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Chapter 40

Women and sleep

JOYCE A. WALSLEBEN*
Division of Pulmonary, Critical Care and Sleep Medicine, New York University School of Medicine, New York, NY, USA

Differences in the sleep of males and females have been documented across multiple studies. Humans begin to form various stages of sleep around the fourth month of life. Sleep architecture continues to evolve throughout childhood and adolescence and subtle differences of architecture between sexes may exist at times during this period. Sleep then reaches a fairly stable period until midlife when gender differences begin to be more noticeable and suggest a female advantage. Objective tests would tend to indicate that women sleep "better" than men. However, subjective studies tend to show that women complain of more insomnia and more pain and stress-related interference of sleep than men (Table 40.1). This chapter will discuss differences in women's sleep compared to men, reasons why differences occur, and how this may affect clinical decisions.

OBJECTIVE DIFFERENCES IN FEMALES' SLEEP

A seminal work examining sleep in normal subjects was reported by Williams et al. (1974) and shows sleep architectural changes across ages and between genders. Noncomplaining sleepers, categorized by decade and gender, were studied with full laboratory-based polysomnography. While not all variables that could influence sleep were controlled for at this early time in our history, this work did attempt to control for the influence of the menstrual cycle by only studying adult women in their follicular phase. Sleep differences between males and females were seen to begin around 9–10 months of age, with female babies sleeping longer. Around age 3 years males showed greater time in bed (TIB), total sleep time (TST), longer rapid eye movement (REM) cycle length and higher percentage of stage 2 sleep. Females demonstrated a trend toward increased slow-wave sleep (SWS) which continued throughout most of their lives. Teenage females tended to show less TIB and in the later teens females slept less than males. In their 20s females demonstrated more TST than men and continued to do so throughout life. Additionally they showed more stage 2 sleep. Males began to show increased levels of arousals and decreased SWS toward the end of the second decade. The decline of SWS continued throughout their life but did not begin in females until the fourth or fifth decade. Females began to show less SWS in their 50s and began to look like males did in their 30s. Females continued to show decreased levels of arousal (compared to men) into their fourth decade. Sleep became fragmented with increased arousals during predicted perimenopausal years. During the sixth decade larger differences were seen in the amount of SWS; only 10% of males showed any SWS while 50% of females did. By the age of 70, few males showed appreciable amounts of SWS. In their seventh decade, females showed more stage changes than males, perhaps simply because they continued to show all stages of sleep. Males tended to show shorter REM cycles than females.

More recently, Walsleben et al. (2004) demonstrated similar findings in a large cohort of adults over age 40 ($n = 470$) using home-based polysomnography. This cohort was well defined as "normative" in that subjects with possible causes of sleep disruption were excluded. Females continued to show "better" sleep. They had longer TST, lower arousal rates, more SWS and less stage 1 and 2 sleep compared to males. Importantly, the data also demonstrated significant subjective excessive daytime sleepiness (EDS) in subjects despite a TST of > 7.2 hours per night.

*Correspondence to: Joyce A. Walsleben, R.N., Ph.D., Sleep Medicine Associates of NYC, 11 East 26th St, New York, NY 10010. Tel: 212-481-1818, Fax: 212-523-0498, E-mail: Joyce.Walsleben@nyumc.org

Table 40.1

Sleep disorders that are more common in women compared to men

Women	Men
Insomnia: 1.4× more than men	Obstructive sleep apnea: 2× more in men
Restless-legs syndrome: 2× more than men	Primary snoring: 2× more in men
Sleep-related headaches: 4× more in women	Rapid eye movement behavior disorder: 88% men
Fibromyalgia: 80% women	Delayed sleep phase syndrome
Nocturnal sleep-related eating disorders: 65% women	Sleep enuresis: 3:2 male/female
Nightmares	Sleep terrors
Familial sleep paralysis	Sudden unexplained nocturnal death

Smaller objective studies of gender differences in sleep have shown few significant differences between men's and women's sleep when studies are visually scored. With more advanced electroencephalogram (EEG) scoring techniques, the finding of increased delta power among women has been confirmed and other differences noted. Dijk et al. (1989) studied gender differences in young adults aged 19–28 years (13 males/15 females) using computer-quantified spectral analysis of EEG. These authors noted an increase of delta power in the EEG (0.25–4 Hz) of females during non-REM (NREM) sleep and higher power densities in women during REM sleep that was consistent across the night.

Armitage (1995) studied young adults (mean age 25 years, 11 males/11 females) using visually scored staging and period analysis algorithms, to examine EEG frequencies during sleep. Her analysis evaluated EEG in five conventional frequency categories: (1) delta (0.5–4 Hz), seen in SWS; (2) theta (4–8 Hz), predominantly seen in other stages of sleep; (3) alpha (8–12 Hz), found in quiet wakefulness; (4) sigma (12–16 Hz), seen in spindle activity of stage 2; and (5) beta (16–32 Hz), seen in lighter stages of sleep and wake. When global delta power of NREM was examined, females again showed significantly more delta across the sleep period. Unfortunately, most of the females in these two studies took oral or injectable contraceptives that may have influenced the findings.

Ehlers and Kupfer (1997) studied young adults aged 20–40 years using visually scored sleep staging and spectral analysis of EEG characteristics to examine the effects of aging on the EEG. Both sexes had a decline in spectral power of spindles with age. No gender differences in SWS or delta wave activity were seen among subjects in their 20s. However, significant reductions of delta activity and percentage SWS were noted for males in their 30s. Additionally, males showed significant reductions of REM time, REM density, activity, and intensity with an increase of stage 2 sleep. These authors suggested this might reflect that males and females age differently over the second and third decade.

Laboratory findings studying 10 older men and 10 postmenopausal women demonstrated a novel measurement technique for polysomnographically recorded sleep. When NREM delta and alpha spectral activity was normalized for the amount of delta in REM sleep, women were shown to have less delta activity and more alpha activity in NREM than men, an objective finding which may reconcile women's subjective complaints of poor sleep (Latta et al., 2006).

To avoid confounds of the laboratory environment, other small studies have objectively evaluated sleep in the subject's home with full polysomnography. Kobayashi et al. (1998) studied 18 older subjects (8 males/10 females, mean aged 60.6 and 61.7 respectively) during two 36-hour sleep/wake periods. Females napped less frequently, had higher sleep efficiency, less stage 1 sleep, more SWS, more REM and fewer state changes than males. However, no mention was made of concomitant sleep disorders such as apnea that could be expected to influence sleep negatively.

Fukuda et al. (1999) evaluated sleep in older subjects (8 males and 8 females aged 54–72 years). Visually scored sleep staging and spectral analysis of two frequency bands (0.5–2 Hz and 2–4 Hz) were analyzed. Visually scored sleep parameters showed that females continued to have higher percentages of SWS. With spectral analysis, females showed larger amounts of delta power and maintained clearer periodicity of delta power across the night. The authors suggest that the SWS generator is better conserved in middle-aged and elderly females compared to same-aged males.

Using sleep logs and actigraphy at home, Reyner and Horne (1995) studied 400 adults (211 female and 189 males) aged 20–70 years for 15 consecutive nights. Actigraphy provided objective confirmation of sleep length and timing as well as sleep continuity. Subjects were divided into three age groups: (1) young, aged

20–34 years; (2) middle-aged, 35–49 years; and (3) older, 50–70 years. Home environmental factors were not controlled in this field study. Overall, there appeared to be minimal effects of aging in both subjective and objective parameters. Females reported longer sleep latency (time to fall asleep). Although both males and females awoke earlier as they aged, there was a significant difference in rise time between middle-aged subjects, with females rising later than males. Young males slept longer than both their middle-aged and older counterparts and middle-aged females slept longer than middle-aged males. Actigraphy confirmed subjective complaints that females, particularly the older ones, had more TIB with more frequent awakenings. Many of these awakenings were noted to be environmental (children's needs). This begins to suggest that women's sleep is also dependent on social issues.

Objective studies of gender differences in circadian rhythmicity

The circadian rhythm of body temperature, oscillating between a nadir at night and maxima in the afternoons, is thought to influence sleep onset and offset. Questions have been posed as to the impact of ovulatory changes in body temperature on females' sleep. Ito et al. (1995) studied the plasma melatonin circadian pattern under controlled conditions with measurements every hour for 24 hours on the third day of each week in 7 females aged 18–19 who spent 3 consecutive days in each of 5 successive weeks in the laboratory. The menstrual cycle was divided into four phases. Plasma melatonin increased in the late luteal phase and rise time was delayed on the first of the 3 days in the laboratory. Additionally, SWS was increased in the follicular phase, as was TIB and TST, suggesting that the menstrual cycle did affect melatonin and sleep/wake rhythm.

Similarly, Parry et al. (1997) studied the nocturnal patterns of melatonin in females with premenstrual dysphoric disorder (PMDD) and controls and noted a delay in the secretion of melatonin and a decrease in melatonin secretion during the luteal menstrual phase as compared to the follicular phase in females with PMDD. The authors suggest that the circadian pacemaker of females with PMDD is more responsive to the hormonal changes of the menstrual cycle. Further they postulate that this sensitivity may render these females more subject to mood, cognitive, and sleep disturbances as a result of endogenous and exogenous stimuli (Parry et al., 2006a).

Baker et al. (2001) studied subjective and objective sleep variables in 8 normally cycling women, 8 women on birth control pills, and 8 males (all aged 21–22 years). All subjects had a screen/adaptation night in the laboratory. Females were alternately studied in their mid follicular and mid luteal phases over a 3-month period. Polysomnography and continuous core body temperature were measured along with levels of estradiol and progesterone in the females. Rectal temperatures of the normally cycling females were elevated, as expected, in the luteal phase of the menstrual cycle compared to that in their follicular cycle and documented blunted nocturnal drops of temperature compared to males. Both groups of females attained temperature minima earlier than males, suggesting a gender effect. Temperatures of the females on exogenous hormones were similar to that of the luteal phase in normally cycling females.

There was no significant difference in the sleep architecture (macrostructure) of males and females; however, more SWS was seen in the luteal phase of normally cycling females. Those on exogenous hormones demonstrated less SWS than normally cycling females, suggesting that, as hormonal supplementation alters the temperature phase, it may also influence sleep. Buysse et al. (1993) studied 17 healthy 20–30-year-old males ($n = 9$) and females ($n = 8$) and 18 healthy 80-year-olds (11 males and 7 females) during a 36-hour constant routine paradigm to evaluate temporal patterns of unintended sleep episodes. During the constant routine, which followed a 24-hour normal routine adaptation period, balanced nutrition was supplied every hour. Online core body temperatures were tracked and cortisol and melatonin levels were sampled over the entire period. All subjects had continuous EEG with measurement of mood and sleepiness every hour. Females showed stronger rhythmic trends for sleep than males. Although all temperature measurements of the younger females were taken during their follicular menstrual phase, older females in this study showed higher temperature amplitudes than the younger females. Unfortunately, 3 of the younger females were taking oral contraceptives which could have blunted their temperature curves. Still, the findings may suggest that changes occur with increasing age.

In a study designed to examine the relationship between age-related changes in sleep and the circadian timing system, Campbell and Murphy (1998) studied 60 subjects (32 females and 28 males) between the ages of 40 and 84 years. For some analyses, the group was divided by age and sleep history. One middle-aged group (40–60 years) and two older groups aged 65–81 years (one a subset who had experienced sleep difficulties for at least 1 year prior to the study) were studied. Polysomnography and measures of core body temperature were performed at an adaptation and baseline night. There was no difference between the sleep

quality of noncomplaining older subjects when compared to middle-aged subjects; however there was an advance in minimum body temperature in older subjects. Although complaining older subjects had decreased TST, sleep efficiency and REM with increased wake after sleep onset compared to noncomplaining older subjects, there was no difference in the rhythm of body temperature. With age controlled for, females again showed significantly higher temperature amplitude than males. In addition, there was a significant age effect on amplitude in females, not males. The authors suggest that these findings argue that a stronger circadian rhythmicity, as measured by temperature curve amplitude, is maintained by older females and that age-related sleep disturbances may have multiple causes.

In addition to the homeostatic and circadian rhythms, an interval timing clock which measures the duration of a period of time, much like a stopwatch, is thought to exist (Virginia, 1996). How this may have an impact on sleep is not yet known. However, work by Morofushi et al. (2001) tends to indicate that estrogen may control the mechanism of the interval clock, affecting time-keeping across the menstrual cycle. Further, Kruijver and Swaab (2002) have shown estrogen and progesterone receptors located in the human SCN with a significantly stronger nuclear estrogen receptor-alpha expression pattern in females compared to males.

SUBJECTIVE DIFFERENCES IN WOMEN'S SLEEP

Despite objective proof that sleep is good, many women continue to complain of poor sleep. A 1997 poll of just over 1000 women by the National Sleep Foundation (1998) found that 50% of women polled complained about insomnia. Seventy percent of menstruating women lost 2.5 nights of sleep per month and 80% of pregnant women complained about disrupted sleep. Forty-four percent of women napped every weekend. Almost a third took over-the-counter or prescription sleep aids.

Similarly, 38% of 12 603 women polled, as part of the Study of Woman's Health Across the Nation, reported difficulty sleeping. This sample studied women between the ages of 40 and 55 years. Those reporting the most sleep difficulty were in the late perimenopausal group or had been oophorectomized. Caucasian women had the highest percentage of complaints and Japanese and Chinese women the least. When compared to Caucasian women, African American women had fewer complaints (Kravitz et al., 2003).

It is unclear why the discrepancy between objective and subjective findings exists. Perhaps we are not looking closely enough when objectively monitoring sleep. Clearly the use of standardized visual scoring (Rechtschaffen and Kales (R&K), 1968) may not adequately mark the subtle disruption, which may have an impact on sleep in women. O'Malley et al. (2003) have shown that approximately 20% more arousals are noted when frontal EEG leads were added to typical R&K montages. Latta et al. (2006) studied healthy nonobese older subjects (10 males and 10 postmenopausal females) and found that women actually had lower delta activity than males when NREM delta activity was normalized for the delta activity in REM sleep, and higher absolute alpha activity. This important finding coincides with women's subjective complaints of poor sleep.

Finally, women may be assessing other aspects of their sleep when complaining of difficulty (Vitiello et al., 2004). For instance, both Cartwright and Knight (1987) and Ultberg et al. (2000) have described the negative impact of a spouse's sleep disorder on one's sleep. When studying partners of apneics, Cartwright & Knight saw poor adjustment on the Marital Satisfaction Inventory and Ultberg et al. noted more insomnia and daytime fatigue/sleepiness among the spouses. Spouses noted improvement of their own sleep when treatment of the apnea occurred (Strawbridge et al., 2004).

Other hormonal and physiological factors as well as psychological and sociological factors are thought to affect women's sleep.

HORMONAL FACTORS

Estrogen level

Limited data suggest that secretions of gonadal hormones influence or modulate sleep physiology in animals and both the physiology and pathology of sleep and its disorders in humans. Neuroendocrine function is influenced by gonadal hormones at both pre- and postsynaptic levels. Animal studies show that neurosteroids (estrogen, progesterone, and testosterone) play a pivotal role in the mediation of stress and the effect on brain functions. Furthermore affects are noted in brain regions related to the control of sleep and wake (medial preoptic nuclei, medial hypothalamus) and limbic areas such as the hippocampus and amgydala (McEwen, 2001). Estrogen has been shown to increase the turnover of norepinephrine in the brainstem, hypothalamus, nucleus accumbens, and locus coeruleus as well as alter expression of c-fos proteins in α_2-adrenergic neurons (for review, see Manber and Armitage, 1999). These effects act to decrease REM sleep but the action appears to depend on the phase of the circadian cycle. Temperature phase may be altered, suggesting that

estrogen may weaken the coupling between the core body temperature and the sleep–wake cycle or otherwise modulate circadian rhythms (Dijk et al., 1989).

Estrogen acts as an excitatory stimulus by increasing the production of and receptor concentrations of neurotransmitters such as serotonin, norepinephrine, and dopamine as well as β-endorphins, and increasing the availability of glutamate, which stimulates the excitatory *N*-methyl-D-aspartate system (Arpels, 1996). Estrogen also regulates the flow of other key hormones that are secreted during sleep, among them growth hormone, prolactin, cortisol, and melatonin. Estrogen can act as an antidepressant, decreasing monoamine oxidase activity while increasing availability of serotonin and norephinephrine, and is a necessary cofactor for memory (Joffe and Cohen, 1998; McEwen, 2001). In theory, increased levels of estrogen occurring as a consequence of hormone replacement therapy (HRT) could increase activity and irritability and lessen sleep. However, studies evaluating HRT in postmenopausal women demonstrate increased sleep times; there was less fragmentation and enhanced REM sleep compared to baseline and placebo controls (Giampiero et al., 1997; Leproult et al., 1998; Moe et al., 2001; Montplaisir et al., 2001; Gambacciani et al., 2005).

Hormones: progesterone

Progesterone has a hypnotic and anxiolytic effect on sleep similar to that of the benzodiazepines.

Progesterone and its metabolites act directly on the $GABA_A$ receptor and, through a complex mechanism, result in either a hyperpolarization and decrease in neuronal excitability (allopregnanolone and pregnanolone) or an antagonistic reaction which limits GABA-induced chloride transport (pregnenolone sulfate) (Mellon, 1994). The sedating action of progesterone is comparable to that of the benzodiazepines and acts in a dose-dependent fashion (Lancel et al., 1997). Progesterone has been shown to decrease latency to sleep, decrease wakefulness, and increase EEG spindle activity in both REM and NREM sleep in both animal and human studies. Furthermore the progesterone antagonist mifepristone (RU-486) has been shown to produce increased wake time, longer sleep latencies, and decreased REM and SWS when administered to healthy men (Wiedemann et al., 1998). Progesterone also acts as an antiestrogen and downregulates the estrogen receptors.

Researchers also see changes in cellular immune function across the menstrual cycle that appear to be associated with fluctuations of progesterone. Moldofsky et al. (1995) have shown that there is less natural killer cell activity during the luteal phase when progesterone is high. During the follicular phase women's natural killer responses are the same as in men. This suggests that progesterone may modify immune function, perhaps having an impact on women's risk of lupus and rheumatoid diseases that may also alter their ability to sleep.

Hormones: testosterone

Animal work also suggests that androgens (testosterone) play a role in the sexual dimorphism of REM sleep during a critical period of brain development around the perinatal time (Manber and Armitage, 1999). Testosterone, excreted by the adrenals in women and converted into estrogen in the brain, has variable effects on sleep. In men testosterone decreases REM sleep but the addition of exogenous testosterone to adult animals has been shown to have little effect on sleep. For women, as estrogen is waning, the ratio of estrogen to testosterone changes such that there appears to be more testosterone. Those sensitive to the effects of androgens will feel symptoms of irritability, sleeplessness, and depression similar to that of estrogen loss. The lessening of progesterone as well as the change in this ratio of estrogen to testosterone may influence the sleep changes around the perimenopause.

PHYSIOLOGIC CHANGES OVER THE LIFESPAN

In addition to women's cyclic sex hormones, there are changing life stages such as menarche, pregnancy, lactation, and menopause which also affect sleep (Parry et al., 2006a, b).

Sleep and the menstrual cycle

Numerous studies and surveys of subjective complaints of sleep disturbance demonstrate large numbers of women with occasional menstrual-related sleep difficulty (National Sleep Foundation, 1998). This includes complaints of bloating, cramping, and pain such that women lose up to two nights of sleep per month. However, few objective studies have confirmed these complaints, perhaps because few studies accurately measured hormonal levels, many dividing the menstrual cycle into a variety of phases which could not be matched for meta-analysis. Furthermore, most studies have few subjects. In studies of sleep, the menstrual cycle has been divided into two to eight phases. If two phases are studied, they are the follicular (preovulation) and luteal (postovulation) phases. If more than two phases are discussed, authors separate the follicular and luteal phases into early or late. They

may also include menstruation and ovulation as phases. This complicates the comparison and interpretation of studies.

Although the findings are not always consistent, generally in the follicular phase, as increased estrogen is triggered by follicule-stimulating hormone (FSH), many women will experience an increased depth of sleep if not actual increased sleep time, increased SWS and TST. At midcycle, after ovulation, the corpus luteum produces progesterone. This increase in progesterone acts to increase body temperature and can blunt circadian rhythm. Additional estrogen is secreted in the early luteal phase, perhaps modulating some of these effects. Over the course of the next 14 days, there is increasing wakefulness and increased sleep disturbance as levels of estrogen and progesterone decline. Less REM sleep occurs but an increase of stage 2 sleep is noted with higher spindle activity (Driver et al., 1996). There is a significant decrease in SWS premenstrually, decreased sleep efficiency, an increase in the time it takes to fall asleep, and decreased sleep quality (Driver, 2008). Because of the blunting in melatonin rhythm, some women tend to advance their circadian phase, getting sleepier early in the evening and awakening early in the morning. The metabolic rate increases across the cycle as well. Sixty-eight percent of menstruating women surveyed felt sleepiest during the week before or the first few days of their periods, compared to the rest of the month. In rare cases, women can suffer debilitating hypersomnia or EDS that begins premenstrually and resolves after menses begins. This may be due to sensitivity to progesterone's sedating effects or the lessening of estrogen secretion and metabolic rate during the menses (Parry et al., 2006a).

Women who experience premenstrual syndrome (PMS) may experience these symptoms to a greater degree. PMS varies from woman to woman. Clinically, PMS symptoms arise in the period between ovulation and menstruation. There may be daytime sleepiness and increased sleep disturbances. Some researchers have likened PMS to jet lag. Both are temporary conditions involving nighttime sleep disturbance and daytime sleepiness, with mood changes and difficulty concentrating. Both also involve shifts in the secretion of melatonin. Melatonin has been found to be higher premenstrually and during menstruation. Low serotonin may also contribute to PMS-related mood swings, depression, and anxiety. For women who suffer PMDD, sleep problems are common and objective differences are more pronounced (Parry, 1989). Despite these general findings, it is important to note the vast individuality of responses among women.

Pregnancy and the postpartum period

Being pregnant and caring for an infant also have an impact on sleep. Due to the rapid rise of progesterone during the first trimester, many women are unable to stay awake during the day. Progesterone also inhibits smooth-muscle contraction and may be responsible for frequent trips to the bathroom during the night. By 11 weeks of pregnancy, sleep becomes disrupted with increased awakenings, a shorter time to fall asleep, and less efficient sleep. Some studies show a slight decline in REM and SWS, perhaps due to more awakenings. Some women may also be bothered at night by nausea (which is hormonally related), and by backaches.

By the second trimester, sleep is the most stable it will be, although less REM and SWS is noted (Lee, 1998). Women are bothered by fetal movements and the emergence of pregnancy-related heartburn. Restless-leg activity may also start during the second trimester and may be due to an imbalance of ferritin in the brain and folate deficiency (Lee et al., 2001) or indirect interference with dopaminergic transmission as a result of an estrogen-driven increased turnover of norepinephrine (Manconi et al., 2004). Despite the normal serum level, brain ferritin may be low. Additional iron in supplement form is frequently helpful (Earley and Connor, 1999).

During the third trimester, there is increasing sleep difficulty, in part because of the physical girth of the body and the inability to be comfortable and in part because of changing hormones prior to delivery. Less TST is noted and sleep becomes lighter with more frequent awakenings (Brunner et al., 1994). Women will tend to dream of the impending birth and care of the baby (Hall et al., 1982). Sleep deprivation and fatigue are major issues late in the third trimester. Women also suffer from shortness of breath, frequent urination, cramps, itching, and frequent nightmares. Heartburn increases along with the size of the belly. Additionally, the growing uterus can press on the sciatic nerve, causing pain. Each of these problems interferes with sleep continuity. However, REM sleep returns to almost normal levels during the last month of pregnancy.

Of interesting clinical note, Lee and Gay (2004) also reported that TST is associated with length of labor and type of delivery such that women who sleep less than 6 hours per night were more likely to have longer labors and 4.5 times more likely to have cesarean deliveries. Those whose sleep was even more fragmented had an even higher rate of cesarean births.

In addition to the hormonal aspects of pregnancy and childbirth, there are the physical stresses of

pregnancy and the demands of taking care of a newborn who needs to be fed on a schedule (day or night). In striving to do their best, parents often put their own sleep needs on the back burner. Sleep issues continue into the postpartum phase for many women. Lee and Zaffke (1999) followed 24 primiparous and 18 multiparous women to evaluate perceived levels of fatigue and energy before, during, and after pregnancy. Studies that were carried out in the subjects' homes during the follicular and luteal phase of menstruation prior to conception served as baseline data. Studies were repeated during each trimester and again at months 1 and 3 of the postpartum period. Measures included polysomnography, scales including: Lee Fatigue Scale, Profile of Mood States and Dupuy General Well-being, Vitality subscale. Serum chemistries included iron (hemoglobin, hematocrit, ferritin, B_{12}, and folic acid) progesterone and thyroid serum triiodothyronine (T_3), serum thyroxine (T_4), T_3 resin uptake, free T_4 index, and thyroid antimicrosomal antibody titer. Complaints of fatigue during the first trimester correlated to subject's younger age and lower levels of iron, hemoglobin, and ferritin. Hemoglobin levels remained at low normal throughout the pregnancy whereas ferritin levels dipped more slowly across trimesters. During the third trimester, fatigue was related to decreased TST. Postpartum fatigue was related to decreased sleep, ferritin, and hemoglobin. Even at 3 months postpartum these women still perceived less energy than their baseline levels. The perception of energy appeared to be influenced by parity, with multiparae having less energy throughout pregnancy. This suggests that pregnancy takes a significant toll on the sleep patterns and energy levels of women. Lee suggests that poor sleep may set women up for profound mood changes and depression during the postpartum period. She suggests that the "baby blues" may be a consequence of prolonged sleep deprivation (Lee et al., 2000). Postpartum depression or anxiety may be overlooked as a cause of sleep problems because we expect disrupted sleep at this time of life. Furthermore, the sleep systems of women with a history of depression may be more sensitive to the psychobiological changes of childbearing. Those women may have an earlier onset or more severe sleep disruption. Clinicians should be alert to the issues of sleep and pregnancy and educate their patients regarding expectations and solutions to improve outcomes.

Pregnancy and apnea

During pregnancy changes in respiration and airway mechanics also occur. Snoring and apnea are not uncommon. To evaluate the extent of this problem Loube et al. (1996) carried out a large survey of pregnant women, asking about snoring status, and compared infant outcomes to examine the impact of self-reported snoring on infant health. A total of 350 pregnant women and 110 age-matched women as controls answered a survey about snoring and daytime sleepiness. Those with reported daytime sleepiness and snoring were given full sleep evaluations. Fourteen percent of pregnant women snored versus 4% of the nonpregnant women. Eleven women reported anecdotal apnea (cessation of airflow). Of these, only four were recorded. Two of them met the criteria for mild apnea, one had positional apnea, and the other only snored. There were no significant differences between infants from either group, perhaps due to inadequate power.

In contrast, Franklin et al. (2000) noted in a study of 500 Swedish women that habitual snoring was a sign of pregnancy-induced high blood pressure (preeclampsia), and was associated with lower birth weights and lower Apgar scores. The study also noted that women started to snore before any sign of hypertension appeared and that snoring was related to sleep apnea. While it may seem reasonable to suppose that the increased abdominal girth of pregnancy (with or without excessive weight gain) underlies the increase in apnea, there is little evidence to support this. A more likely explanation is that the frequent nasal congestion experienced by pregnant women predisposes to upper-airway collapse due to the large negative pressure in the airway needed to overcome the nasal obstruction. Fortunately, for many this is countered by the increase in minute ventilation and the fact that most pregnant women sleep in the lateral position during the later trimesters (Pien and Schwab, 2004). That position and the lessening of REM sleep may be protective as REM and supine positions may predispose to developing increased upper-airway resistance syndrome and sleep apnea. Clearly, care must be taken to assess the important aspect of snoring during late pregnancy whether or not women complain of disrupted sleep.

Perimenopause and menopause

Menopause, marked by a permanent cessation of menstruation (>12 months), elevation of luteinizing hormone and FSH, and decrease of androgens, is preceded by many years of hormonal changes. This period has been called the perimenopause and can stretch 5–10 years before the onset of menopause. Perimenopausal women frequently note mood changes and sleep disruption during this time.

Physical and psychological symptoms such as hot flashes and depression can take their toll on sleep.

The hot flash typically is characterized by peripheral vasodilatation, profuse sweating beginning on the face and upper body, and subsequent chilling. The flash is thought to be a disorder of thermoregulation. They may occur 2–20 times a day and last 3–5 minutes, with a peak acrophase around 6 p.m. When flashes occur at night they are accompanied by wake either preceding or following the event (Freedman and Krell, 1999). Alterations in central catecholamines occur. Levels of plasma 3-methoxy-4-hydroxyphenylglycol are higher in women who experience hot flashes (Woodward and Freedman, 1994). In a sense the hot flash is a general alerting mechanism which interrupts sleep and requires time to settle before sleep can comfortably recur. The phenomenon results in sleep loss and daytime consequences, such as mood changes and loss of concentration and memory (Baker et al., 1997). The addition of estrogen and estrogen replacement therapy (ERT/HRT) reduces the hot flash and has been seen to increase SWS in postmenopausal women (Leproult et al., 1998). Despite findings from the Women's Health Initiative (Writing Group for the Women's Health Initiative Investigators, 2002) and subsequent warnings about the risks involved with supplemental hormones, they still remain an effective treatment for menopausal symptoms. Patients are encouraged to use the lowest doses for the shortest amount of time to relieve symptoms.

Menopause is also a stage of life-altering changes which can produce stress and mood changes (Parry et al., 2006b). Children are leaving, parents are requiring more care, marriages are being renegotiated, and women may be redefining their roles. These stresses add to a hormonally volatile time in women's lives and may take a toll. Shaver and Paulsen (1993) reported on subjective and objective studies of 135 healthy women aged 37–59 years. Women were grouped as premenopausal and menopausal, each with and without poor sleep. The authors noted that women with objectively documented poor sleep had higher psychological distress rather than active menopausal symptoms. This suggests that the sleep disruption in the menopausal years may not be totally due to hormonal changes. Women's perception of poor sleep during the pre-, peri-, and postmenopausal years is not always consistent with objective data. Examining data on 589 women from her Wisconsin Sleep Cohort Study, Young et al. (2003a) found that menopausal status was not associated with diminished sleep quality as measured by polysomnography. In fact, postmenopausal women slept better than premenopausal women. Postmenopausal women showed 3.4% more SWS and 13.4 minutes more TST with less wake after sleep onset.

DIFFERENCES IN FEMALE PSYCHOSOCIAL ISSUES AND THE IMPACT ON SLEEP

Psychosocial issues, particularly at the midlife period, are different for women and men and affect them in significant ways. Part of this effect may be due to hormonal influence. It is known that oxytocin, a neurohormone stimulated by estrogen, acts to enhance bonding, particularly in new mothers when the amount of oxytocin increases. This also influences aspects of women's "tend and befriend" psychology, perhaps making it difficult to "let it go" when nighttime falls. Additionally, part of the midlife woman's stress may be due to the different roles women may be expected to play in society. Women are typically the caregivers to the extended family as well as the main caregiver to the immediate family. More women now work outside the home and may be single mothers attempting to survive on lower-paying jobs than men, with few social supports. Many work the night shift, suffering the effects of circadian misalignment and sleep deprivation. Most work "the second shift" of home and family. There are just so many hours in the day and something has to give. That something is usually sleep. These phenomena beg for education so that women understand the importance of adequate sleep time and the consequences of poor sleep.

Stressors are also different between the sexes. What may profoundly affect a woman will have little to no effect on a man. In a study of 1179 working individuals (623 women), Nordin et al. (2005) note that "women's sleep may be more vulnerable to poor emotional support and poor social integration than men's sleep." In this study matrixes were developed to measure network (number of helpful friends), emotional support (perception of closeness of friends/relatives), work control, and work demand indexes. Subjective quality of sleep was determined. Twenty-five percent of the women compared to 16% of the men rated their sleep quality to be poor. Women with low scores of network and emotional support but with high scores on work demand index complained of poorer-quality sleep. None of the indexes were associated with poor sleep in the men. Although stressors have been shown to affect sleep differentially, this paper points out the unique associations between stress and sleep in women.

Further, literature has again taken up the issues of a midlife crisis for women which involves significant life changes, which had previously been economically unavailable to them. More women who question their happiness or position during the midlife years (generally 40–60 years) are now able to afford changes which

may have an impact on the entire family as well as the woman herself. This issue has been well described in *The Breaking Point: How Female Midlife Crisis is Transforming Today's Women* (Shellenbarger, 2005). How these changes will affect women's sense of power, well-being, and sleep remains to be seen. Awareness of the impact of these and other psychosocial variables such as simple safety may help clinicians in their attempt to improve women's sleep.

Sleep disorders common in women

Far more women than men complain of insomnia – difficulty falling or staying asleep (Leger et al., 2000). This increase may be related to the increase in depression in women or at least the reporting of somatic symptoms related to sleep difficulties, which is increased among depressed women both acutely (Angst and Dobler-Mikola, 1984) and chronically (Kornstein et al., 2000). While it is still unclear as to the causation of symptoms, i.e., whether sleep difficulties precede mood symptoms or not, studies suggest a strong association (Joffe and Cohen, 1998). Furthermore, women may be more subjected to the entrainment of poor sleep habits first developed during years of parenting.

Clearly, insomnia may also be caused by physical syndromes such as fibromyalgia and pain. Medications may affect one's ability to sleep. Simple environmental issues such as safety may also play important causative roles. Because insomnia is so multifactorial, care should be taken to evaluate women for all the possible causative factors.

The increase of reports of insomnia among women is especially true during the perimenopausal years when hormone levels are rapidly shifting and continue to be prominent as women age. Maggi et al. (1998) evaluated 2398 (867 males and 1531 females) community-living older (>65 years) subjects with questionnaires. The prevalence of insomnia was 54% in women compared to 36% in men. There was an increased odds ratio for insomnia (1.69) and depression (1.93) in women even when results were controlled for potential risk factors such as health status and smoking and alcohol habits. Night waking was the most common complaint.

Differences in treatment of women's insomnia

As we know, the pathophysiology of insomnia is multifactorial. Treatments should be designed to alleviate the cause when possible. In addition to behavioral changes and medications, studies have also shown that ERT/HRT improves the sleep of perimenopausal depressed women irrespective of the presence of hot flashes (Scharf et al., 1997; Schmidt et al., 1997) and may continue to be helpful in postmenopausal women (Giampiero et al., 1997; Hays et al., 2003; Gambacciani et al., 2005). Caution should be exercised when considering this treatment, especially in women >60 years of age (Board of the North American Menopause Society (NAMS), 2003).

Obstructive sleep apnea (OSA) and sleep-disordered breathing (SDB)

Once thought to be a man's disease, OSA is also common among women and frequently overlooked as a possible cause for poor sleep. The estimated prevalence of SDB, which is defined as an apnea–hypopnea score over 5/hour of sleep, is 24% in men and 9% in adult women. Four percent of men and 2% of women will have the apnea–hypopnea syndrome, which includes daytime sleepiness (Young et al., 1993). There is an increased likelihood of developing OSA/SDB postmenopausally. Young et al. (2003b) reported an increased odds ratio (2.6 (1.4, 4.8)) of developing five or more apnea episodes per hour and an increased odds ratio of 3.5 (1.4, 8.8) of developing an apnea–hypopnea index of 15 events per hour in postmenopausal women.

Symptoms of OSA in both men and women include dramatic snoring (although many women do not know if they snore and may not report it), gasping during sleep, restlessness, and daytime sleepiness. Unfortunately, despite giving the classic symptoms of OSA to their health care provider, many women go undiagnosed. It is not clear whether this results from a bias of the health care worker or the concurrent reporting of psychologically oriented symptoms such as insomnia, depression, and anxiety, which attract more attention in women (Young et al., 1996). Women with OSA do report far more symptoms of depression and anxiety as measured with the Symptom Check List-90 than men, regardless of the severity of their OSA. Furthermore, Pillar and Lavie (1998) note that complaints of depression and anxiety were higher in women with severe OSA compared to women with mild OSA/SDB.

There has been much speculation as to why there is a sexual dimorphism in this disorder. Popovic and White (1998) suggested it is due to an increase in pharyngeal dilator muscle activity, probably related to levels of progesterone in awake females, such that genioglossus tone is increased in the luteal menstrual phase as well as in those postmenopausal women taking ERT. During sleep, Thurnheer et al. (2001) noted no such difference. They did note an increase in total respiratory resistance at sleep onset in men compared to women. The authors suggested that the waking

increase in upper-airway resistance previously seen in women reflected the narrower size of their airway. Vgontzas et al. (2001) note that SDB is more common among women with polycystic ovarian disease, perhaps reflecting the role of hormones.

Obesity tends to be a large factor in the development of obstructive apnea. However, for equal degrees of obesity, a man would probably have more sleep apnea than the woman, perhaps because of the placement of male fat in the midtorso area. Buyse et al. (2003) also notes that obese women < 55 years of age (presumably premenopausal) had a positive effect of weight gain on chemosensitivity, which may have been protective. However, women who are severely overweight are in jeopardy at any age. They may not have apnea from airway obstruction but may suffer hypoventilation, a decreased effort to breathe, particularly in REM, allowing significant hypoxia to develop (O'Connor et al., 2000). As previously mentioned, women can also develop a temporary form of OSA during pregnancy.

Unfortunately the consequences of OSA are the same, if not worse, for women compared to men (Peppard et al., 2000). Snoring alone increases the likelihood of the metabolic syndrome in women (Leinweber et al., 2003). Treatment options are the same for both sexes; however, several studies have indicated that HRT may be a useful treatment of sleep apnea (Pickett et al., 1989; Bixler et al., 2001; Polo-Kantola et al., 2003; Shahar et al., 2003; Wesstrom et al., 2005). Given the recent controversy over the risk factors of HRT, it may be premature to consider HRT as a treatment option for SDB.

Restless-legs syndrome

Restless-legs syndrome, described as crawly sensations in the legs which cause the sufferer to move them constantly, is more common in women than men and may have an impact on one's ability to fall asleep (Lavigne and Montplaisir, 1994). Restless-legs syndrome has a circadian rhythm which worsens the symptoms in the evening hours, just as one tries to settle down. Symptoms generally increase with age but are two to three times more common in pregnancy (Manconi et al., 2004). A National Sleep Foundation poll (2005) showed that restless-legs syndrome is "significantly associated with medical and psychiatric conditions, other sleep disorders, unfavorable life style behaviors and adverse effects on daytime function." Clinicians should explore symptoms of restlessness with their patients. Treatments include supplemental iron with vitamin C (when serum iron levels are low) and dopaminergic agents/agonists.

CONCLUSIONS

In summary, subtle differences in sleep architecture exist between males and females, particularly as they age. Most of these differences appear to be influenced by the gonadal hormones estrogen and progesterone in females and changes in the ratio of estrogen to testosterone as menopause approaches. Females' cyclic hormonal nature and physiologic changes significantly influence sleep architecture across their reproductive lifetime. Estrogen seems to increase REM sleep in humans and improve sleep continuity in menopause. Progesterone is known to be sedating and similar to the benzodiazepines in that it decreases REM sleep and increases spindling and stage 2 sleep in humans. This effect is most notable in the first trimester of pregnancy.

Although data suggest that women have a propensity for "better/deeper" sleep, subjective reports do not agree. Recent work demonstrating a novel measurement technique for sleep shows that women have less delta activity and more alpha activity in NREM, an objective finding which may reconcile subjective complaints.

Furthermore, certain sleep disorders appear to favor one sex over the other. Sleep disorders are common in women and have a negative impact on their quality of life. Insomnia, restless legs, and apnea all act to disrupt sleep. Women have a risk of depression that is twice that of men. This may influence the prevalence of insomnia in women. Other sleep disorders such as apnea appear frequently in women, yet are still underdiagnosed, leaving women subjected to the significant health outcomes of hypertension, diabetes, and profound daytime sleepiness.

Awareness of these issues and attention to incorporating questions about sleep and daytime alertness into a woman's care will optimize treatment. Treatment of sleep complaints and disorders in women will need to consider their unique physiology and psychology. Attention to stressors and life stage is necessary. While HRT can improve sleep in many women, individual risk/benefit ratios should be considered before incorporating this therapy.

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