REVIEW ARTICLE

# Sleep in Women

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## Introduction

Sleep in women can best be described as a dynamic process that varies with the physiological stages that occur within the lifespan of the female gender. There has been a growing interest in this previously less well studied domain and this has led to enhanced understanding and proved to be an exciting area of upcoming research.

The three major changes that occur are that unique to women are menstrual cycle, the childbearing years-pregnancy and menopause.

Sleep disturbances reported in women are highly prevalent and this was brought to light in the National Sleep Foundation Poll in 2007 in which only 3 in 10 women reported a good night's sleep in a few nights per month or less. Forty six percent of women stated that they had a "sleep problem" almost every night. 84% of pregnant and post-partum women had sleep problems at least a few nights per week

## The menstrual cycle and its effect on sleep

### Overview of Physiology

The menses phase day 1 to day 5 is the time when the lining of the uterus is shed out if pregnancy has not occurred.

### The follicular phase

Between days 6 and 14 the level of the hormone estrogen rises, causing the lining of the uterus i.e. endometrium to grow and thicken. In addition, follicle-stimulating hormone causes follicles in the ovaries to grow. Between days 10 and 14 only one of the developing follicles will form a fully mature egg or ovum.

### Ovulation

On day 14 a sudden increase in luteinizing hormone causes the ovary to release its egg. This event is called ovulation.

### The luteal phase

Between days 15 and 28 the egg travels through the fallopian tubes to the uterus. The level of the hormone progesterone rises to help prepare the uterine lining for pregnancy.

If pregnancy does not occur, estrogen and progesterone levels drop and the thickened lining of the uterus is shed during the menstrual period.

## Effect of sex hormones on sleep

**Progesterone**: Progesterone acts as a sedating agent, acting in an agonistic manner on the same receptors ($GABA_A$) as benzodiazepines and barbiturates, though it may act in a unique binding site. Similar to these medications, this hormone also affects REM sleep, prolonging the latency to REM sleep and reducing the amount of REM sleep. It appears to act via progesterone metabolites (5-alpha-pregnanolone and 5-beta-pregnanolone), increasing the frequency and duration of chloride channel openings[2].

**Estrogen**: Estrogen increases the turnover of norepinephrine in the brainstem, the hypothalamus, locus coeruleus and nucleus accumbens, which appears to be the method of REM sleep decrease. Estrogen also appears to interact with GABA and serotonin receptors. The effect of estrogen on REM sleep was demonstrated by ospherectomy in adult female rats, which caused an increase in REM sleep. This increase was suppressed by the exposure to estradiol. Women who are

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perimenopausal and are treated with estrogen tend to report decreased sleep latency, decreased nocturnal waking, and increased total sleep time. When comparing humans who are receiving estrogen exogenously, they appear to have increased REM sleep time and decreased REM sleep latency.

**Testosterone**: Testosterone appears to decrease REM sleep when given to female neonatal mice. Neonatal castration was shown to increase REM sleep in mice.

## Circadian effects of sex hormones

The circadian effect of estrogen is evident by the daily running activity in female rats and hamsters that is enhanced when estradiol secretion is maximal.

Free running rhythm periods in male mice are lengthened by castration and shortened by chronic testosterone treatment.These effects may be mediated by hormone binding within the suprachiasmatic neurons or by hormonal effects on locomotor activity or other behaviours.

## Sleep Architecture in relation to the Menstrual Cycle

In general, sleep appears quality to improve (fewer arousals) in the early luteal phase when hormones are increasing. As these hormones recede, the number of arousals increase, leading to worse sleep. When comparing the luteal and follicular phase, there is a higher percentage of NREM sleep in the luteal phase (decreasing REM percentage)[3]. REM sleep onset latency tends to decrease with increasing progesterone levels.Some reports have mentioned a correlation between progesterone and slow wave sleep such that the mid luteal phase i.e. the period that has the highest progesterone level is associated with the longest luteal phase.

## Upper airway resistance: Impact of menstrual cycle

Upper airway patency is dependent on the interaction between anatomy and upper airway dilator muscle activity. This finding may suggest that progesterone is related to decreased upper airway muscle activity[4].Another study demonstrated that the muscle activity of the tongue appears to be greater in the luteal phase, thereby suggesting that the airway will remain more open during that portion of the menstrual cycle. When upper airway resistance was measured in 11 women in the 2 phases (via catheter measurement of supraglottic pressure and pneumotachometer measurement of airflow), the resistance was lower in the luteal phase (when progesterone rises).

## Menstrual related hypersomnia

A clinical sub-type of the Recurrent Hypersomnias (ICSD-2)[5] is characterized by recurrent episodes of sleepiness that occur in association with the menstrual cycle. The disorder begins within the first months after menarche. Typical episodes last approximately one week with rapid resolution at the time of menses

## Sleep During Pregnancy

In 2007, the National Sleep Foundation polled a group of pregnant women to assess the self-reported severity of their sleep disturbance.Pregnant women report having significant sleep disturbances. These numbers, particularly the 40% with symptoms of snoring, apneas and restless legs syndrome, suggest that more attention should be spent evaluating and addressing these sleep disorders. Pregnant women were more likely to awaken during the night (74%) and/or wake up early and unable to get back to sleep (46%).

In fact, 30% of pregnant women and 42% of post partum women report rare or never getting a good night's sleep, Pregnant (31%) and post partum (35%) women were significantly more likely than women in general (22%), and specifically perimenopausal (18%), postmenopausal (20%) and menstruating (21%) women, to have sleepiness interfered with daily activities at least a few days a week.

The first trimester of pregnancy is notable for increasing progesterone levels, which may increase the woman's sleepiness level. In addition, nocturnal sleep may be disrupted due to the physiological changes in a woman's body and the resultant effects. Sleep usually improves in the second trimester, followed by a return of sleep difficulties in the third trimester.[6]

**1st Trimester**

- Increased total sleep time
- Possibly due to the sedative properties of progesterone

- Sleep disruptors: Nausea/vomiting, frequent urination

**2nd Trimester**

- Many report improved sleep and daytime alertness
- Decreased nausea
- Normalization of total sleep time

**3rd Trimester**

- Decreased total sleep time
- Increased insomnia / nocturnal awakenings
- Increased daytime sleepiness.
- During the third trimester many women report more difficulty falling asleep and maintaining sleep.
- Common complaints include general physical discomfort, frequent urination, back, joint and neck pain, vivid dreams, nasal congestion, leg cramps, fetal movements and contractions.[7]

Total sleep time and sleep efficiency decline throughout pregnancy regardless of parity.

There was a significant decline in SWS in the first trimester as compared to pre-pregnancy. There was a significant increase in SWS postpartum as compared to the last trimester. There is no significant change in REM sleep before, during and post partum.

Women with severely disrupted sleep (WASO 15%+) had longer labors, and were 5.2 times more likely to have C-sections). Women who slept < 6 hrs had longer labors and were 4.5 times more likely to have C-sections.

## Post partum

Sleep does not immediately return to normality after birth. This finding may be related to the needs of the infant, but also may involve a number of physiological and psychological changes.

Post partum women are most likely to wake up feeling un-refreshed (72%) and/or awake a lot during the night (68%). Overall, about three in ten women (29%) say they have used a sleep aid at least a few nights a week. Postmenopausal women tend to be most likely to use a sleep aid at least a few nights a week (41% vs. 33% perimenopausal, 11% pregnant, 8% post partum). The vast majority of post partum women say they are awakened during the night to give care to the child (90%). Forty seven percent women report no help in child care, which may lead to significant sleep disruption and resultant daytime sleepiness.

## Menopause

Menopause is the period of absence of menstruation for 1 year. Hormonal changes begin 7-10 years before the final menses. During this perimenopausal period the pituitary-gonadal axis changes with decreasing estradiol and progesterone and rising FSH and LH. As the ovarian source of estrogen fades, there is an increase in the extragonadal production of estrone from the conversion of androstenedione.

After menopause the prevalence of sleep disturbances further increases to 35-60% of women surveyed. Part of this escalation may be explained by increased risk for sleep disordered breathing with menopause in the absence of hormone replacement therapy. It is also possible that restless legs syndrome contributes as well (especially the secondary forms which are more common in the older aged population).

There are many factors interacting to influence both the direct effects on sleep and the perceptions of sleep and sleep quality at this time of a women's live, such as greater susceptibility to depression, psychosocial factors, responsibilities (home, children, spouse) and work (homemaker and salaried employment coexist), Life-style (retirement active vs. sedentary), Increased life expectancy (care for ailing parents, spouse) and sharing a bedroom with ailing spouse may contribute .

Increased prevalence of SDB in men leads to environmental sleep disorder.

## Sleep architecture changes in menopause

Baker et al found a non-significant overall reduction in total sleep time (by 18 minutes) with increased fragmentation of the sleep period. Their main finding was more arousals and more awake time with arousals.

They also measured subjective sleep quality. Comparing ratings on questions in the sleep questionnaire the perimenopausal subjects reported significantly greater dissatisfaction with sleep quality than the premenopausal group. The perimenopausal group reported more spontaneous awakenings, more nights per

week ($p<0.05$), feeling drowsy on significantly more days ($p<0.05$), and needing extra sleep more often than did premenopausal subjects ($p<0.05$). Subjective assessment of the need for extra sleep was significant with the perimenopausal groups reporting needing 1 hour and 28 minutes more than did the premenopausal subjects ($p<0.05$). Mood scores on the State-Trait Anxiety Inventory (STAI) were also significantly higher in the perimenopausal group.

## Circadian changes in the elderly

Aging is associated with advanced sleep and core temperature phases. Light, as a *zeitgeber,* may be less able to maintain the circadian cycle. Age related reduced photic inputs due to macular degeneration, cataracts; and other pathology of the eye or neuronal losses at the level of the suprachiasmatic nucleus (SCN) play a role. It is known that the elderly with visual impairments are 30-60% more likely to have impaired nighttime sleep than those with unimpaired vision.

In the older population, the acrophase of melatonin is shifted earlier and the peak is shallower. Walters et al. looked at the effect of menopause on the melatonin acrophase in 10 women in menopause (mean age 55) and 11 premenopausal women (mean age 42). He found that melatonin onset was advanced in menopause by 1.1 hours. The cause is not known but may be more due to aging effect than gender effect as other studies demonstrate similar shifts in older men.

Weakening of both circadian and homeostatic processes interact to result in sleep disturbances.

An additional factor influencing sleep and sleep quality is hot flushes. Hot flushes affect 75 - 85% of perimenopausal and postmenopausal women. For most the symptoms dissipate within 1 year but for 25% the symptoms may last 5 years and, for a small minority, the rest of their life[9]. Hot flushes are due to central and peripheral vasomotor manifestations presenting as palpitations, diaphoresis, skin redness, warmth of the face spreading to the chest. The hot flush is believed to be mediated through the preoptic area of the anterior hypothalamus, and is associated with an increase of brain norepinephrine metabolism and also seems to be associated with luteinizing hormone pulses.

Treating hot flushes in a nonpharmacological approach includes consuming cold drinks, and using fans and air conditioning. Weight loss,smoking cessation and beneficiary relaxation techniques may also help. Paced respiration (slow deep abdominal breathing) has been shown to reduce hot flush frequency by approximately 50% when implemented at symptom onset.

Of the medications used for treatment of hot flushes such as clonidine, gabapentin, methyldopa and Bellergal (belladonna, ergotamine, and phenobarbital), there are only a few small randomized controlled studies on the impact of the drug on sleep and hot flushes.

Estrogen replacement has been studied for impact on sleep and has demonstrated benefit in reduced sleep disturbances and improved quality of life. But there are significant risks associated with estrogen replacement that make it undesirable for long term therapy of sleep complaints.

Decrease in progesterone secretion is noted after menopause. With progesterone use, the total duration of awakenings was 50 percent lower than with placebo and slow-wave sleep increased by 44 percent compared with placebo

The risk benefit ratio of hormone replacement therapy must be weighed heavily. Women's Health Initiative findings of increased incidence of breast cancer, blood clots, stroke and heart disease are real risks which may well outweigh the benefit of sleep and quality of life.

## Obstructive sleep apnea

OSA is found in 2% of middle aged women and about 4% of middle-aged men (AHI>15). OSA tends to be less severe by total AHI with shorter respiratory events in women. However, the absolute REM-related RDI is similar (women had a higher percentage of REM events). Apparently women are symptomatic at a lower RDI than men (potentially due to the disruption of REM).[11]

Theories have been described that suggest the difference between men and women is purely an anatomical one; i.e., men are predisposed to have OSA based primarily on their upper airway, while anatomical differences may occur, there was no clear correlation between the change in upper airway anatomy and severity of OSA. In fact, it appeared that though cross-sectional area in the upper airway was smaller in women, it did not correlate with apnea severity.

Loube et al. found that 14% of pregnant women snore, compared to 4% of non-pregnant women. 7% of this same pregnant group reported witnessed apneic spells.

Snoring is more common in obese pregnant women than non-obese pregnant women. Significant predictors of apnea symptom score were BMI and change in neck circumference.

Women may suffer more from morning headaches and have depressive symptoms. Women appear to have more hypopneas and fewer overt apneas. This finding may be related to the reason that women were under-recognized for having OSA in the early years of research, where hypopneas were not recognized as a significant factor in OSA.

The severity of OSA was documented to be significantly improved after childbirth. Reduction of OSA from 65±18 to 18±4 events/hr in NREM; 64±11 per hour to 22±4 per hour in REM. Minimum mean $O_2$ 86%±2% antenatally improved to 91%±1% in the post-natal period. Arterial blood pressure responses to apnea peaked 170 to 180 mm Hg antenatally, while they only peaked at 130 to 140 mm Hg postnatally.

Risk of OSA for women is less than that of men until menopause when it then approximates that of men. 2.7% (menopausal women) as compared to 3.9% (men). Prevalence peaks at 65 year for women (as compared to 55 year in men).

The treatment options for obstructive sleep apnea are independent of gender, though women may make different treatment choices than men. In one study, 86% of men took CPAP home whereas to 31% of women refused CPAP.

## Insomnia in women

The menstrual cycle, pregnancy and menopause are important considerations in evaluation and treatment of insomnia in women.

Insomnia can be experienced at various times as hormonal changes occur during the menstrual cycle. Thirty six percent of women reported that their sleep was most disturbed during the first few days of their menstrual periods. Premenstrual Syndrome (PMS) symptoms such as bloating headaches, mood alterations, and abdominal cramps contribute to difficulty falling or staying asleep or non-restorative sleep. 50% of menstruating women report that discomfort related to bloating disturbs their sleep.

As was noted earlier, pregnancy involves hormonal, physical and emotional changes that can contribute to sleep disruption. Leg cramps, vivid dreams, frequent urination, heartburn, snoring and nasal congestion associated with swelling of the nasal passages can cause discomfort and difficulty falling or staying asleep, especially during second and third trimesters.

Of note, approximately 15% of women develop restless legs syndrome (RLS) during the third trimester, often resulting in difficulty falling asleep. During the post-partum period, the newborn's rapidly cycling and often erratic sleep cycle can disrupt the mother's sleep and post-partum depression can develop, further disrupting sleep and contributing to fatigue during the day. Depression also occurs more commonly in women during menopause (about 20%), a time in later life when women undergo major hormonal, physical, social and psychological changes. The depression is often accompanied by insomnia. Hot flushes, night sweats, and mood swings occur during menopause and can disrupt sleep[12].

Co-morbid conditions more common in women are pain syndromes and fibromyalgia, depression, restless legs syndrome and nocturnal sleep-related eating disorder.

An initial reasonable step is to provide education and sleep hygiene instructions for patients with insomnia. Behavioral and psychological measures should be used.

When pharmacologic treatment is indicated, the first line of treatment in almost all cases should include a short acting benzodiazepine receptor agonist.A low dose of a sedating antidepressant is another reasonable strategy.

Restless legs, due to the discomfort and need to move, may reduce total sleep time (TST). In one study, it was demonstrated that TST was best in the healthy group (404 minutes±129) and worst in new onset of RLS during pregnancy (345 minutes±123).

## Restless legs syndrome

Epidemiological studies have consistently found that RLS is more prevalent among females. RLS is a common disorder seen in 5-10% of the population. Prevalence for those severe enough to warrant medical attention is estimated to be around 2.7%

Pregnancy is often associated with transient RLS. Manifestation in the third trimester is the most likely time of onset and symptoms usually resolve around the time of delivery. Twenty to 25% of pregnant women experience RLS[13].

Multiparous women with three or more children are three times more at risk for developing RLS compared to men. Symptoms were slightly more common in teenage pregnant women and pregnant women in their 40's.Various etiologies include iron deficiency, folate deficiency and hormonal changes. Always investigate for and treat iron deficiency.

Ferritin < 18 ng/ml; percent iron saturation <16%, but levels less than 50 ng/ml have been associated with increased symptoms. The goal of therapy should be to maintain ferritin > 50 ng/ml Pregnancy related RLS may be risk factor for later development of RLS.

Treatment for RLS encompasses non-pharmacological treatments such as massages, hot baths and stretching. Pharmacological interventions include dopamine agonists, GABA agonists, opiates (safest in view of fetal effect) and iron replacement.

## Narcolepsy

Symptoms of narcolepsy often start in adolescence, though they may be unrecognized for many years. Women appear to have the disorder slightly less frequently than men. The ratio of male to female is 1.2:1 is for narcolepsy with cataplexy and 1.6:1 is for narcolepsy without cataplexy.

In women, cataplexy may develop at a younger age; other manifestations of narcolepsy i.e. excessive daytime somnolence, sleep paralysis hypnogogic hallucinations do not exhibit significant gender differences.

Narcolepsy has a clear negative effect on quality of life, most profoundly affecting bodily pain, social function and general health, with women expressing more social limitations than men.

Considerable amount of weight gain associated with this disorder, is more frequent in women. Leptin levels are influenced by sex hormones and cytokines. Female rats have shown higher levels of preprohypocretins mRNA in the hypothalamus, and leptin affects its signaling. The underlying mechanism of this gender difference may help us understand obesity.

## Parasomnias

Dreams and nightmares are recalled at a higher frequency by women and they have a higher level of distress associated with negative dreams Adolescents and young adult females commonly report having nightmares more than twice a week. Posttraumatic stress disorder (PTSD) is diagnosed more frequently in women.

Parasomnias, or abnormal behaviors during sleep, can occur throughout the lifespan, though perhaps more dramatically in childhood/adolescence and in the elderly. In the younger age group, girls tend to be less likely to suffer from enuresis than boys. In an older population, men are more likely to suffer from catathrenia (nocturnal groaning) and REM sleep behavior disorder[14]. Sleep related eating disorder (SRED) is reported most commonly in females

## Melatonin and its proposed role in cancer

Melatonin (MLT) is secreted by the pineal gland in cyclical periods. In mammals, MLT is involved in physiological processes, such as sleep/wake regulation in the circadian cycle. It has antioxidant and anti-inflammatory properties, functions as an immunomodulator, and stimulates bone metabolism. MLT is also involved in tumour processes in breast, prostate, liver, and bone cancers. Reduced melatonin may increase breast cancer risk through several mechanisms, including increased estrogen production and altered estrogen receptor function.

## Summary

Sleep disorders occur in women and often appear related to age, hormones, and pregnancy. Effects of these disorders can impact a woman's role in both the workplace and at home. Treatment options are generally gender-neutral for the majority of these disorders. Further research is necessary for potentially gender-specific treatments.

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