

# Sleep-Disordered Breathing and Pregnancy-Related Cardiovascular Disease

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## Abstract

Sleep-disordered breathing (SDB) is a serious medical condition characterized by intermittent episodes of airflow limitation, intermittent hypoxia, and sleep disturbance triggering a pattern of autonomic dysfunction associated with hypertension, diabetes, and other adverse health conditions. SDB incidence is two to three times higher during pregnancy and is associated with an increased risk of cardiometabolic complications, including pre-eclampsia and gestational diabetes. Treatments to protect breathing during sleep are available, pointing to SDB as a potential therapeutic target to reduce maternal cardiometabolic morbidity. However, in clinical practice, the majority of SDB cases in pregnancy are undiagnosed, indicating a need to improve screening for SDB risk factors and referral for diagnostic testing. Furthermore, definitive clinical trials are needed to determine the extent to which SDB intervention reduces the risk of adverse cardiovascular and neonatal outcomes in pregnancy. This review article discusses an accumulation of research pointing to SDB as a prevalent risk factor for gestational cardiometabolic disease, as well as a potential therapeutic target to reduce cardiometabolic morbidity.

**Keywords:** sleep-disordered breathing, gestational hypertension, pre-eclampsia, pregnancy

## Introduction

**S**LEEP IS A FUNDAMENTAL REQUIREMENT for health and mediates essential molecular and physiological functions, including gene expression, energy metabolism, immune response, inflammatory signaling, and vascular endothelial function. Nearly a third of adults in the United States report insufficient sleep on a regular basis.<sup>1</sup> Sleep disorders (*e.g.*, obstructive sleep apnea [OSA] and insomnia) and sleep deficiency (*i.e.*, short sleep duration, irregular sleep timing, and poor sleep quality) are independently associated with an array of adverse health outcomes, including cardiometabolic disease.<sup>2</sup>

Sleep disturbance is more common among pregnant women than in the general population of women of childbearing age.<sup>3–5</sup> A particular concern is sleep-disordered breathing (SDB), a serious medical condition characterized by repeated episodes of partial (hypopnea) or complete (apnea) airway obstruction during sleep, oxygen desaturation–reoxygenation (*i.e.*, intermittent hypoxia), and sleep fragmentation. SDB triggers elevated sympathetic tone, oxidative stress, systemic inflam-

mation, endothelial dysfunction, and glucose dysregulation.<sup>2</sup> This pathophysiology is associated with hypertension, heart failure, stroke, arrhythmia, and metabolic impairment in non-pregnant adults.<sup>2</sup> SDB-associated mechanisms overlap with pathophysiology implicated in pregnancy complications—such as pre-eclampsia, cardiomyopathy, thromboembolism, and gestational diabetes—suggesting that SDB contributes directly to the risk of maternal cardiometabolic morbidity.

## Prevalence of SDB in Pregnancy

Habitual snoring is a hallmark symptom of SDB, indicating upper airway restriction during sleep and increased risk of sleep apnea. Self-reported snoring is two to three times more prevalent during pregnancy than nonpregnancy and may be higher in women with cardiovascular pathology during gestation, such as high blood pressure and pre-eclampsia.

Franklin et al.<sup>6</sup> published one of the earliest studies examining SDB symptoms during pregnancy, revealing that 23% of women reported snoring every night in the week before

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delivery, compared with 4% during prepregnancy. Cohort studies of >1000 women who were healthy at pregnancy onset reported habitual snoring in 33% and 35% of women in the third trimester.<sup>7,8</sup> Cai et al.<sup>9</sup> identified a threefold increase in the prevalence of habitual snoring across trimesters (9.5%, 13%, and 26%) in a cohort of ~2000 women with normal body mass index (BMI) at enrollment. In a prospective study comparing nonpregnant, healthy pregnant, and pre-eclamptic women, “habitual snoring” was reported by 17%, 35%, and 59% of women in the third trimester.<sup>10</sup> Cross-sectional studies indicate high rates of snoring among women with and without gestational hypertension (61% vs. 19% and 82% vs. 38%).<sup>11,12</sup>

Studies using objective assessments of breathing during sleep confirm the high prevalence of SDB in pregnancy. Using polysomnography, Pien identified an increase in SDB from 10.5% in the first trimester to 27% in the third trimester.<sup>13</sup> An in-home overnight assessment of breathing in >3000 healthy nulliparous women identified SDB in 3.6% of women who were 6–15 weeks pregnant, with a 2.5-fold increase by 22–31 weeks.<sup>14</sup> In this study, ~25% of women with BMI >30 at pregnancy onset exhibited SDB by 32 weeks of gestation, compared with women with BMI <25 (2%) and BMI <30 (7%).

In high-risk groups, SDB is a prevalent comorbidity.<sup>15</sup> In a number of studies, SDB was detected more often in women with hypertensive disorders of pregnancy than in nonhypertensive women (53% vs. 12% and 41% vs. 19%).<sup>12,11</sup> Cross-sectional analysis identified SDB in 22% of women with gestational diabetes, compared with 9% in nondiabetic women, matched for age, BMI, race, and parity.<sup>16</sup> The high prevalence of SDB in pregnancy and comorbidity with pregnancy conditions implicates SDB as a risk factor for maternal cardiometabolic disease.

### SDB as a Risk Factor for Gestational Cardiovascular Disease

Cardiovascular disease is a leading cause of maternal morbidity and mortality, which continues to occur at a high rate in the United States, compared with other developed countries.<sup>17</sup> Safe and effective therapeutic strategies to prevent and treat cardiovascular disease in pregnancy are limited. Delineating risk factors and modifiable targets to prevent and treat cardiovascular complications in pregnancy is an urgent research and clinical need. Managing pregnancy conditions may have long-term health benefits for women as well, because pre-eclampsia and gestational diabetes are associated with increased risk of cardiovascular and metabolic disease for years after pregnancy.<sup>18,19</sup>

SDB triggers autonomic, immune, and vascular pathobiology in adults<sup>2</sup> that potentially contributes to mechanisms of cardiovascular disease during gestation.<sup>20</sup> Impaired placental vascularization is a critical mechanism in the etiology of pre-eclampsia. The sympathetic and peripheral vasoconstrictive effects of SDB may contribute to poor uteroplacental vascular development, releasing proinflammatory and hypoxic factors into the maternal circulation and increasing cardiovascular stress.<sup>21–24</sup> Indeed, an accumulation of epidemiological findings indicates that SDB is independently associated with increased maternal cardiovascular disease risk.

Franklin et al.<sup>6</sup> provided early evidence of increased gestational hypertension (14% vs. 6%) and pre-eclampsia (10% vs. 4%) among women reporting habitual snoring during pregnancy compared with nonsnorers. O’Brien identified an association between pregnancy-onset snoring and gestational

hypertension (OR 2.36, 95% CI 1.48–3.77) and pre-eclampsia (OR 1.59, 95% CI 1.06–2.37).<sup>7</sup> Similarly, habitual snorers were more likely than nonsnorers to develop a hypertensive disorder of pregnancy in the third trimester (OR 2.3, 95% CI 1.4–4.0), independent of early pregnancy BMI, age, parity, and other pregnancy conditions.<sup>8</sup> Several studies show that gestational diabetes, which occurs in ~7% of pregnancies, is two to three times more likely in women who snore than in nonsnorers, after controlling for several factors, including age, BMI, race/ethnicity, and other sleep disturbances.<sup>8,16,25,26</sup>

National databases of pregnancy outcomes and clinical studies using objective measures of clinically defined SDB (e.g., polysomnography and ambulatory devices) also provide evidence of SDB-associated risks to maternal cardiovascular health. Analysis of the National Perinatal Information Center database (2010–2014, >1.5 million records) showed that a diagnosis of SDB was associated with increased cardiometabolic disease risk, including pre-eclampsia (OR 2.22, 95% CI 1.94–2.54), eclampsia (OR 2.95, 95% CI 1.08–8.02), cardiomyopathy (OR 3.59, 95% CI 2.31–5.58) heart failure (OR 3.63, 95% CI 2.33–5.66), and gestational diabetes (OR 1.51, 95% CI 1.34–1.7) in fully adjusted models.<sup>27</sup>

Similarly, in the Nationwide Inpatient Sample database (1998–2009, >55 million records), SDB diagnosis was associated with increased risk of pre-eclampsia (OR 2.5, 95% CI 2.2–2.9), eclampsia (OR 5.4, 95% CI 3.3–8.9), cardiomyopathy (OR 9.0, 95% CI 7.5–10.9), pulmonary embolism (OR 4.5, 95% CI 2.3–8.9), and gestational diabetes (OR 1.89, 95% CI 1.67–2.14), as well as a fivefold increase in maternal in-hospital mortality.<sup>28</sup> These findings are consistent with several cross-sectional clinical studies evaluating SDB and maternal cardiovascular risk.<sup>29</sup>

Facco et al.<sup>14</sup> conducted the largest prospective study to date, with objective in-home assessments of breathing during sleep in nulliparous women in early pregnancy (6–15 weeks gestation) and mid-pregnancy (22–31 weeks gestation). SDB (apnea-hypopnea index [AHI]  $\geq 5$  events per hour of sleep) in early pregnancy was associated with incident pre-eclampsia (OR 1.94, 95% CI 1.07–3.51), composite hypertensive disorders of pregnancy (OR 1.46, 95% CI 0.91–2.32), and gestational diabetes mellitus (OR 3.47, 95% CI 1.95–6.19), independent of age, BMI, pregnancy weight gain, race/ethnicity, and chronic hypertension. SDB detected at mid-pregnancy was similarly associated with pre-eclampsia (OR 1.95, 95% CI 1.18–3.23), hypertensive disorders (OR 1.73, 95% CI 1.19–2.52), and gestational diabetes (OR 2.79, 95% CI 1.63–4.77). In this cohort, the majority of SDB identified was in the mild range (i.e.,  $\geq 5$  AHI < 15), yet still notably associated with cardiometabolic conditions. Furthermore, a dose response between AHI severity and cardiometabolic risk was identified at both early and mid-pregnancy time points. These findings indicate that evaluation for SDB should be considered throughout the course of pregnancy and that even mild breathing abnormalities during sleep warrant consideration as clinically significant to maternal health.

### Mechanisms Contributing to SDB in Pregnancy

Pregnancy invokes several physiological changes that could underlie increased susceptibility to SDB during gestation.<sup>30</sup> Estrogenic effects on vascular smooth muscle increase mucosal edema and nasal congestion, which contribute to airflow limitation during sleep. Increased blood volume during pregnancy

may contribute to fluid shifts from the lower extremities to the upper airway while in the sleeping position, decreasing airway patency. The diaphragm is elevated in pregnancy because of an enlarging uterus, reducing lung functional residual capacity and maternal oxygen reserve. Progesterone, a respiratory stimulant, upregulates respiratory drive, which generates an inspiratory negative pressure gradient against a collapsible airway, predisposing to obstruction.

In women with normal prepregnancy BMI, the cross-sectional diameter of the nasopharyngeal junction is narrowed in the third trimester, even in the waking state.<sup>31</sup> Increased adiposity with fat deposition in the upper airway and tongue further increases susceptibility to airway obstruction. Other mechanisms contributing to the development of SDB include impaired neural output to airway dilator muscles and altered chemoreceptor function, although it is not clear to what extent these mechanisms are involved in SDB etiology during pregnancy.<sup>32</sup>

### Diagnosis and Screening of SDB in Pregnancy

SDB is notably underdiagnosed in perinatal clinical care. Louis et al.<sup>28</sup> examined a database of >55 million pregnancy-related discharge records between 1998 and 2009, and found a diagnosis of SDB in only 0.003% (3/10,000) of women. Similarly, SDB was noted in 0.012% (12/10,000) of women in the National Perinatal Information Center database of >1.5 million pregnancies between 2010 and 2014.<sup>27</sup> These findings notably contrast with the 10% to 50% SDB prevalence identified in several epidemiological and clinical studies and are particularly concerning given the risk associations between SDB and maternal cardiovascular morbidity.<sup>11,13,33</sup>

In a survey of >700 women, 30% reported habitual snoring in the last 3 months of pregnancy, but only 5% were asked about snoring by their perinatal physician.<sup>34</sup> This heralds an urgent need to improve SDB diagnosis and referral in women during pregnancy, which necessitates both educating health care professionals about SDB and improving the availability of accurate and easily implemented screening tools to identify women at risk.

Commonly used screening tools for SDB in the general population (*e.g.*, Berlin Questionnaire, STOP-BANG, and Epworth Sleepiness Scale) do not accurately identify SDB in women during pregnancy.<sup>35–37</sup> These tools, based primarily on symptoms typical in men (*e.g.*, excessive daytime sleepiness), include items likely not predictive of SDB in women and exclude symptoms commonly reported by women, such as fatigue, anxiety, and depression. A few studies have aimed to develop a predictive screening tool in pregnancy.

Facco et al.<sup>36</sup> identified a four-variable model—including frequent snoring, age, continuous BMI, and chronic hypertension—that predicted OSA with >85% accuracy when validated against objective SDB assessment in 100 high-risk women. In a cohort of 3000 healthy nulliparous women, a three-variable model incorporating frequent snoring, age, and BMI produced a high level of accuracy (AUC >80%) for predicting SDB validated against objective measures in early and mid-pregnancy, as well as new-onset SDB during gestation.<sup>38</sup> Another three-variable model—using BMI, age, and a measure of tongue enlargement—predicted polysomnography-verified SDB in the first and third trimesters with >85% accuracy.<sup>39</sup> Bourjeily et al.<sup>40</sup> examined 100 women with self-reported snoring and BMI >30

during early pregnancy and found a model combining neck circumference and Mallampati classification (a score based on visual assessment of upper airway space) performed with >80% accuracy in identifying SDB.

Practical screening tools using easily available information are needed for risk stratification in pregnancy to prioritize the need for referral for a clinical evaluation of SDB. However, the same screening tool may not be generalizable between healthy and high-risk women or across trimesters, and a tool may vary in its ability to detect existing SDB versus the risk of developing it later in pregnancy. Continued research is needed in this critical area.

If SDB is suspected, women can be referred to a sleep disorder specialist for evaluation. Sleep clinic polysomnography represents the most comprehensive assessment of SDB, but it is expensive, requires an overnight stay in the clinic, and may take several months to schedule. Alternatively, home SDB testing with U.S. Food and Drug Administration–approved devices is a reliable, convenient, and cost-effective approach for assessing and diagnosing SDB.

### Treatment of SDB

Effective treatments exist for managing SDB. In adults, continuous positive airway pressure (CPAP) is the first line of treatment for mild, moderate, and severe SDB. CPAP is effective in reversing airway obstruction, thereby improving AHI, nocturnal oxygen saturation, and sleep quality. SDB treatment is efficacious in lowering blood pressure in adults with hypertension, improving glucose and insulin response in diabetes, and reducing complications in other cardiovascular diseases. However, few SDB intervention studies have been conducted during pregnancy.

In a study of 11 women with pre-eclampsia and mild SDB, one night of CPAP reduced mean systolic (128 ± 3 vs. 146 ± 6 mmHg) and diastolic (73 ± 3 vs. 92 ± 4 mmHg) blood pressure compared with a baseline night without treatment in the same women.<sup>41</sup> Poyares et al.<sup>42</sup> reported a reduction in blood pressure and hypertensive medication doses across pregnancy in women with mild SDB and chronic hypertension treated with CPAP (*n* = 7), where blood pressure and medication doses increased in the non-SDB-treated group (*n* = 9). In 12 women with pre-eclampsia, a single night of CPAP in the third trimester improved cardiac output and reduced peripheral vascular resistance, whereas no improvement occurred in a nontreated pre-eclampsia group (*n* = 12).<sup>43</sup> Whitehead et al.<sup>44</sup> published a case report of a woman presenting with severe SDB and pre-eclampsia at 30 weeks gestation. After initiation of CPAP, blood pressure and the placental antiangiogenic marker, s-flt-1, decreased, and pregnancy was extended by an additional 30 days.

Although these studies demonstrate that CPAP is safe and can improve intermediate maternal and placental measures, they are limited by small sample sizes and not powered to assess gestational outcomes. A Phase III clinical trial is underway to examine whether treating SDB in pregnancy reduces the risk of gestational hypertensive disease.<sup>45</sup> This trial will randomize >2700 women with clinically defined SDB (AHI >5) in early pregnancy to CPAP versus perinatal standard of care and will evaluate the efficacy of the intervention on the incidence of gestational hypertensive disorders and an array of secondary cardiovascular, metabolic, and neonatal outcomes.

## Conclusion

The incidence of SDB is two to three times higher among pregnant women than among nonpregnant women of child-bearing age. SDB in pregnancy is an independent risk factor for gestational hypertension, pre-eclampsia, and gestational diabetes. Despite the danger posed to maternal health, the risk of SDB is rarely evaluated in perinatal medicine, and no guidelines currently exist for treating SDB in pregnancy. Effective treatment of SDB itself is available and routinely used in the nonpregnant adult population. With regard to pregnancy, evidence is urgently needed from definitive clinical trials that treating maternal SDB will make a difference in gestational cardiovascular and metabolic outcomes. If confirmed, SDB treatment could be added as a therapeutic strategy to prevent or mitigate the progression of cardiometabolic disease across gestation, resulting in improved perinatal, postpartum, and future health in a substantial number of women.

## Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the U.S. Department of Health and Human Services.

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