Sleep and Sleep Disorders in Women

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The Menstrual Cycle and the Effects on Sleep

Hormonal and Sleep-Related Changes Across the Menstrual Cycle

Cyclical changes in four reproductive hormones—luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen, and progesterone—and in body temperature occur in a normal, ovulatory menstrual cycle. The cycle lasts 28 days on average (Fig. 53.1) but may range from 25 to 35 days. When menstruation starts (day 1), levels of all four key reproductive hormones are low. As FSH and estrogen rise, ovarian follicles develop and mature. This follicular phase precedes ovulation and may vary in length. LH peaks about 16 h prior to ovulation, and the appearance of LH in urine is a reliable marker of ovulation. At ovulation, an oocyte is released from the follicle. The corpus luteum then evolves from the ruptured follicle and secretes progesterone and estrogen during the luteal phase. If ovulation occurs, body temperature, measured at the same time every morning, increases by about 0.4 °C; this effect is mediated by progesterone [1–3]. In the absence of pregnancy, about 7 days after ovulation, the corpus luteum degenerates and hormone production begins to decline. The luteal phase lasts 14–16 days. Most negative menstrual symptoms are experienced as hormone concentrations decline toward the end of the luteal phase and during the first days of menstruation.

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Subjective Reports of Sleep Across the Menstrual Cycle

Normally, subjective sleep quality is reduced both premenstrually and at menstruation [4–6]. Retrospective surveys have found that 16–32 % of women report increased fatigue, difficulty in concentrating, or lethargy in the premenstrual period [1, 7–9]. A telephone survey of 514 women for the National Sleep Foundation (NSF) in 1998 found that approximately 70 % of women report that their sleep is adversely affected on average 2½ days every month by menstrual symptoms such as cramps, bloating, tender breasts, and headaches [10].

Increased sleep disturbance around menstruation has been confirmed in some, but not all, prospective studies [4–6]. In a study of 32 women who kept daily diaries across two menstrual cycles, although there was no change in sleep duration in the late luteal compared to the mid-follicular phase, sleep disturbances increased, with poorer sleep quality. In the premenstrual period, sleep onset was delayed and there was an increased number of awakenings [5]. In contrast, there was no change in sleep quality or sleep duration in 30 young women with normal menstrual cycles [6]. In our study based on daily self-reports across one menstrual cycle, ovulation was confirmed in 26 young women without significant menstrual-associated complaints, sleep quality was reduced in the 3–6 premenstrual days and during the first 4 days of menstruation [4]. These studies, and other reviews [1, 7–9], highlight the challenges

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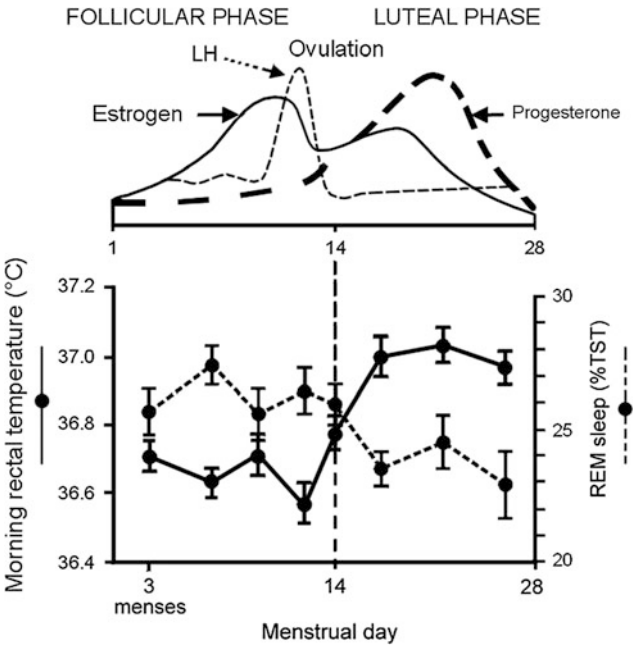

Fig. 53.1 Menstrual cycle changes across a 28-day ovulatory cycle. The day menstruation begins is generally considered the first day of the menstrual cycle, and ovulation occurs around day 14. *Top* The profile for luteinizing hormone (*LH*), which peaks before ovulation (*dotted line*), and the ovarian hormones estrogen and progesterone. *Bottom* Morning core body temperature (*solid line*, axis on the *left*) and REM sleep as a percentage of total sleep time (TST; *dashed line*, axis on the *right*) (Modified from Driver et al. [2] and Driver and Baker [1])

inherent in studying menstrual cycle effects, including variability in cycle length, the presence of ovulation, individual and cycle-to-cycle differences, changes with age, and the frequency of data sampling. Given the cyclical, though modest, reduction in sleep quality around the time of menstruation in women without sleep complaints, assessment of insomnia in naturally cycling women should consider the temporal relationship of sleep complaints and the phase of the menstrual cycle.

Polysomnographic Studies Across the Menstrual Cycle

Early laboratory studies were based on small sample sizes, usually in young women (<30 years of age), with heterogeneous groups including those with affective symptoms or those taking oral contraceptives (OCs), often without verification that ovulation had occurred [1, 7, 9]. Two studies addressed these issues [2, 11] by conducting more frequent recordings, at 3 nights per week [11] and every other night [2], in nonsymptomatic good sleepers with verified ovulatory cycles. These polysomnographic (PSG) studies included spectral analysis of the sleep electroencephalogram (EEG) and core body temperature measurements. Both studies revealed an increase in sleep spindle frequency [2, 11] in the mid- to late-luteal phase compared with the follicular phase. This effect on sleep spindles was reflected in a menstrual-associated variation in stage 2 sleep (higher in the luteal phase). Increased stage 2 sleep in the luteal phase compared to the follicular phase was also reported by Shechter and colleagues [12] who recorded sleep every third night in the laboratory in five healthy women and seven women with premenstrual dysphoric disorder (PMDD). This luteal phase increase in stage 2 and sleep spindle power may represent an interaction between endogenous progesterone metabolites and γ-aminobutyric acid (GABA) type A membrane receptors [2]. However, in a group of 16 healthy women and 18 women with severe premenstrual syndrome (PMS), Baker et al. [13] found no correlation between EEG sigma (12 to <15 Hz) power (i.e., sleep spindle frequency) and progesterone based on one night laboratory recording in the mid-follicular and the late-luteal phase.

No significant effect of menstrual cycle phase on slow-wave sleep (SWS, now N3) [2, 11–14] or EEG slow-wave spectral activity [2] has been reported suggesting that sleep homeostatic mechanisms are not altered by menstrual phase. With the higher nocturnal temperature of the luteal phase, rapid eye movement (REM) sleep is slightly reduced [2, 3, 14] particularly in the early-luteal compared to the early-follicular phase [12], with shorter REM sleep episodes in the first 3–4 cycles if not the whole night [13, 15]. No significant menstrual phase effect on sleep latency or sleep efficiency based on PSG has been reported. The few controlled PSG studies in young women with no menstrual-associated complaints show that sleep across the menstrual cycle is remarkably stable, aside from variation in sleep spindles and subjectively disturbed sleep in the premenstrual and menstrual periods [1–4, 7–9, 11].

Oral Contraceptives and Their Effect on Sleep

OCs are used by approximately 100 million women worldwide [16, 17], yet few studies have examined their effects on sleep. Studies are complicated by different levels of synthetic estrogen and progestin within the various OCs, which are available as monophasic and triphasic pills [16, 17]. OCs contain synthetic estrogen and/or progestin that prevent ovulation by suppressing endogenous reproductive hormones. While the progestin is responsible for the contraceptive effects, the estrogen component is included for cycle control, and ethinyl estradiol is a potent suppressor of pituitary gonadotropins. Side effects are reported by about half of the women who start taking OCs [17]. Among the most commonly reported are weight gain, painful periods, swollen legs, and heavy menstrual bleeding; a change in sleep is not a commonly reported side effect [16, 17].

Women taking monophasic combination OCs, which provide the same dosage of hormones through the entire 21-day active cycle followed by 7 days of inactive placebo, had persistently raised body temperatures when taking either the active OC or the placebo [3]. This increase in temperature with OCs has also been reported in a study of circadian rhythms during 24 h of sleep deprivation with 8 women in the follicular phase, 9 in the luteal phase, and 8 who were taking OCs (pseudo-luteal phase) in an environment free of time cues using a modified constant routine procedure [18]. There was also an increase in melatonin levels in the OC group when compared to the women studied in the follicular phase [18]. Women taking OCs had significantly more stage 2 sleep in the active phase of the OC compared to the placebo, and more stage 2 compared to the naturally cycling women in both menstrual cycle phases [3]. OC users also had less SWS than naturally cycling women in the luteal phase [3]. A reduction in SWS with OC use was reported based on an archival analysis that compared women diagnosed with major depressive disorder and healthy controls, although menstrual phase or type of contraceptive was not controlled [19]. Reduced REM latency has also been reported in healthy women taking OCs [19], but OC use does not affect sleep efficiency [3, 19] or subjective sleep quality [3].

On balance, because OC effects on sleep appear modest, for women with premenstrual and menstrual symptoms as described in the next sections, attenuation of pain and mood symptoms by OCs may improve sleep.

Premenstrual-Related Effects on Sleep: Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Starting from puberty and lasting until menopause, women are at twice the lifetime risk of developing major depression as are men [20, 21]. Approximately 60 % of women experience mild premenstrual symptoms, referred to as premenstrual syndrome (PMS), but for 3–8 % of women, the cyclical pattern of symptoms is severe enough to be diagnosed as premenstrual dysphoric disorder (PMDD) [21]. Common symptoms that occur in the last week of the luteal phase and lessen after the onset of menstruation include irritability/anger, anxiety/tension, depression and mood swings, change in appetite, bloating, weight gain, fatigue, and problems with sleep [22]. Complicating the comparison of studies of sleep in premenstrual mood disturbance is the fact that definitions and severity of symptoms vary considerably as do the duration of symptoms [21, 23, 24]. Sleep disturbances include problems falling or staying asleep, hypersomnia, unpleasant dreams, wakening during the night, failure to wake at the expected time, and tiredness in the morning. Women with PMS perceive their sleep to be poor in the symptomatic phase with a decline in subjective ratings of sleep quality [13], with more unpleasant dreams [25]. These women report tossing and turning, frequent awakenings, and taking a long time to fall back asleep after an awakening during the night. Perhaps as a consequence of the disturbed sleep, or reflecting an underlying need for more sleep, women with severe PMS have increased daytime sleepiness [25–29]. Subjectively poorer sleep quality in women with severe PMS has been related to anxiety indicating the relationship of mood with sleep quality ratings [13].

Laboratory studies in symptomatic women have yielded conflicting findings, and only a small number of women have been studied [24]. There are reports of significantly more stage 2 sleep [14, 27] and less SWS [14] or more SWS [2, 12] and less REM sleep [27] compared to asymptomatic women in both phases of the menstrual cycle. Other studies show no objective change in sleep [28]. The finding of increased SWS (N3) in women with PMS/PMDD compared to controls while sleep efficiency was unaltered has been associated with psychological state [2] and with reduced nocturnal melatonin secretion [12] suggesting changes in homeostatic and circadian processes.

Women with increased severity of premenstrual symptoms have been found to have an increase in luteal phase daytime sleepiness [5]. In a study by Lamarche et al. [29], 10 women with significant emotional/behavioral premenstrual symptoms when compared with 9 women with minimal symptoms (mean age 26 years) were more sleepy and less alert in the late luteal phase than in the follicular phase. No menstrual phase change in sleepiness was found in the women with minimal symptoms. Women with more severe symptoms were significantly sleepier and less alert than women with minimal symptoms during the late luteal phase but not the follicular phase of the cycle. Using a midafternoon 40-min nap intervention, there were no group differences in sleep-onset latency, with both groups falling asleep within an average of 7 min. The short sleep-onset latency found for both groups of women suggests a high sleep need during the late luteal phase regardless of symptom severity, but may also be indicative of chronic sleep restriction in this age group.

Changes in nocturnal temperature rhythms and melatonin secretion suggest that women with PMDD have underlying circadian rhythm abnormalities that could impact sleep [20]. As reviewed by Baker et al. [24] in the symptomatic (luteal) phase, women with PMDD tend to have higher nocturnal temperatures and decreased melatonin secretion than normal controls; compared to their follicular phase, women with PMDD have delayed and decreased melatonin secretion. Therapeutic mood benefit has been reported by Parry et al. [30] from 1 night of partial sleep deprivation (4 h of sleep,

either 9:00 P.M. to 1:00 A.M. or 3:00 A.M. to 7:00 A.M.), with further improvements reported after a subsequent recovery night of sleep (11:00 P.M. to 7:00 A.M.). Initial findings indicate that appropriately timed light therapy may be a treatment strategy for PMDD, reducing depression, irritability, and physical premenstrual symptoms compared to a placebo condition. Thirty minutes of light therapy in the evening for 2 weeks during the luteal phase resulted in a significant improvement in premenstrual symptoms in women with PMS compared to baseline levels [31]. Larger trials with light therapy in this population are needed.

Painful Menstrual Conditions: Dysmenorrhea and Endometriosis

As many as 50 % of women suffer from dysmenorrhea and experience extremely painful cramps during menstruation, the pain is very severe in approximately 10–25 % of women [24, 32]. Similarly, women with endometriosis—who have misplaced uterine (endometrial) tissue in the abdominal and pelvic area—suffer extreme menstrual pain. Not surprisingly, these women report poorer sleep quality and higher anxiety during menstruation compared to symptom-free women.

Baker et al. [33] found that dysmenorrheic women had more disturbed sleep and subjective sleepiness than controls. Their sleep efficiency was reduced when experiencing menstrual pain, with increased wakefulness, movement, and stage 1 sleep compared with pain-free phases of their cycle. In a subsequent study of 10 women with primary dysmenorrhea, when experiencing menstrual pain, sleep efficiency was reduced with less REM sleep, and more stage 1 sleep during the night compared with a pain-free mid-follicular phase of their menstrual cycle [34]. Women with dysmenorrhea (like those with PMS/PMDD) had decreased REM sleep and increased core temperature during the luteal and menstrual phases compared to normal controls. Although progesterone concentrations in the luteal phase were similar to those in asymptomatic women, dysmenorrheic women had elevated morning estrogen levels in the follicular and luteal phase and higher prolactin levels in the luteal phase [21, 33]. Prostaglandins have been implicated as the mediators of the pain of primary dysmenorrhea, with the most common pharmacologic treatment for dysmenorrhea being nonsteroidal anti-inflammatory drugs (NSAID) [35]. Indeed, when dysmenorrheic pain was treated with the NSAID diclofenac potassium, given as two doses of 50 mg during the day and a 50 mg dose in the evening before bedtime, menstrual pain was attenuated and both objective and subjective sleep quality was restored with increased sleep efficiency and REM sleep compared to placebo [34].

Fibromyalgia (FM) and Functional Somatic Syndromes

Fibromyalgia is more common in women than in men, as are the other chronically widespread and regional painful, multi-symptom syndromes: irritable bowel syndrome, chronic pelvic pain, low back pain, temporomandibular joint disorder, and tension-type headache [36]. These conditions are sometimes referred to as functional somatic syndromes when pain hypersensitivity and stress-immune dysregulation are evident with emotional arousal and physiologic activation but no clear pathologic indicators [36]. With FM, painful regions and tender points have been associated with poorer sleep and increased alpha EEG [36, 37]. Complaints of pain and insomnia are more prevalent in women than in men, though little is known about the physiologic and behavioral mechanisms involved [37]. In chronic pain conditions, objective PSG measures show lighter and less consolidated sleep, possibly with more arousals, but no specific marker aside from a characteristic alpha EEG (7.5- to 11-Hz) intrusion into non-REM delta sleep (alpha-delta sleep, ADS); in patients with fibromyalgia, ADS was first described in 1975 by Moldofsky and colleagues [38]. However, not all studies have found differences in objectively measured sleep parameters. A recent study of female adolescents (n = 10, aged 16 years) with juvenile primary fibromyalgia syndrome revealed poorer sleep efficiency, more arousals/awakenings, and more ADS (70.3 % of total SWS versus 21.9 % SWS) than controls [39]. In the adolescent women, completion of a multidisciplinary pain treatment program over approximately 4 weeks that included intensive exercise therapy, improved pain, disability, and subjective sleep quality, but neither ADS nor other objective measurements of sleep quality changed after treatment [39]. Combining data from two randomized placebo-controlled double-blind trials of pregabalin (Lyrica®) for the management of FM in adults (n = 748 and 745, 95 % females, mean age 50 years), in addition to pain relief, improvements in subjective sleep quality and the severity of sleep disturbance compared to placebo showed clinically important differences [40].

Fibromyalgia has also been associated with a high prevalence of inspiratory flow limitation [41]. Conceivably, cortical arousability in response to increased upper airway resistance (UAR) may be reflected as increased EEG frequency and sleep fragmentation, causing more somatic

symptoms than those more commonly associated with obstructive sleep apnea (OSA), namely excessive daytime sleepiness and snoring.

Polycystic Ovarian Syndrome

Women with polycystic ovary syndrome (PCOS), a condition of irregular or anovulatory menstrual cycles, increased androgen production, and metabolic consequences related to insulin resistance and weight gain [42, 43], are more likely to develop OSA [42–46]. Sleep apnea is described in more detail in the next section on sleep-disordered breathing (SDB).

Four percent to 10 % of women of reproductive age may suffer from PCOS [42–47]. About half of these women are overweight [48] with metabolic-related disorders and visceral obesity [47]. Approximately 15 % of obese normal women have OSA [49], but in obese women with PCOS, the incidence of OSA is markedly increased at 41–58 % [42] interestingly their body mass index (BMI) itself does not correlate with their OSA severity [43–45]. In obese women with PCOS, fat distribution follows a male pattern, with increased waist-to-hip ratio [45, 46]. However, in adolescent girls (15 years) with PCOS (n = 31) compared with healthy obese girls without PCOS (n = 19) neither group had significant OSA although total sleep time (TST), percentage of REM sleep, and sleep efficiency were lower in the girls with PCOS [47]. Symptoms of PCOS usually begin in adolescence and perhaps OSA develops in a subgroup of females over time along with worsening insulin resistance. A relationship of OSA severity with waist-to-hip ratio, elevated serum testosterone [44], and higher fasting insulin levels [45] indicates the contribution of androgenization and insulin resistance to the higher prevalence of OSA in women with PCOS [42, 46].

Sleep-Disordered Breathing in Women

The range of SDB includes snoring, the upper airway resistance syndrome (UARS), OSA, and the obesity-hypoventilation syndrome (OHS) as well as central sleep apnea (CSA) and periodic breathing (Cheyne–Stokes respiration). Women with SDB may report snoring less frequently than men [50] but they report more fatigue [51] and nonspecific complaints [52, 53]. Young premenopausal women (<30 years) in particular more often present with these nonclassical symptoms of OSA such as insomnia and depression, as well as cranio-facial findings [54]. One study found that women were more likely than men to be treated for depression and have hypothyroidism at the time of diagnosis [55]. As reviewed by Banno and Kryger [56], women with a diagnosis of OSA had higher obesity and comorbid psychiatric conditions and received more antidepressants, hypnotics, and anxiolytics before OSA diagnosis, compared to men with OSA matched for age, BMI, and apnea-hypopnea index (AHI) [57].

The prevalence of CSA in women and OSA in premenopausal women is quite low, with women showing about half the prevalence of OSA as men, although this discrepancy declines in postmenopausal women [58–60]. More recent large cohort studies in the general population, coupled with changes in technology (e.g., more accurate airflow measurement via nasal cannula pressure transducers than with thermocouples), the increase in obesity with higher prevalence in women than men [48], and the referral bias in favor of men [55], indicate that OSA is more common in women than previously recognized. An association between lighter sleep (more high-frequency EEG beta) that is more fragmented and of lower sleep efficiency with the metabolic syndrome was reported in a group of 368 midlife women (age 46–57 years) enrolled in the SWAN study [61]. Sleep-disordered breathing, as measured by a clinical cutoff score AHI $\geq$ 15, and lower sleep efficiency were found to be independent correlates of the metabolic syndrome and were independent of race and menopausal status [61].

There is evidence that upper airway resistance (UAR) during sleep is higher in men [62], and the male airway is more collapsible than in women. Premenopausally, women are protected from developing sleep apnea. Indeed, there is a menstrual phase effect on UAR, with UAR being lower during the luteal phase than in the follicular phase [63], possibly related to progesterone effects. A number of other factors may contribute to the gender differences in SDB, such as differences in anatomy, upper airway collapsibility, the arousal response to increased inspiratory resistance, and ventilatory control [62, 63]. The clinical effect of lower airway resistance and less collapsibility in women is apparent in PSG differences: Women with OSA have more hypopneas than frank apneas with a shorter duration of apneas than in men [64], and lower apnea severity in the luteal versus follicular phase [65]. Women with OSA tend to have a clustering of respiratory events during REM sleep [66, 67], the frequency of which is related to BMI in both men and women [67]. The magnitude of the increase in blood pressure after apnea termination compared with immediately prior to apnea termination was higher during the luteal phase than during the follicular phase, despite lower OSA severity in the luteal phase [65]. The augmented luteal phase pressor response to apneas may effectively be enhancing the arousal response due to a combination of centrally mediated and peripheral sympathetic responses [65]. The arousal response in UARS to airflow limitation results in daytime sleepiness due to fragmented sleep [52]. Excessive sleepiness is a key presenting complaint for OSA. However, in women with recently

diagnosed OSA, insomnia was more likely to be a presenting complaint than it was in men [55, 68].

Clinically there is the potential that in some women, polysomnographically significant SDB may manifest in the follicular phase and could be missed by a diagnostic study in the luteal phase. Menstrual-related variability in the severity of sleep apnea may require a corresponding adjustment in management, such as varying the pressure requirement of continuous positive airway pressure (CPAP) therapy as could be achieved using long-term auto-adjusting positive airway pressure (APAP).

Sleep Disorders Associated with the Menstrual Cycle

There is very limited research on premenstrual sleep disorders, and its inclusion is based on isolated case reports. Three forms of "menstrual-associated" sleep disorders—premenstrual insomnia, premenstrual hypersomnia, and menopausal insomnia—were listed under the category of Proposed Sleep Disorders in the revised International Classification of Sleep Disorders (ICSD) published in 1997 [69]. In the second edition of the ICSD from 2005 [70], the only two disorders carried over were menstrual-related hypersomnia and menopausal insomnia. The third edition of the ICSD published in 2014 eliminated these as separate categories and listed menstrual-related hypersomnia as menstrual-related Kleine-Levin Syndrome (see Chap. 27).

Difficulty falling asleep or staying asleep, usually in the week before menstruation (premenstrual insomnia), should be distinguished from PMS and PMDD. Insomnia as the only premenstrual symptom is not considered sufficient to receive a diagnosis of PMS. Premenstrual hypersomnia occurring periodically around menses, preceding and into the early-follicular phase, has been successfully treated with hormonal treatment (conjugated estrogen or oral contraceptives) [71]. In another case of periodic hypersomnia, prolactin was elevated but did not respond to hormone replacement therapy and was symptomatically treated with methylphenidate [72].

Sleep During Pregnancy

Sleep disruption during pregnancy is a common and multifaceted problem [73, 74]. Contributing factors include hormonal changes, fetal movement, bladder distention, gastrointestinal discomfort, vomiting, and temperature fluctuations. There are significant changes in sleep architecture, and primary sleep disorders such as OSA and restless legs syndrome (RLS) may be more common. Most women accommodate to the changes in sleep, but for a proportion of them, the disruption will prove problematic and may result in medical and psychiatric complications.

Subjective Changes in Sleep

A large percentage (66–94 %) of women note alterations in their sleep during pregnancy [75–77]. During the first trimester, subjective sleep quality decreases and the number of nocturnal awakenings increases. Daytime sleepiness is more problematic. During the second trimester, women report that sleep normalizes, although 19 % of women continue to experience difficulties at this stage [77]. By the third trimester, women experience worsening insomnia, increased daytime sleepiness, and decreased alertness [76]. Reasons cited for the increased sleep disturbances were mainly urinary frequency, backache, fetal movement, abdominal discomfort, leg cramps, and heartburn. A survey of sleep disruption across pregnancy found that 97 % of women identified themselves as having disrupted sleep, while a third felt they had a "sleep disorder" [78]. The latter group may be biologically or psychologically more vulnerable to the detrimental effects of disrupted sleep. Factors such as a prior history of a psychiatric disorder, lack of a social support network, poor coping skills, and difficulty adjusting to the impending role of motherhood are likely important in this regard.

The 1998 NSF survey found that 79 % of women reported that their sleep was, or had been, disturbed during pregnancy [10]. Women who were currently pregnant or had been pregnant recently were more likely to report frequent insomnia (64 %) when compared to premenopausal or menopausal women. Of the women reporting sleep disturbance during pregnancy, 70 % reported that it interfered with daily functioning on at least a few days per month. It is unclear for what proportion it represented a *serious* problem. There are limitations to this survey, such as the fact that not all women were pregnant at the time of reporting and were hence providing retrospective accounts of their sleep during pregnancy, but it does shed light on the extent of subjective sleep disruption during pregnancy. The NSF 2007 "Sleep in America" telephone poll of 1003 women included 150 pregnant (second trimester, $n = 47$; third trimester, $n = 91$) and 151 postpartum women [79]. More pregnant women (84 %) experienced insomnia symptoms at least a few nights a week, compared to 67 % of the overall group. In response to whether they were getting a good night's sleep at least a few nights a week, 82 % of pregnant women felt they were doing so before their current pregnancy, compared to 60 % who felt this to be the case during their ongoing pregnancy. More women in their second trimester (72 %) said they got a good night's sleep at least a few nights a week than those in their third trimester (54 %). Reasons for sleep disturbance were to go to the bathroom (92 % in the third trimester and 75 % in the second trimester), and pain in their back, neck, or joints (66 and 47 % of third and second trimester women,

respectively). Two other reasons for disturbed sleep in the third trimester are leg cramps (54 %) and heartburn (51 %).

Objective Changes in Sleep

Pregnancy has a significant impact on sleep architecture and on the quantity and quality of sleep. Several excellent reviews [9, 80–82] show that the findings are not fully consistent and that more research into the changes in sleep architecture that accompany pregnancy is necessary. However, there is consensus that there is a "lightening" of sleep as pregnancy progresses, with a decrease in sleep efficiency, decreased total sleep time, increased wakefulness after sleep onset, and decreased REM sleep. Most studies show a decrease in SWS, especially in the third trimester [83, 84]. One study reports an *increase* in SWS from early to late pregnancy [85]. This last finding may relate to the fact that only primiparous women were included, while the other studies included both primiparous and multiparous subjects. The sleep of these two groups of women appears to differ; exactly in what way remains to be determined. According to one study, multiparous women have lower sleep efficiency at all time points across pregnancy [84]. Immediately postpartum, primiparous women have lower sleep efficiency, but at 3 months postpartum, their sleep had improved but did not revert to its prepregnancy baseline. This finding would suggest that pregnancy and childrearing has a prolonged impact on sleep architecture. Another study, following women's sleep using actigraphy during pregnancy and at 1 and 6 weeks postpartum, reported that primiparous women have lower sleep efficiency in general during pregnancy and postpartum, when they also had fewer sleep episodes than their multiparous counterparts [86]. Again, the discrepancy in findings could be secondary to varying assessment techniques (PSG, actigraphy) and relatively small sample sizes.

Primary Sleep Disorders Associated with Pregnancy

The risk for OSA increases substantially with obesity [48, 87] but the prevalence with the weight gain during pregnancy is unclear. Changes in respiratory physiology during pregnancy, such as decreased functional residual capacity [88], changes in the airway mucosa [89], and hyperventilation with increased sensitivity to CO_2 [90], may predispose to obstructive or central apneic events. Some investigators have found no decrease in nocturnal arterial oxygen saturation during pregnancy [91, 92]. Others, however, report significantly more nocturnal desaturation in pregnant women compared with controls [93, 94]. Hypertension in the mother at the time of birth and lower Apgar scores in the infant are significantly more common in women who reported snoring during pregnancy as compared to nonsnorers [95]. A large (n = 1091) prospective study of pregnant women suggests that severe snoring in the third trimester is a significant risk factor for fetal growth restriction and preterm birth [96]. A number of case series, using small numbers and relying on clinical examination rather than PSG, indicate that OSA may be associated with intrauterine growth retardation, especially if other complications such as maternal obesity and diabetes mellitus are present [97]. The control of partial upper airway obstruction and snoring using nasal CPAP in women with preeclampsia has been shown to decrease blood pressure significantly [98]. Edwards and Sullivan [99] have reviewed the risks and treatment options of SDB during pregnancy and with preeclampsia.

Restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) increase during pregnancy [81, 100]. Women cite restless legs as a common cause of sleep disruption during pregnancy [74]. Complaints of leg cramps during waking in the middle of the night should raise the possibility of RLS-PLMS, especially if the woman is experiencing daytime sleepiness or fatigue.

Risks Associated with Sleep Disruption During Pregnancy

The role of sleep disturbance in the development of psychiatric illness is a grave concern. Patients with persistent insomnia are at significant risk for developing depression [101]. This holds true even when there is a medical cause, such as sleep apnea, for the insomnia. Women with sleep disruption during pregnancy and in the weeks postpartum may be at higher risk for depressive symptoms during pregnancy [76] and for postpartum mood disorders, especially where there is a previous history of mental illness [102, 103]. Parity may play a role in this regard. One study which compared sleep and mood in primiparous women and multiparas noted that both parameters were better in the latter group [104].

Sleep disruption often heralds the onset of a manic or hypomanic episode among patients in the general population who suffer from bipolar illness [105, 106]. The risk of new-onset mania or recurrence of a preexisting illness during the postpartum period is significant. Women with a history of bipolar affective disorder (BAD) have a twofold increase in risk for symptom exacerbation during the immediate postpartum period. Furthermore, women with a prior history of BAD have a sevenfold increase in risk for a psychiatric admission in the puerperum when compared with nonpostpartum and nonpregnant women [107]. Even fathers with BAD are at increased risk of relapse in the postpartum period [108]. This suggests that the sleep disruption associated with

caring for a neonate may play an important role in the development or recurrence of postpartum psychiatric illness. The challenge for the clinician is to identify those women for whom sleep loss, an inevitable part of childbearing, will have serious consequences.

Patients with insomnia often resort to the use of alcohol and over-the-counter remedies. The NSF report [10] found that 7 % of pregnant women used over-the-counter medications and 7 % used alcohol at some point in the pregnancy to help them sleep, while 4 % used prescription medications for this purpose. The use of such sleep aids during pregnancy could have significant consequences for the developing fetus.

Research is being carried out on the impact of pregnancy-related sleep complaints and inflammatory markers. A study by Okun et al. [109] on 19 women during mid- and late-trimester pregnancy examined subjective sleep reports and the levels of circulating (naturally occurring) and secreted (experimentally stimulated peripheral blood mononuclear cells) interleukin-6 (IL-6). Complaints of shorter sleep duration and poor sleep efficiency at both stages of pregnancy were associated with higher levels of stimulated IL-6; while in late pregnancy, sleep complaints were also associated with higher levels of circulating IL-6. The implications of these findings for maternal well-being and fetal development remain to be determined.

Management of Pregnancy-Related Sleep Disruption

Significant sleep disruption during pregnancy is likely underreported by women. Hence, it is imperative that the primary caregiver inquire about it and determine to what extent it warrants further assessment and intervention. Potential medical causes should be considered (e.g., medications, thyroid problems, psychiatric illness) and treated where appropriate. Primary sleep disorders such as OSA and RLS/PLMS should be ruled out.

Significant respiratory disturbance can be treated with CPAP, which has been shown to be safe during pregnancy [97, 98]. Milder respiratory disturbances may respond to conservative measures such as positional therapy.

There is a relationship between low serum ferritin levels and RLS/PLMS. Iron supplementation should be instituted where this is the case. Conservative measures such as reducing caffeine intake or wearing supportive stockings should be implemented. The use of any form of medication during pregnancy must be approached with caution, and the patient must be made fully aware of the risks and benefits. Pregnant women are not included in drug trials, and the safety of many medications during pregnancy has not been determined. The safety of certain medications used to treat RLS/PLMS (e.g., pramipexole, gabapentin, ropinirole) is unknown. The benzodiazepine clonazepam carries concern about possible teratogenicity when used in the first trimester. However, judicious use in the second and third trimesters may be warranted. There is a risk of "floppy baby syndrome" if used close to the time of delivery, and the patient should be educated accordingly. Some patients with RLS/PLMS respond well to opioids such as codeine and oxycodone, and there is no evidence of teratogenicity, although there is a risk of a withdrawal syndrome or respiratory depression in the neonate.

During the postpartum period, the sleep of women with a history of a mood disorder must be protected since a recurrence at this time can have disastrous consequences for both mother and infant [106]. Prolongation of the hospital stay to enable the new mother to recover from the impact of labor and birth may be beneficial. The patient's partner and other family members should be encouraged to play an active role in nocturnal feeding.

Where no primary cause for the sleep disruption can be determined, nonpharmacologic treatments should be the primary intervention. Attention to sleep hygiene factors, such as a regular sleep–wake schedule, avoiding caffeinated beverages, reducing the amount of fluids consumed in the evening, and ensuring the temperature in the bedroom is comfortable, should be highlighted. There are no data concerning the efficacy of cognitive and behavioral techniques, such as cognitive behavioral therapy or stimulus control therapy, for insomnia during pregnancy. However, given that they are efficacious for insomnia in general, we would expect that they would be beneficial when applied during pregnancy.

The majority of women are likely to resist the use of sleeping medications, but where insomnia is having a severe effect, the use of a sleep aid may be warranted. The antihistamine dimenhydrinate has not been associated with fetal effects in animal studies. The nonbenzodiazapine hypnotics, zopiclone, zaleplon, and zolpidem, all considered Class C drugs by the America Academy of Pediatrics (AAP), should be limited during pregnancy until more data are available. A study of pregnancy outcome in 40 women exposed to zopiclone during the first trimester did not find an increase in the rate of major malformations when compared with a nonexposed group [110]. A population-based study in Taiwan compared the rates of adverse pregnancy outcomes (preterm delivery, small for gestation age, low birth weight infants) in a large number of women who were exposed to zolpidem during pregnancy with those in women who were not exposed. All adverse outcomes were significantly higher in the exposed group but the rate of *major congenital malformations* did not differ between the 2 groups [111]. There are many potential confounding factors that could not be accounted for (e.g., adherence with the medication, other medical or psychiatric factors, social factors such as

smoking, alcohol use, and nutrition status of the mother) but these data highlight the need to use this class of medications during pregnancy with caution.

The antidepressant trazodone may be beneficial for reducing sleep-onset latency and improving sleep quality in depressed patients [112]. The AAP stated that data are too limited to provide a recommendation on the use of this and other sedating antidepressants, such as mirtazapine and nefazadone (not available in Canada), during pregnancy [113]. No difference in pregnancy outcome (including rate of major malformations and gestational age at birth) has been found between patients taking nefazadone and trazodone during the first trimester when compared with women taking other nonteratogenic antidepressants or other nonteratogenic drugs (e.g., sumatriptin, dextromethorphan), matched for age, smoking, and alcohol use [114]. Both antidepressant groups, however, had a trend toward a higher rate of spontaneous abortion, although the difference was not statistically significant. The tricyclic antidepressant amitriptyline has considerable sedating properties, does not appear to have teratogenic effects, and is considered safe for use in pregnancy [113].

Benzodiazepines are frequently used to treat insomnia in the general population. The AAP [113] recommends that their use be limited during pregnancy since they can induce sedation, withdrawal signs (including restlessness, hypertonia, irritability, seizures, and abdominal distention), and floppy baby syndrome (muscular hypotonia, low Apgar scores, neurologic depression) in the neonate, effects that can last for up to 3 months. Hence, when benzodiazepines are used, they should be slowly tapered over a number of weeks prior to delivery. Use during the first trimester should be avoided if possible because of concerns about congenital malformations such as cleft palate [115]. However, no congenital defects have been associated with lorazepam or alprazolam [113]. Use of the former is preferred since it lacks active metabolites and is less likely to be associated with a withdrawal syndrome in the neonate.

Menopause and the Climacteric

Changes in menstrual cycle frequency and menstrual flow reflect the changing hormone milieu in the perimenopausal period. Menstrual cycle length decreases from 28 days for women in their 20 s to 26 days for women in their 40 s [116]. Between the ages of 45 and 55 years, production of estrogen and progesterone decreases, FSH levels increase, and menstrual cycles become irregular [116]. This transition occurs over a few years (mean 3.8 years) prior to the last menstrual period. There is no definitive way to distinguish transient amenorrhea from menopausal amenorrhea, and generally menopause is only confirmed when menstrual periods have stopped for a year (average age 51 years) [117]. The term *climacteric* is used to refer to the transition period (usually 7–10 years) preceding the last menses when ovarian function decreases, and afterward, when women experience hormonally induced physical and/or psychological changes [116].

Sleep Disturbance and Climacteric Symptoms

Women of any age are more likely than men to report dissatisfaction with their sleep and to experience daytime consequences. Insomnia is more prevalent in women than men [118] and this gender disparity increases with age [119]. Comparing the sex difference in the prevalence of insomnia among young adults (15–30 years), middle-aged (31–64 years), and elderly ($\geq$ 65 years), the overall relative risk (RR) for females compared to males increased from 1.28 in young adults to 1.46 in middle age and 1.73 in elderly [119]. In a Canadian survey of 2000 adults, by Morin and colleagues, 15.6 % of women and 11 % of men met all the criteria for insomnia showing that women have 1.5 times (95 % Confidence Interval: 1.15–1.95) the risk of presenting with insomnia syndrome than men [120]. This gender disparity increases with age—the female:male ratio of insomnia symptoms after 45 years of age is 1.7:1 [121]. There is evidence that the higher prevalence of affective disorders among women contributes toward their insomnia symptoms. Data from 148,938 postmenopausal women who were enrolled in the Women's Health Initiative study revealed that the strongest independent risk factors for sleep disturbance were depression, somatic symptoms, lower emotional well-being, and restlessness [122].

Menopause is often cited as the underlying cause for the gender disparity in sleep complaints in middle-aged individuals. Complaints of sleep disruption are higher in perimenopausal than in premenopausal women [121, 123, 124]. Sleep disturbances include waking at night (the most common problem) [124], waking early, and difficulty falling asleep [123]. Trouble sleeping has been associated with more depressive symptoms, vasomotor symptoms, mood swings, higher levels of stress, tension and anxiety, and palpitations, particularly during perimenopause [116, 123–127]. Furthermore, midlife women with disturbed sleep were found to have a twofold increase in menopausal symptoms [124].

Other menopausal symptoms that can be disruptive to sleep either directly or indirectly include weight gain, vaginal dryness and irritation, and urinary problems. Nocturia in postmenopausal women is reportedly improved with estrogen therapy [128]. However, as in men, the prevalence of nocturia increases with age (9 % in women <39 years old to 51 % of women $\geq$ 80 years old) [128], and OSA can

increase nocturnal diuresis through increased atrial natriuretic peptide production. Thus, aside from menopausal symptoms disturbing sleep, underlying chronic physical conditions or sleep disorders should also be considered.

The terms *hot flush, hot flash*, and *vasomotor symptoms* are used to describe the same phenomenon. Nocturnal hot flashes (also called night sweats) that can soak bedclothes, followed by chills as the body cools down, lead to sleep disruption [23, 129]. Vasomotor symptoms, including night sweats and hot flashes, are the primary reason for women to seek treatment at the time of menopause [130]. Up to 85 % of women experience hot flashes [116, 127, 129], with variation depending on ethnicity and culture [127, 129]. In a large (n = 14,906) multisite, multiethnic study in the USA of women's health across the nation (SWAN), the population group with the lowest incidence of night sweats were Japanese women at 9 % and the highest was African women at 32 % [131]. A further analysis from the SWAN study found that 38 % of all women reported subjective difficulty sleeping; the incidence was lowest in Japanese women (28 %) and highest in Caucasian women (40 %), and difficulty sleeping was associated with hot flashes [129]. In the SWAN study, an odds ratio for sleep problems in women with vasomotor symptoms was 2.0 compared to asymptomatic women. Furthermore, in a smaller study (n = 63) based on healthy women who had undergone hysterectomy, those with subjectively impaired sleep had more hot flashes and palpitations as well as mood-related symptoms (anxiety, depression, mood instability, memory problems) [132]. A study of 15 perimenopausal women who reported increased awakenings and dissatisfaction with sleep quality showed an increased number and duration of arousals and more movement activity on wrist actigraphy compared to 13 age-matched premenopausal controls [125].

Interestingly, PSG studies do not consistently show worse sleep quality peri- and postmenopausally than premenopausally [126, 132–136], or an association with climacteric vasomotor, somatic, or mood symptoms [132, 134, 135]. Although no significant differences in sleep were apparent, for 39 symptomatic versus 32 nonsymptomatic women, there was a trend toward lower sleep efficiency [133]. Young et al. [134] compared objective sleep data from a single night in 589 women of known menopausal status but, despite postmenopausal women reporting more dissatisfaction with their sleep than premenopausal women, PSG sleep efficiency was not lower in peri- and postmenopausal women. Indeed, the proportion of SWS was higher in postmenopause than premenopause. A study by Freedman and Roehrs [135] also found that 12 symptomatic versus 8 asymptomatic postmenopausal women and 11 premenopausal women did not have more sleep disturbance. Clearly there is a disconnect between objective and subjective sleep that merits further investigation.

Potential factors contributing to the disparity between subjective dissatisfaction with sleep and objective measures include (1) the severity of climacteric symptoms and the presence of hot flashes during the sleep recording, (2) effects on sleep microstructure—arousals, alpha EEG intrusion [37], and EEG cyclic alternating pattern (CAPS) [136]—rather than macrostructure, and (3) sympathetic activation. The association of hot flashes with subjectively poorer sleep suggests that they should be monitored during PSG studies. One study that used skin conductance to monitor hot flashes in women with nightly complaints of sweating found that after 4 weeks of conjugated estrogens (0.625 mg), there was a reduction in hot flashes associated with polysomnographically documented reduced CAPS rate and improved sleep efficiency [136]. Similarly, when monitoring hot flashes in breast cancer survivors with insomnia (n = 24), more sleep disruption and wake time around the time of hot flashes was observed; sleep efficiency was lower on nights with than on nights without hot flashes [137]. However, no association of sleep disturbance around the time of hot flashes measured by skin conductance has been found [135].

Hormone and Estrogen Replacement Therapy: A Role for Improving Sleep?

Vasomotor symptoms are reduced with estrogen alone (estrogen replacement therapy, ERT) [136, 138, 139] or in combination with progesterone therapy (hormone replacement therapy, HRT) [140–143], but in laboratory studies, they have not been found consistently to improve sleep. Findings from three studies highlight these inconsistencies. Polo-Kantola et al. [138] reported subjective sleep improvement with transdermal estrogen preparations compared with placebo (n = 70), associated with reduced hot flashes and sweating, but estrogen was no better than placebo in terms of sleep on PSG. Antonijevic et al. [144] in contrast found reduced wakefulness and increased REM sleep with an estradiol patch (n = 11). In a third study, an HRT with estrogen (Premarin 0.625 mg) and two different progesterone preparations—either micronized progesterone (Prometrium 200 mg) (n = 10), which gives rise to sedative metabolites, or medroxyprogesterone (Provera 5 mg) (n = 11)—showed improved sleep efficiency with micronized progesterone [143]. Despite the sleep improvement, daytime vigilance was unchanged with the micronized progesterone, whereas it improved with medroxyprogesterone. Overall, most studies of HRT on sleep show favorable effects including improved subjective sleep quality and reduced sleep fragmentation and wake on PSG [145, 146].

Clearly, more detailed studies of the effects of HRT are needed before firm conclusions can be drawn regarding their effects on sleep.

For those women whose menopausal symptoms and sleep may be alleviated on hormone therapy, safety concerns with HRT from the Women's Health Initiative (WHI) [139] posed a dilemma [130]. The large (n = 16,608), randomized, placebo-controlled WHI trial on the effect of conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) revealed increased risks for stroke, venous thromboembolism, coronary heart disease, and breast cancer [139]. These risks have been subsequently confirmed in other clinical trials that used a variety of estrogen and progestin products [147]. Given the fear of adverse events, over 50 % of women stop therapy after 1 year [148]. However, in the WHI trial, the average age of women at enrollment was 63 years (range 50–79), and women with severe menopausal symptoms were excluded, yet symptom relief is the reason most women initiate HRT. The choice of whether to use hormone therapy or not is a balance between age, symptoms, current quality of life, and potential risk [130, 149].

Subsequent analysis of health-related quality of life in nonsymptomatic women from the WHI trial [150] showed there was only a small and not clinically meaningful reduction in sleep disturbance in the first year that was not evident after 3 years. In contrast, from the Heart and Estrogen/Progestin Replacement Study (HERS)—another large (n = 2763) randomized, placebo-controlled trial of the same hormone concentrations as the WHI trial—women who experienced hot flushes had improved mental health and depressive symptoms [151]. Thus, the effects of HRT on quality of life appear to depend on the presence of menopausal symptoms with negative effects in women without vasomotor symptoms and improvements in women with vasomotor symptoms [151]. For women who experience significant disruptive menopausal symptoms, the smallest effective dose of estrogen may serve a useful short-term role in symptom management [147, 149, 152]. Family history and potential risk of disease should be taken into account when considering HRT for relief from disturbed sleep [130, 146, 147, 152].

Alternatives to Hormone Replacement Therapy for Sleep Disruption

With a decrease in HRT prescriptions since July 2002, there has been an increase in prescriptions of serotonergic antidepressants [153]. Some antidepressants that block the release of serotonin and norepinephrine (e.g., fluoxetine, paroxetine, venlafaxine) have been reported to alleviate climacteric symptoms [153, 154]. Norepinephrine and serotonin have a central role in the pathophysiology of hot flashes [149]; clonidine, an α_2-adrenergic agonist, has also been found to alleviate climacteric symptoms and accordingly related sleep problems.

An age-related decline in melatonin secretion occurs between 17 and 45 years in premenopausal women, with an increase during perimenopause (46–50 years), and a decline postmenopause [155]. In the first 15 years of postmenopause, there is a steep decline in melatonin, followed by a more gradual decline. The timing of melatonin secretion is also advanced in postmenopausal compared with premenopausal women [156]. Melatonin has chronobiotic (circadian effect) and hypnotic properties. Exogenous melatonin, as well as a controlled-release formulation of 2 mg melatonin Circadin®, and the melatonin agonist Ramelteon have been reported to promote sleep onset and improve sleep quality in middle-aged and elderly insomniacs [157].

Given the safety concerns related to hormone therapy, many women seek alternative therapies to relieve sleep disturbances. Hot flashes occur more frequently in warmer than cooler environments [127]; reducing ambient temperature (to 16–19 °C) may provide relief from hot flashes and sleep disruption [142, 149].

A telephone survey of 866 women on the use of eight alternative therapies to manage menopause symptoms found that 76 % of women had used at least one type of alternative therapy [158]. Women who experienced trouble sleeping were more likely to use alternative therapies such as dietary soy and stress management. Soy isoflavones are estrogen-like substances that have been investigated as an alternative therapy to relieve menopausal symptoms but have not been found consistently to have an appreciable effect [159].

Valerian is commonly used as a sleep aid and has been tested with conflicting results in small groups of older individuals. For example, Taibi et al. [160] found no improvement in sleep in 16 older women (69 years) who took 300 mg concentrated valerian extract for 2 weeks compared with placebo. Whereas Taavoni et al. [161] found that 50 menopausal women (aged 50–60 years) given 160 mg valerian with 80 mg lemon balm for one month improved subjective sleep quality (based on the Pittsburg Sleep Quality Index, PSQI) compared to a placebo control group. A meta-analysis of 18 RCTs of valerian (300–600 mg/d) suggested that it improves subjective sleep quality based on yes/no responses [162].

Though not well studied, black cohosh (a root extract from a North American perennial plant) may relieve hot flash symptoms, and gabapentin (a GABA analog) has been found to have a favorable effect compared to placebo [154] but concerns have been raised about liver toxicity [see 163]. Linseed (flaxseed) extract as well as Mediterranean pine bark extract have been reported to reduce vasomotor symptoms [163]. The hop-flavonoid (the hop flower is an ingredient in

beer) 8-prenylnaringenin, a stronger estrogen than soy isoflavones, has been studied in two RCTs for effectiveness in reducing vasomotor symptoms with conflicting findings suggesting no advantage over placebo [163]. Hypnotic drugs such as zolpidem (10 mg) in women with menopause-related insomnia (n = 141) reduced wake after sleep onset and improved subjective sleep quality [164].

Chronic heavy smoking in adulthood is a significant risk factor for insomnia. Compared with nonsmokers, midlife women who were chronic heavy smoker were more likely to report insomnia at mean age 65 (Adjusted OR = 2.76; 95 % CI = 1.10–6.92) [165]. However, women who quit smoking in midlife (43–48 years) by the age of 65 years did not have any more insomnia symptoms that a nonsmoking group.

Yoga has been found to improve insomnia severity scores and menopausal symptoms after 4 months of practice in 15 postmenopausal women not taking hormone therapy compared to passive stretching and a wait-control group [166]. Consistently high physical activity rated as sports/exercise (e.g., participation in recreational activity or sports) for 6 years preceding assessment has been associated with better sleep efficiency on PSG and better PSQI scores in 339 midlife women (mean age 52 years) in the SWAN study [167]. In menopausal women (mean age 54 years) with vasomotor symptoms, nonsupervised aerobic training four times per week for 50 min for 6 months improved subjective sleep quality and vasomotor symptoms in a group of 73 women compared with a control group of 76 women [168]. Thus, a more active lifestyle is recommended to improve sleep disruption in menopause.

Sleep-Disordered Breathing in the Menopause

Menopause increases the risk of SDB by three to four times, even after adjusting for known risk factors such as age and BMI, compared to premenopausal women [59, 169]. Increased age, hormone-related changes, and weight gain—including a change in fat distribution [116] with more visceral adiposity—are all contributing factors for increased OSA. Older, overweight women with high blood pressure, insomnia, disturbed sleep, or "fatigue" should be considered at high risk for having OSA.

Progesterone is a respiratory stimulant and, in women receiving HRT, the prevalence of OSA and SDB was found to be lower than women not taking HRT [59]. This finding needs to be confirmed in larger clinical trials. The prevalence of moderate-to-severe OSA in women in the Sleep Heart Health Study (n = 2994, age $\geq$ 50 years) among women using hormone replacement (either ERT or HRT) was half the prevalence in nonusers [170]. The reduction in SDB (estimated odds ratio, 0.55) for hormone users corresponded to the predicted effect of reducing BMI by 6.8 kg/m^2 [170]. Before recommending menopausal hormone replacement to treat apnea in women, however, many other factors need to be considered. The focus should instead be on using standard therapy such as weight loss, CPAP, an oral appliance, or positional therapy (side sleep) for milder OSA.

Other Factors Influencing Sleep During Menopause

The secretion of other endogenous hormones, such as thyrotropin, decreases with age: 25 % of postmenopausal women show clinical or subclinical thyroid disease, which often causes symptoms similar to those of the climacteric [149]. The cause of sleep problems around menopause is not always evident and possibly is multifactorial. Factors aside from menopause—such as systemic diseases, medications, depressed mood, stress, behavioral or cognitive factors, social and family situations, pain, and aging-associated increases in RLS and PLMS—may explain, or contribute to, decreases in sleep quality.

Conclusion

The changing hormone profile across the reproductive life of a woman, from puberty through the reproductive period to the postmenopausal years, has a significant influence on sleep. Abrupt changes in, or withdrawal of, female hormones may lead to sleep disruption. During pregnancy, however, multiple factors contribute to sleep disruption, and these will vary according to the stage of pregnancy. Certain sleep disorders such as OSA and RLS are influenced by stage of menstrual cycle or life cycle. This chapter has highlighted the impact of the reproductive and menstrual cycles on sleep. It is imperative that sleep clinicians take these factors into account when working with women. Women should be encouraged to track whether there is a cyclical change in their symptoms in association with hormone changes or if the symptom changes are due to age-related changes in hormonal profile.

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