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## Sleep-disordered breathing and pregnancy: potential mechanisms and evidence for maternal and fetal morbidity

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### Abstract

**Purpose of review**—This article reviews current data on pathophysiologic mechanisms by which sleep-disordered breathing during pregnancy may cause harm, and explores biological pathways for associated adverse maternal and fetal outcomes, especially pregnancy-induced hypertension and gestational diabetes.

**Recent findings**—Accumulating data indicate that snoring and sleep apnea during pregnancy are likely to increase the risk for gestational hypertension and preeclampsia. Several new studies have observed that sleep-disordered breathing and short sleep duration also increase the risk of gestational diabetes, similar to observations in the general population. There are varying levels of emerging evidence for potential mechanisms, including oxidative stress, increased sympathetic activity and inflammation, adipokine levels and insulin resistance, linking sleep-disordered breathing events during pregnancy to adverse outcomes.

**Summary**—Sleep-disordered breathing and adverse maternal–fetal outcomes such as preeclampsia and gestational diabetes share a number of mechanistic pathways, and growing data in pregnant women indicate that snoring and sleep apnea increase the risk of these and other complications for both the mother and the fetus. Nevertheless, direct evidence of the pathophysiologic mechanisms by which sleep-disordered breathing during pregnancy exerts negative effects remains sparse.

### Keywords

gestational diabetes; gestational hypertension; preeclampsia; sleep apnea; sleep-disordered breathing

### Introduction

Sleep-disordered breathing (SDB) is a common sleep disturbance among pregnant women. The term SDB refers to the spectrum of breathing disorders during sleep, ranging from uncomplicated snoring to the most severe forms of SDB, obstructive sleep apnea (OSA) and the obesity–hypoventilation syndrome [1]. These breathing disturbances are characterized by repeated episodes of partial or complete upper airway obstruction during sleep and can result in disruption of normal ventilation, intermittent hypoxemia, and arousals from sleep

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[2,3]. Physiologic and hormonal changes occur during pregnancy that increase the likelihood of developing SDB and magnify its effects, including gestational weight gain, pregnancy-associated nasopharyngeal edema, decreased functional reserve capacity and increased arousals from sleep [4,5] (a review of diagnosis and management of pregnancy-associated SDB is beyond the scope of this paper, but is covered by these reviews).

During the third trimester, when gestational SDB is most likely to occur, the prevalence of habitual snoring has been estimated to be 10–27% of pregnant women [5]. The prevalence of OSA in pregnancy has not been systematically evaluated. There is growing evidence that SDB is associated with adverse pregnancy outcomes, especially pregnancy-induced hypertension and gestational diabetes [6–8]. This article reviews current data on pathophysiologic mechanisms by which SDB during pregnancy may cause harm, and explores biological pathways for associated adverse maternal and fetal outcomes.

## Potential mechanisms for adverse perinatal outcomes

In the nonpregnant population, SDB and short sleep duration are strongly associated with diabetes [9,10], hypertension [11–15], and cardiovascular disease [16–18]. Similarly, in pregnant women, evidence suggests that snoring, sleep apnea and short sleep duration are likely to increase adverse outcomes, including gestational diabetes and preeclampsia [19–22]. Among pregnant women with OSA, chronic intermittent hypoxia and sleep fragmentation with sleep loss are thought to be key factors [3,9,19,23,24]. The primary affected domains include sympathetic activity, oxidative stress and inflammation, adipokines, and the hypothalamic–pituitary–adrenal (HPA) axis [3,23,25,26]. Most adverse pregnancy outcomes, aside from early pregnancy loss, emerge in the third trimester. Thus, sleep disturbances during the first two trimesters may potentially disrupt placental and fetal development.

### Oxidative stress owing to intermittent hypoxia

During sleep, individuals with SDB experience recurrent episodes of intermittent hypoxia, alternating between hypoxia and reoxygenation. In animal studies, intermittent hypoxia leads to oxidative stress, inflammation, and reductions in antioxidant levels (reviewed by Lavie, [27]). Increased oxidative stress caused by intermittent hypoxia appears to play an important role in the mechanism for insulin resistance and thus, potentially, in the onset of gestational diabetes. For instance, mice exposed to intermittent hypoxia demonstrated increased pancreatic beta cell proliferation and cell death owing to oxidative stress [28].

There is also increasing evidence that preeclampsia is associated with increased oxidative stress owing to ischemia–reperfusion events and with reduced antioxidant defences [29]. During hypoxia/reperfusion, the initial response is an increase in the generation of reactive oxygen species. When the generation of reactive oxygen species generation exceeds antioxidant capacity, oxidative stress damages cells and tissues [27,30,31]. It is possible that, among pregnant women with SDB, intermittent hypoxia and abnormal sympathovagal balance contribute to the development of preeclampsia [30].

### Sympathetic activity

Upper airway obstruction during sleep results in recurrent brief awakenings or microarousals that reduce slow wave and total sleep time and increase sympathetic activation, with effects carrying over into daytime [32,33]. Such increases in sympathetic activity may be responsible, at least in part, for acute blood pressure (BP) changes and glucose intolerance seen in patients with OSA [34]. Intermittent hypoxia in early gestation can also contribute to increased sympathetic activity [15,19,35]. As women with preeclampsia have been observed

to have elevated levels of sympathetic activity [36], these data suggest that women with SDB and intermittent hypoxia during pregnancy may be at increased risk for preeclampsia.

Gestational hypertension and preeclampsia are characterized by vasoconstriction, which is due to increased sympathetic nerve activity. Sympathetically mediated vasoconstriction of skeletal muscle is markedly greater in preeclamptic women compared with normotensive pregnant women [36]. SDB events leading to increased sympathetic activity could, therefore, be a mechanism for vasoconstriction in some pregnant women.

### Inflammation

Intermittent hypoxia induces increased oxidative stress and elevated levels of proinflammatory cytokines [37]. Once inflammation occurs, it can trigger further oxidative stress [38,39]. In an animal model, both oxygen desaturations and respiratory efforts contributed to systemic inflammation; hypoxia–reoxygenation also induced endothelial dysfunction [40].

Habitual poor sleep quality or shortened sleep duration owing to gestational SDB may also contribute to increased inflammation. Poor sleep quality and continuity were associated with elevated C-reactive protein levels in healthy young women even after controlling for covariates [41]. Furthermore, higher levels of circulating tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) were observed in mothers with subjective sleep complaints during the third trimester [42]. Short sleep duration and poor sleep efficiency, common features of sleep in patients with SDB, have been associated with higher levels of interleukin-6 (IL-6), but not TNF- $\alpha$ , in mid and late pregnancy [43]. This is important because IL-6 has been reported to be involved in the pathogenesis of insulin resistance and type 2 diabetes [44].

Increased inflammation has been associated with adverse pregnancy outcomes [45–48], and increased IL-6, TNF- $\alpha$ , C-reactive protein levels and leukocyte counts are reported in gestational diabetes mellitus (GDM) [49], preeclampsia [50], intrauterine growth retardation [51], and preterm delivery [52]. Thus, the inflammatory response induced by SDB could provide a biological pathway between SDB and adverse pregnancy outcomes.

### Changes in the HPA axis

Hypoxia and sleep fragmentation caused by SDB can lead to increased secretion of plasma cortisol [25,26] and abnormalities in insulin and glucose metabolism [53,54]. Inflammatory responses are also regulated by the HPA axis through cortisol secretion. Proinflammatory cytokines can trigger the HPA axis to produce more cortisol [55], shutting down the inflammatory response [56,57]. Continual cortisol secretion decreases glucocorticoid receptor sensitivity, weakening cortisol's suppressive effects [56]. Thus, intermittent hypoxia, disrupted sleep and inflammation can lead to chronic HPA activation, causing decreased glucocorticoid sensitivity and increased inflammatory responses [19].

### Changes in adipokines

OSA potentially affects adipokine levels through oxidative stress [58,59], inflammation [60], and sympathetic activation [61]. Abnormalities in levels of leptin, an adipokine that regulates body weight through the control of appetite and energy expenditure, have recently been associated with adverse effects on weight control, cardiovascular health and glucose regulation [3]. However, in a study of pregnant women with severe preeclampsia, leptin levels were highly correlated with BMI, but not with the subsequent onset of preeclampsia [62]. Thus, although intermittent hypoxia may affect leptin levels in pregnant women with SDB, leptin may not play a direct role in the pathogenesis of preeclampsia, and its association with obesity must be considered.

Adiponectin is an active polypeptide hormone with insulin-sensitizing, antiatherogenic, and anti-inflammatory properties that is secreted by adipose tissue [63]. Oxidative stress, TNF- $\alpha$ , and IL-6 all reduce adiponectin production, and levels are lower in patients with OSA, GDM, hypertension, coronary artery disease, and type 2 diabetes compared with normal individuals [63,64]. Although plasma adiponectin is an independent determinant of homeostasis model assessment of insulin resistance in OSA patients, it is more closely related to obesity than to sleep apnea [63]. Whether adiponectin levels are lower among pregnant women with OSA than normal pregnant women and how this affects women's risk for GDM bears further investigation.

### Insulin resistance

Insulin resistance has been reported to contribute to the onset of both diabetes and hypertension [10–12]. It is associated with short sleep duration and can occur in the setting of SDB due to increased sympathetic nervous activity [65,66]. Insulin resistance increases in normal pregnancy [64]. This physiological insulin resistance is not accompanied by a rise in overall sympathetic activity, but there is evidence of moderate sympathetic overactivity in muscle and the heart [67]. In women with GDM, studies in skeletal muscle and adipose tissue demonstrate additional defects in insulin signaling [64].

In the nonpregnant state, increased sympathetic nervous system activation owing to arousals is thought to contribute to the increased prevalence of diabetes in patients with SDB [9]. When the sleep of normal volunteers was fragmented for two nights using auditory and mechanical stimuli, a 20–25% decrease in insulin sensitivity and glucose effectiveness (the effect of glucose on its own disposal independent of insulin response) and increases in morning cortisol and sympathetic activity were seen [68\*\*]. Punjabi and Beamer [10] also described lower insulin sensitivity among individuals with OSA compared with nonapneic controls, suggesting that obstructive events are associated with impaired insulin sensitivity and pancreatic beta cell dysfunction. If similar events occur in the gravid state, microarousals and intermittent hypoxemia in pregnant women with sleep disruption could lead to alterations in glucose metabolism that increase the risk of gestational diabetes.

Preeclampsia is a state of increased insulin resistance and sympathetic overactivity. Insulin resistance is associated with microvascular dysfunction, and inflammation has also been noted to be involved in the onset of hypertension, coronary artery disease and preeclampsia [69,70]. As insulin resistance, sympathetic overactivity and inflammation are all commonly observed in SDB [69], snoring or sleep apnea during pregnancy may potentially precipitate or exacerbate events associated with the development of preeclampsia.

### Adverse pregnancy outcomes: possible biological pathways

SDB during pregnancy may be associated with adverse pregnancy outcomes via the mechanisms outlined in Fig. 1. Recently, a number of studies have examined the relationship between SDB and gestational diabetes [71\*\*,72\*\*]. Both new and older studies have demonstrated that SDB may increase the risk for the hypertensive disorders of pregnancy [6,73\*]. Studies have also examined the relationship between SDB and other adverse outcomes including fetal outcomes and preterm labor [6,74]. Possible biological pathways for the development of these outcomes and supporting evidence of involvement of these mechanisms are reviewed.

### Glucose dysregulation

Glucose dysregulation, which spans a continuum from milder abnormal glucose tolerance to GDM [75,76\*,77], has been estimated to occur in 1–14% of pregnancies [75,77–79]. GDM and even mild maternal hyperglycemia without GDM are associated with increased risks for

maternal and fetal complications such as preeclampsia and fetal growth retardation, and future diseases such as type 2 diabetes, obesity and cardiovascular disease in both mothers and children [76,78–81].

Numerous epidemiological, clinical and experimental studies in the general population have reported that snoring and OSA are associated with increased risk of type 2 diabetes, glucose intolerance and insulin resistance independent of obesity and other risk factors [10,65,68, 82–84]. Preliminary studies have examined whether there is an analogous relationship in pregnancy between SDB and glucose intolerance or gestational diabetes. Several survey studies have reported that pregnant snorers are 2–7 times more likely to develop gestational diabetes than nonsnoring women [71,72,73]. Additionally, we recently demonstrated that moderate OSA (Apnea–Hypopnea Index>15) is associated with maternal hyperglycemia [22]. These findings suggest that OSA and self-reported habitual snoring are associated with an increased risk of gestational diabetes. However, the underlying mechanism is not clear.

Findings from studies in the general population show that poor-quality sleep and sleep loss can also increase the risk of obesity and diabetes by impairing glucose regulation and the neuroendocrine control of appetite [3,65]. Preliminary studies in pregnant women have observed that short sleep duration ( < 4 vs. >9 h or <7 vs. >7 h) is associated with increased risk of GDM independent of other risk factors [71,72]. We recently observed that napping, which can reflect nocturnal sleep loss, is associated with higher maternal glucose levels [22].

These data suggest that hypoxia and sleep loss due to SDB may play a role in the development of gestational diabetes. Hypothetically, disturbed sleep/wake cycles or sleep at unusual times may also cause hormones that regulate glucose metabolism and appetite to fluctuate excessively, disrupting the sympathetic–parasympathetic balance.

Among the potential mechanisms for the relationship between SDB and GDM, at present, there is only limited evidence of a direct relationship between GDM and oxidative stress. The release from placental tissue of 8-isoprostane, a biomarker for oxidative stress [85], is greater in women with GDM compared with healthy pregnant women [86] and the response of placental tissue to oxidative stress in women with GDM is reduced [87]. Release of 8-isoprostane from incubated placenta, adipose, and skeletal muscle tissues is also higher in women with GDM compared with pregnant controls [88].

Recent studies demonstrate that low circulating levels of the insulin-sensitizing protein adiponectin and higher serum concentrations of the inflammatory biomarker C-reactive protein may be associated with a higher risk of GDM [89–92]. Lower levels of adiponectin, Th1 cytokines, and inflammatory cytokines such as IL-6, IL-10 and TNF- $\alpha$  have been observed in mothers with GDM compared with controls [93] and, as reviewed above, in individuals with obstructive sleep apnea. However, the relationship between SDB, cytokines and GDM in pregnant women has not been elucidated.

In summary, the limited available data suggest that the mechanisms of injury associated with SDB, including oxidative stress, inflammation and sympathetic activation, are also important in the pathogenesis of GDM. The contribution of specific oxidative stress and inflammatory pathways to alterations in glucose metabolism in pregnancy remains to be investigated.

### **Pregnancy-induced hypertension**

Pregnancy-induced hypertension is usually defined as repeated BP recordings of more than 140/90 mmHg, diagnosed after 20 weeks' gestation in previously normotensive women [94].

When unaccompanied by proteinuria, this condition is called gestational hypertension, but if it includes proteinuria it is called preeclampsia [94]. Pregnancy-induced hypertension is associated with maternal and neonatal morbidity and mortality, including future hypertension, metabolic syndrome, stroke, and premature cardiovascular death [95].

Snoring during pregnancy has been independently associated with an increased risk of developing pregnancy-induced hypertension [6,73\*,96\*,97,98]. Women with preeclampsia have also been observed to have smaller upper airways [7], which are associated with SDB and may be due to pharyngeal edema.

The pathophysiology of preeclampsia is multifactorial. Oxidative stress is likely a key factor. Endothelial dysfunction or inappropriate endothelial cell activation is the most common clinical manifestation in preeclampsia [99]. Reactive oxygen species, which have been implicated in preeclampsia [100], have been observed in some but not all studies to be released during intermittent hypoxia events [27,101] and are likely involved in endothelial cell activation [102]. Both SDB and endothelial dysfunction occur more frequently in women with preeclampsia than those with uncomplicated pregnancies [8], suggesting that intermittent hypoxia may cause oxidative stress, leading to endothelial dysfunction as is seen in preeclampsia.

The increased levels of proinflammatory cytokines that occur in SDB are another important potential contributor to the causal pathway in preeclampsia. The oxidative stress associated with SDB can increase inflammatory cytokines and activation of endothelial cells, leading to endothelial dysfunction and cardiovascular disease [103]. Similarly, the normal maternal inflammatory response to pregnancy [95] could be exacerbated by SDB, predisposing pregnant women to preeclampsia. Plasma concentrations of cytokines including C-reactive protein, IL-6, TNF- $\alpha$ , and 8-isoprostane have all been found to be significantly higher in women with preeclampsia than in healthy pregnant women [104\*]. Inflammatory cytokines such as TNF- $\alpha$  are also important in the pathogenesis of preeclampsia, as they interfere with trophoblast implantation [105,106], which has been observed in preeclamptic pregnancies [107]. However, whether levels of inflammatory cytokines are higher in women with SDB during pregnancy and are associated with a greater risk of preeclampsia independent of other risk factors is unknown.

Preeclampsia is characterized by a marked increase in peripheral vascular resistance, leading to elevated BP [95]. Among pregnant women with SDB, increased sympathetic vasoconstrictor activity owing to hypoxemia and arousals during sleep may cause increases in peripheral vascular reactivity. Such increases, in turn, could lead to elevations in systemic arterial BP and reductions in maternal cardiac output accompanying compromises in uteroplacental blood flow, as is observed in preeclampsia [108–110].

### **Fetal complications**

Maternal sleep is important for fetal well-being, because uteroplacental blood flow and the secretion of neurohormones, especially growth hormones, are at their peak during sleep [109,111]. Women residents, working long hours compared with controls, and presumably sleeping less, had higher rates of preterm labor (11 vs. 6%) and preeclampsia (8.8 vs. 3.5%). Residents who worked 100 h or more per week during the first trimester also had a 9.8% risk of preterm delivery, compared with 4.6% for residents who worked less [112]. In case series and mostly small studies, SDB has been associated with increased risks of premature delivery, intrauterine growth restriction, lower infant Apgar scores and even infant mortality [4,6,21,109,113\*\*].

The maternal hormonal and metabolic alterations observed in SDB can negatively impact the uterine environment. Pregnant women with SDB can develop hypoxemia during sleep owing to decreased cardiorespiratory reserve. Even small declines in maternal oxygenation can endanger oxygen delivery to the fetus. Furthermore, any cause of maternal hypercapnia leads quickly to fetal respiratory acidosis. Fetal heart decelerations and accompanying acidosis have been recorded during maternal apneic episodes with oxygen desaturation [4,114,115]. Nevertheless, although lower infant Apgar scores and higher rates of intrauterine growth restriction have been observed among snorers compared with nonsnorers [6], other studies found no association between maternal snoring and infant birth weight [116,117].

In an animal model, reductions in fetal growth associated with maternal intermittent hypoxia were readily reversible after birth [118]. However, the pups demonstrated sustained postnatal alterations in respiratory control, leading to speculation that similar changes in humans could place them at risk for conditions such as sudden infant death syndrome. Studies in humans have not tested this hypothesis.

Fewer fetal movements have been observed in preeclamptic women with SDB, though they were compared with women with normal pregnancies rather than other preeclamptic women [74]. Case studies have reported that, when women with SDB received treatment before the third trimester, they delivered infants with normal birth weight and high Apgar scores [4,98,119]. However, causality has not been established.

### Other pregnancy complications

In a retrospective cohort study, women with OSA were more likely to have preterm and cesarean deliveries, probably owing to maternal comorbidities [113\*\*]. Snoring women have also been reported to be more likely to require an emergency cesarean delivery than nonsnorers [73\*,120].

### Conclusion

In summary, many of the pathways via which SDB causes injury leading to increased risks for hypertension, cardiovascular disease and diabetes mellitus in the general population have also been implicated in the pathogenesis of preeclampsia, GDM and other adverse outcomes in the pregnant population. Although evidence of increased risks for preeclampsia and GDM among pregnant women is accumulating, data that explicitly examine the impact of gestational SDB on these mechanistic pathways –oxidative stress, increased sympathetic activity, inflammation, change in the HPA axis, adipokines and insulin resistance – and links them to pregnancy outcomes remain sparse. The need exists for additional studies to promote an improved understanding of how SDB during pregnancy promotes adverse maternal–fetal outcomes, the magnitude of these effects, and interventions that effectively mitigate increased risk.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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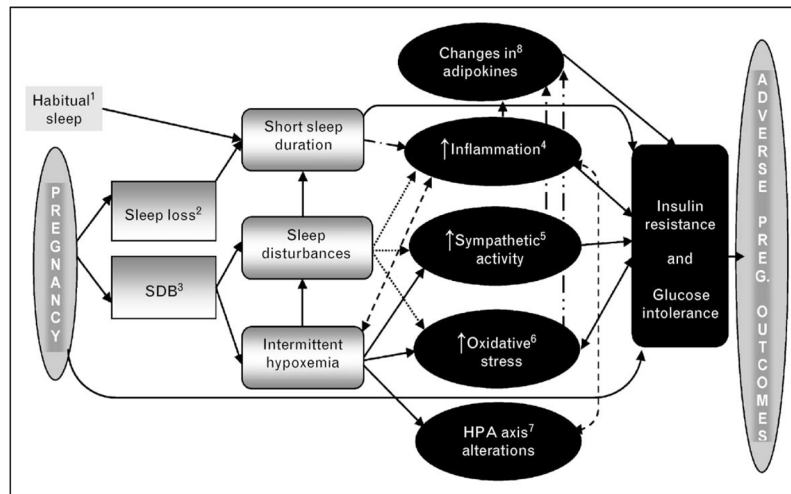
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**Figure 1. Possible pathways for impact of sleep-disordered breathing on maternal and fetal outcomes**

We propose that a number of causal pathways may link sleep during pregnancy with adverse pregnancy outcomes. 1) In the present model, short sleep duration (as a trait factor) may be a predisposing factor for adverse pregnancy outcomes. 2) Sleep loss may contribute to sleep disturbances and reduce sleep duration. 3) SDB can cause repeated arousal from sleep and intermittent hypoxemia. It should be noted that each of these phenomena (2 and 3) is probably not directly related to the various aspects of sleep disturbance, but instead has its own mediators and moderators. For the sake of simplicity, these are not contained in the schematic and include, but are not limited to, pregnancy-related physical changes affecting the respiratory system; pregnancy-related weight gain; and pregnancy-related changes in gonadotrophic hormones. 4) Short sleep duration due to sleep habits or sleep fragmentation and intermittent hypoxemia during pregnancy are associated with increased inflammatory cytokines such as tumor necrosis factor  $\alpha$ , interleukin 6 and so on. Other predisposing factors, such as obesity and neuroendocrine changes, may also contribute to sleep disturbances and/or increased inflammation. 5) Arousals and nocturnal hypoxia due to complete or partial upper airway obstruction during sleep are linked with a reduction in both total sleep time and increased sympathetic activation. Elevated sympathetic activity is likely to be directly responsible, at least in part, for the glucose dysregulation and preeclampsia. 6) Increased oxidative stress due to the cyclical nature of hypoxia–reoxygenation has been shown to be an important mechanism for insulin resistance, the onset of diabetes and preeclampsia. 7) Intermittent hypoxia, disrupted sleep and inflammation lead to chronic HPA activation, which, in turn, causes decreased glucocorticoid sensitivity and increased inflammatory responses. 8) Adipokine levels are affected by oxidative stress, inflammation and sympathetic activation seen in SDB and may play a role in the pathogenesis of gestational diabetes mellitus and preeclampsia. These maternal metabolic and hormonal alterations associated with SDB may be implicated in the pathogenesis of adverse maternal and fetal complications. It should be noted that each of these phenomena (4, 5, 6, 7 and 8) is not likely directly related to the various adverse outcomes, but instead has its own mediators and moderators. HPA, hypothalamic–pituitary–adrenal; SDB, sleep-disordered breathing.