26 Sleep disorders and pregnancy

Pradeep Sahota and Sanjay Jain

INTRODUCTION

Pregnancy is associated with several hormonal, physiologic, physical, and behavioral changes that can cause alterations in sleep architecture, quality, and duration. As a result, it is not surprising that a majority of women report sleep disruption during pregnancy. In addition, pregnancy can affect preexisting sleep disorders such as insomnia, sleep-disordered breathing, and restless legs syndrome (RLS). The intimate relation between sleep and pregnancy has been well recognized and has, especially within the last few years, seen an increased interest in this field. This chapter aims to review changes occurring during pregnancy, which may have a bearing on sleep, and sleep disorders during pregnancy.

HORMONAL CHANGES DURING PREGNANCY THAT MAY AFFECT SLEEP

Pregnancy is characterized by hormonal changes that are aimed toward successful maturation of the fetus. These changes can affect normal sleep patterns directly and indirectly. There are increases in levels of circulating estrogen and progesterone throughout pregnancy. Estrogen production progressively increases in pregnancy, and levels during the last few weeks prior to delivery may be 1000-fold higher than that in ovulatory premenopausal women (1). Level of estrogen decreases abruptly after delivery of the fetus and placenta. Estrogen has been shown to reduce rapid eye movement (REM) sleep in animal studies. This may be due to its ability to increase brainstem norepinephrine (2). Progesterone levels gradually increase from 25 ng/mL at 6 weeks to 150 ng/mL at 37 weeks of pregnancy (3). Exogenously administered progesterone is associated with decreasing wakefulness, shortened latency to non-REM sleep, and increased duration of non-REM sleep (4). The effects of progesterone appear to be mediated by the action of its metabolites on brain GABA_A receptors (4,5).

Levels of other hormones that can influence sleep patterns such as prolactin and cortisol are also elevated during pregnancy. Overall, the effect of hormonal changes on sleep during pregnancy is unpredictable due to the wide variation in circulating levels of different hormones as well as the effect of other physical and physiologic changes that occur during pregnancy.

PHYSIOLOGIC CHANGES IN PREGNANCY THAT MAY HAVE A BEARING ON SLEEP

The expectant mother undergoes a variety of physiologic and physical changes that may lead to alteration of sleep during pregnancy. Majority of these changes occur as a result of the hormonal changes described above, but other factors play a role as well. Renal blood flow increases to a level of 50% to 85% above baseline throughout the first and second trimesters (6).

Dilatation of the renal pelvis and ureters occurs due to hormonal changes and mechanical effects of the enlarged uterus (7). These changes predispose to frequent micturition and therefore to several nocturnal awakenings to go to the bathroom.

Lower esophageal sphincter pressure begins to decrease in the first trimester of pregnancy, reaching a nadir in the 36th week. Gastrointestinal reflux symptoms are common, particularly in late pregnancy (8), and may be associated with frequent arousals from sleep.

Upper airway hyperemia, mucosal edema, hypersecretion, and increased friability may occur as a result of increased estrogen levels (3). Progesterone reduces the integrity of the vascular endothelium leading to fluid leakage from the intravascular to the extravascular space, causing tissue edema (9). Additionally, during pregnancy, there is an increase in the level of relaxin, an insulin-like growth factor hormone. It is both a muscle relaxant and a powerful vasodilator (10), properties that increase airway collapsibility and decrease airway caliber. Thus the increased levels of these hormones can potentially reduce the size of the upper airway significantly. Furthermore, progesterone increases phrenic nerve activity with consequent increase in diaphragmatic drive (11), and its property as a powerful respiratory stimulant has been recognized since the 1940s (12). An increase in metabolic CO₂ production and the increase in respiratory drive cause a significant increase in minute ventilation (13). This ventilatory augmentation, which is in excess of the increased CO₂ production, produces a respiratory alkalosis. The reduced arterial CO₂ of pregnancy may be a potential source of respiratory instability during sleep (14). Moreover, augmented respiratory drive may induce obstructive sleep-disordered breathing by increasing negative suction pressure on narrowed upper airway structures (15). In addition to changes in respiratory drive, pulmonary function in pregnancy is also affected by changes in the airways and thoracic cage. Chest wall and total respiratory compliance are reduced in late pregnancy (16). The expanding uterus produces a cephalad displacement of the diaphragm, causing a progressive 10% to 25% decrease in functional residual capacity (FRC) toward term (3,17). As a result of increased fetal demands and metabolic alterations in the mother, oxygen consumption increases by 20% to 33% by the third trimester (18). The combination of a reduced FRC and increased oxygen consumption results in a lowered oxygen reserve. Conditions that may cause further lowering of this reserve may potentially affect fetal oxygenation with adverse consequences.

SLEEP ARCHITECTURE CHANGES DURING PREGNANCY

Nonpregnant women of childbearing age have total sleep times on average of 7 to 9 hours per night, with 55% of the time

spent in light sleep, 20% in slow wave sleep (SWS), and 20% to 25% in REM sleep (19).

Numerous studies have examined changes in sleep architecture during pregnancy with variable findings (20–24). Most of these studies were however consistent in noting lighter and more disrupted sleep as pregnancy progresses. Wake after sleep onset increased from the second to third trimester, whereas REM sleep decreased from the first trimester to second (24,25). Brunner et al. also found, by spectral analysis, a progressive decrease in EEG power density in non-rapid eye movement sleep (25).

SLEEP DISORDERS AND PREGNANCY

The mother-to-be is predisposed to a number of sleep disorders due to the hormonal and consequently the physical and physiologic changes occurring during pregnancy. Insomnia, parasomnias, sleep-related movement disorders, sleep-related breathing disorders, and hypersomnolence have all been reported in pregnant patients.

INSOMNIA

The American Academy of Sleep Medicine, in its diagnostic and coding manual, defines insomnia as repeated difficulty with sleep initiation, duration, consolidation or quality that occurs despite adequate time, and opportunity for sleep and results in some form of daytime impairment. Insomnia is very commonly reported during pregnancy. In a survey of 192 pregnant women, 88% reported alteration in sleep as compared with their usual experience (21). The most frequent reasons for sleep disruption during pregnancy are urinary frequency (26), heartburn, and backache or ache in hips (21). In addition, there may be disruption of sleep due to nausea and vomiting during the first trimester and because of fetal movements during the third trimester of pregnancy.

Maternal factors such as maternal age (27), parity (28,29), altered circadian rhythm (30), and pregnancy-related disorders such as pre-eclampsia could also influence sleep during pregnancy. Parity may have a bearing on sleep quality and architecture. Compared with primiparas, multiparas had reduced sleep efficiency at all time points (19).

Nonpregnancy-related factors such as maternal smoking, inadequate sleep hygiene, and adjustment disorder may contribute to insomnia independent of the pregnant state.

Ohida and colleagues (31) reported that women exposed to passive smoking were likely to have sleep disturbances, such as subjective insufficient sleep, difficulty in initiating sleep, short sleep duration, and snoring loudly/breathing uncomfortably. Smoking pregnant women had an even greater prevalence of same sleep disturbances and also experienced excessive daytime sleepiness and early morning awakening (31).

SLEEP-DISORDERED BREATHING DURING PREGNANCY

Although snoring and apneas occur in pregnancy (32), there is lack of data regarding incidence and prevalence of sleep apnea in pregnant women. Most studies investigating sleep-disordered breathing were in the form of questionnaires with variable results (33–37). Despite conflicting results, there is agreement regarding higher prevalence of snoring in pregnant women as opposed to nonpregnant women.

Loube et al. (34), in their survey of 350 pregnant women and 110 age-matched nonpregnant women, found that snoring was more frequent (14%) in pregnant women as opposed to nonpregnant women (4%). They concluded that snoring was not associated with fetal compromise or adverse outcome. By contrast, the study by Franklin and Holmgren (35) suggests that snoring may be independently predictive of maternal hypertension and fetal growth retardation. Of the 502 pregnant women, 23% in their study reported snoring every night during the last week of pregnancy. Hypertension and pre-eclampsia were more common, and the incidence of infants born with Apgar score less than or equal to 7 was higher in women who habitually snored.

Obesity has been shown to have a causal association with sleep apnea (38,39). Pregnancy is associated with weight gain, which may exceed 20% or more by term (40). A recently published study suggests that the prevalence of pre-gravid obesity (defined as BMI > 29 kg/m²) in the United States has increased significantly from 13% immediately before pregnancy in 1993 to 22% immediately before pregnancy in 2002/2003 (41). Rapid gain in weight is known to be associated with a higher incidence of obstructive sleep apnea (OSA). It has not, however, been established by sleep studies whether excessive weight gain during pregnancy causes sleep apnea. In 1992, Feinsilver et al. (42) reviewed the physiologic adaptations in pregnancy and suggested an increased likelihood of sleep-disordered breathing in pregnant women. Upper airway changes, as described earlier, would predispose the patient to snoring and OSA. In addition, the respiratory alkalosis resulting from augmented minute ventilation and the enhanced sensitivity of the respiratory center to CO₂, as occurs in pregnancy, could predispose to central sleep apnea. On the other hand, there are physiologic adaptations, such as increased minute ventilation and pharyngeal muscle tone, due to elevated progesterone levels during pregnancy (43), which may be protective against sleep-disordered breathing. There is reduction in REM sleep (22) during pregnancy, which may protect against sleep apnea. Additionally, in late pregnancy, there is a greater tendency for women to sleep on their sides, thereby reducing the tendency to manifest severe sleep apnea.

The increased possibility of OSA occurring in pregnancy and its possible adverse effect on the fetoplacental unit has been hypothesized (44). There is evidence that pregnant women with preexisting obesity have a higher apnea-hypopnea index (45) and they may be at increased risk of OSA. In pregnant women who do have sleep apnea, it is felt that due to the lowered oxygen reserve in these patients, occurrence of OSA with oxygen desaturation can have undesirable consequences for the fetus. There are isolated reports of increase in incidence of babies with intrauterine growth retardation in pregnant women diagnosed with OSA (45,46). Other case reports suggest that treatment of the mother to be resulted in delivery of babies with normal birth weight (47). There are, however, no systematic studies of adverse outcomes of OSA during pregnancy.

Despite a lack of conclusive evidence of poor outcomes of pregnancy in women with OSA, pregnant women, especially those with preexisting obesity, and those giving a history of loud snoring, excessive daytime somnolence, or witnessed apneas should be considered to be at increased risk for sleep

apnea with possibility of adverse consequences for the fetus. There should, for this reason, be a low threshold for obtaining an overnight sleep study and initiation of treatment with nasal continuous positive airway pressure (CPAP) even if the patient has mild sleep apnea.

SLEEP-DISORDERED BREATHING AND PRE-ECLAMPSIA

Pre-eclampsia is a condition arising in the third trimester of pregnancy. It affects approximately 7% of all pregnancies and is characterized by abrupt hypertension, proteinuria, and edema of the hands, feet, and face. Risk factors for pre-eclampsia include family history, primiparity, advanced maternal age, multiple gestation, obesity, chronic hypertension, and renal disease (48). Sleep architecture is altered in women with pre-eclampsia, with a markedly increased time spent in SWS as compared with primigravidas with normal pregnancies (49). Women with pre-eclampsia were noted to have upper airway narrowing in both upright and supine postures as compared with nonpregnant and pregnant women (50). This predisposes women with pre-eclampsia to snoring and as many as 75% of women with pre-eclampsia were reported to snore by Iczl et al. Sleep studies in a subgroup of pregnant women with pre-eclampsia revealed higher prevalence of inspiratory flow limitation in these patients without associated oxygen desaturation (51). It is unclear whether this may have implications in the pathophysiology and treatment of this disorder. There is evidence that snoring is associated with increased blood pressure in women who suffer from pre-eclampsia, and it has been suggested that using a nasal mask to deliver CPAP may reduce obstruction and improve nocturnal blood pressure control.

RLS

RLS is a sensorimotor disorder characterized by a strong, nearly irresistible, urge to move the legs. This urge to move is often accompanied by other uncomfortable paresthesias felt deep inside the legs. The urge to move, or the unpleasant sensations, begin or worsen during periods of rest and are partially or totally relieved with movement. Symptoms typically occur in the evening or night.

Pregnancy is a known cause of secondary RLS. In a study by Nikkola, 4 out of 10 women were diagnosed with RLS after becoming pregnant (52). Sleep studies in these patients showed periodic limb movements in all 10 mothers-to-be, with an average frequency of 21.7 movements per hour. In another study, 23% women were noted to develop symptoms of RLS after becoming pregnant (Lee).

PARASOMNIAS

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep. These events are manifestations of central nervous system activation transmitted into skeletal muscle and autonomic nervous system channels, often with experiential concomitants. Parasomnias, such as sleepwalking, and night terrors occurring during pregnancy and exacerbated by the condition have been reported. Hedman and colleagues, however, found that the frequency of most parasomnias decreases during pregnancy. They found a significant decrease

in sleepwalking, sleep talking, bruxism, and hypnagogic hallucinations from the prepregnant state. Prevalence of sleep paralysis was noted to decrease during the first trimester, but it increased during later pregnancy from 5.7% to 13.3% in the second trimester.

NARCOLEPSY

Narcolepsy is a condition characterized by excessive daytime sleepiness, with or without cataplexy. Other features such as hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disruption may commonly occur in these patients. Narcolepsy is usually diagnosed in patients during adolescence or young adulthood. There is a paucity of data regarding effect of pregnancy on the course of narcolepsy. It is likely that symptoms of narcolepsy may be exacerbated by the sleep disturbances associated with pregnancy and also due to the fact that medicines typically used to treat narcolepsy have to be stopped, causing a withdrawal effect. Cataplexy, in severe cases, may be disabling, predisposing the pregnant patient to injury and jeopardizing the fetus.

MANAGEMENT OF SLEEP DISORDERS IN THE PREGNANT PATIENT

General management consists of advice regarding regular sleep schedules and practice of adequate sleep hygiene. Patients with insomnia should be counseled regarding stimulus control and relaxation techniques. Recognition of etiologic factors is important and every attempt should be made to optimally manage any underlying medical condition. For example, patients with gastrointestinal reflux symptoms may benefit from life style modification changes such as sleeping with the head end of bed elevated and by limiting portion sizes as well as avoiding oral intake at least 2 hours prior to bedtime.

Understandably, there are no clinical trials of pharmacologic treatment modalities for sleep disorders during pregnancy. Pharmacologic options therefore must be viewed with caution because of safety issues associated with use of medicines during pregnancy. Short-term zolpidem or diphenhydramine may be considered in patients with severe insomnia not responding to other measures.

Patients with narcolepsy should discontinue treatment with stimulants such as dextroamphetamine or methamphetamine. They may have to accept less stringent control of excessive daytime sleepiness and allow time for more frequent daytime naps. REM sleep suppressing medicines such as paroxetine or fluoxetine, which are pregnancy category B agents, may be used for control of cataplexy.

Similarly, medicines for RLS such as dopaminergic agents and benzodiazepines should ideally be discontinued. Patients may benefit from avoidance of caffeinated beverages and heavy exercise too close to scheduled bedtime. Administration of iron and folate supplements as is usually the practice during pregnancy may be helpful.

Patients with prior history of sleep apnea or those newly diagnosed with sleep apnea should be advised to use CPAP regularly. Despite theoretical concerns regarding diminished cardiac output and placental flow, there are no reports to suggest adverse effects from CPAP to the mother or the fetus. There may, however, be difficulty in tolerating CPAP due to factors such as intolerance to pressure, nasal congestion, and

stuffiness, which may decrease adherence to CPAP regimen. This may be overcome by measures such as saline nasal rinses and use of topical nasal steroids, lowering of pressure to a more tolerable level, and sleeping with the head end of bed elevated.

CONCLUSION

Sleep disturbance is frequently reported during pregnancy (53). This is due to the several hormonal, physiological, physical, and behavioral changes that occur during the pregnant state. As a result of these changes, the pregnant woman may develop or have worsening of pathologic sleep conditions such as insomnia, sleep-disordered breathing, sleep-related movement disorders. Many of these conditions may be effectively treated, and lack of treatment may have adverse consequences for the mother and the fetus. Sleep evaluation should, therefore, be a part of routine prenatal checkup. Particular attention should be given to obese pregnant women and those who gain excessive weight during pregnancy, and to women who develop gestational hypertension or pre-eclampsia. There should be a low threshold for obtaining an overnight polysomnogram in these patients and treatment with CPAP should be considered even in patients who have mild sleep apnea. Treatment should also focus on adequate sleep hygiene techniques.

There is need for larger, multicenter studies with clinical and polysomnographic evaluation to improve our understanding of association between pregnancy and sleep disorders and to determine whether (i) sleep disorders influence the outcome of pregnancy and (ii) pregnancy influences the course of certain sleep disorders such as narcolepsy.

REFERENCES

- Cunningham GF, Macdonald PC, Gant NF. Williams Obstetrics, 18th edn. Appleton & Lange, 1989: 67–85.
- Heritage AS, Stumpf WE, Sar M, et al. Brainstem catecholamines are target sites for sex hormones. *Science* 1980; 207: 1377–9.
- Elkus R, Popovich J. Respiratory physiology in pregnancy. *Clin Chest Med* 1992; 13: 555–65.
- Lancel M, Faulhaber J, Holsboer F, et al. Progesterone induces changes in sleep comparable to those of agonistic GABA_A receptor modulators. *Am J Physiol* 1996; 271: E 763–72.
- Edgar DM, Seidel WF, Gee KW, et al. Ccd-3693: an orally bioavailable analog of the endogenous neuroactive steroid, pregnanolone, demonstrates potent sedative hypnotic actions in the rat. *J Pharmacol Exp Ther* 1997; 282: 420–9.
- Davison JM, Dunlop W. Renal hemodynamics and tubular function in normal human pregnancy. *Kidney Int* 1980; 18: 152–61.
- Merchant DJ. Alterations in anatomy and function of the urinary tract during pregnancy. *Clin Obstet Gynaecol* 1978; 21: 855–62.
- Van Thiel DH, Gavalier JS, Joshi SN, et al. Heartburn of pregnancy. *Gastroenterology* 1978; 72: 666–8.
- Stachenfield NS, Taylor HS. Effects of estrogen and progesterone administration on extracellular fluid. *J Appl Physiol* 2004; 96: 1011–18.
- Sherwood OD. Relaxin's physiological roles and other diverse actions. *Endocr Rev* 2004; 25: 205–34.
- Bayliss DA, Millhorn DE, Gallman EA, et al. Progesterone stimulates respiration through a central nervous system steroid receptor-mediated mechanism in cat. *Proc Natl Acad Sci USA* 1987; 84: 7788–92.
- Dempsey J, Olson EB, Skatrud J. Hormones and neurochemicals in the regulation of breathing, Vol. 2. Washington, DC: American Physiological Society, 1986.
- Lapinsky SE, Kruczynski K, Slutsky A. Critical care in the pregnant patient. *Am J Respir Crit Care Med* 1995; 152: 427–55.
- Skatrud JB, Dempsey JA. Interaction of sleep state and chemical stimuli sustaining rhythmic ventilation. *J Appl Physiol* 1983; 55: 813–22.
- Remmers JE, DeGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978; 44: 931–8.
- Marx GF, Moorthi PK, Orkin LR. Static compliance before and after vaginal delivery. *Br J Anaesth* 1970; 42: 1100–4.
- Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. *Br J Obstet Gynaecol* 1978; 85: 518–24.
- Artal R, Wiswell R, RomemY, et al. Pulmonary responses to exercise in pregnancy. *Am J Obstet Gynecol* 1986; 154: 378–83.
- Sloan EP. Sleep disruption during pregnancy. *Sleep Med Clin* 2008; 3: 73–80.
- Schweiger MS. Sleep Disturbances in Pregnancy. A subjective survey. *Am J Obstet Gynecol* 1972; 114: 879–82.
- Suzuki S, Dennerstein L, Greenwood KM, et al. Sleeping patterns during pregnancy in Japanese women. *J Psychosom Obstet Gynecol* 1994; 15: 19–26.
- Driver HS, Shapiro CM. A longitudinal study of sleep stages in young women during pregnancy and postpartum. *Sleep* 1992; 15: 449–53.
- Karacan I, Wayne H, Harman AW, et al. Characteristics of sleep patterns during late pregnancy and the postpartum periods. *Am J Obstet Gynecol* 1968; 101: 579–86.
- Hertz G, Fast A, Feinsilver S, et al. Sleep in normal late pregnancy. *Sleep* 1992; 15: 246–51.
- Brunner DP, Munch M, Biedermann, et al. Changes in sleep and sleep electroencephalogram during pregnancy. *Sleep* 1994; 17: 576–82.
- Baratte-Beebe KR, Lee K. Sources of midsleep awakenings in childbearing women. *Clin Nurs Res* 1999; 8: 386–97.
- Worth J, Oneyeje CI, Ferber A, et al. The associations between fetal and maternal sleep patterns in third trimester pregnancies. *Am J Obstet Gynecol* 2002; 186: 924–5.
- Waters MA, Lee KA. Differences between primigravidae and multi-gravidae mothers in sleep disturbances, fatigue and functional status. *J Nurse Mid-wifery* 1996; 41: 364–7.
- Oga M, Shono H, Kohara M, et al. Chronological changes in subjective symptoms during pregnancy in nulliparous and multiparous women. *Acta Obstet Gynecol Scand* 1995; 74: 784–7.
- Labyak S, Lava S, Turek F, et al. Effects of shift work on sleep and menstrual function in nurses. *Health Care Women Int* 2002; 23: 703–14.
- Ohida T, Kaneita Y, Osaki Y, et al. Is passive smoking associated with sleep disturbance among pregnant women? *Sleep* 2007; 30: 1155–61.
- Kowall J, Clark G, Nini-Murcia G, et al. Precipitation of obstructive sleep apnea during pregnancy. *Obstet Gynecol* 1989; 74: 453–5.
- Schutte S, Gross A, Segal J, et al. Self reported snoring and sleep in high-risk pregnancies. *Sleep Res* 1995; 24: 342.
- Loube DI, Poceta JS, Morales MC, et al. Self-reported snoring in pregnancy. Association with fetal outcome. *Chest* 1996; 109: 885–9.
- Franklin KA, Holmgren PA, Jonsson F, et al. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Chest* 2000; 117: 137–41.
- Hedman C, Pohjasvaara T, Tolonen U, et al. Effects of pregnancy on mother's sleep. *Sleep Med* 2002; 3: 37–42.
- Pien GW, Fife D, Pack AI, et al. Serial assessment of symptoms of sleep-disordered breathing in pregnant women using the multivariable apnea prediction index. *Sleep* 2002; 25: A 467–8.
- Dixon JB, Schachter LM, O'Brien PE. Predicting sleep apnea and excessive daytime sleepiness in the severely obese: Indications for polysomnography. *Chest* 2003; 123: 1134–41.
- Kyzer S, Charuzi I. Obstructive sleep apnea in the obese. *World J Surg* 1998; 22: 998–1001.
- Gunderson EP, Abrams B. Epidemiology of gestational weight gain and body weight changes after pregnancy. *Epidemiol Rev* 1999; 21: 261–75.
- Kim SY, Dietz PM, England L, et al. Trends in pre-pregnancy obesity in nine states, 1993–2003. *Obesity (Silver Spring)* 2007; 15: 986–93.
- Feinsilver SH, Hertz G. Respirations during sleep in pregnancy. *Clin Chest Med* 1992; 13: 637–44.
- Popovic RM, White DP. Upper airway muscle activity in normal women: influences of hormonal status. *J Applied Physiol* 1998; 84: 1055–62.
- Schoenfeld A, Ovadia Y, Neri A, et al. Obstructive sleep apnea (OSA) – implications in maternal-fetal medicine. A hypothesis. *Med Hypotheses* 1989; 30: 51–4.
- Maasilta P, Bachour A, Teramo K, et al. Sleep-related disordered breathing during pregnancy in obese women. *Chest* 2001; 120: 1448–54.

46. Joel-Cohen SJ, Schoenfeld. Fetal response to periodic sleep apnea: a new syndrome in obstetrics. *Eur J Obstet Gynecol Reprod Biol* 1978; 8: 77–81.
47. Lewis DF, Chesson AL, Edwards MS, et al. Obstructive sleep apnea during pregnancy resulting in pulmonary hypertension. *South med J* 1998; 91: 761–2.
48. Zhang J, Zeisler J, Hatch MC, et al. Epidemiology of pregnancy induced hypertension. *Epidemiol Rev* 1997; 19: 218–32.
49. Edwards N, Blyton DM, Kesby GJ, et al. Pre-eclampsia is associated with marked alteration in sleep architecture. *Sleep* 2000; 23: 619–25.
50. Izci B, Riha RL, Martin SE, et al. The upper airway in pregnancy and preeclampsia. *Am J Respir Crit Care Med* 2003; 167: 137–40.
51. Connolly G, Razak AR, havanga A, et al. Inspiratory flow limitation during sleep in pre-eclampsia: comparison with normal pregnant and nonpregnant women. *Eur Respir J* 2001; 18: 672–6.
52. Nikkola E, Ekblad U, Ekholm E, et al. Sleep in multiple pregnancy: breathing patterns, oxygenation, and periodic leg movements. *Am J Obstet Gynecol* 1996; 174: 1622–5.
53. Sahota P, Jain S, Dhand R. Sleep Disorders in Pregnancy. *Current Opinion in Pulm Crit Care Med* 2003; 9: 477–83.