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Sleep Disorders During Pregnancy

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Abstract: This paper reviews the topic of sleep disorders in pregnant women. We describe changes in sleep architecture and sleep pattern during pregnancy, discuss the impact of the physical and biochemical changes of pregnancy on sleep in pregnant women and examine whether maternal-fetal outcomes may be adversely affected in women with disordered sleep. The literature on common sleep disorders affecting pregnant

women, including insomnia, sleep-disordered breathing and restless legs syndrome, is reviewed and recommendations are made for the management of these disorders during pregnancy.

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INTRODUCTION

DURING PREGNANCY, THE MAJORITY OF WOMEN EXPERIENCE ALTERATIONS IN SLEEP.¹⁻⁹ Changes in sleep pattern and sleep duration are commonly reported, as are sleep complaints associated with the physical changes of pregnancy. The physiologic and biochemical changes of pregnancy may place women at risk for developing specific sleep disorders such as obstructive sleep apnea and restless legs syndrome (RLS).

This review describes common sleep problems in pregnant women, including changes in maternal sleep architecture and pattern during pregnancy, insomnia, snoring and sleep-disordered breathing (SDB), and RLS. We will explore the reported association between SDB and adverse pregnancy outcomes.¹⁰ Finally, we will make recommendations for the management of common sleep disorders in pregnant women.

METHODS

Articles were chosen for inclusion in this review by searching the MEDLINE and PubMed databases for relevant studies using the term "pregnancy" in combination with each of the following: sleep, sleep disorders, insomnia, snoring, sleep apnea, pulmonary, lung, anoxia, narcolepsy, restless legs disorder, periodic limb movement, and parasomnia and were supplemented by our own experience and research in this area. Cross-references from these articles, conference proceedings, and bibliographies from review articles and book chapters were also examined for appropriate citations. Only English-language articles were considered for inclusion.

Disclosure Statement

Drs. Pien and Schwab have indicated no financial conflicts of interest.

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DISCUSSION

Changes in Sleep during Pregnancy

Sleep disturbances and changes in sleep pattern begin occurring during the first trimester of pregnancy^{6,8,9} and are likely to be influenced by some of the dramatic changes in reproductive hormone levels that accompany pregnancy. Levels of estrogens and progesterone rise throughout pregnancy and peak at term, falling rapidly after delivery.¹¹

In animal studies, progesterone administration has been observed to have hypnotic effects, decreasing wakefulness and shortening the latency to non-rapid eye movement (REM) sleep, while decreasing the amount of REM sleep.¹² Similarly, sedating or anesthetic effects have been demonstrated when progesterone administration is administered,^{13,14} and an increase in non-REM sleep has been observed.¹⁵ Progesterone appears to exert its effect not by activating intracellular progesterone receptors, but by the action of its metabolites on brain GABA_A receptors.^{12,16} Estrogen, like progesterone, selectively suppresses REM sleep in animal studies,¹⁷⁻¹⁹ an effect attributed to its ability to increase brainstem norepinephrine turnover.²⁰ In contrast, increased REM sleep has been observed in human studies of perimenopausal women receiving estrogen replacement therapy,^{21,22} making it difficult to ascertain the specific effects of estrogen in human pregnancy. In an animal model, total sleep time increased during pregnancy, with an early but transient increase in REM sleep time, a sustained increase in non-REM sleep over the course of pregnancy, and increased diurnal sleep during late gestation.^{23,24}

In human pregnancy, sleepiness is a common first-trimester complaint that may precede the realization of pregnancy.²⁵ Corresponding to this period of heightened sleepiness, women surveyed by Hedman et al about their sleep habits during pregnancy reported a mean increase in sleep duration of 0.7 hours during the first trimester, compared to the prepregnancy period.²⁶ Similarly, a mean increase of more than 30 minutes of total nocturnal sleep time was recorded at 11 to 12 weeks of gestation in 33 women who underwent in-home polysomnography prior to conception and during each trimester of pregnancy.⁶ However, sleep efficiency and the percentage of slow-wave sleep decreased significantly compared to the prepregnancy period.⁶ First trimester sleep disturbance is commonly associated with complaints of fatigue or nausea and vomiting.⁸

By late in the second trimester (23-24 weeks of gestation), total nocturnal sleep time falls.⁶ Although a significant increase in the percentage of slow-wave sleep compared to the first trimester is observed,² the prevalence of restless sleep and sleep complaints increases.⁸

During the third trimester, the majority of women report altered sleep.⁷⁻⁹ Only 1.9% of women fail to experience nocturnal awakenings in the third trimester of pregnancy.²⁶ In terms of sleep architecture, decreases in the percentages of slow-wave sleep^{4,6,27} and REM sleep^{1-3,6} are observed, which may be offset by increased stage 1 sleep.³ Despite increased wake time after sleep onset and decreased nocturnal sleep time compared to the first 2 trimesters,^{1,6} total nocturnal sleep time approximates prepregnancy sleep time.^{6,26} Furthermore, the majority of pregnant women report taking daytime naps,^{5,7} which may add more than an hour to the total 24-hour sleep time.^{7,28} Thus third-trimester total sleep time may exceed prepregnancy sleep time.²⁹ Nevertheless, gravid women maintain a clear diurnal rhythm in serum melatonin levels during pregnancy, without evidence of a shift in circadian phase.³⁰ In the last trimester, common etiologies of sleep disturbance include general discomfort (including backache), urinary frequency, and spontaneous awakenings or restless sleep. Fetal movement, heartburn, leg discomfort, fatigue, and difficulty falling asleep or maintaining sleep are also regularly reported.^{3,5,8,31}

Following delivery, the greatest degree of maternal sleep disturbance occurs during the first month,⁶ with a mean 24-hour total sleep time at 2 weeks postpartum of less than 6 hours, including more than an hour of nap time.²⁸ Total maternal sleep time and sleep efficiency increase gradually as the infant's circadian rhythm matures, with a transition from interrupted to uninterrupted sleep usually occurring at approximately the 12th postpartum week.³² In a study comparing sleep architecture in women breastfeeding their infants to women bottle-feeding their infants and nongravid controls, the percentage of slow-wave sleep time was noted to be dramatically higher for lactating women compared to the other 2 groups (43% ± 7% in breastfeeding women vs 15% ± 6% in bottle feeders and 19% ± 4% in controls, $P < .001$).³³ Increased slow-wave sleep has been reported in patients with prolactinomas compared to controls.³⁴ Therefore, increased amounts of slow-wave sleep observed in lactating women have been attributed to their high levels of circulating prolactin, although hormone levels were not recorded in this study.³³ Shortened latency to the onset of REM sleep has been noted in women at 1 month postpartum compared to the third trimester and was attributed to the return of serum progesterone to prepregnancy levels³⁵; as the authors point out, however, the possibility that sleep loss in the postpartum setting may lead to decreased REM latency should also be considered.

Characteristics potentially associated with poor sleep among pregnant and postpartum women have been examined by a number of authors. For instance, Hedman et al observed that during the third trimester, women over the age of 30 years reported less total sleep time than did their younger counterparts, although the results did not control for the number of children at home or other potential confounders.²⁶ Waters and Lee,³⁶ in reporting on the sleep patterns of pregnant primiparous women compared to pregnant multiparous women, found that while the sleep efficiency of these groups was similar during the third trimester, primiparous

women experienced a significant decline in sleep efficiency during the first postpartum month (89.76% ± 4.11% vs 77.25% ± 5.74%, $P < .0001$) while multiparous women did not (86.76% ± 7.04% vs 83.99% ± 7.845, $P < NS$). The authors attributed this difference to the challenges associated with new maternal role acquisition for women having a first child.³⁶

Sleep quality and sleep architecture in women with pathologic conditions have not been extensively examined but are reported for preeclampsia in 2 case series. The data from these studies suggest that sleep quality is impaired in preeclamptic women³⁷ but that the amount of slow-wave sleep may increase compared to pregnant controls.³⁸ Coble et al³⁹ found that women with a history of affective disorder did not appear to have significant differences in sleep time or sleep architecture during pregnancy compared to controls, although they experienced an earlier onset of sleep disruption. The severity of many other chronic medical conditions, such as asthma⁴⁰ and migraine headaches,⁴¹ is often affected by pregnancy, and these may in turn impact sleep; nevertheless, effects on sleep measures have generally not been evaluated.

Management of Insomnia During Pregnancy

The *International Classification of Sleep Disorders* has proposed that the occurrence of either insomnia or excessive sleepiness that develops in the course of pregnancy be termed *Pregnancy-associated sleep disorder*,²⁵ in recognition of the association of sleep disturbance with the gravid condition and the self-limited nature of these complaints. Despite moderate to high levels of fatigue⁵ and the high prevalence of disturbed sleep among pregnant women, however, the majority of women do not report these complaints to their physicians.^{9,42} In nonpregnant populations, chronic partial sleep restriction of approximately 5 hours per night has been observed to adversely impact both mood and performance^{43,44}; furthermore, sleep restriction can place individuals at increased risk for adverse events such as motor vehicle accidents.⁴⁵ Several authors have speculated about whether postpartum sleep disruption or sleep deprivation may increase the risk for mood disorders ranging from postpartum depression to overt psychosis.⁴⁶⁻⁴⁹ Nevertheless, little is known about the effects of sleep restriction and sleep disturbance on either pregnant and postpartum women.⁵

For women who request assistance in managing general sleep complaints during pregnancy, a combination of usual sleep hygiene techniques and therapies targeted at pregnancy-associated complaints can be recommended, once specific sleep disorders have been excluded through a careful history and, when indicated, further testing. Specifically, education about maintaining sleep hygiene during pregnancy, adjusting fluid intake to reduce nocturia, and managing physical discomfort using pillow support and local heat application are likely to be useful.^{5,9}

Occasionally, women may experience severe persistent insomnia during pregnancy that fails to respond to sleep hygiene measures or targeted therapies and causes serious impairment of daytime function. Although a trial of behavioral therapies (eg, relaxation techniques, stimulus control therapy) can be attempted, pharmacologic therapy (see Table 1) may be considered for short-term use in refractory cases after discussion between the provider and patient of potential risks and benefits. Two hypnotic agents have been designated class B in pregnancy (ie, fetal harm possi-

Table 1—Pregnancy Safety Classification for Commonly Used Medications for Sleep Disorders

DRUG	Drug Class	Pregnancy Category*	COMMENTS^{51,52}
<u>Insomnia</u>			
Diphenhydramine	Antihistamine	B	No evidence of fetal harm in animal studies
Zolpidem	Imidazopyridine	B	No evidence of fetal harm in animal studies
Amitriptyline	Tricyclic antidepressant	C	Animal teratogen at high doses, insufficient human data
Doxepin	Tricyclic antidepressant	C	Possible association with major birth defects, polydactyly
Trazedone	Antidepressant	C	Fetal toxicity & teratogenicity in animals at high doses
Zaleplon	Pyrazolopyrimidine	C	Increased stillbirths in animal studies, insufficient human data
Lorazepam	Benzodiazepine	D	“Floppy infant syndrome,” respiratory depression, possible association with anal atresia
Estazolam	Benzodiazepine	X	May have adverse effects similar to other benzodiazepines
Flurazepam	Benzodiazepine	X	No reported major adverse effects in animals or humans, but known adverse effects of other benzodiazepines
Quazepam	Benzodiazepine	X	May have adverse effects similar to other benzodiazepines
Temazepam	Benzodiazepine	X	Potential interaction with diphenhydramine, causing stillbirth in animals and 1 human case
Triazolam	Benzodiazepine	X	May have adverse effects similar to other benzodiazepines
<u>Restless legs syndrome</u>			
Oxycodone	Opioid	B	No evidence of teratogenic effects in animal studies; potential neonatal respiratory depression, withdrawal symptoms
Pergolide	Dopamine-receptor agonist	B	No evidence of fetal harm in animal studies
Carbidopa-levodopa	Dopaminergic	C	Teratogenicity and toxicity in animals, limited human data showing no adverse effects
Gabapentin	Anticonvulsant	C	Some fetal toxicity in animals, limited human data
Levodopa	Dopaminergic	C	See entry for Carbidopa-levodopa
Pramipexole	Dopamine-receptor agonist	C	Pregnancy disruption & early embryonic loss in animals, insufficient human data
Ropinirole	Dopamine-receptor agonist	C	Teratogenicity and toxicity in animals at high doses, insufficient human data
Codeine	Opioid	C/D	Neonatal respiratory depression, neonatal withdrawal symptoms
Hydrocodone	Opioid	C/D	Teratogenicity in animals, possible association with human fetal malformations
Propoxyphene HCl	Opioid	C/D	Neonatal withdrawal symptoms
Carbamazepine	Anticonvulsant	D	Increased incidence of major & minor malformations, including spina bifida
Clonazepam	Benzodiazepine	D	Neonatal respiratory depression
<u>Narcolepsy</u>			
Excessive somnolence			
Pemoline	CNS stimulant	B	No evidence of teratogenicity, but increased stillbirths in animal studies; limited human data.
Dextroamphetamine	Amphetamine	C	Increased risk of premature delivery and low birth weight, neonatal withdrawal symptoms
Methylphenidate	CNS stimulant	C	Teratogen in animals at high doses, inadequate human data
Methamphetamine	Amphetamine	C	See entry for Dextroamphetamine
Modafinil	Wake-promoting agent	C	Fetal toxicity in animals at high doses, inadequate human data
Cataplexy, other REM-related symptoms			
Sodium oxybate	CNS depressant	B	No evidence of teratogenicity in animal studies
Fluoxetine	Selective serotonin reuptake inhibitor	C	Increased stillbirths in animal studies, inadequate human data
Protryptiline	Tricyclic antidepressant	Unclassified	No adverse effects on reproduction in animal studies, inadequate human data

* Classifications as designated by the Food and Drug Administration⁵⁰

Pregnancy category A: Adequate and well-controlled studies in pregnant women have failed to demonstrate fetal risk. Possibility of fetal harm appears remote.

Pregnancy category B: Animal studies have failed to demonstrate fetal risk, and no adequate studies in pregnant women exist or animal studies have shown adverse fetal effects, but studies in pregnant women have failed to demonstrate risks to the fetus. Possibility of fetal harm is remote.

Pregnancy category C: Animal studies have shown adverse fetal effects, and no adequate studies in humans exist. Benefits from use of the drug may be acceptable despite potential risks.

Pregnancy category D: Clear evidence of human fetal risk. Potential benefits from use may be acceptable despite risks, e.g. for serious disease when safer drugs cannot be used or are ineffective, or in life-threatening situations.

Pregnancy category X: Clear evidence of human or animal fetal abnormalities, or human fetal risk. Risk of use clearly outweighs any possible benefit.

CNS refers to central nervous system.

ble but unlikely⁵⁰): (1) zolpidem, a nonbenzodiazepine hypnotic⁵¹ and (2) diphenhydramine, an antihistamine with a strong sedative effect and a long duration of action.⁵¹ Zolpidem is preferable, as it is short acting and does not have anticholinergic effects. Zaleplon is Class C (possible adverse fetal effects based on animal studies, no evidence of adverse fetal effects in humans⁵⁰) in pregnancy⁵² and therefore should be used with caution. Most other sedative-hypnotics (see Table 1) should be avoided as they have been labeled pregnancy Class D (human data show risk, though benefits may outweigh these⁵⁰) or X (benefit unlikely to outweigh clear evidence of increased human or animal risk⁵⁰).⁵¹ Benzodiazepines, for instance, have been associated with an increased risk of congenital malformations early in pregnancy and with neonatal flaccidity and respiratory problems when administered late in pregnancy.^{51,53}

The Effect of Pregnancy on the Risk of SDB

The term *sleep-disordered breathing* describes a spectrum of abnormal respiration during sleep that ranges from primary snoring to obstructive sleep apnea (OSA) and obesity hypoventilation syndrome. Many of the known risk factors for SDB have been described most convincingly in middle-aged men⁵⁴; whether they impose the same risk in young women, a population at low overall risk for SDB,⁵⁵ is largely unknown. Nevertheless, in nonpregnant individuals, weight change, age and alcohol or sedative use can all contribute to movement along the spectrum of SDB.⁵⁶ During pregnancy, hormonal and physiologic changes may alter respiration during sleep, also moving women along this spectrum of disease. Although some of these changes may reduce the likelihood of SDB, others are likely to contribute to its development. We will focus primarily on central and obstructive SDB events, given the paucity of literature on entities such as Cheyne-Stokes respiration, obesity hypoventilation, or central alveolar hypoventilation⁵⁷ in pregnant women or animal models of pregnancy.

Changes during pregnancy that may offer protection against SDB (Table 2) include increased respiratory drive, preference for the lateral sleep posture, and changes in sleep architecture (specifically, a reduction in REM sleep).^{2,58,59} During pregnancy, augmented progesterone production¹¹ either stimulates respiratory drive directly or enhances the sensitivity of the brain's respiratory center to CO₂.⁶⁰ Larger tidal volumes and higher minute ventilation result,⁶¹ accommodating the increased O₂ consumption demands and CO₂ production of normal pregnancy.^{61,62}

The possibility that increased respiratory drive during pregnancy may reduce the occurrence of central apneas during sleep has been explored.⁶³ Brownell et al⁶³ demonstrated, in a study of 6 normal subjects who underwent polysomnography at 36 weeks of pregnancy and again several months postpartum, that the mean apnea-hypopnea index (AHI, the number of apneas and hypopneas per hour of sleep) was significantly lower during than after

pregnancy (1.13 ± 0.42 vs 2.71 ± 0.76 events per hour), although the number of SDB events was not clinically significant at either time point. Although the investigators concluded that the elevated progesterone levels of late pregnancy conferred protection against central apneas and episodic hypoxemia, progesterone levels were not directly measured. However, it should be noted that, in nonpregnant individuals, increased ventilatory drive also enhances respiratory instability⁶⁴; whether a similar effect occurs in pregnant women is unresolved at present.

In the general population, the severity of SDB can vary with changes in sleep posture and sleep state.^{65,66} Obstructive events can increase in the supine sleep posture compared to the lateral or prone positions.⁶⁵ During late pregnancy, the majority of women prefer the lateral sleep posture,⁵⁹ which avoids uterine compression of the inferior vena cava and potential compromise of cardiac output.⁶⁷ The lateral sleep posture may also decrease the occurrence of SDB by averting supine apneas.⁶⁵ Preservation of cardiac output and O₂ delivery during sleep in the lateral position should also help to maintain adequate oxygenation should apneas or hypopneas occur.

Changes in sleep architecture during pregnancy may also offer protection against apneic events. During REM sleep, muscle tone in the upper airway decreases, respiratory variability increases, and ventilatory responses to hypercapnia and hypoxia are diminished.⁶⁸ Obstructive apneas and hypopneas are frequently more common during REM than non-REM sleep, a difference that appears more pronounced in women than men.⁶⁶ As previously noted, REM sleep time declines in late pregnancy.¹⁻³ Other changes in sleep architecture that may affect the frequency of SDB events include increased stage 1 sleep in late pregnancy and frequent awakenings from sleep.^{3,31} Increased respiratory instability at sleep onset in the setting of sleep-state instability and during changes from arousal to sleep has been well described in nongravid individuals⁶⁹ and may increase the risk of SDB events in pregnant women. However, whether the occurrence of apneic events is directly affected by these changes in sleep architecture requires further study.

During pregnancy, hormonal and anatomic changes that promote SDB also occur (Table 2). Pregnancy is the only normal adult physiologic process in which body weight routinely increases by 20% or more over a relatively short period of time.⁷⁰ Whether the rate of weight gain affects SDB progression is currently unknown. In the general population, an independent longitudinal association between weight change and SDB severity has been documented in a large prospective cohort study of SDB in which subjects were followed over 4 years.⁷¹ In this study, a 20% weight gain predicted an approximate 70% increase in AHI (the number of apneas and hypopneas per hour of sleep), independent of baseline AHI.⁷¹ Baseline body mass index was also an independent predictor of change in AHI.⁷¹ We speculate that if gestational weight gain acts analogously to weight gain in the general

Table 2—Changes in Pregnancy That May Influence the Development of Sleep-Disordered Breathing

Pregnancy-Associated Changes that Increase Risk of Sleep Apnea

Gestational weight gain
Nasopharyngeal edema
Decreased functional reserve capacity
Increased arousals from sleep

Pregnancy-Associated Changes that Decrease Risk of Sleep Apnea

Increased minute ventilation
Preference for lateral sleep posture
Decreased rapid eye movement sleep time

population, it may precipitate or worsen SDB, particularly in obese women.

Like progesterone, estrogen levels rise throughout pregnancy.¹¹ High estrogen levels can cause vasomotor rhinitis, which occurs in 20% of pregnancies, most commonly in the last trimester when estrogen levels are highest.⁷² Hyperemia and edema of the nasal and pharyngeal mucosa can lead to increased airflow resistance and airway narrowing, eliciting or exacerbating SDB.⁷³

Finally, during pregnancy, uterine enlargement, diaphragmatic elevation, and relaxation of the costochondral ligaments lead to alterations in thoracic shape and dimensions.⁵⁸ Declines in expiratory reserve volume and residual volume result, with accompanying decreases in functional residual capacity and O₂ reserve.⁵⁸ In late pregnancy, airway closure can occur above functional residual capacity, leading to ventilation-perfusion mismatch.⁵⁸ Mild supine hypoxemia (PaO₂ < 90) has been observed in 25% of healthy third-trimester pregnant women during wakefulness⁷⁴; during sleep, arterial oxyhemoglobin saturations are lower in pregnant women in the third trimester than in nonpregnant controls.⁷⁵ Although hypoxemia does not contribute to the development of SDB, it can magnify the adverse consequences of abnormal breathing events, especially in the setting of respiratory instability during sleep.

Thus, multiple factors influence the likelihood of developing SDB during pregnancy. Although preference for the lateral sleep posture and decreased REM sleep time may diminish the impact of obstructive events, gestational weight gain, increased stage 1 sleep and sleep fragmentation, rhinitis and decreased functional residual capacity and O₂ reserves are likely to contribute to the development of SDB in pregnant women.

Snoring and Sleep Apnea in Pregnant Women

Until recently, the literature on SDB during pregnancy consisted largely of case reports of gestational sleep apnea.⁷⁶⁻⁸² Although these women were uniformly obese, none had been previously diagnosed with OSA. In several cases, complications, including preeclampsia and low fetal birth weight, ensued.⁷⁷ These reports generated interest in further exploration of pregnancy-associated SDB.

In 1995, Schutte et al⁸³ observed that 27% of a group of normal women reported third-trimester snoring. A subsequent study of 350 pregnant women noted that 14% of pregnant subjects reported frequent snoring during the second or third trimesters, compared to 4% of nongravid age-matched controls.⁸⁴ A third study examined the time course of incident self-reported snoring in 502 women who completed a questionnaire on the day of delivery.¹⁰ Only 4% of subjects reported habitual snoring prior to pregnancy. By the final week of pregnancy, however, the prevalence of habitual snoring had increased significantly, to 23%. Seven percent of subjects reported that snoring started or increased during the first trimester, 6% during the second trimester, and 24% in the third trimester. Although a similar study performed in a Finnish population noted that self-reported regular snoring increased in prevalence during pregnancy from 5% prepregnancy to 10.4% in the third trimester, the difference was not statistically significant.²⁶ By 3 months after delivery, the prevalence of snoring had decreased significantly from the third trimester (4.4% vs 10.4%, $P = .004$) and returned to approximate prepregnancy levels.²⁶

We surveyed 155 women recruited prospectively over the course of pregnancy about whether they had snoring and other symptoms of SDB, such as gasping or choking and self-perceived or witnessed apneas, using a validated self-report measure of sleep-apnea symptoms.⁸⁵ Not only did SDB symptoms increase significantly during pregnancy for the group as a whole, but more than 10% of subjects reported a large clinical increase in symptoms indicating they may have been at risk for developing sleep apnea during pregnancy.⁸⁵

The study by Franklin and colleagues¹⁰ suggests that the development of SDB may be accelerated by pregnancy. Habitual snorers were significantly heavier than nonsnorers prior to pregnancy, supporting the idea that this process is likely to be accentuated in obese women.¹⁰ Although obese women generally gain less weight during pregnancy than do women of normal baseline weight,⁸⁶ habitual snorers in Franklin's study also gained significantly more weight than did the nonsnorers.¹⁰ These observations suggest that both initial body mass index and gestational weight gain are important to the development of snoring in pregnancy.

To examine the relationship between obesity and gestational SDB, polysomnography was performed during early (> 12 weeks) and late (> 30 weeks) pregnancy in a case-control study in which obese women were compared to healthy controls ($n = 22$).⁸⁷ Mean AHI increased significantly in obese subjects by late pregnancy (1.7 vs 2.6 events per hour, $P < .01$), although these increases in AHI were not clinically meaningful. In contrast, control subjects experienced no change in AHI. Nevertheless, 1 obese subject developed mild sleep apnea (AHI = 12 events per hour). This study demonstrates that SDB events increase slightly in obese women during pregnancy and suggests that some obese women develop gestational sleep apnea. However, the prevalence of pregnancy-associated sleep apnea cannot be determined from this study due to its small size.

These studies establish that incident habitual snoring is common in pregnancy, especially among obese women. Although individuals with primary snoring do not exhibit significant decrements in airflow or oxyhemoglobin saturation, snoring frequently accompanies clinically significant SDB.⁵⁶ However, as studies of the prevalence of SDB in community populations have demonstrated that young, nongravid, premenopausal women are at lower risk for developing SDB than are men or postmenopausal women,^{55,88} whether a substantive proportion of pregnant snorers is likely to have sleep apnea is unknown. Further studies are needed to explore whether incident habitual snoring, obesity, or other characteristics identify women at risk for developing pregnancy-associated OSA.

Relationship Between SDB and Adverse Pregnancy Outcomes

SDB has been proposed as a risk factor for adverse maternal-fetal outcomes including pregnancy-induced hypertension and small-for-gestational-age births. Pregnancy-induced hypertension is characterized by development of hypertension after 20 weeks of gestation, with regression following delivery.⁸⁹ It is divided by severity into designations including gestational hypertension (blood pressure elevation without proteinuria or other features of preeclampsia; 6%-7% of pregnancies); preeclampsia (hypertension with proteinuria of ≥ 300 mg per 24 hours, potential multisystem involvement; 5%-6% of pregnancies); and, rarely, eclampsia (hypertension with seizures; < 1% of pregnan-

cies).⁸⁹ Pregnancy-induced hypertension increases the risk of adverse outcomes such as premature delivery, fetal growth retardation, and maternal morbidity and mortality.⁸⁹

Known risk factors for preeclampsia include family history, primiparity, advancing maternal age, multiple gestation, obesity, chronic hypertension, and renal disease.⁸⁹ The pathogenesis of pregnancy-induced hypertension in women without preexisting conditions has not been fully elucidated but appears to be related to oxidative stress and endothelial dysfunction.⁹⁰

Speculation about the relationship between SDB and pregnancy-induced hypertension arises from clinical observations in pregnant women with sleep apnea and compelling evidence in the general population of an association between SDB and hypertension. This latter relationship has been substantiated by 2 large cohort studies demonstrating increased risks for hypertension among individuals with OSA^{91,92} and numerous smaller studies.⁹³⁻⁹⁷ The odds of hypertension increase with escalating AHI in a graded dose-response fashion, placing individuals with even mild OSA at increased risk.⁹¹

To examine whether an analogous relationship may exist between pregnancy-associated snoring and blood pressure, polysomnography and 24-hour blood-pressure monitoring were performed in 26 nonsnorers and incident snorers at 6 months of gestation.⁹⁸ Although mean AHI was slightly higher in snorers (2.5 vs 1.2 events per hour) and snorers had higher systolic and diastolic blood pressures than nonsnorers (118/79 vs 110/71 mmHg), these data were cross-sectional and did not reach statistical or clinical significance. However, the absence of the normal nocturnal dip in systolic blood pressure, a feature of preeclampsia,⁹⁹ was noted in snorers.

Several studies have examined whether preeclamptic women manifest SDB. In these studies, mild upper airway inspiratory flow limitation was commonly noted in preeclamptic women, but these low-frequency oscillations did not meet standard apnea-hypopnea definitions and were not reported to cause arousals, as would be expected in upper airway resistance syndrome.^{100,101} Examination of the oropharyngeal junction area using acoustic reflectance techniques has demonstrated a narrowed upper airway in preeclamptic women compared to pregnant controls.¹⁰² However, whether upper-airway changes and SDB precede and potentially contribute to blood-pressure elevation, or whether inspiratory flow limitation develops due to preeclampsia-associated edema, has not been determined.

In the general population, altered peripheral chemoreceptor sensitivity and enhanced activation of the sympathetic nervous system due to nocturnal hypoxia are believed to underlie the association between SDB and hypertension,^{103,104} leading to impaired endothelium-dependent vasodilation.¹⁰⁵ Levels of venous endothelin-1, a potent long-acting vasoconstrictor implicated in the development of hypertension,¹⁰⁶ are not only significantly elevated in patients with untreated sleep apnea compared to healthy controls,¹⁰⁷ but the levels rise during sleep and decline acutely after treatment with continuous positive airway pressure (CPAP).¹⁰⁸ Oxidative stress may also increase the expression and activation of adhesion molecules on the surfaces of endothelial cells and leukocytes,¹⁰⁹ leading to enhanced release of superoxide from polymorphonuclear neutrophils and vascular damage in patients with OSA.¹¹⁰

Endothelial dysfunction also appears to be central to the devel-

opment of preeclampsia.⁹⁰ Observations of reduced antioxidant capacity and increased lipid peroxidation in the placentas of preeclamptic women suggest that oxidative stress mediates or contributes to endothelial dysfunction.¹¹¹ Although abnormal development of the placental vascular bed is observed in preeclampsia,⁹⁰ whether placental ischemia ensues, releasing placental factors that damage maternal vascular endothelium, or occurs as a manifestation of end-stage disease, remains under debate.⁹⁰

During pregnancy, intermittent hypoxia induced by SDB could potentially exacerbate placental ischemia, precipitating oxidative stress and endothelial activation. Such a relationship has not been investigated and at present remains speculative. In animal models, chronic or prolonged intermittent maternal hypoxia can cause fetal growth restriction.¹¹² Fetal bradycardia and decreased fetal breathing movements are observed during even brief periods of maternal hypoxia.¹¹² In humans, fetal heart rate decelerations have been described in response to maternal apneic events.⁷⁶ Three observational studies have examined maternal-fetal outcomes in pregnant women with symptoms of SDB.^{10,26,84} After identifying snorers ($n = 49$) and nonsnorers ($n = 301$) by self-report, Loube et al⁸⁴ did not find significant differences between groups in mean birth weights or Apgar scores. However, 1-time survey completion in the latter 6 months of pregnancy may have led to misclassification bias, obscuring potential differences in outcomes. Similarly, Hedman et al²⁶ did not find a significant relationship between snoring and infant birth weight in a prospective survey of sleep symptoms in 325 Finnish pregnant women, although a large portion of the original sample was lost to follow-up.

In contrast, Franklin and colleagues found that self-reported habitual snorers developed significantly higher rates of gestational hypertension (14% vs 6%, $P < .01$), preeclampsia (10% vs 4%, $P < .05$), and delivery of small-for-gestational-age infants (7.1% vs 2.6%, $P < .05$) than did nonsnorers.¹⁰ Differences remained significant after adjustment for age, weight, and smoking status. Subjects were not evaluated for sleep apnea, so it is unknown whether increased risk for these outcomes could be attributed to uncomplicated snoring alone. In addition, as these data were collected retrospectively, differential symptom recollection may have biased results.

Studies of pregnant animals exposed to intermittent hypoxia have demonstrated adverse fetal outcomes.¹¹³⁻¹¹⁵ For instance, when pregnant rats were exposed to 1 hour each day of hypoxia (FIO₂ 0.09-0.095) during days 15 to 19 of gestation, rat pups had decreased fetal weight and length compared to control animals.¹¹⁵ When pregnant rats were exposed to conditions more closely simulating the brief repetitive episodes of intermittent hypoxia observed in OSA, their offspring were noted to weigh significantly less than unexposed pups^{113,114} and to have impaired ventilatory and resuscitative responses under hypoxic¹¹⁴ and anoxic conditions.¹¹³ Nevertheless, by 30 and 120 days after birth, pups exposed to intermittent hypoxia during gestation were able to perform as well as control animals during acquisition and retention of a spatial task (water maze performance), implying either that maternal intermittent hypoxia does not lead to detectable neurobehavioral deficits in the offspring or that such changes do not impose long-lasting changes in the ability of these offspring to perform such tasks.¹¹⁴

Only preliminary evidence exists to suggest that SDB is associated with the hypertensive conditions of pregnancy or that SDB increases the risk of adverse maternal-fetal outcomes. Nevertheless, oxidative stress and endothelial dysfunction are mechanisms important in the development of both sleep apnea-associated hypertension and preeclampsia. The effect of intermittent hypoxia on placental and fetal development may bear further exploration as evidence for a clinical association between SDB and pregnancy-induced hypertension grows.

Evaluation and Treatment of SDB during Pregnancy

How should pregnant women with symptoms of SDB be evaluated and managed? Guidelines for the treatment of pregnancy-associated sleep apnea have not been developed. However, published guidelines for the treatment of SDB in the general population¹¹⁶ may be used as a reference.

Who Should Be Evaluated for OSA During Pregnancy?

As in the nonpregnant population, pregnant women with symptoms suggestive of SDB, such as excessive daytime somnolence, loud snoring, or witnessed apneas, should be evaluated for sleep apnea with overnight polysomnography (Figure 1). In addition, it may be useful to review symptoms of SDB with patients who develop gestational hypertension or preeclampsia, particularly those with known risk factors for SDB such as obesity. At present, uncomplicated snoring, pregnancy-induced hypertension, or intrauterine growth retardation alone are insufficient clinical indications for ordering polysomnography.

As previously described, it is known that the severity of SDB can worsen with weight gain in the general population.⁷¹ Therefore, although excessive sleepiness may accompany normal pregnancy,⁵ a low threshold for determining the adequacy of current treatment and for adjusting therapy (eg, CPAP retitration) should be maintained in pregnant women with known OSA. For instance, 6 of 12 women diagnosed with upper airway resistance syndrome or OSA prior to or during early pregnancy required an increase in CPAP therapy when polysomnography was repeated at 24 to 27 weeks of gestation.¹¹⁷ Nevertheless, the increase in CPAP level required was small (1-2 cm H₂O) and most of the patients' bed partners (5 of 6) had noticed recurrent snoring.¹¹⁷ Similarly, for women with known OSA who develop gestational hypertension, symptom recurrence should be assessed and polysomnography repeated if insufficient treatment is suspected. Overnight oximetry performed in the home may be considered for screening purposes but is unlikely to be efficient in patients with obvious disease progression, given the anticipated need for CPAP retitration if oximetry should demonstrate recurrent disease.

Who Should Receive Treatment for SDB during Pregnancy?

For individuals with severe sleep apnea (AHI > 30), general consensus exists regarding the need for treatment, independent of pregnancy. However, there is considerable debate over treatment indications for patients with mild to moderate SDB.¹¹⁸ Given potential adverse effects of maternal hypoxia such as fetal growth retardation,^{114,115,119-121} we believe an important goal during pregnancy should be to abolish maternal oxyhemoglobin desaturations below 90%. Accepted indications for therapy in milder

SDB, such as daytime somnolence in patients with an AHI of 5 to 30 events per hour, should also apply.¹¹⁶

For pregnant women with largely position-dependent OSA without significant oxyhemoglobin desaturations or hypertensive complications, positional therapy may be adequate. Nevertheless, the most effective therapy for sleep apnea in pregnancy is likely to be CPAP, which can be obtained and adjusted easily. Although theoretical concerns have been raised over the ability of CPAP to lower cardiac output, a clinically significant decline is unlikely to occur in individuals with normal cardiac function,¹²² especially given the normal physiologic hypervolemia of pregnancy. Furthermore, excellent adherence to therapy (> 80% use) was reported in a small (n = 12) series of pregnant women utilizing CPAP for the treatment of OSA and upper airway resistance syndrome.¹¹⁷

In contrast, oral appliances are relatively impractical during pregnancy, as multiple fitting sessions would be necessary in a short period of time. Supplemental O₂ can be considered for pregnant women unable to utilize more effective therapies. However, O₂ does not significantly blunt increases in arterial pressure following apnea termination¹²³ and may prolong apnea duration with associated hypercapnia.¹²⁴ Its utility in the treatment of OSA remains unproven.¹²⁴

Surgical therapies for OSA such as uvulopalatopharyngoplasty carry risks¹²⁵ that are likely to be magnified during pregnancy. Because uvulopalatopharyngoplasty is effective in only half of OSA cases,¹²⁵ this procedure should not be routinely performed during pregnancy. Likewise, although tracheostomy for sleep apnea in pregnancy has been reported,⁸² it is unlikely to be necessary except under unusual circumstances.

In the general population, CPAP therapy has been shown to lower blood pressure in patients with OSA.¹²⁶ The use of nasal CPAP in the hypertensive conditions of pregnancy hypertension has been examined in only 1 uncontrolled trial.¹⁰¹ In this investigation, when 11 women with severe preeclampsia (mean gestational age 35 weeks) received autotitrating nasal CPAP to abolish inspiratory airflow limitation, mean nocturnal blood pressure was significantly reduced (149/93 baseline, vs 129/73 with CPAP).¹⁰¹ These results should be interpreted cautiously, given the lack of a control group or placebo arm and potential order effect, because treatment and nontreatment nights were not randomized. Daytime blood pressure was not monitored to ascertain whether the effect was sustainable. The magnitude of the blood-pressure reduction was much larger than that observed in a blinded randomized trial of CPAP in hypertensive men with sleep apnea (-3.3 mm Hg compared to placebo)¹²⁶ or in an efficacy study of overnight CPAP use in hypertensive subjects with OSA (mean nocturnal BP, 132/86 with CPAP, vs 139/92 without).¹²⁷ Without additional evidence, we do not recommend CPAP use in the treatment of preeclampsia without objective evidence of sleep apnea.

What Should Be Done Postpartum?

Pregnancy-associated sleep apnea has been reported to improve or resolve following delivery.^{81,82} Since estrogen and progesterone levels fall dramatically after delivery,¹²⁸ estrogen-induced nasopharyngeal edema should improve quickly postpartum. In general, 75% to 80% of gestational weight gain is lost within 2 to 6 weeks.¹²⁹ Nevertheless, as weight loss may continue up to 6 months postpartum,¹²⁹ SDB may persist beyond the

puerperium.

Thus, the postpartum management of pregnancy-associated OSA must be individualized (See Table 3). Daytime somnolence is unlikely to be a useful clinical indicator, given the maternal sleep deprivation associated with infant care. Women with mild to moderate gestational OSA who fail to return to within 10% to 15% of baseline weight or experience nocturnal OSA symptoms may require polysomnographic reevaluation to determine if they have persistent sleep apnea. Women with severe (AHI > 30 events per hour) gestational OSA or with antenatal symptoms consistent with OSA are likely to require maintenance therapy. We believe these patients should undergo repeat polysomnography after weight stabilization (eg, ≥ 2 months postpartum) to determine baseline AHI and further management options.

Finally, women with preexisting OSA may resume their maintenance therapy after weight stabilization, with reassessment as necessary if weight retention is excessive or symptoms recur. All women with gestational sleep apnea should be monitored for recurrence during subsequent pregnancies.

RLS in Pregnancy

RLS is a sensorimotor disorder in which patients experience an irresistible desire to move the legs (akathisia) that is often accompanied by an uncomfortable or frankly painful sensation within the legs.^{26,130-132} Although RLS occurs with relatively infrequency in young, otherwise healthy, individuals without a family history,¹³⁰ it is common among pregnant women.^{42,131,132} The diagnosis of RLS is based on the clinical history: in addition to akathisia, patients usually report that their symptoms are brought on by rest, relieved with moving or walking, and characterized by circadian variation, so that the symptoms occur primarily at night or in the evening.¹³⁰ Symptoms of RLS can both delay nocturnal

sleep onset and make it difficult to return to sleep if awakened, decreasing sleep efficiency.¹³³ Furthermore, approximately 85% of individuals with RLS exhibit periodic limb movements of sleep (PLMS), involuntary clonic-type movements of the lower extremities¹³³; arousals due to PLMS can further exacerbate sleep disruption.¹³⁴

Although RLS is infrequently recognized by physicians taking care of pregnant patients,⁴² the prevalence of RLS has been observed to increase during pregnancy^{26,131,132} and to resolve rapidly postpartum.⁴² In a group of women (n = 41) recruited prior to pregnancy and followed prospectively, the prevalence of RLS symptoms (0% prepregnancy) increased from 12.5% in the first trimester to 23% by the third trimester¹³²; however, a quarter of the sample failed to complete the study. Nevertheless, additional studies have confirmed these findings.^{26,131} In a large cross-sectional study of approximately 16,000 pregnant women in Japan, Suzuki et al¹³¹ observed a significant relationship between RLS and the duration of pregnancy, with 15% of patients reporting RLS symptoms at 3 to 4 months of gestation and increasing to 23% at term. Furthermore, women with RLS reported significantly lower average sleep time, more difficulty in initiating and maintaining sleep, more early morning awakenings, and more excessive daytime somnolence than did women without RLS.¹³¹ In multiple regression analysis, risk factors for RLS included primiparity, duration of pregnancy, less than 7 hours of sleep, no daytime napping, current employment, smoking, and use of medication or alcohol.¹³¹

Although PLMS are common in individuals with RLS,¹³³ whether PLMS contribute significantly to sleep disruption during pregnancy is just beginning to be studied. When assessed in a series of 10 women with multiple gestations in the third trimester of pregnancy, PLMS were present in all subjects, with a frequen-

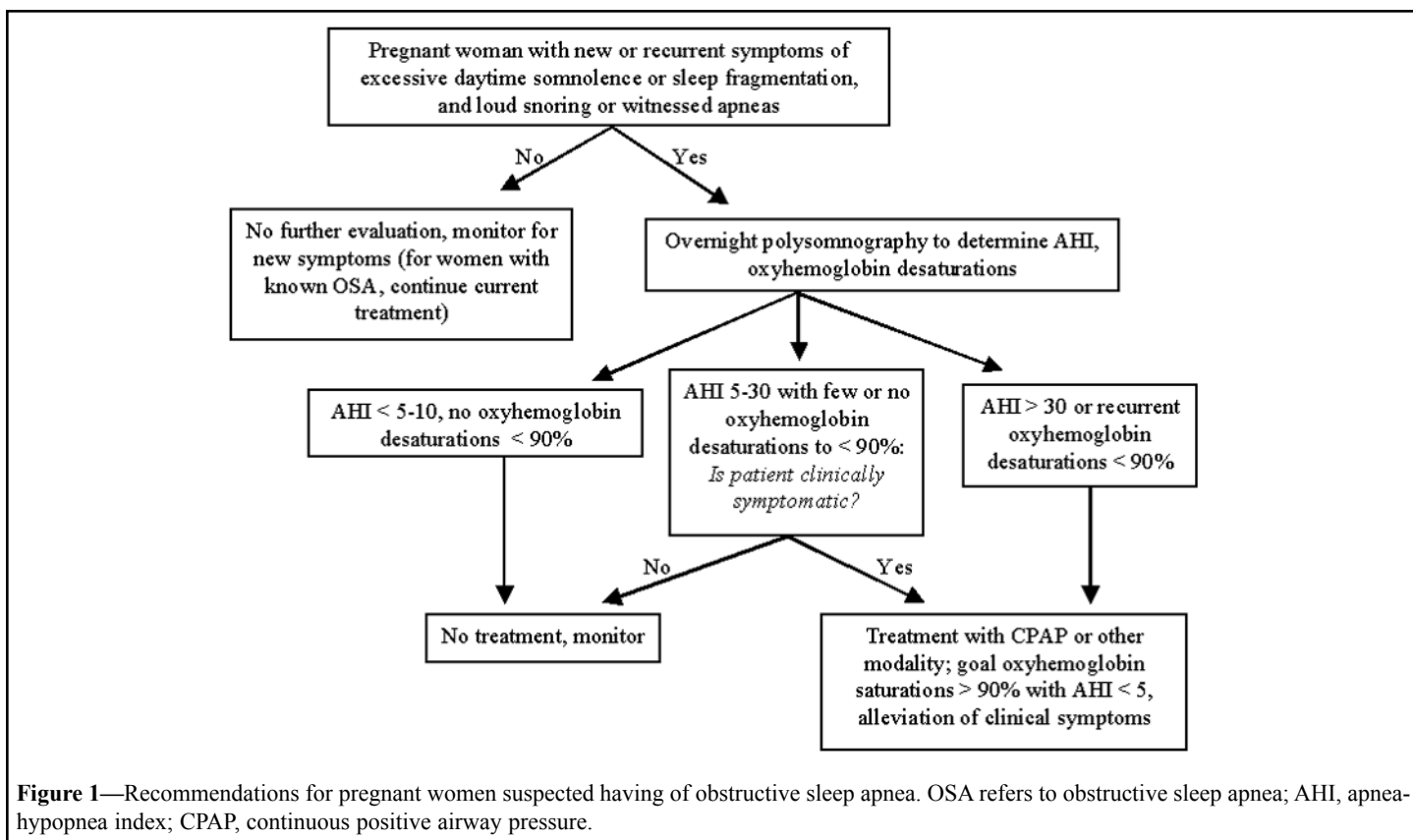


Figure 1—Recommendations for pregnant women suspected having of obstructive sleep apnea. OSA refers to obstructive sleep apnea; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

cy of 21.7 events per hour.¹³⁵ Only 4 subjects reported symptoms of RLS associated with the pregnancy,¹³⁵ suggesting that PLMS may be present even in the absence of RLS. However, the frequency of arousals due to PLMS was not reported.

In nonpregnant patients, RLS is often noted in association with iron deficiency.¹³⁶ Reduced serum ferritin levels, the most specific marker for iron deficiency,¹³⁷ have been demonstrated in pregnant women with RLS.¹³² However, pregnant women without RLS symptoms have similar reductions in ferritin, an observation attributed to the normal hemodilution that accompanies pregnancy.¹³² In contrast, although serum folate levels remain within the normal range in pregnant women with RLS, levels are consistently lower than in controls.¹³²

Treatment of RLS in Pregnant Women

Although folate supplementation specifically for pregnancy-associated RLS has been reported in only 1 small preventative trial,¹³⁸ oral folate is widely recommended during the periconception and early pregnancy period for the prevention of fetal neural tube defects.¹³⁹ Iron supplementation of 30 to 60 mg per day throughout the second and third trimesters of pregnancy is also recommended,¹⁴⁰ and iron is included in most prenatal multivitamins. As symptoms of RLS become more common over the course of pregnancy, a trial of folate supplementation and evaluation for iron deficiency with a serum ferritin level is a reasonable approach in pregnant women who develop RLS. Conservative treatments, such as walking, stretching, massaging the affected limbs, applying heat, and performing relaxation techniques, may also be helpful. Abstinence from tobacco and alcohol should be reinforced, and adequate time should be set aside for sleep, as these may be risk factors for RLS in pregnant women.¹³¹

For women with severe symptoms who continue to experience clinically significant sleep disruption, consideration may be given to standard pharmacologic therapies for idiopathic RLS, such as dopaminergic, opiate, and benzodiazepine medications.¹³⁰ However, there are no controlled clinical trials upon which to base treatment recommendations. For short-term use, oxycodone and pergolide are currently classified as Class B in pregnancy; of note, pergolide use has been recently reported in

association with valvular heart anomalies in several nonpregnant patients.¹⁴¹ Most benzodiazepines, anticonvulsants, and other opioids and dopamine agonists have been classified as Class C, D, or X in pregnancy (see Table 1).

By 10 days after delivery, the majority of patients with pregnancy-associated RLS report symptom resolution.⁴² In a few women, symptoms may persist beyond the month following delivery.^{42,132} These cases can be managed using standard therapies, although consideration should be given to the excretion of opioids, benzodiazepines, and anticonvulsant medications in breast milk and to the possibility that lactation may be diminished by the use of dopaminergic medications.¹⁴²

Other Sleep Disorders

Little information exists about how pregnancy affects the course of other sleep disorders, such as narcolepsy¹⁴³ and the parasomnias.¹⁴⁴ The clinical presentation of narcolepsy usually occurs during adolescence or young adulthood,¹⁴⁵ and symptoms may be exacerbated by the sleep disturbance associated with pregnancy. Individuals with narcolepsy often require medication for excessive daytime somnolence (eg, modafinil, methylphenidate, amphetamines) or REM-related symptoms including cataplexy (eg, tricyclic agents, fluoxetine, sodium oxybate). However, prematurity, low birth weight, and withdrawal symptoms have been reported in infants born to women taking amphetamines,¹⁴⁶ and many of these drugs are designated Class C in pregnancy (see Table 1). Similarly, the widely used wakefulness-promoting agents modafinil and methylphenidate have been labeled Class C.⁵² Pemoline, a central nervous system stimulant with a chemical structure dissimilar to the amphetamines, is Class B in pregnancy,⁵¹ but its use has been associated rarely with liver failure (nonpregnant patients)¹⁴⁷; because of its potential toxicity, it is rarely indicated in the treatment of narcolepsy.¹⁴⁶ Selegiline, which has both alerting and anticataplectic effects, and fluoxetine, which has anti-REM effects, are also Class C.¹⁴⁸

Given the limited treatment options, the reduction or discontinuation of stimulant drugs has been advised for women attempting to conceive and for pregnant women, except in cases where potential benefits to the patient clearly outweigh risks to the fetus.¹⁴⁸ Therefore, whenever possible, narcolepsy should be

Table 3—Postpartum Recommendations for Women with Pregnancy-Associated Sleep Apnea

	Initial Postpartum Management	If Symptoms Recur with Withdrawal of Therapy, or Weight Gain Persists
Mild to moderate pregnancy-associated sleep apnea	Postpartum withdrawal of therapy with close follow-up for symptom recurrence; if asymptomatic, monitor for recurrence in future pregnancies	Obtain overnight PSG to determine baseline AHI; assess need for treatment and therapeutic options based on findings
Severe pregnancy-associated sleep apnea	Continue therapy and obtain overnight PSG when weight within 10% to 15% of baseline to rule out persistent OSA	Obtain repeat overnight PSG to establish baseline AHI (consider split-night study with CPAP titration) and need for continued therapy
Preexisting sleep apnea	Consider return to prepregnancy therapy when weight within 10% to 15% of baseline, with close follow-up for symptom recurrence	Repeat overnight PSG (with split-night study if using CPAP at baseline) to determine new baseline AHI; modify prepregnancy therapy based on findings

PSG refers to polysomnography; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

managed during pregnancy by maintenance of good sleep hygiene and adequate sleep time; scheduled naps; and, if necessary, a reduction in work and family responsibilities. Women with disabling cataplectic episodes or who must maintain daytime alertness (eg, who must drive) may, however, continue to require medication.

Among 325 women who participated in a recent longitudinal study of parasomnias during pregnancy, symptoms of common mild parasomnias, including sleepwalking, sleep talking, hypnagogic hallucinations and sleep bruxism, generally declined compared to the 3-month prepregnancy period.¹⁴⁴ No symptoms of REM behavior disorder were reported,¹⁴⁴ consistent with the low prevalence of this condition to be expected in a sample of young women. Although frightening dreams about pregnancy or the infant have been reported by at least 25% of women during pregnancy,¹⁴⁹ overall nightmares declined significantly in this sample.¹⁴⁴

CONCLUSION

During pregnancy, most women experience sleep disturbance and daytime fatigue despite total sleep times that often equal or exceed prepregnancy sleep time. Changes in sleep architecture and sleep disruption result from high circulating hormone levels and the physical changes of pregnancy. When necessary, treatment should focus on sleep-hygiene measures and behavioral therapies targeted at managing physical discomfort; severe cases may require short-term pharmacologic intervention.

Although sleep complaints are extremely common among pregnant women, we are just beginning to learn about the potential adverse effects of sleep disturbance and sleep disorders on maternal-fetal health. A relationship during pregnancy and the postpartum period between poor sleep and negative mood and performance, or outcomes such as postpartum depression, has been proposed; however, as yet, there are not compelling data to support this relationship. Growing evidence does suggest that SDB is common among pregnant women and can negatively impact maternal-fetal outcomes. Nevertheless, risk factors for the development of SDB during pregnancy have not been clearly defined, and a large prospective study of the incidence and prevalence of gestational sleep apnea and the effects on pregnancy has not yet been performed.

Finally, although RLS affects nearly a quarter of pregnant women in the third trimester of pregnancy and may indicate relative folate or iron deficiency, it frequently goes unrecognized by physicians. Improved knowledge among healthcare providers about sleep disorders during pregnancy is also needed. Future studies to elucidate the relationships between sleep disorders and the health and well-being of pregnant women and their infants have important implications not only for sleep medicine, but also for obstetrics and women's health.

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