



Understanding Unique Sleep Problems in Women

While women overall sleep better than men do, they may experience various sleep difficulties throughout life.

By Antonio Culebras, MD

In general, women sleep better than men do.¹ They have more deep sleep, a slower age-related decline in delta activity, the marker of deep sleep, and twice as many sleep spindles.^{2,3,4} And yet, only 40 percent of women sleep well almost every night, while 46 percent of women complain of trouble sleeping almost every night.⁵ Women go through phases in their life-cycle that increase the risk of sleep disturbance. The menstrual cycle, pregnancy and menopause are the principal modifying factors. Here, we take a closer look at issues unique to women and how to approach them.

Menstruation

Menstruation is controlled by hormonal changes, which in turn may affect sleep. Estrogen levels are higher in the follicular phase between days six and 14 of the cycle, when the

endometrium grows and thickens. Simultaneously, the ovarian follicles grow in response to the action of follicle-stimulating hormone (FSH), but only one follicle will develop into a mature egg. On day 14, the ovary releases the egg in response to an increase in luteinizing hormone (LH), a process that is known as ovulation. The luteal phase ensues as the egg travels via the fallopian tubes to the uterus where it finds a receptive lining facilitated by increasing levels of progesterone. When pregnancy fails to occur, estrogen and progesterone levels drop, and the lining of the uterus is shed into the vagina during days one to six of the menstrual cycle, a phenomenon identified as menstruation. On average, the cycle is 28 days long with a range between 21 and 35 days.

Estrogen decreases REM sleep in rats, but in humans exogenous exposure to estrogen increases REM sleep.⁶ Progesterone

increases the latency to REM sleep and decreases the proportion of REM sleep. Progesterone is related to decreased upper airway muscle activity.⁷ In the luteal phase, when the influence of progesterone is maximum, upper airway muscle activity decreases and the tongue muscle activity increases, improving the opening of the upper airway during that portion of the cycle.⁸ Measurements of upper airway resistance have shown a lower resistance in the luteal phase.

Pregnancy

Thirty percent of pregnant women rarely or never get a good night's sleep, while 84 percent experience a sleep problem a few nights per week, compared to 67 percent of women overall. Forty percent of pregnant women report symptoms of sleep disorders; snoring, sleep apnea or restless legs syndrome.⁹

During the third trimester of pregnancy women see a decrease in total sleep time, while increased insomnia and nocturnal awakenings as well as increased daytime sleepiness are common. Many women report more difficulty falling asleep and maintaining sleep. Sleep is commonly disrupted by general physical discomfort, frequent urination, back and neck pain, vivid dreams, nasal congestion, leg cramps, fetal movements, and uterine contractions. These sleep issues may be a barometer of what to expect in the delivery room: women with severely disrupted sleep (Wake After Sleep Onset -WASO 15 percent or more) may have longer labors, and are 5.2 times more likely to have C-sections.¹⁰

Snoring increases during pregnancy.¹¹ As many as 14 percent of pregnant women snore, compared to four percent of non-pregnant women, and seven percent report witnessed apneic spells. Predictably, snoring is more common in obese pregnant women than in non-obese pregnant women¹² and for obvious anatomical reasons, symptoms of sleep apnea increase significantly from the first trimester to the month of delivery. In the few studies that have been conducted, predictors of sleep apnea were high Body Mass Index (BMI) and change in neck circumference. Following parturition, sleep apnea improves significantly, both in REM (64 ± 11 per hour to 22 ± 4 per hour) and non-REM sleep (65 ± 18 to 18 ± 4 events/hr).¹³

Pregnancy may be associated with sleep-disordered breathing, in general known as sleep apnea. The condition is characterized by repetitive collapse of the upper airway causing lapses in respiratory activity, hypoxemia, and sympathetic activation. Sleep apnea may lead to arterial hypertension and endothelial dysfunction. During the third trimester of pregnancy, reduced functional respiratory residual capacity due to weight gain and changes in the shape of the diaphragm and thorax increase the incidence and severity of sleep apnea. Up to 10 percent of pregnant women are at risk for development of sleep apnea;¹² overweight women and women with the metabolic syndrome are at particularly high risk.

An emergent body of literature has reported a distinct association between sleep apnea and preeclampsia.¹⁴ Preeclamptic toxemia is characterized by hypertension, proteinuria and edema. Preeclampsia may affect seven to 10 percent of all pregnancies in the US¹⁵ and constitutes a major cause of fetal and maternal morbidity and mortality. Sleep apnea in pregnancy may also cause placental hypoxia. It has been hypothesized that placental ischemia is the triggering event in preeclampsia.¹⁶ Placental ischemia precipitates a cascade of active factors from the placenta that generate profound effects on the maternal cardiovascular system causing hypertension and endothelial dysfunction. At the very least, sleep apnea is a significant contributing factor for the development of preeclampsia, in particular in pregnant women who are at high risk.

A recent study carried out in Buenos Aires, Argentina¹⁷ investigated the relationship between snoring, witnessed sleep apneas, and pregnancy-induced hypertension in 456 women. The authors utilized a questionnaire that was administered on the day of delivery. After they gathered information about complications of pregnancy and blood pressure measurements, the authors found that 156 (35 percent) of 447 women with singleton pregnancies who answered the questionnaire snored at some time during pregnancy. Snoring was related to pregnancy-induced hypertension and preeclampsia combined, with an adjusted odds ratio of 1.82 (95% CI: 1.16-2.84; $p < 0.01$). The results were independent of BMI before pregnancy, weight gain during pregnancy, neck circumference, smoking, alcohol and age. The authors also found that daytime sleepiness was more prevalent in snoring women and concluded that snoring and witnessed sleep apneas were independently related to pregnancy-induced hypertension.

In another study,¹⁶ the authors studied 17 women with preeclamptic toxemia and 25 matched women with uncomplicated pregnancy. All subjects underwent a nocturnal ambulatory sleep study (using Watch_PAT100) and noninvasive evaluation of endothelial function utilizing the reactive hyperemia test (using Endo_PAT 2000). Preeclamptic women were evaluated at night for sleep apnea in the hospital and control women were studied at home. The authors found that endothelial dysfunction and sleep apnea coexisted in women with preeclamptic toxemia compared with controls, and suggested that endothelial dysfunction and sleep-disordered breathing were associated with each other without proving causality.

Although the ultimate study has not been done in pregnant women, it stands to reason that the clinical protocols used to treat sleep apnea in adult non-pregnant women should be considered also in pregnant women. Guilleminault, et al.¹⁸ conducted a study based on the premise that a significant overlap exists between risk factors for preeclampsia and sleep-disordered breathing. The work was a prospective, longitudinal investiga-

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tion designed to characterize sleep-related breathing patterns in pregnant women with risk factors of preeclampsia and to describe the effects of early nasal CPAP therapy in these patients. Twelve pregnant women with risk factors of preeclampsia underwent polysomnography to identify sleep-related breathing abnormalities and measure baseline blood pressure. Patients with sleep apnea underwent nasal CPAP titration and were treated with optimal pressures. In addition, they received periodic assessments of CPAP compliance and tolerance, sleep quality, and blood pressure control until delivery or onset of preeclampsia. Additional CPAP retitration was performed between weeks 20 and 22 of pregnancy.

Based on the results of the study, the authors concluded that early application of nasal CPAP in pregnant women alleviated sleep-related breathing disturbances but was not sufficient to prevent negative pregnancy outcomes. Obesity and prior preeclampsia were associated with the worst complications. In their view, nasal CPAP applications may still be beneficial to decrease severity of outcomes, particularly if individualized to risk factors, like hypertension at the onset of pregnancy.

In a parallel study conducted in Sao Paulo, Brazil, Poyares, et al.¹⁹ evaluated the possible benefit of CPAP applications in pregnant women with chronic snoring and hypertension early in pregnancy. Subjects were randomized to receive either CPAP with standard prenatal care (treatment group) or standard prenatal care alone (control group) with routine obstetric follow-up. Hypertension was treated with alpha-methyl dopa. Nocturnal polysomnography was performed in all patients randomized to the treatment group for initial CPAP titration. The authors found in the control group (n=9) a progressive rise in blood pressure with a corresponding increase in requirement of alpha-methyl dopa doses, beginning at the sixth month of pregnancy. Preeclampsia occurred in one subject, while the remaining eight patients had normal pregnancies and infant deliveries. In the treatment group (n=7), blood pressure was noted to decrease significantly as compared to the control group, with associated decreases in doses of antihypertensive medications at six months of gestation.

All treated patients experienced uncomplicated pregnancies and delivered infants with higher APGAR scores compared to those of controls. The authors concluded that in pregnant women with hypertension and chronic snoring, nasal CPAP applications during the first eight weeks of pregnancy combined with standard prenatal care are associated with better blood pressure control and improved pregnancy outcomes.

Although the studies included a small number of women, the results are provocative and difficult to ignore. Overnight ambulatory non-tended polysomnography, recently endorsed

by the American Academy of Sleep Medicine, is a reasonable test to use in the third trimester of pregnancy at home in women who snore, report sleepiness, and show hypertension. The aim would be to objectively demonstrate and measure clinically significant sleep apnea. A sleep apnea-hypopnea index (AHI) of five/hour of sleep or more might lead to the indication of continuous positive airway pressure treatment.

Further, Gay, et al. explored the sleeping habits of new parents and found that 84 percent of women experience insomnia a few nights per week. Forty-two percent rarely or never get a good night's sleep, while 19 percent experience post partum blues or depression.²⁰

Menopause

Menopause officially ensues one year following cessation of menstrual periods but hormonal changes begin seven to 10 years before the final menses. Estradiol and progesterone secretion decrease, while FSH and LH increase. Postmenopausal sleep complaints increase to reach 35 to 60 percent of all women. In the absence of hormone replacement therapy²¹ there is increased risk of developing sleep apnea, and, in fact, post-menopausal women tend to equalize the sleep apnea severity with men.

However, the cause of poor sleep quality in menopause is likely multi-factorial. Women have greater susceptibility than men to develop depression. In addition, psychosocial factors such as responsibilities towards home, children, spouse, and jobs, as well as life-style changes imposed by retirement coupled with increased life expectancy contribute to sleeplessness in the post-menopausal years. Loss of estrogen and progesterone leads to difficulty with sleep maintenance, but the significant finding has been more arousals and more time awake with arousals.²²

Sleep alterations caused by the aging process interact with the sleep disturbances precipitated by menopausal changes. Aging is associated with advanced sleep onset and core temperature phases, at a time when light as a Zeitgeber becomes less influential in maintaining the circadian cycle. Weakening of circadian and homeostatic processes contributes to sleep disturbances. In post-menopause, older women experience a phase advancement of 1.1 hours in melatonin acrophase.

Menopausal hot flashes display a circadian variation with peak frequency in late evening and are related to a change of unknown etiology in the central thermoregulatory response. Eighty percent of peri- and post-menopausal women with severe hot flashes have chronic insomnia.²³ Recommendations to improve hot flashes include regulating the core body temperature, cooling ambient temperature, dressing in layers, drinking cold liquids, avoiding caffeine and nicotine, and losing weight. Estrogen replacement, administration of gabapentin or clonidine, along with relax-

ation techniques have been recognized as effective remedies. Hormone replacement therapy (HRT) users report better quality of sleep than nonusers, even three years after HRT, perhaps through modulation of the reticular activating system. Women should be aware that there are significant risks associated with HRT, including increased risk of breast cancer, stroke, heart disease and vascular dementia.^{24, 25, 26}

Sleep Apnea in Women

Outside pregnancy, sleep apnea syndrome of moderate to severe intensity (AHI > 15 respiratory events/hour of sleep) is found in two percent of middle aged women and about four percent of middle-aged men.²⁷ For mild cases (AHI > 5/hr) the ratio changes to men 15 percent and women 10 percent. Gender differences in sleep apnea are related to anatomical differences with more upper body fat distribution in men, and increased ventilation and upper airway muscle activity in women caused by the hormonal action of progesterone.²⁸

In general, the risk of sleep apnea increases after menopause, presumably when the influence of progesterone declines and anatomical differences with men become less marked, and tends to approach that of men until the age of 65 years—the age at which the prevalence of sleep apnea peaks in women. Central sleep apnea occurs in women with congestive heart failure (odds ratio 3.5 for women) but with much lower frequency than in men.^{29,30} Women with sleep apnea complain of headaches in the morning more frequently than men, perhaps related to allodynia (lowering of pain threshold) in women with migraines,³¹ a condition that is well known to affect women more often than men at all ages. On the other hand, men with sleep apnea have a higher risk of suffering motor vehicle accidents, a feared complication of sleep apnea syndrome.³²

Special Considerations

In general, women without sleep complaints sleep objectively better across age than men, and the sleep of young women is more resistant to external stressors. Also, gonadal hormones exert a beneficial effect on women's sleep. Conversely, women are exposed to biologic circumstances that have a powerful influence on sleep. Pregnancy and menopause are strong sleep modifiers with a unique pathology that deserves additional independent study and therapeutic intervention. Sleep apnea affects 10 percent of pregnant women, particularly if obese, with the incidence reaching a peak in the third trimester of pregnancy. The notion of a pathogenic link between sleep apnea and preeclampsia opens opportunities for prevention and treatment. **PN**

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