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Sleep in women across the life cycle from adulthood through menopause

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In the last decade, more research interest has focused on the sleep of women across the life cycle. A significant body of literature has endorsed the view that the sleep of women differs in many respects from that of men. Beyond gender differences, however, are questions about sleep within cohorts of women. For example, in adult women ages 20–45 years, there are women with regular menstrual cycles, women taking oral contraceptives, pregnant and lactating women, and women entering menopause. Given that each of these states is associated with a unique hormonal environment, it is important to determine whether there are clinically significant differences in the sleep of women in these phases of life. This article presents what is known currently about the sleep of women from adulthood through menopause and provides recommendations for evaluation and treatment.

Several recurring themes become evident. First, there is the difficulty of generalizing because of the complexity of factors that affect study design. Second, many of the studies discussed in each of the sections have been limited by small sample sizes. Finally, there is a lack of longitudinal data that would begin to clarify risk factors, if any, for the development of sleep disturbances.

Sleep during the menstrual cycle

The menstrual cycle is characterized by cyclic alterations in the production of the gonadal steroids (estradiol and progesterone), pituitary hormones (gonadotropins, prolactin, growth hormone), melatonin and

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cortisol, and in temperature rhythms. The sections that follow summarize studies of sleep parameters across the menstrual cycle in normal women, followed by descriptions of studies in women with premenstrual syndrome (PMS), the more serious premenstrual dysphoric disorder (PMDD), and dysmenorrhea. Research on sleep in women taking oral contraceptives and with specific sleep disorders related to the menstrual cycle are also described.

Sleep in women with normal menstrual cycles

Studies of the influence of phase of the menstrual cycle on sleep began in 1966 with the article by Williams' group [1]. The literature since that time is small and divergent. The latter features result from numerous methodologic issues that make designing studies in this area a challenge. Lee and Shaver [2] discussed many of the concerns that remain relevant for current research. First, there is the definition of menstrual phase. Because menstrual cycles are not uniform in length in an individual or among women, the research study must define carefully the phases under study and how the data are assigned to them. This point is important, because the hormonal conditions are changing continuously and may differ markedly even across several days and across cycles. Next, the timing of ovulation, demarcating follicular from luteal phase, has not always been measured, or alternatively ovulation confirmed with measurement of the luteinizing hormone (LH) surge, for example. As women reach their early forties, the perimenopausal interval begins, with changes in hormonal production despite apparently normal cycling. Other women take oral contraceptives, which leads to regular menstrual cycles, but with an underlying artificial hormonal milieu.

In part because of the cost of recruitment effort, methods to assess and control timing, and polysomnography, many studies of women across the menstrual cycle have been performed on small samples [3,4]. The number of menstrual phases during which women could be studied has been also limited.

Other issues to be considered include the subjects' life situations. The sleep of a woman with normal menstrual cycles and young children at home may be different from that of a woman without children. This may translate into differences observed in the laboratory between "normal" cohorts. The artificial nature of the laboratory also may affect data [5], but this consideration is not unique to studies of women. Another point is the use of paper records versus computerized data. Subtle changes in certain parameters may be addressed more comprehensively with additional analyses made possible by way of the latter technique.

Despite these concerns, some progress has been made in identifying possible menstrual cycle effects on sleep in normal women. Data from survey studies and studies using polysomnography have been reported.

The early studies [6,7] reported that subjective sleep was most disturbed premenstrually. More recently, Manber and Bootzin [8] collected data from 32 premenopausal women across two menstrual cycles. The luteal phase was

associated with significantly longer sleep latency, lower sleep efficiency, and subjective sleep quality compared with the follicular phase. Of note, however, was the finding that 4 of the 32 women actually experienced an improvement in sleep efficiency premenstrually. Severity of premenstrual symptoms did not correlate with sleep parameters, but was correlated significantly with an increase in daytime sleepiness in the luteal phase. The investigators point out that the decreased sleep efficiency found in the subjects in the luteal phase may be more common than recognized previously and has therapeutic implications for the treatment of women with insomnia. Their data suggest that the temporal relationship of sleep complaints to the phase of the menstrual cycle should be an important consideration in a sleep disorder evaluation.

The results of the polysomnographic studies have been inconsistent with respect to sleep stages between [9–13] and within [9,14–16] groups.

Taken together, the conflicting results of these studies suggest that there are no clear-cut major differences in sleep architecture (except sleep spindle frequency) across the normal menstrual cycle, despite subjective reports of sleeping difficulties in the late luteal phase [17]. Although this would seem to be encouraging to researchers who theoretically would not need to control for phase of cycle in their study designs, a note of caution is needed. First, these were studies with few subjects, and many reported data only from young adult women. That leaves women 30–45 years of age unstudied. Another point is that mood symptoms also should be tracked, because some studies noted that data differed between women with and without affective symptoms, even when the women did not formally report PMS. Additional research with cohorts of regularly cycling women in different age groups therefore still needs to be performed to confirm the apparent lack of major menstrual cycle effects on sleep.

Sleep in women with premenstrual syndrome and premenstrual dysphoric disorder

PMS is a common problem of women with ovulatory menstrual cycles and is characterized by mood or physical symptoms that appear regularly in the luteal phase and remit on or shortly after menses. When a woman's symptoms are severe, predominantly affective, and cause a marked negative impact on her ability to function at home or the workplace or in her relationships with others, she may receive a second diagnosis, premenstrual dysphoric disorder (PMDD). Sleep complaints, either insomnia or hypersomnia, comprise 1 of the 11 symptoms listed in DSM-IV for PMDD, 5 of which must be considered positive for the diagnosis to be given.

Sleep researchers are interested in studying women with PMS and PMDD for several reasons. First, as summarized by Mauri [18], women with PMS report sleep-related complaints including "insomnia, hypersomnia, tiredness or fatigue, disturbing dreams or nightmares, lethargy, and inability to concentrate." Second, because PMDD is believed to be a variant of an affective

disorder and because patients with major depression have well characterized sleep abnormalities, it is of interest to compare the sleep of women with premenstrual conditions with those with major depression. Third, there are suggestions that women with PMDD may have underlying circadian rhythm abnormalities in temperature [19,20], melatonin [21,22], or the coupling of rhythms [23] that could affect sleep.

An additional set of methodologic issues should be considered together with those mentioned earlier. Manber and Armitage [4] call attention to the fact the definition of PMS differs among studies. Although the DSM-IV criteria for PMDD simplified the diagnostic process greatly by articulating the criteria, this is not the case for PMS. Some studies of PMS also may include patients who meet criteria for PMDD. Further, not all studies documented symptoms prospectively, a process that is generally considered fundamental in the diagnostic evaluation. Prospective ratings help exclude the high number of women who report premenstrual symptoms and who subsequently are found not to have PMS or PMDD after daily ratings [24]. These and other methodologic concerns complicate interpretation and generalizations across research studies.

As with research on sleep across the menstrual cycle, there have been survey [8,25,26] and polysomnographic studies of sleep in women with PMS or PMDD. The survey studies suggest that the late luteal phase may be associated with more frequent subjective sleep disturbances, including restless sleep, sleep disturbances, unpleasant dreams, and unrefreshing sleep. There has been limited research using polysomnography [9,10,12,15,18,27,28].

These groups did not report major reproducible differences in sleep architecture in women with PMS/PMDD compared with control women. As in the studies of normal women across the menstrual cycle, study samples have been small, procedures and diagnostic methods varied markedly, and the findings were inconsistent among groups and within the same group over time. Future research thus should address design and size of study issues to resolve the issue of whether objective assessments support the subjective complaints of disturbed sleep and wakefulness in women with PMS/PMDD.

It is worth noting that some women may experience premenstrual exacerbations of underlying chronic mood disorders, such as dysthymia. In this case, some consideration could be given to adjunctive therapy in the luteal phase, for example by increasing the number of sessions of psychotherapy or augmenting doses of antidepressant medication, especially given recent data on the luteal phase dosing of SSRIs for PMDD (see Physician's Desk Reference for fluoxetine and sertraline).

Sleep in women with dysmenorrhea

Dysmenorrhea refers to severe pain associated with menstruation. It also can include painful cramping before the onset of menstrual flow. Despite the fact that dysmenorrhea is common, apparently only one article on this

population has been published in the sleep literature [29]. In this well designed study, women with dysmenorrhea reported more subjective fatigue than control subjects. Notable was the finding of decreased rapid-eye-movement (REM) sleep and increased core temperature across the luteal and menstrual phases compared with normal control subjects. This increase in temperature is reminiscent of that reported by Severino et al [19] across the cycle in women with PMDD.

This study points out the need for more research in this area, with a reminder that phase of cycle is a key variable in many types of studies of women, and not simply in research in which mood disorders like PMDD are being evaluated.

Sleep and oral contraceptives

Little is known about the effects of oral contraceptives (OCs) on sleep. By comparison, far more is known about the effects of estrogen and progesterone on sleep in peri- and postmenopausal women (see later sections). For obvious reasons, women taking OCs would be excluded from research on sleep across the menstrual cycle. Studies are needed on this population, however, to understand the sleep of women during the reproductive years, because OCs are used so widely. Further, studies of women taking OCs with sequential progestin allows for the evaluation of possible gonadal steroid hormone effects on sleep. Over time the doses of the estrogen and progestin components have changed, and the product may be of the fixed progestin or sequential variety. These factors are important to consider when comparing data across studies and unfortunately are not always mentioned in detail in design sections.

The studies to date have used small sample sizes and the findings are inconsistent [9,10,17,28,30]. No conclusions thus can be drawn yet about OCs and sleep. Future studies should be mindful of factors including doses of the estrogen and progestin components, whether the progestin dose is constant or sequential, and when in the monthly administration cycle the sleep recordings occur (active drug or hormone-free week).

Disorders of sleep related to the menstrual cycle

The International Classification of Sleep Disorders (ICSD) lists several sleep disorders related to the menstrual cycle (1990) in their own category: menstrual-associated sleep disorder. These include premenstrual insomnia, premenstrual hypersomnia, and menopausal insomnia. The rationale for the latter inclusion is not clear, because by definition, menopausal women have no menstrual cycles. Schenck and Mahowald [31] recommended adding another disorder, premenstrual parasomnia, to the category, based on their clinical observations.

Premenstrual insomnia

Despite its listing in the ICSD, Manber and Armitage [4] discussed the lack of research on this problem. In apparently the only research study focusing on this issue, Manber's group [32] used sleep logs and actigraphy to study 13 women with psychophysiologic insomnia across the menstrual cycle. They found that daily irregularity in the insomnia pattern outweighed any menstrual cycle effect. A recent case report [33] documented a phase delay in core temperature in association with premenstrual insomnia. More research thus is required to validate this diagnosis. Phase of menstrual cycle should be taken into account when evaluating women with sleep complaints. Premenstrual symptoms such as anxiety and pain from cramps, headache, or bloating have the potential to affect the quality of sleep.

Premenstrual hypersomnia

There have been several reports in the literature regarding hypersomnia episodes that were linked temporally to the menstrual cycle. Billiard et al [34] reported a case study of a 13-year-old girl whose hypersomnia before menses was treated successfully with conjugated estrogens, thereby blocking ovulation. Sachs et al [35] described a patient who was followed for 3 years beginning at age 16 years. Hypersomnia also began before menses, but continued into the early follicular phase. As in the Billiard et al case [35], hormonal treatment, in this case with oral contraceptives, was successful in preventing the periodic hypersomnia.

A more recent report [36] was the case of a 42-year-old woman with rheumatoid arthritis and diabetes mellitus who had experienced hypersomnia since age 38 years during the week before menses. When the patient's menstrual cycles ceased secondary to the use of medications such as metoclopramide, the hypersomnia episodes became shorter and more erratic. Unlike the previous cases, hormonal replacement therapy did not prevent somnolent episodes; successful symptomatic relief was obtained with methylphenidate. Clearly a much larger case series is required to understand the cause and treatment of this type of hypersomnia.

Premenstrual parasomnia

As mentioned, premenstrual parasomnia currently is not listed in the ICSD. Schenck and Mahowald [31] reported two female patients who each had sleep terrors and injurious sleepwalking that were linked to the premenstrual phase. With treatment (in the younger woman by self-hypnosis and in the older woman by self-hypnosis and medication), symptoms were minimized. This limited case series highlights the need for future reports. In addition, it is hoped that clinicians who encounter female patients who are past menarche and who have complaints of parasomnias will include questions regarding the temporal association of symptoms with

menstrual cycle events that may have an important impact on etiology and treatment of the parasomnia.

Sleep during pregnancy and postpartum

Although pregnancy, childbirth, and postpartum can be a fulfilling and exhilarating experience for a woman, they are also fraught with considerable sleep disruption. Reports of altered sleep during pregnancy range from 13%–80% in the first trimester and increase to 66%–97% by the third trimester [37,38]. The marked increase in gonadal steroid hormones during the first trimester, the added physical discomfort associated with the growing fetus during the second and third trimesters, the precipitous decrease in hormones after delivery, and the infant's irregular feeding and sleep schedules are all obvious reasons for sleep disturbance. The recent addition of the diagnosis of pregnancy-associated sleep disorder in the ICSD validates these problems during pregnancy. As Santiago et al point out [39], however, physicians may presume a sleep problem is caused by normal physiologic changes during pregnancy and overlook the possibility of a primary sleep disorder, such as sleep apnea or restless legs syndrome.

As with the menstrual cycle, sleep research during pregnancy and postpartum has been limited by varying data collection procedures, small and often nonrepresentative samples, poorly controlled studies, pooled data that may obscure individual variation, cross-sectional designs, and studies that are descriptive rather than hypothesis driven. Unfortunately few generalizations exist beyond women's almost universal complaints of disrupted sleep and fatigue during the first trimester, varying degrees of a grace period in the second trimester, and considerable sleep disruption during the third trimester and postpartum. As Lee discusses in a comprehensive review of the literature [40], research of sleep during childbearing has received little attention since the pioneering work on Karacan et al in the 1960s. Furthermore, little research exists on possible treatments for sleep disruption and safe, effective treatment of primary sleep disorders during pregnancy and postpartum.

Anatomic and physiologic changes affecting sleep during pregnancy

The progressive increase in sex steroids during pregnancy, particularly estrogen and progesterone, has a profound effect on sleep and wakefulness. Estrogen has been shown to decrease REM sleep and to exert its influence by increasing turnover of brainstem noradrenaline [41]. In a longitudinal study of 31 women, Lee and Zaffke [42] showed that progesterone levels increased exponentially from 9.7 ng/mL during the non-pregnant luteal phase to 179 ng/mL during the third trimester. It is likely that progesterone's thermogenic and sedative-like effects have a more profound influence on sleep and sleepiness. Indeed, administration of progesterone directly to the

preoptic area of the forebrain in rats produces sleep [43], and when given exogenously to women, has a sedating effect [44]. In addition, progesterone inhibits smooth muscle action, causing an increase in urinary frequency as early as the first trimester. Changes in prolactin, oxytocin, melatonin, and cortisol during pregnancy also affect sleep [45].

By the second and third trimesters, the growing fetus compresses the bladder and reduces bladder capacity, resulting in a progressive increase in urinary frequency during sleep and wake. Additionally, fetal activity and acid reflux cause awakenings, and discomfort from the large gravid uterus makes turning over during sleep a more effortful and alerting behavior. A multitude of hormonal and physical factors thus adversely affect women's sleep during the course of pregnancy.

Subjective and objective sleep studies during pregnancy

In one of the earliest subjective studies [37], women in late pregnancy were asked if their sleep had been "normal" during the pregnancy. Those responding "no" then were asked to indicate which trimester they experienced poor sleep and to generate reasons why. Schweiger found that 68 of 100 women reported having altered sleep during pregnancy; 13% during the first trimester, 19% in the second trimester, and 66% in the third trimester. Although only 11 of the 100 reported that their sleep was altered throughout the pregnancy, this finding may have been in part a confound of the design. Twelve women who had never taken sleep aids before took sleep medication during some part of their pregnancy. The most common reasons cited for altered sleep depended on the trimester. In the first trimester, women complained of nausea and vomiting, urinary frequency, feeling uncomfortable, and backaches. By the second and third trimesters, fetal movements, heartburn, cramps, or tingling in the legs and shortness of breath were reported additionally. Only one woman reported that her other children kept her awake, but the total number of multiparous women in the study was not reported.

A more recent survey [38] that included an expanded questionnaire of sleep habits and disturbances and symptoms associated with sleep disorders found an increase in prevalence of sleep problems. Mindell and Jacobson surveyed 127 women divided into four groups depending on "quarter" of pregnancy (8–12 weeks, 18–22 weeks, 25–28 weeks, and 35–38 weeks). They found that the most common sleep disturbance was night waking (80% of women in the first quarter and 97% by the last quarter) and that the number and duration of awakenings also progressively increased by quarter. Likely in response to sleep disruption, women in the last quarter of pregnancy were more likely to awaken later in the morning and take more naps, especially on weekends. Women at the beginning of pregnancy were also more likely to nap.

As in Schweiger's study, reasons for sleeplessness during pregnancy were primarily physical discomfort, urinary frequency, and fetal movement.

Women also endorsed answers that revealed that more emotional concerns, however, such as dreams about the fetus and anxiety over the eminent change in lifestyle, were playing a role in their insomnia. There was also strong evidence that symptoms of snoring, sleep apnea, and restless legs syndrome increased during pregnancy. For instance, 30% reported snoring during pregnancy (although most did not report snoring beforehand) and 22% reported leg twitching or jerking. A most provocative finding was that despite the fact virtually all women at the end of pregnancy reported poor sleep, only one third of women considered they had a current sleep problem. The authors suggest that pregnant women may resign themselves to poor sleep because they believe it is an expected and perhaps untreatable part of pregnancy. The authors add that it also may represent a larger issue of poor recognition of sleep disorders in general.

In the largest longitudinal survey study [46], 325 women were interviewed during and after pregnancy to evaluate changes in sleep. At their first prenatal check-up, women filled out two questionnaires (one regarding the 3 months before becoming pregnant and one for the first trimester) and thereafter filled out a questionnaire at each subsequent trimester and at 3 months' postpartum. Reported total sleep time at night before pregnancy was 7.8 hours; it increased to 8.2 hours in the first trimester and decreased to 8.0 hours in the second and back to a baseline of 7.8 hours in the final trimester. Napping showed a similar pattern of increasing precipitously during the first trimester. Night wakings increased progressively over pregnancy. During late pregnancy, women older than 30 years of age were found to sleep for less than 7 hours, although it is unclear whether this was mainly from having other children. Symptoms of snoring, sleep apnea, and restless legs progressively increased during the course of pregnancy.

In an effort to understand the physiologic changes in sleep, polysomnography has been used to assess the impact and course of pregnancy on sleep. In one of the earliest studies on pregnant women, Karacan et al [47,48] recorded sleep in 13 Caucasian women (mean, 24.5 years; range, 22–30 years) during late pregnancy and postpartum. A subset of 3 of the 13 women also were studied every 2 weeks beginning at 4–6 weeks' gestation and found to have increased total sleep time and napping in the first trimester. In late pregnancy, stage 2 sleep, wake after sleep onset (WASO), and number of awakenings were increased significantly and stage 4 sleep was decreased significantly compared with a nonpregnant control group. The finding of disrupted sleep in late pregnancy in addition to lowered total sleep time several months postpartum compared with the nonpregnant group led Karacan et al to suggest the possibility of a permanent physiologic adjustment in the sleep process during pregnancy that anticipates the eventual sleep disruption from the infant's erratic sleep [47]. It also was suggested that late-pregnancy insomnia could be a manifestation of a subclinical depression and, furthermore, that stage 4 suppression may be a marker for the subsequent development of postpartum depression.

Unfortunately more recent sleep studies using longitudinal designs have produced equivocal results. Driver and Shapiro [49] found a progressive increase in SWS over the course of pregnancy in four first-time mothers (18–29 years of age) but only the first 6 hours of sleep were analyzed. In contrast, Brunner et al [50] found a progressive decrease in SWS activity in all nine women (mean, 30.6 years; range, 27–35 years) studied during the course of their pregnancies using spectral analysis. Hertz et al [51] found significantly increased WASO and stage 1 sleep, lower sleep efficiency, and decreased percentage of REM sleep in 12 women (mean, 30.5 years; range, 22–40 years) during late pregnancy when compared with a nonpregnant control group. There was also a nonsignificant decrease in SWS in the pregnant women. The authors suggest that the pregnant women's most frequent complaints of restless sleep, lower back pain, leg cramps, and frightening dreams were consistent with the pattern of sleep maintenance insomnia seen on polysomnography.

Lee et al [42,52] present more comprehensive, naturalistic data on 33 women studied in their own homes from prepregnancy, at each trimester, and postpartum (discussed in a later section). In addition to sleep studies, subjective and physiologic measures of fatigue were obtained. Changes in sleep were evident by 11–12 weeks' gestation, with a significant increase in total sleep time (from 6.9 hours at prepregnancy to 7.4 hours), an increase in WASO, and a decrease in SWS when compared with prepregnancy measures. By late pregnancy, total sleep time decreased to baseline levels (6.9 hours), in part because of awakenings, and SWS remained lower than baseline levels. Subjective fatigue increased during the first trimester, improved by the second, and then decreased in the third trimester. Prepregnancy levels of iron, ferritin, and hemoglobin and younger age all were correlated with subjective fatigue in the first trimester. Higher levels of fatigue in the third trimester were associated with lower folic acid levels and less total sleep time.

The effect of parity (primiparous versus multiparous) on sleep before and during pregnancy revealed unexpected findings [52]. At all time points, the 16 experienced mothers with children sleeping through the night had more total sleep than the 13 novice mothers, although differences were not statistically significant. On the other hand, the experienced mothers' sleep efficiency was significantly lower because of frequent awakenings when compared with the nulliparous women. This suggests that multiparous mothers compensate for increased awakenings by spending more time in bed.

Interesting patterns also emerge when prior history of a psychiatric disorder is considered. It is known that the period of childbearing, particularly postpartum, is associated with increased risk for psychiatric morbidity. In a longitudinal study, Coble et al [53] monitored in-home sleep in 18 pregnant women without and 13 pregnant women with a prior history of affective disorder. Although all women were psychiatrically healthy

during pregnancy, women with a history of affective disorder had an earlier onset and greater changes in sleep during the course of their pregnancy and reported more sleep disturbances and somatic distress. In addition, there was a decreased latency to the first REM period in the women with a prior history of affective disorder. These findings led Coble's group to suggest that women with a prior history of affective disorder may have a more "fragile" sleep system and that the shortened REM latency may represent a marker of past affective episodes. Because only 1 of the 13 women at risk actually developed a depressive episode postpartum, they suggested that if women are healthy at the time of pregnancy, the impact of childbearing on psychiatric symptoms may be modest.

In sum, subjective and objective studies concur that early in pregnancy most women become sleepier and their nighttime sleep is more disrupted. Mean sleep durations are 7.5–8.5 hours and total sleep time increases roughly 0.5–1.0 hour per 24-hour day when compared with prepregnancy levels. As the pregnancy progresses, however, sleep becomes more fragmented, with a resulting decrease in total sleep time back to prepregnancy levels. Most sleep studies show either no change or a slight decrease in SWS, likely because of the fragmentation that occurs from frequent awakenings. To compensate for disrupted nighttime sleep and the soporific effects of increasing hormones, pregnant women alter their sleep habits by sleeping later, especially on weekends, and napping more often. Studies agree that the most commonly endorsed complaints are of physical discomfort, but reported prevalence of sleep problems can vary widely and depend to some degree on the format of the survey studies (eg, self-report, questionnaires, sleep logs, Likert scales). Although hormonal and physical changes contribute profoundly to sleepiness and sleep disruption, age, parity and history of mood disorders also affect sleep. Alterations in sleep and wake schedules, anxiety, and sleep disorders also contribute to an unknown extent.

Unfortunately research on behavioral and pharmacologic treatment of sleep problems during pregnancy is lacking in part because of obvious considerations of the effects on the developing fetus. Anecdotal reports from pregnant women suggest that certain interventions such as antacids for heartburn, a reduction of fluid intake in the evenings to decrease nocturia, and pregnancy pillows for discomfort may improve their sleep. Although it is assumed that altering sleep schedules in response to sleep disruption likely worsens the insomnia and that good sleep hygiene treatment benefits the pregnant woman and her developing fetus, there are no behavioral treatment studies to support this assertion.

It is thus imperative that research is conducted on treatment alternatives, that consciousness be raised regarding pregnancy-related sleep problems, and that women discuss their sleep with informed health care providers and appropriate recommendations are made. It is also important that sleep disorders, such as sleep-disordered breathing and restless legs syndrome, are diagnosed and treated whenever possible.

Sleep disorders during pregnancy

Given the changes in pulmonary mechanics during pregnancy, the incidence of sleep-disordered breathing during pregnancy has become a topic of interest. Although progesterone, a respiratory stimulant, may play a protective role, there are at least theoretic concerns that narrowed upper airways coupled with increased body habitus may result in compromised breathing during sleep in pregnancy. It is well known that snoring increases in pregnancy, with estimated frequencies increasing from 4% in the nonpregnant woman to ranges of 14%–23% during pregnancy [54,55]. These findings are potentially important, because snoring during pregnancy has been linked to maternal hypertension and pre-eclampsia and fetal growth retardation [55].

Although increased incidence of snoring suggests that sleep apnea also should be on the increase, results of sleep studies in pregnant women have been largely equivocal. Brownell et al [56] found a marginal reduction in respiratory disturbance index (RDI, number of respiratory events per hours of sleep) in pregnant women with no prior history of sleep apnea when compared with their own postpartum levels. To evaluate whether obesity predisposes a woman to sleep apnea, Maasilta et al [57] studied the sleep and breathing of obese pregnant women with pregnant women of normal weight during early and late pregnancy. At both time points, obese pregnant women snored more and had higher RDIs.

Guilleminault et al [58] conducted polysomnography using esophageal manometry to assess for upper airway resistance (UAR). They studied 26 pregnant women, 13 of whom snored loudly and 13 who did not. Although none of the 26 women presented with frank obstructive sleep apnea, chronic snorers were more likely to have higher systolic and diastolic blood pressure increases and exhibit abnormal breathing patterns associated with UAR. In 10 women with multiple pregnancies, Nikkola et al [59] found no significant sleep apnea or episodes of hypoxemia, but their study did not measure UAR.

In addition to sleep apnea, restless legs syndrome (RLS) increases during pregnancy, particularly during the final trimester, and then decreases after delivery. Mindell and Jacobson found that none of the women in early pregnancy reported restless legs, but by late pregnancy there was an increase to 14%. Twenty percent of pregnant women in a survey study in Japan endorsed the symptom of restless legs [60]. Lee et al [61] found that the prevalence increased from 0% of the 30 women preconception to 13% in the first trimester, 18% in the second, and 23% by the third trimester. Only one subject continued to have restless legs after delivery. When compared with those without complaints, the women with restless legs had lower ferritin levels and significantly lower folate levels before and during pregnancy. They suggest that these findings support the role of iron and folate in the etiology of RLS during pregnancy. Although Nikkola's study [59] did not investigate the incidence of restless legs, they found that periodic leg

movements (PLMs) were prevalent in mothers with multiple pregnancies (mean, 22 PLMs per hour of recording).

In sum, definitive conclusions are lacking regarding the incidence of sleep-disordered breathing because of the need for larger prospective, longitudinal studies. The data suggest, however, that sleep apnea may develop in pregnant women who have a pre-existing tendency toward sleep-disordered breathing and may worsen in those women who already have sleep apnea [62]. Nasal continuous positive airway pressure (CPAP) has been used effectively in a number of pregnant women and was found to reduce nocturnal blood pressure increments in women with pre-eclampsia [62]. Future research should assess for UAR by using more sophisticated breathing equipment and should investigate the possible relationship of sleep-disordered breathing with maternal and fetal complications. Given the known increase in RLS, an investigation should be undertaken to address possible nutritional supplements for this problem. Conservative treatments include avoidance of caffeinated beverages, treatment of anemia (if present), and vitamins with folate. Indeed, Botez and Lambert [63] found that the prevalence of RLS in pregnant women taking vitamins with folate (9%) was lower than those taking supplements without folate (80%).

Alterations in postpartum sleep

The postpartum period, which is associated with considerable sleep disruption, begins with delivery and ends for most women approximately 6–12 months later when the infant is sleeping through the night. Following delivery of the fetus and afterbirth, there is a rapid decrease in placental-derived hormones that is mainly responsible for the short-lived ''postnatal blues'' experienced by most women (75%–80%) 3–5 days after birth. In addition, the hormonal changes may have a profound effect on sleep.

Although postpartum sleep loss is intuitive and well documented, interpretation of objective sleep studies using polysomnography is challenging for some of the same reasons as pregnancy research and for some different reasons. First, data collection procedures vary widely, especially the earlier research in which the mother's sleep was studied without the infant present. More recent postpartum sleep studies have been conducted in a natural setting with the infant at home or in the hospital room. Second, there is great variability in prior sleep deprivation and sleep/wake patterns. Finally, other important variables (eg, parity, length of labor, time of day, type of delivery, feeding method, postpartum day studied) often are not considered.

Karacan et al [47] conducted laboratory polysomnography in 13 women without their infants following delivery. They found a significant increase in awakenings and WASO in the postpartum group when compared with a nonpregnant control group. In contrast to late pregnancy, stage 4 sleep

increased to a level commensurate with the control subjects. They suggested that the increase in stage 4 sleep is caused by increased energy expenditure during labor and delivery and hormonal factors, but recovery from prior sleep loss also plays a role. Zaffke and Lee [64] conducted ambulatory sleep studies in the hospital rooms of nine breastfeeding mothers on the first postpartum night. Compared with the control subjects, the postpartum group had significantly lower sleep efficiency (74%) and a shorter latency to REM sleep (71 minutes).

At 3–4 weeks postpartum, Lee et al [65] showed continued decrements in sleep efficiency (81%) and total sleep times (379 minutes) in 29 women when compared with the late third trimester (89% sleep efficiency, 415 minutes TST). SWS was slightly increased, stage 2 sleep was decreased, and REM latency was significantly decreased from pregnancy levels. Lee et al propose that these findings support the early sleep deprivation research in showing that recovery sleep preferentially includes SWS because the restorative function of sleep takes precedence over REM sleep. One to 6 weeks postpartum, Nishihara and Horiuchi [66] also found diminished sleep efficiency and a high correlation between maternal wakefulness and infant activity in 10 younger women studied polysomnographically while their infants were studied with ankle actigraphs. SWS and REM measures, however, were not significantly different from late pregnancy. Two of the 10 women had extreme difficulties with sleep; one because of unusually high activity in her infant (''day–night rhythm reverse'') and one attributed to difficulty adjusting to her new maternal role. In a later study, the investigators also showed that the infant's sleep–wake rhythm also depended on the mother's schedule [67].

Although the most common reason cited for maternal awakenings in postpartum studies is the infant's sleep and feeding schedule [68,69], there is considerable discrepancy in the average total sleep times reported because of small sample sizes and the variability of sleep during the first few postpartum weeks. Using actigraphy and sleep logs, Kang et al [70] studied 10 women (5 primiparous) from the fifth prepartum to the fifteenth postpartum week. As in Lee's study, total sleep time decreased precipitously after delivery and progressively increased, although still below late pregnancy levels by the fifteenth postpartum week. Of interest, estimates of sleep from sleep logs were higher than from actigraphy after delivery when there was more variability in the data, in general. As in pregnancy, women compensated for lost nighttime sleep by sleeping on a more irregular schedule and napping to some extent while the infant napped [71], although the ability to nap is known to be affected by parity. Beyond the obvious sleep disruptions caused by the infant, however, recent studies suggest a myriad of other factors (eg, emotional and physical health of mother, parity, methods of birth and feeding, infant's sleep–wake rhythm, co-sleeping) that can further affect postpartum sleep.

The impact of sleep deprivation on postpartum mood remains largely unstudied. Mead-Bennett [72] did not find a relationship between late

pregnancy sleep loss and depressed mood through surveys on the first postpartum day, but Wilkie and Shapiro [73] found a significant relationship between accrued sleep loss and depressed mood during the first postpartum week. Of note, prior sleep loss did not affect labor and delivery outcome (eg, length of labor, type of delivery) in one study [74]. In the only study to look at postpartum cognitive function [75], modest decrements in memory and psychomotor performance tasks were found in 30 primiparous women compared with 28 nonpostpartum women. In addition, higher levels of dysphoric mood were found in the postpartum group. When the investigators controlled for ''time awake'' at night, the significant effect of dysphoric mood was eliminated [75]. In contrast, partial sleep deprivation was shown to be effective in improving mood; however, this was found in a group of women with postpartum depression [76].

More serious psychiatric disorders (ie, postpartum depression and psychosis) may occur 2–4 weeks after birth but may not reach peak intensity until 3–5 months postpartum. Approximately 10%–15% of new mothers develop postpartum depression and of that group, only one third of the women have a prior history of affective disorder [77]. In Coble's study [77], the control group reported symptoms of mild depression in the early postpartum period, but the women with a prior history of depression reported more depressive symptoms manifested in sleep disturbances and somatic complaints. The finding of a shortened REM latency found in the third trimester in women with a prior depressive episode persisted through the eighth postpartum month. Lee et al [65] also found shortened REM latency and sleep disturbances in postpartum women with elevated depressive symptoms.

Although Coble's study did not show a psychiatric history as a risk factor (only 1 of the 13 women at risk developed a major depression postpartum), other studies have shown that approximately one quarter of women with a prior psychiatric history go on to develop postpartum depression. Larger studies thus need to be conducted to assess the interrelationships among mood before pregnancy, sleep deprivation, and postpartum depression. In addition, infant sleep disturbance has been shown to affect maternal mood adversely [78], but studies also show that there exists a bidirectional causal relationship between these two factors, possibly mediated by sleep deprivation and the quality of mother–infant interaction [79]. Elaboration of this complex system could have important public health consequences.

In a large prospective study on women's postnatal health [80], 1193 women completed four questionnaires beginning on the fourth postpartum day and then at 8, 16, and 24 weeks postpartum. Thompson et al [80] found that such health problems as exhaustion/tiredness, backache, bowel problems, lack of sleep/baby crying, perineal pain, excessive/prolonged bleeding, urinary incontinence, mastitis, and other urinary problems improved between weeks 8 and 24. Even at the 6-month evaluation, however, health problems continued for many of the women (exhaustion or extreme tiredness, 49%;

backache, 45%). When method of birth was compared, women having cesarean sections were more likely to report exhaustion, lack of sleep, and bowel problems and to be readmitted to the hospital and were less likely to report perineal pain and urinary incontinence at 8 weeks when compared with those women with unassisted vaginal deliveries. Forty percent of the women reported that they would have liked more education and advice regarding the care of their infants. When method of birth was controlled, interesting effects of parity were found; primiparas were more likely to report perineal pain and sexual problems and were less likely to have resolution of depressive symptoms. Also, primiparas had higher rates of assisted deliveries.

In a polysomnographic study comparing 12 primiparas with 18 multiparas, Waters and Lee [81] found that first-time mothers had a decrease in sleep efficiency from 90% (third trimester) to 77% (one month postpartum), whereas multiparas' sleep efficiency remained stable (87% in third trimester, 84% 1 month postpartum). Total sleep times during late pregnancy were not significantly different in these two groups. Another study [69] reported that, whereas women with other children had fewer sleep periods than novice mothers, there were no significant differences in total sleep time. This likely reflects the difficulty multiparas have taking a nap when other children are in the home, but also suggests the possibility that experience helps mothers learn how to sleep more efficiently.

A most provocative finding in the Waters and Lee study is that new mothers had more fatigue than experienced mothers, yet scored lower on an operationalized measure in household chores. The authors propose that the differences in sleep and fatigue found in novice and experienced mothers reflect the new challenges in maternal role acquisition in the primigravida group. They also suggest that the process of integrating and achieving competence in mothering behaviors together with the sleep deprivation may put new mothers at risk for developing postpartum depression.

Feeding method also may affect the sleep of mothers with infant children, although this subject has not been well studied [40]. Quillin's study of 44 mothers during the fourth postpartum week [82] showed that the 32 mothers who breastfed had more awakenings and tended to sleep less during the night than women who bottle fed. In another study [83], however, lactation was associated with significant increases in SWS in 12 women who breastfed (SWS, 182 minutes) when compared with 7 women who bottle fed (SWS, 63 minutes).

Cultural differences in sleeping arrangements also play a role in postpartum sleep. Mosko et al [84] conducted laboratory polysomnography on 20 routinely bedsharing and 15 routinely solitary-sleeping, breastfeeding Latino infant (11–15 weeks old) and mother pairs. Mothers were able to care for their infant ad libitum, and each mother–infant pair slept in the solitary and bedsharing conditions in a counterbalanced design. They found a significant increase in arousals and decrease in SWS by 4% in the bedsharing condition. Because of the shorter duration of arousals in the

bedsharing condition, however, overall nocturnal wakefulness was no different between the conditions and thus, total sleep time was no different between the two conditions.

Although all of the variables mentioned affect mother and baby's sleep, studies show that ultimately mothers' sleep improves together with the baby's development. Subjective and objective studies conducted on new mothers and their infants show that by approximately 3 months the infants' sleep and wake patterns become more regular and, in turn, the mothers' sleep becomes more continuous [69,85]. A careful study of the development of sleep and circadian rhythms in a single human infant from birth to 6 months of age [86] showed that periods of sustained wakefulness first appeared in concert with increased melatonin levels at sunset at day 45. The sleep circadian rhythm appeared last (at approximately day 56) of all the physiologic parameters that were monitored. In Nishihara et al's study [67], the amplitude of the 24-hour peak in the infant's movements was detected at the third week and increased from the sixth to the twelfth week. Although internal factors promoting a more organized sleep–wake rhythm are developing between 3 and 6 months of age, data and experience show that many children continue to have difficulties sleeping through the night. According to Ferber, bothersome nocturnal awakenings continue to occur in 23%–33% of 1- and 2-year-old children [85].

In closing, postpartum sleep in new mothers is seriously disrupted. This disruption is likely attributable to the influence of a multitude of factors that include parenting approaches (bedsharing, parity, breastfeeding, how and where an infant is readied for sleep, the tenor of the parents' interaction with the child, and the general household demeanor). The parents' general health (physical and emotional, cumulative sleep deprivation) and their ability to bounce back from severe sleep disruption also must be considered. In a study evaluating first-time parents, Gjeringen and Center [87] found that mothers and fathers experienced a decline in their perceived quality of life at 6 months postpartum. Of note, both parents' postpartum health was associated with the mothers' partner satisfaction and work characteristics (eg, balance of work between mothers and fathers). Many of the factors affecting the infant and mother's sleep are likely amenable to intervention that benefits the mother without compromising the infant. Yet in common with research on sleep during pregnancy, there are few data on treatment for postpartum sleep disruption aside from the old adage of "sleep when you can." A better understanding is needed of how this sleep disruption affects mood and functioning in new parents. Equally important is research on how the consequences of parental sleep disruption ultimately may affect the healthy development of the infant. Finally, greater knowledge of effective methods for minimizing sleep loss is essential, together with dissemination of what is known already. Clinical practice should strive to raise consciousness and institute effective treatments for this most exciting and challenging period in a woman's life cycle.

Sleep and menopause

Menopause is defined strictly as 1 year following cessation of menstrual periods. Hormonal changes, however, begin 7–10 years before the final menses. During this time, there is a decrease in estradiol and inhibin with an increase in FSH and a lesser increase in LH. Circulating estrogens shift from estradiol to estrone, predominantly produced by the extraglandular conversion of androstenedione, and there is only a minimal decrease in testosterone production [88].

Menopause is associated with hormonal, physiologic, and psychologic changes that affect sleep. Insomnia becomes common during this time. The literature on sleep during menopause focuses primarily on two questions: (1) Is sleep worse with menopause and if so, what are the causes and effective treatments? and (2) Is obstructive sleep apnea more prevalent with menopause and if so, what are the causes and effective treatments? The answers to the first parts of both of these questions is ''Yes''; however, the mechanisms remain obscure, the efficacy of hormone replacement therapy (HRT) is debated, and there is no clear answer as to the appropriate treatments (although an approach to the menopausal woman with insomnia may be found at the end of this article).

Menopausal insomnia

Subjectively, sleep becomes worse with menopause. Although insomnia generally is increased in women when compared with men, there is an increased prevalence of insomnia in postmenopausal women when compared with premenopausal women. Estimates of complaints of insomnia in peri- and postmenopausal women range from 44% [89] to 61% [90], clearly significantly more than the 33%–36% incidence seen in premenopausal women [89]. Of recent interest has been the finding in a large population-based polysomnographic study that postmenopausal women were *less satisfied* with their sleep than premenopausal women but had *better sleep* documented on full-night polysomnography (longer total sleep times, increased amounts of SWS, less time awake in bed) [91]. One explanation is that the findings may reflect an increased drive to sleep from greater daytime sleepiness caused by the lack of estrogen in the postmenopausal population [92] or that the differences, although statistically significant, are not physiologically significant (eg, the increase in total sleep time is 13.4 minutes). There seems to be a discrepancy between the subjective experience of sleep by postmenopausal women and the objective data, which makes evaluating the efficacy of estrogen in treating menopause-related insomnia difficult.

Four main causes of sleep disruption during the perimenopausal and postmenopausal states have been studied: hot flashes, mood disorders, primary insomnia, and sleep-disordered breathing. The first three causes are described later, followed by a discussion of the effects of HRT. A thorough

discussion of sleep-disordered breathing follows. Of note, restless legs syndrome as an issue in the sleep of menopausal women rarely is mentioned but is discussed later.

Hot flashes affect 75%–85% of perimenopausal and postmenopausal women. Most women experience hot flashes for only 1 year, but approximately 25% experience them for 5 years [93] and a small minority may have them lifelong [94]. An elevation in core body temperature precedes the hot flashes [95] and the frequency of hot flashes can be affected by the ambient temperature before bedtime, being decreased in cooler temperatures and increased in warmer temperatures [96]. Hot flashes are experienced as warmth beginning around the face and spreading to the chest, often accompanied by skin redness, diaphoresis, and palpitations. Other symptoms include nocturnal awakenings, nausea, dizziness, and headache [93]. The awakenings generally precede the peripheral vasomotor manifestations [97]. There seems to be an association with LH pulses [94], although this is controversial [98]. The hot flash is believed to be mediated through the preoptic area of the anterior hypothalamus and is associated with an increase of brain norepinephrine metabolism; hence, the increase in hot flashes with alpha$_2$-agonist therapy [93,94].

The significance of hot flashes in menopause is not yet resolved. On polysomnography, some investigators found an association of hot flashes with nocturnal awakenings [97] and decreased sleep efficiency [98,99], whereas others found no correlation between the presence of hot flashes and polysomnographic measures of poor sleep [100]. In the most recent study of climacteric symptoms and sleep quality, however, a high frequency of hot flashes was associated with impaired *subjective* sleep quality. There are thus polysomnographic arguments for and against the role of hot flashes in the insomnia of menopause.

Mood disturbances are well known to affect sleep. Depression and anxiety can be associated with less refreshing and more fragmented sleep [101]. The hormonal changes of menopause may contribute to depression and anxiety in this population [94], or the depression and anxiety that can be associated with menopause may be caused in part by a response to life circumstances [102], unresolved grief [103], or to the presence of hot flashes [88,103]. Nonetheless, there are patients for whom psychotherapy is necessary to treat insomnia despite diminution of hot flashes with HRT [104]. Addressing psychiatric causes of insomnia is important in this population.

Finally, Krystal et al [103] in their excellent review of this topic raise the possibility of a primary menopausal insomnia. The theory is that a symptom of menopause, such as hot flashes, initiates insomnia (the precipitating factor). Once the symptom is treated, however, the insomnia persists because of perpetuating factors and behavioral conditioning. The insomnia then would be treated best by the applicable insomnia therapies—sleep restriction, education about the principles of good sleep hygiene, and

relaxation techniques. Please see the article by Sateia and Pigeon elsewhere in this issue for a more detailed discussion of the treatment for insomnia.

Menopausal restless legs syndrome

There is little in the literature about the effect of menopause on RLS. This relative paucity of research may have occurred in part because many polysomnographic studies did not include leg EMG electrodes. There is, however, an increase in the incidence of RLS with age in the general population. Unfortunately a survey study of midlife women that noted an increased incidence (10/23 subjects) of self-reported periodic limb movements of sleep (PLMS), one of the behavioral components of RLS, did not report whether or not the PLMS were reported more frequently by the menopausal or premenopausal subjects [105]. Nonetheless, RLS should be considered in the differential diagnosis of insomnia in most cases.

Treatment of sleep disorders in menopausal women with hormone replacement therapy

The use of HRT for menopausal insomnia is a source of current debate. Because of the results of the Women's Health Initiative (WHI) [106], the use of HRT now is being widely discussed. The results of this seminal study apply only to oral conjugated equine estrogen and oral medroxyprogesterone, however, and thus may not apply to transdermally delivered estradiol and oral unconjugated progesterone. Other forms of HRT therefore may return as a popular treatment in the future. Because there are still women who choose to remain on HRT, the effect of HRT on the sleep of menopause and the problems mentioned previously should be discussed. As with the WHI, the conclusions reported later apply only to the hormones used, which are for the most part oral synthetic estrogens and oral medroxyprogesterone, although some of the more recent articles do use transdermal estrogen. The reader is referred to the earlier review by the authors for the exact medications and dosing [107].

Although the older literature suggests a beneficial effect of HRT on sleep, newer studies contradict this finding. The classic articles from the 1970s found improvement in polysomnographic sleep parameters in menopausal women treated with oral synthetic estrogens for at least 8 weeks in placebo-controlled trials [108,109]. In contrast, more recent studies using transdermal estrogen for 2 weeks (no placebo group) [110] or 3 months (placebo-controlled trial) [111] showed no objective, polysomnographic improvements (although the latter study reported a decrease in the intensity but not the frequency of arousals). In both of these studies, however, the women using estrogen noted a *subjective* improvement in their sleep. One recent placebo-controlled study looking at oral conjugated estrogen and an oral progestin [112] similarly found no difference in sleep parameters

between treatment and placebo over 12 weeks. Another trial comparing 6 months of oral conjugated estrogen with a synthetic progestin (0.625 mg Premarin with 5 mg of Provera) versus oral conjugated estrogen with progesterone (0.625 mg Premarin with 200 mg Prometrium) found no objective improvement with the former but a decrease in wake after sleep onset with the progesterone. As mentioned earlier, both groups subjectively believed that their sleep improved significantly [113]. As with the perception of sleep, there is thus a discrepancy between some of the objective and subjective data. There is also the suggestion that using the newer, more natural form of pure progesterone (versus the synthetic compound that up until recently has been used more commonly, medroxyprogesterone) may have better results.

Equally debated is the role of HRT, particularly estrogen, in its treatment of nocturnal hot flashes. For the most part, HRT generally is shown to decrease hot flashes in sleep, but many of the studies rely on self-reports and not objective data. Despite this information, there are studies with objectively quantifiable hot flashes that arrive at opposite results.

Two articles analyzing the effect of estrogen therapy on objectively determined hot flashes (using measures of skin resistance) and sleep found improvements in both. These studies used oral synthetic estrogens for approximately 4 weeks and found a statistically significant decrease in objectively measured hot flashes. These studies used few subjects, however (seven or fewer) [97,114], and only one was placebo-controlled [114]. In contrast, a slightly larger placebo-controlled study (17 in each group) that looked at the *combination* of estrogen and progesterone for 12 weeks [112] found no difference in hot flashes (measured by an increase in skin temperature, skin humidity, and pulse) between treatment and placebo. There was a decrease of hot flashes in the treatment and the placebo arms, but no statistically significant difference between the two (although there was a trend toward a greater decrease in the treatment group).

Not only do the objective studies disagree, but those studies looking at patient self-reports of hot flashes also conflict. Two double-blind crossover studies, one with transdermal estrogen used for 3 months [111] and one with oral synthetic estrogen for 1 month [108], found a decrease in subjectively reported hot flashes. On the other hand, a double-blind [109], placebo-controlled study using oral synthetic estrogen for 8 weeks did not result in a greater decrease in hot flashes.

The efficacy of HRT in treating affective disorders seen with menopause also presents conflicting results. One of the placebo-controlled studies mentioned previously [109] of oral synthetic estrogen found no difference in improvement in scales of mood and anxiety when compared with placebo treatment. Similarly, the large placebo-controlled study of the effect of transdermal estrogen for 3 months [111] found that hot flashes and sleep complaints improved with estrogen, but the decrease in subjective reports of depression was barely not statistically significant ($P = 0.055$). A statistically significant improvement was noted with oral conjugated estrogen versus

placebo given for 3 months [115] in one study. This study, however, was performed on women who were not depressed at baseline. The authors conclude that there is an effect on mood even in a subject without perceived depression.

The data on the combination of an estrogen and a progestin similarly provide no simple answer and, in fact, one study suggests that adding a progestin actually worsens depression. A 12-week, placebo-controlled study of oral synthetic estrogen with cyclic progestin found an improvement in depression and anxiety (despite no improvement in sleep) [112]. In contrast, when a progestin was added to transdermal estrogen use in a study looking at a comparison between the efficacy of estrogen alone (estradiol-17-β, 3 mg/day) and estrogen with a progestin (lynestrenol, 5 mg/day) over 6 months, the women receiving the progestin noted an increase in depression and irritability, despite a subjectively reported greater decrease in hot flashes [116]. This study was not blinded nor was there a placebo group. Finally, as mentioned previously, one 6-month trial of transdermal estradiol with a progestin found that symptoms of insomnia did not improve with the HRT alone but required the addition of psychotherapy. The investigators noted that combination therapy was more effective than HRT alone, although there was some beneficial effect of HRT noted on some psychologic measures [98].

Sleep-disordered breathing in menopausal women

The final proposed mechanism for poor sleep in postmenopausal women is sleep-disordered breathing. Although earlier it had been believed that sleep-disordered breathing was much more common in men than in women (a male:female ratio of 8:1 was calculated from a clinic population) [117], more recent polysomnographic studies of a large general population (the Wisconsin Sleep Cohort data) suggest that the male:female ratio is only 2.67:1 [118]. The overall prevalence in women aged 30–60 years is 9%. In fact, further analysis of these data confirmed that menopause is itself an independent risk factor for sleep-disordered breathing. After controlling for age, BMI, and several lifestyle factors [119], postmenopausal women were 2.6 times more likely than premenopausal women to have an apnea-hypopnea index greater than 5 and 3.5 times more likely to have an apnea-hypopnea index greater than 15. From another large polysomnography-based study, the exact prevalence of sleep-disordered breathing defined as an apnea-hypopnea index greater than or equal to 15 per hour of sleep was estimated as 3.9% in postmenopausal women, statistically greater than the 0.6% found in premenopausal women [120].

Proposed mechanisms for this apparent increase have included a change in the distribution of body fat [121] and a decrease in progesterone [122]. With menopause, there is a redistribution of body fat with an increase in the waist:hip circumference ratio. When analyzing the Wisconsin Sleep Cohort

data by gender, controlling for either the waist:hip circumference ratio or neck girth, men were no longer at an increased risk for having an apnea-hypopnea index (AHI) greater than 5 [121]. Because women increase their abdominal fat with menopause [88], it seems possible that this fat redistribution alone may play a role in the development of sleep-disordered breathing.

Another proposed mechanism is the change in hormones. A large cross-sectional polysomnographic study [123] (1315 women not using HRT) found an increase in the prevalence and severity of sleep-disordered breathing in postmenopausal versus premenopausal women, even after controlling for BMI and neck circumference, implicating hormonal changes as the cause of this increase. Although these investigators did not speculate on the exact hormonal mechanism, many have suggested that progesterone loss may be playing a role. Progesterone is a known respiratory stimulant in awake women [124]. Progesterone treatment of men with sleep apnea, however, has shown limited effect [125,126] and not much more effectiveness in women [127]. There does seem to be a correlation of progesterone levels with motor tone of one upper airway dilator muscle when women at different hormonal states were studied awake. If this differential in genioglossus tone persists during sleep, postmenopausal women may have reduction in pharyngeal area compared with premenopausal women, setting them up for sleep-disordered breathing [128] (of note, however, despite the decrease in genioglossus tone, there was no increase in upper airway resistance noted).

Research on the effectiveness of hormone therapy in treating sleep-disordered breathing in women is difficult to analyze because each study used different hormonal regimens and often presented different parameters (some used indices and others total numbers of respiratory events) with different definitions of hypopnea. In general, the literature on HRT and sleep-disordered breathing is divided into cross-sectional analyses and prospective clinical trials. Most of the results from the large cross-sectional studies favor a positive effect of HRT on sleep-disordered breathing. A large polysomnographic study of a general population of women (1000 subjects) [120] found that for postmenopausal women taking HRT (either oral estrogen or oral estrogen and a progestin), the prevalence of sleep apnea (1.1%) was not statistically different from the premenopausal group (0.6%). The postmenopausal group without HRT had a prevalence (5.5%) that was similar to that of men determined from a previous study (7.2%). The results of the Sleep Heart Health Study also showed a protective effect of HRT [129]. Women who used either estrogen or estrogen and progesterone (doses and vehicles not specified) had half the prevalence of sleep-disordered breathing as postmenopausal women who did not use HRT. The Wisconsin Sleep Cohort Study [119] found that women using HRT (drugs not specified) had decreased odds of having sleep-disordered breathing, but the difference was not statistically significant. Epidemiologic data thus suggest a therapeutic effect of HRT.

Despite the previously mentioned information, the prospective drug trials have been more disappointing. Some have shown no effect and others a statistically significant effect without elimination of the sleep-disordered breathing. Two studies have evaluated the effect of HRT on women with moderate to severe sleep-disordered breathing, producing contradictory results. One prospective but not placebo-controlled study looking at subjects with moderate sleep-disordered breathing treated with HRT found a statistically significant effect with HRT but not resolution of the sleep-disordered breathing [130]. This study evaluated five subjects given an oral estrogen alone for 3–4 weeks and then after 10–12 days of additional treatment with medroxyprogesterone. The initial average apnea-hypopnea index was 34 per hour of sleep, consistent with moderate sleep-disordered breathing (generally considered an AHI between 20 and 40). The mean AHI decreased from 34 to 25 with estrogen alone, and from a mean of 30 to 17.6 with estrogen and progesterone. Unfortunately, although the results were statistically significant, the residual level of sleep-disordered breathing was still in the high mild to moderate range, suggesting only a limited treatment effect. A second study similarly looked at 15 subjects before and after HRT, with a baseline average AHI of 43 [131]. After 50 days of treatment, the subjects being placed on different HRT regimens (oral or transdermal estrogen, alone or with varying doses of medroxyprogesterone), the average AHI decreased to only 40. The only statistically significant effect seen was a decrease in the REM AHI. These findings, however, are not particularly surprising, because the gold standard of treatment for moderate to severe sleep-disordered breathing is nasal CPAP.

There may, however, be a role for HRT in the treatment of mild sleep-disordered breathing. This population sometimes does not tolerate treatment with nasal CPAP, and having alternative treatments can be helpful. A recent pilot study using the newer, more physiologic forms of HRT recently available in a population of postmenopausal women with mild to low–moderate sleep-disordered breathing found an effect with estrogen but, again, did not normalize the AHI [132]. The average AHI at baseline was 22.7, which decreased to 12.2 with transdermal estradiol 50 mg/day, given for 7–12 days with a placebo pill. Oral pure micronized progesterone 200 mg/day was added for 7–13 days and the average AHI actually increased to 16.2, no longer statistically different from baseline. The interesting question this study raises is whether or not the investigators might have achieved a greater treatment effect if the hormones had been in place for longer. Many studies prescribe the hormones for 2–3 months to achieve a sufficient response. It is unclear why estrogen would be more effective than estrogen plus progesterone, because progesterone is the known respiratory stimulant and estrogen is known to potentiate progesterone receptors. One possibility is that the small sample size of six women may have contributed to these preliminary findings.

Finally, a brief word should be mentioned about two older and oft-quoted articles. The first article is sometimes referenced as proof that HRT

is effective in mild sleep-disordered breathing [133]. Unfortunately this may be a misreading of the data. First, the nine postmenopausal women were described as not having complaints suggestive of sleep-disordered breathing and were not obese. Second, the results were a decrease in the total number of respiratory events and not a decrease in the current standard measurement, the AHI. The study compared 7 days of placebo to 7 days of high doses of HRT (conjugated equine estrogen, 1.25 mg twice daily with medroxyprogesterone acetate, 20 mg three times daily) and recorded a decrease in average number of *respiratory events* (not AHI) from 15 to 3, which corresponds to a decrease in retro-calculated AHI from 2.4 (normal) to 0.5 (also normal) events per hour of sleep.

An old study that predated the use of AHI [127] often is quoted as proof that progesterone does not work in sleep-disordered breathing in women. The investigators performed polysomnography on 21 subjects (10 weeks of 30 mg of medroxyprogesterone acetate in 11 subjects and 10 weeks of placebo in 10 subjects). The only statistically significant effect was a decrease in the duration of apneas in a sub-sample of six subjects with sleep-disordered breathing (not clearly defined) when compared with control subjects. The failure to see an effect may implicate medroxyprogesterone, a single agent without estrogen and as a synthetic progestin, as ineffective rather than progesterone, per se. Estrogen priming is necessary for the development of progesterone receptors in the uterus and hypothalamus. Estrogen therefore may be necessary also for progestins to have a beneficial effect on nocturnal respiration. Second, medroxyprogesterone has some testosterone-like properties. Because testosterone has been shown to exacerbate sleep apnea, use of medroxyprogesterone actually may negate the potential treatment effect of progesterone therapy.

Although the literature does not prove that HRT can be used as definitive treatment for sleep-disordered breathing in postmenopausal women, there is a suggestion that the newer, more physiologic hormone preparations may be effective in mild sleep-disordered breathing. The definitive studies that would use transdermal estradiol and pure progesterone on menopausal women with mild to low–moderate sleep-disordered breathing over a period of a few months have not been done.

What should the clinician do when faced with a menopausal woman complaining of unrefreshing sleep or excessive daytime somnolence? First, the clinician should take a thorough sleep history to look for symptoms that would suggest the intrinsic sleep disorders, such as sleep-disordered breathing (does she snore or gasp at night?) or restless legs syndrome (does she experience an indescribable feeling in her limbs and have to move them at night) and treat them as usual, bearing in mind the possible efficacy of HRT for mild sleep-disordered breathing. Then one should assess whether or not she is experiencing hot flashes—even if she is unaware of them occurring at night—and treat these appropriately. Mood disorders also should be addressed. Finally, one should look for an initiating event (hot flashes,

personal trauma) that has since been treated, but that may have resulted in an irregular sleep–wake schedule or elements of inadequate sleep hygiene. These problems also should be treated. Finally, alternative therapies may be helpful. A recent study looking at the efficacy of stretching versus exercise on symptoms of insomnia in a group of postmenopausal women not using HRT found that stretching and exercise were effective, stretching more so [134].

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