or whether the phase of the menstrual cycle might be a factor in women's adaptation to shift-work or jet-lag.

Similar to our hypothesis that a sharp drop in progesterone levels might induce sleep disruption, Wagner, Moline, and Pollak\(^{134}\) have suggested that periods of rapid sleep are associated with low progesterone levels. Further studies that examine sleep and body temperature across the menstrual cycle in women may provide insight into the clinical significance of this relationship.
gonadal hormone changes, such as those occurring just prior to ovulation and menstruation, can induce internal desynchronization of the sleep-wake rhythm from the temperature and from the cortisol rhythms.

**Melatonin rhythm.** A pineal-ovarian feedback system was hypothesized to exist in humans. This hypothesis is supported by the evidence from animal research, by the presence of gonadal steroid receptors in the human brain, and by early findings of altered levels of melatonin secretion across the menstrual cycle with higher levels during the luteal phase than during the follicular phase and lowest levels just before ovulation. However, most studies conducted in the last decade found no significant menstrual phase differences in melatonin levels in healthy participants, but did find phase difference among women with premenstrual dysphoric disorder. This inconsistent picture might reflect differential methodology with respect to assessment of both ovarian and melatonin secretion. The inconsistent picture might also be related to the fact that estrogen and progesterone appear to have opposite effects on melatonin secretion. Exogenous administration of sex steroids appears to affect melatonin secretion. Exogenous synthetic progestin administered in a tri-phasic oral contraceptive was associated with increased melatonin secretion. Exogenous administration of estradiol decreased pineal activity.

Total melatonin output appears to be relatively less important to sleep than the timing of melatonin onset, peak and offset. Recently, Cagnacci et al. examined melatonin rhythm in relation to the menstrual cycle and found that although melatonin levels were comparable during the two phases of the menstrual cycle, nocturnal melatonin onset was delayed by 90 minutes during the luteal phase compared with the follicular phase. This phase difference in melatonin rhythm was accompanied by the following changes in the circadian temperature rhythm: a delay of the nadir, a 0.3°C elevation of the mean 24-hour temperature, and a 40% blunting of amplitude.

Given that melatonin is readily available over the counter and commonly used without the supervision of a physician, and given its role in the regulation of seasonal reproduction in several species, it is important to understand the effects of exogenous melatonin on human reproduction. At levels commonly found in over-the-counter preparations, melatonin has a differential effect on body temperature during the two phases of the cycle, producing a decrease during the follicular phase but having no effect during the luteal phase. Similarly, exogenous melatonin stimulates LH secretion during the follicular, but not during the luteal phase. On the other hand, chronic daily administration of high levels of melatonin (300mg) significantly deceased LH levels which was most pronounced at the fourth (and last) month of administration suggesting an inhibitory effect of melatonin on ovarian function.

Unfortunately, there are no data on the effects of chronic use of over-the-counter melatonin preparations, usually taken when sleep is disturbed, on fertility.

**Menstrual phase effects on sleep in clinical samples**

**Insomnia.** There is only one study that examined the effect of the menstrual cycle on sleep of women with psychophysiological insomnia. These authors used sleep diaries to study the sleep of eight regularly menstruating women with psychophysiological insomnia and found no significant menstrual phase effect on measures of sleep continuity or sleep quality. Actigraphy based sleep data of eight participants in the same sample of female insomniacs have also failed to show a significant effect of the menstrual cycle on sleep continuity or sleep efficiency. Thus, although the menstrual cycle might affect sleep of insomniacs just as it affects sleep of non-insomniacs, this effect is overshadowed by the day-to-day variability in sleep continuity reported by insomniacs. As was the case in the sample of healthy women, a small subset of women (13% of the sample) did experience marked decrease in sleep continuity. Moreover, for this portion of the sample, sleep efficiencies below 85% (the clinical cut-off) were present during the luteal but not the follicular phase. Attention to menstrual phase effects on sleep continuity and sleep quality in clinical settings may have an impact on treatment because understanding the temporal pattern of the symptom is likely to reduce distress in the patient and lead to a more conservative, pattern-specific treatment approach.

**Sleep apnea and respiration during sleep.** There is a significant gender effect on the prevalence of sleep-disordered breathing with approximately 10:1 male to female ratio among patients in sleep disorder clinics and approximately 2:1 ratio in epidemiological sample of mid-life adults. Both physiological factors (e.g., body fat distribution, body mass index, facial morphology, or neck circumference) and hormonal factors have been hypothesized to account for the gender differences in the prevalence of sleep apnea in young and middle-aged adults. We focus here only on hormonal factors. Because sleep apnea increases in post-menopausal women, it has been suggested that gonadal hormones, particularly progesterone, might protect women from sleep-disordered breathing during their reproductive years. Exogenous administration of medroxyprogesterone appears to decrease the apnea/hypopnea index and to improve oxygenation during obstructive events in untreated apnea patients, and when combined with Premarin reduces the number of respiratory disturbance events in women in surgical menopause. It has also been demonstrated that regularly menstruating women have the least number of hypopneas during the mid-luteal phase when progesterone and estrogen are highest. A recent study identified one possible mechanism by which gonadal hormones affect respiration.
during sleep. This study indicates that female hormones have a significant impact on the upper airway dilator muscle (the genioglossus) activity during sleep with peak activity during the luteal phase, lower activity during the follicular phase, and lowest activity among postmenopausal women. They also report that treatment with a combination of estrogen and progesterone significantly increased activity in the upper airway dilator muscle.

The relationship between sleep apnea and gonadal hormones appears to be bi-directional. In other words, not only is there an effect of gonadal hormones on the prevalence of sleep-disordered breathing, there is also an effect of sleep disordered breathing on menstruation. A report from the Stanford Sleepiness Clinic Disorder Center noted the 45% of premenopausal women with sleep disordered breathing reported dysmenorrhea or amenorrhea that disappeared after treatment with CPAP.

Premenstrual Dysphoric Disorder (PMDD). The symptoms of PMDD might represent differential sensitivity to the hormonal changes that occur during the course of the menstrual cycle. These symptoms can be conceptualized on a continuum. On the one end of the continuum are women with PMDD and Premenstrual Syndrome (PMS), and on the other end of the spectrum are women who actually experience positive changes premenstrually. There is evidence that women with and without PMS or PMDD may differ on some objective and subjective sleep measures. For example, throughout the menstrual cycle, women with negative premenstrual affect have a higher percent of stage 2 sleep, less stage 3 sleep, a lower percent of REM sleep, and higher nocturnal body temperatures than women without premenstrual affective symptoms. Women with premenstrual symptoms do not differ from asymptomatic women with respect to the phase of the temperature, the amplitude of the temperature rhythm, or the daytime maximum of temperature rhythm. However, women with PMDD did have altered melatonin rhythm during the luteal phase compared with the follicular phase, with later nocturnal melatonin onset, and decreased area under the curve, amplitude and mean levels, whereas healthy controls did not exhibit significant menstrual phase differences in melatonin rhythm. Women with premenstrual symptoms report more insomnia symptoms, increased difficulty waking up in the morning, heightened mental activity during the night, more frequent and more unpleasant dreams, and increased sleepiness during the day. Only one of these studies examined the correlation between changes in sleep parameters and the severity of premenstrual symptoms. It found that whereas measures of premenstrual change in sleep disturbance were not significantly correlated with severity of premenstrual symptoms, self-reported daytime sleepiness did.

Not all the studies reported here agree on which sleep parameters differ between symptomatic and asymptomatic women. In addition to the methodological difficulties that were discussed earlier in this article, the studies also differed in the definition of premenstrual symptoms. Whereas some studies rely on at least two months of prospective daily recordings of symptoms, other studies define symptomatic women as those who meet DSM-III-R criteria for major depression except for the duration criteria. Yet others studied women with premenstrual dysphoria as defined by at least 30% worsening in total POMS score in luteal compared with the follicular phase. Although the methodological differences make it difficult to compare the results from different studies, the evidence suggests that the severity of premenstrual symptoms might be an important factor to consider in the study of sleep in women.

**Major depressive disorders (MDD)**

Women are at twice the lifetime risk for the development of MDD compared to men. This gender difference in rates of depression begins at puberty and continues until menopause. As a result, several researchers have suggested that the increased risk for MDD among women is related to gonadal hormones, most notably estrogen and progesterone. Sleep disturbances are key features of major depressive disorders (MDD), present in more than 80% of depressed inpatients. Those with MDD show alterations in the timing of REM sleep, with an early onset of the first REM period, and a shift in REM toward the first part of the night. Decreased slow-wave sleep, and reduced delta activity, have also been reported in MDD, in addition to poor sleep consolidation, and early morning insomnia. Sleep findings have been interpreted as reflecting a primary biological rhythm disturbance in MDD. Phase-shifted or blunted rhythmicity in other neuroendocrine systems including cortisol, growth hormone, melatonin, and testosterone, have also been described in those with MDD.

However, sleep disturbances in MDD and associated biological rhythm abnormalities appear to be strongly influenced by gender. Sleep architecture may also show strong gender differences in MDD. In a large scale study, Reynolds et al. have shown that depressed men have less slow-wave sleep and lower delta wave counts than depressed women, but not on other sleep variables. However, this study did not include a comparison control group. A more recent study indicates that men with depression show an abnormal time course of delta amplitude compared to controls and depressed women, accompanied by more stage 1 sleep, more awake time, and less slow-wave sleep. By contrast, depressed women do not appear to show delta sleep abnormalities compared to controls. However, depressed women do show reduction in temporal coherence of ultradian EEG rhythms in beta and delta activity during sleep. Depressed women have also been
shown to have more fast-frequency EEG activity during sleep than depressed men, despite less disturbed sleep.\textsuperscript{177}

These findings are consistent with greater EEG dysregulation during sleep in depressed women than men and support the view that the pathophysiology of depression differs between the sexes.\textsuperscript{178} Moreover, the relevance of EEG regulation during sleep for explaining gender differences in the pathophysiology of depression is supported by findings that gender differences in EEG regulation during sleep are substantially greater in depressed patients\textsuperscript{177} than those observed in healthy controls.\textsuperscript{7,8,177,179} Several lines of evidence converge to make a convincing the argument that gonadal hormones are involved in sleep regulation, and neurotransmitter regulation in humans.

There is ample evidence that depression is associated with dysregulation of the catecholamine, acetylcholine, and GABA neurotransmitter systems.\textsuperscript{180} For example, 5-hydroxytryptophan, a precursor of serotonin, and 5-hydroxyindoleacetic acid, a serotonin metabolite, are reduced in the cerebrospinal fluid of depressed patients. As mentioned previously, gonadal hormones exert a strong influence on serotonin and other receptors. As stated by Janowsky et al.,\textsuperscript{180} phase of the menstrual cycle can orchestrate very different effects on serotonin sensitivity in depression. Evidence of catecholaminergic influence on depression is also drawn from both the mood-enhancing effects of monamine oxidase inhibitors and selective serotonin inhibitors. Gender differences are also evident in response to these classes of antidepressants,\textsuperscript{181} particularly with regard to sleep effects.\textsuperscript{166} Again ovarian hormones influence the synthesis of catecholamines catecholamines, their release, uptake metabolism, and receptor activity.\textsuperscript{182}

Taken together, these data provide strong evidence that the increased prevalence of depression and the large gender differences reported in sleep EEG regulation in this clinical population are related modulated by to gonadal hormone regulation. Regrettable, however, few studies have evaluated phase of the menstrual cycle effects on sleep in women with MDD or how cycle phase may influence gender differences in those with depression. Much additional research is necessary in this area.

**DISCUSSION**

The accumulation of data reviewed here strongly suggests that both endogenous and exogenous steroid hormones can have an impact on sleep. At the same time, this article clearly indicates that the relationship between gonadal hormones and sleep is very complex and that our understanding of this relationship is limited. Although we identified several open questions in the body of this article, we proceed with a brief discussion of general directions for future research in this area and a summary of the main results.

**Exogenous hormones.** There is compelling evidence that exogenous administration of sex hormones does affect brain systems that are involved in the regulation of sleep and does impact sleep and associated circadian rhythm. Progesterone affects primarily NREM sleep whereas estrogen affects primarily REM sleep. Progesterone has a sedating effect and it alters human and animal sleep architecture in a manner similar to benzodiazepines, including shortening the latency to sleep onset and reducing wakefulness after sleep onset. Estrogen suppresses REM sleep in rats but enhances REM sleep in humans (both increase amount of sleep and decreased latency to REM sleep were observed). Given that data on the effects of estrogen on human sleep architecture are sparse and relatively old, there is a clear need for contemporary research to clarify the inconsistency. There is also a need to study the effects of concomitant administration of progesterone and estrogen on sleep. The endocrinology literature and the relatively new literature on the effects of sex steroids on the brain indicate that there is a complex interaction between these two hormones. There are obvious clinical implications to this line of research because HRT, particularly combination therapies, are becoming increasingly more common. To further improve HRT we need to understand the conditions under which these therapies alleviate sleep difficulties, reduce the risk for breathing-related sleep disorders.

**Endogenous hormones.** It is less clear what the impact of endogenous sex hormones is on sleep. Data has consistently demonstrated dampening of the amplitude of the body temperature rhythm during the luteal phase. In contrast, although menstrual phase effects were observed for sleep continuity, spindle activity, slow-wave sleep, REM sleep, and sleep quality, the agreement among the different studies is low. It is difficult to integrate these results into a converging clear conclusion regarding the effect of the menstrual cycle on sleep. Small sample sizes are not sufficient in the face of large within and between individual differences in sleep in menstrual cycle physiology. Normative data on sleep across the menstrual cycle are greatly needed. In their absence, neither the researcher nor the clinician have a reference point to assess whether the sleep parameter under investigation is affected by the phase of the menstrual cycle. Consequently, the researcher does not know if a control for the menstrual phase needs to be introduced and the clinician inquiring about menstrual phase effect does not know which parameters to focus on.

It is evident that the effect of the menstrual cycle on sleep is not experienced by all women of child bearing age. In each of three samples studied by Manber and her colleagues (healthy women, insomniacs, and women with PMDD), significant (more than 30\% increase in sleep disturbance premenstrually was experienced by approximately 15\% of the sample. The challenge is to collect sufficient data to examine prevalence in clinic-based samples, to
understand causes, and to improve treatment when sleep disturbances are exacerbated premenstrually. One specific etiological theory that remains untested is that premenstrual sleep disruption in sleep continuity is caused by abnormally sharp premenstrual drop in progesterone. 110

Another important open area of investigation is the relationship between the monthly premenstrual rhythm and the daily rhythms (body temperature, melatonin, and sleep). Though we know that the amplitude of the temperature rhythm is dampened during the luteal phase, we do not know the implication of the continual fluctuation in the amplitude of the temperature rhythm on women's ability to adapt to shift work or the impact of shift work on the reproductive system. We similarly do not know what are the effects of melatonin administration on the reproductive system.

Finally, understanding the influence of sex hormones on sleep is essential to developing and testing theories of sleep regulation. As stated by Fang & Fishbein (11 [p.283]) "it seems clear that our knowledge about sleep mechanisms can never be complete if it applies to only half the population."

REFERENCES


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