

A role for sleep disorders in pregnancy complications: challenges and opportunities

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Sleep and sleeplike states have been identified in all mammalian species, other vertebrates such as birds,¹⁻⁴ and invertebrates (eg, fruit fly or *Drosophila melanogaster*).⁵ The key features of sleep are that it is a reversible quiescent state, during which there is decreased sensitivity to environmental stimuli, and is homeostatically regulated. Conservation of sleep during evolution points to its importance in the survival of all species. Indeed, experimental sleep deprivation leads to death.⁶

The lowest morbidity/mortality for human beings occurs with sleep duration ranges from 7–9 hours per 24-hour period⁷⁻¹¹ (Figure 1). “Sleep deficiency” includes: (1) sleep deprivation or insomnia; (2) sleep fragmentation due to abnormal breathing disorders or periodic leg movements; and (3) sleep circadian misalignment caused by shift work or other rhythm-related disorders.¹¹

We spend one-third of our life sleeping¹¹⁻¹⁴; yet, fundamental questions as to the function of sleep and its regulation remain unanswered. Despite evidence that pregnancy is associated with sleep disturbances,¹⁵⁻²³ the assessment of sleep quality and quantity during pregnancy and its consequences has not received the attention it deserves. Indeed, assessment of sleep has not been an integral part of prenatal care, even though many sleep disorders that affect pregnant women (eg, obstructive apnea) are amenable to treatment, and therapy can have benefits.²⁴⁻²⁸

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Evidence has emerged suggesting that sleep disorders may be associated with complications of pregnancy,^{22,29} such as gestational diabetes,^{21,22,30-33} gestational hypertension,^{22,31,34-39} preeclampsia,^{22,31,34,37,39-48} fetal growth disorders,^{22,39,42,49,50} preterm birth,^{32,47,49} and stillbirth.⁵¹ Animal studies indicate that maternal sleep deprivation may have long-term effects in the offspring.^{52,53}

Two systematic reviews and metaanalyses (one of which is published in this issue of the Journal⁵⁴) provide evidence of an association between sleep-disordered breathing and adverse pregnancy outcome.^{54,55} Moreover, recent groundbreaking studies about the effect of sleep on the brain have made the subject topical.

The purpose of sleep

Sleep is thought to be essential to clear the brain of metabolic waste products, which accumulate during wakefulness.⁵⁶ All tissues produce metabolic waste during the course of normal activity—in the brain, this has particular significance. Neurons produce β -amyloid, which is excreted into the extracellular space.^{56,57} When this protein accumulates, it undergoes structural changes and can result in protofibrils and fibrils, which confer local toxicity.^{58,59} The sleep-wake state plays a key role in the clearance of β -amyloid—sleep deprivation results in accumulation of amyloid, and chronic sleep restriction leads to the formation of an amyloid plaque that is characteristic of Alzheimer’s disease.^{60,61}

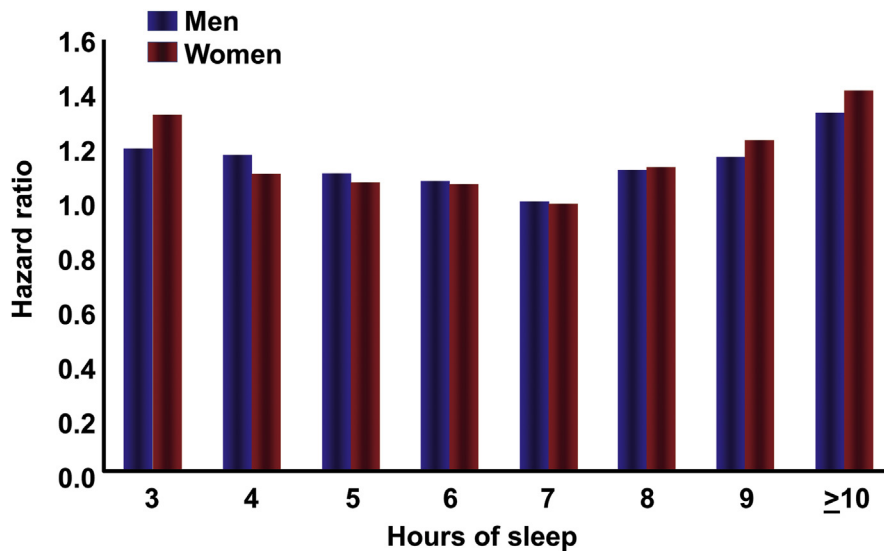
A fundamental question is how this clearance takes place. The brain was thought not to have a lymphatic system; hence, the question of how the organ disposed of metabolic waste.⁶² The answer came with the discovery of a draining system called “glymphatics,”⁵⁶ considered by Maiken Nedergaard⁶² to be the “garbage truck of the brain” (Figure 2). The breakthrough is that, during natural sleep or anesthesia, there was a 60% increase in the interstitial space, and increased clearance of β -amyloid; hence, the proposal that the purpose of sleep is to remove neurotoxic waste products formed while we are awake⁶³ (Figure 3). The potential implications are major: sleep deprivation is a risk factor for neurodegenerative diseases.⁶⁴⁻⁶⁶

Changes in the patterns of sleep in society: sleep debt

The mean duration of sleep has changed over the last century: in 1910, it was 9 hours; in 1975, 7.5 hours; and in 2000, 6.9 hours.^{67,68} Occupational and social demands of modern life have been implicated. Although people in many developed countries (except those committed to napping as a cultural practice) believe that one must sleep for 8 consecutive hours,

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FIGURE 1
Mortality hazard ratios according to sleep duration for men and women



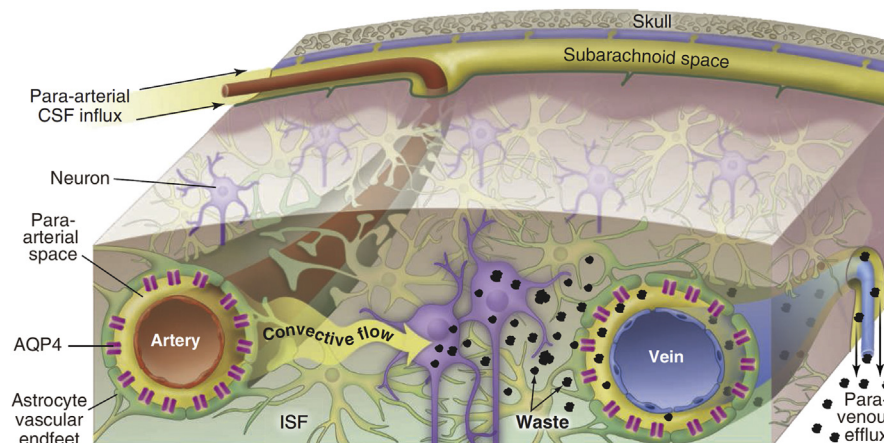
Data collected from 636,095 men and 480,841 women in Cancer Prevention Study II (1982-1988). Both men and women with usual sleep duration of 7 hours had best survival. Participants reporting sleep durations ≤ 6 hours and ≥ 8 hours had significantly increased mortality hazard.⁷

Reproduced, with permission, from Luyster et al.¹¹

there is experimental and historical evidence that the current habit is an adaptation. In 1992, Thomas Wehr⁶⁹ reported an experiment in which people were placed into darkness for 14 hours every day for a month. By the fourth week, people developed a pattern of sleep characterized by a “first sleep” for 4 hours, then waking for 1-2 hours, and subsequently had a “second sleep” for 4 hours.⁶⁹ This biphasic pattern is

considered the natural tendency for humans, and is consistent with the historical record.^{70,71} Prior to the availability of artificial light, the hours after the “first sleep” were not spent in solitude, but were often social events. The initial impetus to shift to a sleep pattern of 8 consecutive hours starting later in the evening is attributed to street and domestic lighting, which extended the period of wakefulness.

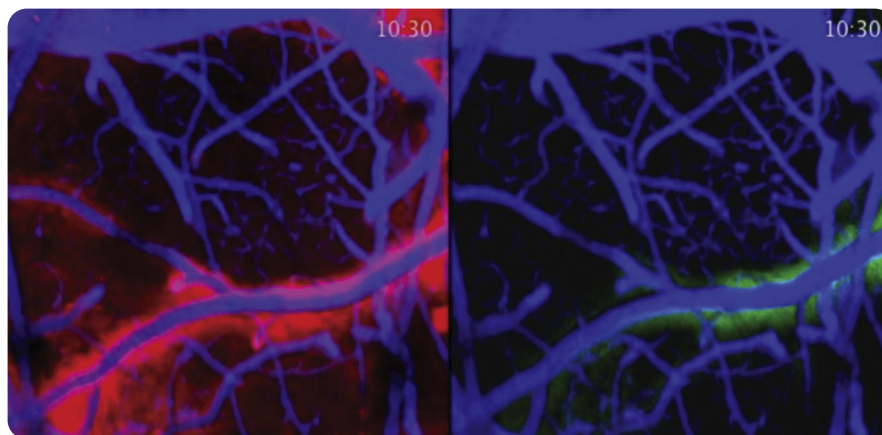
FIGURE 2
Pathway to clear cellular waste from the brain using the glymphatic system



Cerebrospinal fluid (CSF) passes through the para-arterial space surrounding the arteries (*top part* of the Figure). This space is bound by the non-luminal surface of the blood vessel and the apical processes of astrocytes. Aquaporin-4 (AQP4) is a water channel that facilitates convective flow out of the para-arterial space into the interstitial space. CSF exchanges with interstitial fluid (ISF) and generates a convective flow that clears the waste using a paravenous route.

Reproduced with permission from American Association for the Advancement of Science, from Nedergaard.⁶²

FIGURE 3
Cerebral spinal fluid influx in a murine model



Difference of cerebral spinal fluid influx in the brain of a sleeping (*left*) and awake (*right*) mouse. Fluorescent dye was injected to enable the study of cerebral spinal fluid dynamics in a live mouse using 2-photon imaging. *Red* represents greater flow in the sleeping animal. *Green* indicates decreased flow in the awake animal.

Images provided by Drs Maiken Nedergaard and Lulu Xie of Division of Glial Disease and Therapeutics, Center for Translational Medicine, Department of Neurosurgery, University of Rochester Medical Center. Work was funded by National Institutes of Health/National Institute of Neurological Disorders and Stroke.

Sleep during pregnancy

Observational studies based on self-reports, as well as a limited number of polysomnography studies, have documented a high number of sleep disturbances during pregnancy, including snoring,^{19,31,44,46,72-75} nonrefreshing sleep,⁷⁶ insomnia,^{73,77} periodic leg movement during sleep,^{19,72,73,78,79} and sleep-disordered breathing.^{80,81} A critical appraisal of the evidence is beyond the scope of this article—the interested reader is referred to the original sources.

Sleep and pregnancy: two challenges to the respiratory system

Sleep is a rest period for most organ systems, including musculoskeletal, gastrointestinal, and cardiovascular.^{14,82-84} In contrast, sleep challenges the respiratory system in multiple ways. For example, during sleep, the upper airways become narrow and lung volume smaller.⁸²⁻⁸⁴ These changes are more pronounced during rapid eye movement, when there is decreased muscular tone.

Pregnancy is a physiologic challenge to virtually every organ system (eg, cardiovascular, metabolic, immune), and in particular, the respiratory system.⁸⁵ The upper airways narrow due to vascular congestion, mucosal edema, and decreased lung volume.^{20,44,74,75,86,87} Elevation of the diaphragm, especially in the third trimester, leads to a reduction in functional residual capacity.^{20,75,85} Thus, the combination of sleep and pregnancy represents a magnified “stress test” to the respiratory system, which can unmask the propensity to develop “sleep-disordered breathing.” This term encompasses obstructive sleep apnea, periodic episodes of hypoxia, central apnea, and sleep hypopnea. Although the mechanisms of disease, consequences, and treatment of each of these

conditions may differ, the term “sleep-disordered breathing” has been widely used, because respiratory therapy (eg, nasal continuous positive airway pressure [CPAP]) is effective for many of these conditions.

The diagnosis of sleep disorders

Methods of varying complexity are used to diagnose sleep disorders. Most studies during pregnancy have used a symptom-based approach, relying on either the patient or partner’s report of snoring, apnea, or excessive leg activity.^{31,88,89} Several questionnaires are available (eg, Berlin or Hawaii questionnaire, Epworth sleepiness scale).^{31,34,35,37,42,44,46,48,49,90,91} The gold standard for the diagnosis of sleep disorders is polysomnography, in which the patient is studied and monitored continuously in a sleep laboratory. This modality consists of a comprehensive recording of biophysiologic parameters by electroencephalography, electrooculography, electromyography, electrocardiography, nasal and oral airflow, as well as pulse oximetry.^{92,93}

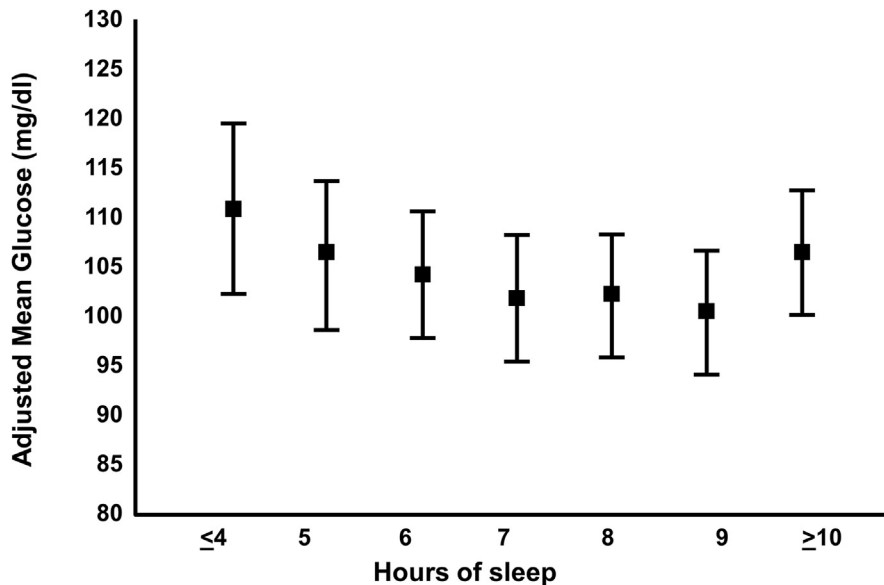
The different approaches to the diagnosis of sleep disorders have varying accuracies when compared to polysomnography; hence, the method of diagnosis can become a confounder when assessing the relationship between sleep disorders and pregnancy complications.⁹⁴

Are sleep disorders during pregnancy associated with gestational diabetes?

In this issue of the *American Journal of Obstetrics and Gynecology*, Pamidi et al⁵⁴ report a systematic review and metaanalysis indicating that maternal sleep-disordered breathing is associated with gestational diabetes (adjusted odds ratio [aOR], 1.86; 95% confidence interval [CI], 1.30–2.45). This association relied on 4 studies in which sleep disorders were diagnosed based on symptoms.^{21,30-32}

FIGURE 4

Maternal mean plasma glucose concentrations after 50-g glucose challenge



Means are adjusted for maternal age and race/ethnicity. Error bars are SE.

Open access article. Qiu et al.³⁰

In October 2013, Luque-Fernandez et al⁵⁵ reported a metaanalysis of sleep-disordered breathing and gestational diabetes based on a total of 9795 pregnant women, and reported that sleep-disordered breathing was associated with a >3-fold risk of gestational diabetes with a pooled body mass index (BMI) aOR of 3.06 (95% CI, 1.89–4.96). In the same month, Reutrakul et al³³ reported a study using polysomnography and noted that women with gestational diabetes had a lower total sleep time, a higher apnea hypopnea index, and a greater frequency of obstructive sleep apnea than pregnant women with a normal glucose tolerance test (73% vs 27%, $P = .01$). This association remained significant after adjustment for prepregnancy BMI (OR, 6.6; 95% CI, 1.15–37.96).

Experimental evidence in human beings that sleep deprivation leads to carbohydrate intolerance

The key observations include the following:

- Partial sleep deprivation in healthy nonpregnant individuals during a single night (only 4 hours of sleep) reduces insulin sensitivity by 19–25%.⁹⁵
- Sleep restriction to 5 hours per night for 1 week in healthy men reduces insulin sensitivity by 11%.⁹⁶
- Progressive sleep restriction in nonpregnant women is associated with increased energy intake and net weight gain.⁹⁷
- In pregnant women, glucose concentrations after a 50-g oral glucose tolerance test decreased 4% for each hour of reduced sleep time.³²

- In pregnant women, the mean glucose concentration varies as a function of hours of sleep³⁰ (Figure 4).

The precise molecular mechanisms linking sleep deprivation with carbohydrate intolerance are complex, and involve hypoxia-induced inflammation, activation of the sympathetic nervous system with up-regulation of counter-regulatory hormones, and high circulating concentrations of leptin (which leads to insulin resistance).⁹⁸

Sleep disorders (including pregnancy-onset snoring) and gestational hypertension/preeclampsia

Pamidi et al⁵⁴ reported that maternal sleep-disordered breathing is associated with an increased risk of gestational hypertension or preeclampsia. This conclusion was derived from 12 studies of symptom-based assessment of obstructive sleep apnea (OR, 3.11; 95% CI, 2.28–4.25), as well as 6 studies utilizing polysomnography (OR, 2.25; 95% CI, 1.13–4.52).

Snoring (the vibration of respiratory structures resulting from turbulent flow when the upper airway is narrowed during sleep)⁹⁹ is more common in pregnant than in nonpregnant women (14–23% vs 4%).^{42,100} The Nurse's Health Study reported that snoring increases the risk of hypertension, independent of age and BMI in nonpregnant women.¹⁰¹ O'Brien et al¹⁰² investigated the clinical significance of pregnancy-onset snoring in a prospective cohort study of 1719 pregnant women (34% of patients had chronic snoring, and 25% pregnancy-onset snoring). New-onset (but not chronic) snoring was associated with gestational

hypertension (OR, 2.36; 95% CI, 1.48–3.77; $P < .001$) and preeclampsia (OR, 1.59; 95% CI, 1.06–2.37; $P = .024$) after adjustment for confounders. The authors estimated that if snoring plays a causal role in hypertensive disorders of pregnancy, 18.7% of gestational hypertension and 11.6% of preeclampsia could be ameliorated by eliminating pregnancy-onset snoring. Interestingly, snoring was not implicated in gestational diabetes.¹⁰² O'Brien et al¹⁰² proposed that 2 questions about snoring and the timing of its onset could be a strategy to identify patients at risk for hypertensive disorders of pregnancy in a clinical setting. The health care implications of this have been the subject of correspondence in this Journal.^{103,104}

The precise mechanisms linking sleep disorders and gestational hypertension/preeclampsia remain to be elucidated. Sleep deprivation is associated with intravascular inflammation, which is also an important feature of preeclampsia.¹⁰⁵⁻¹⁰⁷ Specifically, poor sleep quality during pregnancy is associated with higher serum concentrations of inflammatory cytokines and chemokines, such as tumor necrosis factor- α ,¹⁰⁸ interleukin (IL)-8,¹⁰⁹ and IL-6, all of which have been in patients with preeclampsia.¹⁰⁹ Intravascular inflammation leading to endothelial cell dysfunction is a common pathway of multiple mechanisms of disease responsible for preeclampsia.^{110,111}

Is there a role for CPAP in preeclampsia?

In a series of fascinating studies using polysomnography, Edwards et al⁴¹ first demonstrated marked alterations in the sleep architecture of patients with preeclampsia compared to that of normal pregnant women. A key finding was that patients with preeclampsia had a significantly increased percentage of time spent in slow-wave sleep (21 ± 2 vs 43 ± 3 ; $P < .001$).

What is slow-wave sleep and is it important? Also known as “deep sleep,” slow-wave sleep is characterized by epochs (30 seconds of sleep) that consist of $\geq 20\%$ of slow-wave (delta) sleep (also known as stage-3 sleep).¹⁴ Slow-wave sleep is considered important for the consolidation of new memories¹¹² and is also involved in the secretion of growth hormone.¹¹³ Women with preeclampsia spend more time in deep sleep. One possible explanation is that cytokines (such as IL-1 and tumor necrosis factor- α) can increase slow-wave sleep,⁴¹ as they are elevated in the maternal circulation of those with preeclampsia.¹⁰⁵⁻¹⁰⁷ Cerebral edema, which can be observed in some patients with preeclampsia, can also play a role.⁴¹

In normal pregnancy, blood pressure is the highest during the daytime. In 1976, Redman et al¹¹⁴ reported that in preeclampsia, there was a reversal diurnal blood pressure rhythm (ie, the nocturnal blood pressure was higher than at daytime).¹¹⁵ Such reversal had also been reported with snoring and obstructive sleep apnea.¹¹⁶⁻¹¹⁹ Therefore, Edwards et al¹²⁰ proposed that nasal CPAP may improve blood pressure in women with preeclampsia and reported that auto-setting nasal CPAP administered through sleep at night resulted in a marked reduction in blood pressure (before treatment, mean systolic

146 mm Hg, and mean diastolic 92 mm Hg; after treatment, mean systolic 128 mm Hg, and mean diastolic 73 mm Hg). The authors concluded that partial upper airway obstruction during sleep in women with preeclampsia was associated with an elevation in blood pressure, which could be treated with nasal CPAP.¹²⁰

Next, a randomized clinical trial tested the effect of nocturnal nasal CPAP on maternal cardiac output.⁴⁵ Twenty-four women with preeclampsia were randomly allocated to receive nasal CPAP or no treatment. Patients allocated to CPAP had a reduction in total peripheral vascular resistance and improvement in cardiac output. It is noteworthy that all of these observations were made in women with preeclampsia without requiring the diagnosis of a specific sleep disorder prior to respiratory treatment.⁴⁵ In a different study, nasal CPAP was shown to increase fetal movements in patients studied with polysomnography and continuous ultrasound.²⁸ These studies have been the subject of an insightful analysis by O'Brien et al.¹²¹

Poyares et al²⁴ recently reported a randomized study in which women with preexisting hypertension (receiving treatment) and snoring were allocated to either standard of care or nasal CPAP in the first 8 weeks of pregnancy. Patients in the control group had a progressive increase in blood pressure which required treatment with α -methyldopa. In contrast, women allocated to CPAP had decreases in blood pressure and doses of antihypertensive medications.

Sleep disorders and fetal growth restriction

The evidence of whether sleep disorders increase the risk of fetal growth restriction has been contradictory. A recent prospective observational study using serial fetal biometry in women who had confirmed obstructive sleep apnea by polysomnography found that the rate of impaired fetal growth (defined as a fall in the customized centile $< 33\%$ between 33 weeks and term) was significantly greater in patients with obstructive sleep apnea than in the control group (43% vs 11%; $P = .04$). After adjustment for BMI, the association between obstructive sleep apnea and fetal growth restriction was borderline significant (OR, 5.3; 95% CI, 0.93–30.34; $P = .06$).¹²² Despite the sample size, a strength of the study rests on the use of a longitudinal approach, which is more sensitive than a cross-sectional approach for the characterization of fetal growth.

Maternal sleep position and late stillbirth

Women are advised to sleep on their left side during pregnancy based on the concept that the supine position can lead to compression of the inferior vena cava and reduce venous return and uterine blood flow. One study using xenon found that intervillous blood flow was lower in the supine position than in the left tilt position (113 ± 48 vs 141 ± 48 mL/min/dL; $P < .01$).¹²³ Whether this has any real consequences on the outcome of pregnancy has not been established. A controversial observation has been reported recently in a case-control study in which women who slept on

their back or on their right side the previous night (before fetal death) had a higher rate of late stillbirth than women who slept on their left side (aOR for back sleeping, 2.54; 95% CI, 1.04–6.18).¹²⁴ An editorial commenting on this article concluded that the study should be considered hypothesis generating, rather than hypothesis testing.¹²⁵ The puzzling observation was that women who got up to go to the toilet once or less on the last night before the diagnosis of stillbirth were more likely to have a late fetal death than those who got up more frequently. Chappell and Smith¹²⁵ proposed that this may be explained by reverse causation. Compromised babies have reduced frequency of fetal movements in the days leading to fetal death, and thus, mothers may sleep for longer periods of time because of decreased fetal activity.¹²⁵ Therefore, the longer sleep would not be the cause, but the consequence of decreased fetal movement. A recent cross-sectional study conducted in Ghana about sleep quality and practices during pregnancy (based on a postpartum questionnaire) found that women who slept in the supine position had an increased risk of stillbirth over those who did not (15.8% [3/19] vs 3% [6/197]; OR, 8.0; 95% CI, 1.5–43.2; $P = .016$).⁵¹ Interestingly, stillbirth was less frequent in women who snored than in those who did not snore (3.8% vs 4.2%), although this was not statistically significant ($P = 1.0$).⁵¹ Prospective studies would be required to determine if an association between sleep position during pregnancy is associated with fetal death. These associations require replication and further study.

Could there be long-term consequences of maternal sleep deprivation in the offspring?

Recent experimental evidence from animals suggests that sleep deprivation during pregnancy may have long-lasting effects on the offspring. One study examined the effect of sleep restriction on pregnant rats, and observed the sexual behavior of the offspring.⁵³ Male offspring were reported to have a lower motivation for sex (longer latency to first mount and a reduced number of mounts within a 30-minute period of observation) than males born to non-sleep-deprived mothers. In contrast, female offspring of sleep-deprived mothers had enhanced proceptivity (hopping, darting, and ear-wiggling) as well as disrupted sexual behavior characterized by mounting of the males during the period of observation, when compared to females in the control group. There were also changes in sexual behavior in male and female offspring when the fathers were exposed to sleep deprivation. That study raises interesting questions about the long-term behavioral consequences and the mechanisms by which they arise in the offspring of parents with sleep deprivation.

Finally, investigators attempted to model chronic intermittent hypoxia, which resembles repetitive obstructive sleep apnea in pregnant rats.¹²⁶ Offspring of mothers exposed to intermittent hypoxia had asymmetric growth restriction at birth, but in adulthood, body weight was greater than in the controls. Moreover, exposed offspring had greater body fat deposition, hyperglycemia, and higher levels of insulin.¹²⁶

Whether the experimental model mirrors obstructive sleep apnea of pregnancy remains to be determined.

Conclusion

Pregnant women have an increased frequency of sleep disturbances and such disorders have been associated with pregnancy complications. Assessment of the quality and quantity of sleep has not been part of routine prenatal care. Whether the association between sleep disturbances and adverse pregnancy outcome is causal needs to be established (using a longitudinal approach, determining a dose response gradient between the severity of the sleep disorder and the subsequent pregnancy complications, and generation of large datasets of observational as well as interventional studies). Practical methods to characterize sleep architecture in pregnancy and define pregnancy-specific screening tools are also needed.¹⁰⁴ The diagnosis and optimal treatment of sleep disorders has potential benefits for: (1) reducing pregnancy complications in the index pregnancy; (2) health of the mother after pregnancy; and (3) short- and long-term consequences for the offspring. Pregnancy may be an ideal time to screen for sleep disturbances and to implement treatment that may have preventive implications and long-term benefits for public health. ■

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