

Obstructive Sleep Apnea in Pregnancy—More Questions than Answers

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Abstract

The role of obstructive sleep apnea (OSA) in pregnancy is not well studied, but an increasing body of literature appears to indicate that there may be adverse maternal and fetal health effects of the disease. OSA is associated with a twofold risk for pre-eclampsia. The small size of the existing investigations still leave unanswered questions about the consequences of OSA as it relates to some other clinically relevant outcomes such as eclampsia, stillbirth, and maternal mortality. A consistent body of literature has emerged demonstrating an increased risk for insulin resistance and diabetes associated with OSA. However, among pregnant women, the association appears to be related to short sleep duration. Well-designed and adequately powered studies are required to further delineate the role of OSA and sleep duration on pregnancy outcome and the mechanisms of those effects.

Keywords

Sleep apnea, pregnancy, short sleep duration, gestational diabetes, obesity, glucose intolerance

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The global obesity pandemic has been well documented and affects both high- and low-income countries.¹ In the US, two-thirds of adults are classified as either overweight or obese.^{2,3} In tandem with the high prevalence of obesity is a change in the prevalence of obesity among reproductive-aged women. Therefore, obesity-related morbid conditions such as chronic hypertension and diabetes are also increasing.^{4–7}

One obesity-related condition, which has received increased attention in recent years, is sleep disordered breathing (SDB). SDB refers to a group of disorders characterized by abnormal respiratory patterns (i.e. apneas) or abnormal gas exchange (i.e. hypoxia) during sleep. SDB ranges in severity from snoring, to the most severe form, obstructive sleep apnea (OSA).⁸ OSA is defined as entirely absent or severely reduced airflow during sleep in spite of respiratory effort. It is characterized by recurrent episodes of complete or partial upper airway collapse during sleep leading to decreased airflow, hypoxemia, and recurrent arousals from sleep.⁹ The medical consequences of OSA in the general population have been well documented and include excessive daytime sleepiness, fatigue, cognitive dysfunction, and impaired quality of life.¹⁰ OSA is frequently associated with cardiovascular and metabolic disorders such as hypertension and diabetes. In addition, OSA may contribute to arrhythmias, heart failure, insulin resistance, diabetes, dyslipidemia, and atherosclerosis progression.¹¹

The role of OSA in pregnancy is not as well studied, but an increasing body of literature appears to indicate that there may be maternal and fetal health effects of the disease. In this article, we will review the published

literature on OSA in pregnancy, associated outcomes, and suggest future directions for research.

Epidemiology

OSA is an increasingly common condition. The prevalence of SDB as defined by an apnea-hypopnea index (AHI) ≥ 15 among women aged 30–39 was 4 % among women in the Wisconsin Sleep Cohort.¹² Subsequent studies have reported prevalence of OSA among reproductive age women that is estimated to be 0.6–7 %, depending on the population and the diagnostic criteria used.^{12,13} That prevalence rises to 11–20 % among pregnant women, with the highest prevalence observed among obese gravidas.^{12,14–16} Determining the true prevalence of OSA in pregnancy is difficult secondary to the diagnostic challenges that pregnancy presents. Validated questionnaires have been demonstrated to be poorly predictive of OSA among pregnant women and may overestimate the prevalence of OSA.^{17–19} This may be secondary to an overlap between symptoms from physiologic pregnancy changes and symptoms of OSA. The gold standard for OSA diagnosis is the nocturnal polysomnogram.⁹ This test is expensive, and the time constraints proved to be inhibitive, in particular to women who may be unable to spend the night away from home. The use of unattended portable monitors in the home is increasing but has been approved for limited populations.²⁰

While this alternative is widely used in research, many of the portable devices have not been validated in pregnant women. However, reports from small groups of women indicate that there is considerable

agreement between portable monitoring and polysomnography (PSG) but the monitors may overestimate the respiratory disturbance index.²¹

Risk Factors

In the general population, obesity and weight gain is recognized as the most significant risk factor for OSA with a 10 % weight gain being associated with a sixfold increased risk for OSA compared with individuals with a stable weight.¹ This finding has also been confirmed in pregnancy, with obesity emerging as the predominate risk factor. Even among obese women enrolled in a screening protocol, women with OSA were on average 10 kg/m² heavier than women without OSA.¹⁵ This finding has been mirrored by retrospective and cohort studies, which have reported that increasing body mass index (BMI), older age and chronic hypertension were also associated with an approximately twofold higher risk for OSA.^{15,19,22}

Physiologic Changes in Pregnancy

During the course of pregnancy, estrogen and progesterone levels rise significantly. Respiratory drive is noted to increase due to increased progesterone levels. Estrogen, on the other hand, induces capillary congestion, hyperemia, nasopharyngeal mucosal edema, vasomotor rhinitis, and increased nasal congestion. This can then lead to narrowing of the upper airway, specifically the oropharyngeal diameters, with increased upper airway resistance to airflow and more negative intra-pharyngeal pressure with inspiration leading to snoring and obstructed breathing in sleep.^{23,24}

Furthermore, as pregnancy progresses, weight gain and the upward displacement of the diaphragm occurs due to the growing fetus. This can lead to increased diaphragmatic effort, which results in greater negative pressure at the level of the upper airway and can potentiate upper airway collapse.

Further changes in the airway can be detected by the increase in oropharyngeal edema and narrowing of the airway. The Mallampati score is a crude assessment of airway crowding, which is predictive of difficulty of intubation.²⁵ Longitudinal studies of pregnant women have indicated that the score increases as pregnancy progresses. The proportion of women with a Grade IV Mallampati, indicating severe airway crowding, increased by 34 % over the course of the pregnancy.^{26,27} All of these changes, in summary, may predispose to the development of SDB or worsening of existing SDB. Currently, there are no published large-scale trials that use objective testing for OSA to report the longitudinal changes in OSA.

Consequences of Obstructive Sleep Apnea

The initial reports regarding OSA and adverse pregnancy outcomes were limited to case reports. In those reports, clinical cases of intermittent hypoxia were reported to be associated with chronic hypertension, diabetes, pre-eclampsia, and fetal growth restriction.^{25,28,29} In more than half of the initial case reports, there was no objective testing for OSA, but rather the subjects were classified based on their clinical picture.²⁵ This led to criticisms of the reported associations because there is significant overlap between obesity-related comorbid conditions are significant confounders for pre-eclampsia and fetal growth restriction. Since that time, there has been a significant increase in the number of scientific studies addressing the adverse effects of SDB on pregnancy.

Among the studies with confirmed OSA diagnosis, the largest one utilized a population-based cohort of 791 Taiwanese women with confirmed OSA and a comparative group of 3,955 pregnant women without the diagnosis. The authors reported an increased risk for gestational hypertension (odds ratio [OR] 3.2; 95 % confidence interval [CI] 2.1–4.7) and pre-eclampsia (OR 1.6; 95 % CI 2.2–11.3) among women with OSA. OSA was also associated with an increased risk for small-for-gestational age infants (OR 1.34; 95 % CI 1.09–1.66). Several small prospective observational cohort studies utilized unattended portable monitoring to identify subjects with OSA. Those studies reported significant associations between OSA and pre-eclampsia of a similar magnitude to the study by Chen et al., but they were statistically underpowered to evaluate certain severe maternal or fetal outcomes.^{15,16,30,31} The small size of those investigations still leaves unanswered questions about the consequences of OSA as it relates to some other clinically relevant outcomes such as eclampsia, stillbirth and maternal mortality.³² The findings of these studies were also similar to the findings from larger studies which used symptom-based screening for SDB.

Obstructive Sleep Apnea and Glucose Intolerance in Pregnancy

A consistent body of literature has emerged, demonstrating an increased risk for insulin resistance and diabetes associated with OSA. Individuals with OSA are more likely to develop diabetes compared with those without OSA and people with diabetes are more likely to have OSA compared with people without diabetes. A worsening of insulin resistance has been demonstrated to be directly related to a worsening of OSA as determined by the AHI. This relationship persisted after controlling for obesity.^{33,34} Therein lays the challenge. Studies of OSA are deeply confounded by the implications of obesity, particularly visceral adiposity and central obesity, which are risk factors for the development of OSA.^{35,36} Untreated OSA has been linked to decreased insulin sensitivity and a correlation between OSA severity and insulin resistance has been described.^{37–39} However, efforts to use treatment with continuous positive airway pressure (CPAP) have demonstrated mixed results, with some studies demonstrating a beneficial effect and others failing to improve normalization of glucose.^{40–44}

All of these described findings have occurred in the nonpregnant population. A relationship between OSA and diabetes would have significant implications for the obstetric population. Insulin resistance and diabetes are associated with adverse pregnancy outcomes, and treatment mitigates that association.^{45–47} Among the reported perinatal consequences of diabetes are increased risks for fetal malformations, pre-eclampsia, macrosomia, cesarean delivery, and their associated morbidities.^{46,48,49} Recent large, multicenter trials have demonstrated that insulin resistance and glucose intolerance even in the absence of obesity are associated with increased maternal and neonatal morbidity. That relationship is linear and without a necessarily definitive cutoff point.^{50,51}

Then it becomes prudent to examine the available evidence about metabolic consequences of SDB. Most of the existing studies that sought to examine the relationship between OSA and insulin resistance or diabetes among pregnant women have relied largely on questionnaires. There appeared to be no significant relationship between self-reported habitual snoring and gestational diabetes.⁵³ However, in a cohort of 990 women who completed the Epworth Sleepiness Scale, a measure of excessive daytime sleepiness, women with a score ≥ 16 were more likely

to have a pregnancy complicated by gestational diabetes compared with women with a score ≤ 16 .^{52,53} Only one study utilized pregnant women with a confirmed diagnosis of OSA. Among the studies that utilized a confirmed diagnosis of OSA, only one demonstrated an association. Outside of the case reports, there has not been a systematic investigation of SDB or OSA and diabetes among pregnant women. Very few studies have examined OSA and diabetes. In the report by Chen et al., women with OSA were more likely to have gestational diabetes (OR 1.63; 95 % CI 1.07–2.48) in the affected pregnancy.³² These conflicted findings underscore the importance for confirmatory diagnosis when attempting to ascertain the role of OSA in pregestational and gestational diabetes.

Short Sleep Duration

Short sleep duration and sleep fragmentation are significant components of OSA and may have a different physiologic effect from the intermittent hypoxia. The impact of short sleep duration and fragmentation on diabetes and insulin resistance has been well documented. This presents a challenge when investigating the association between OSA and hyperglycemia. It is uncertain if any observed effects are secondary to the short sleep duration and sleep restriction or due to the hypoxemia of OSA.⁵⁴ This is an important consideration in the obstetric population. Various changes in pregnancy will predispose to sleep fragmentation and short sleep duration. These include nocturia, fetal movement, and back and pelvic discomfort that may result in frequent arousals from sleep. The studies that have examined the metabolic consequences of short sleep duration have found a more consistent impact on insulin resistance and diabetes than the studies of OSA. In a cohort study of pregnant women who underwent polysomnogram and completed questionnaires, SDB symptoms (OR 3.37; 95 % CI 1.44–8.32) and increasing nap duration (OR 1.64; 95 % CI 1.00–2.681.02) were associated with hyperglycemia on a 1-hour glucose challenge test. However, the primary exposure measure, the AHI in the first trimester was not significantly associated with hyperglycemia (OR 1.03; 95 % CI 0.83–1.28).⁵⁵ This finding has been mirrored by other studies. In the largest of these studies, Qiu et al. conducted a pilot study where they assessed associations of maternal self-reported sleep duration and snoring during early pregnancy with gestational diabetes diagnosed using a two-step screening process. Women who reported sleeping on average 4 hours per night compared with those who slept 9 hours per night had 5.56-fold increased risk for gestational diabetes.⁵⁶ These findings were mirrored in other smaller prospective studies

that also sought to evaluate the correlation between short sleep duration and hyperglycemia among pregnant women.^{57,58} The sum of these findings indicates that among pregnant women, the metabolic effect of short sleep duration may be similar to that observed in the nonpregnant population.

Other Mechanisms of Disease

The pathophysiologic consequences of the recurrent intermittent hypoxia and sleep fragmentation associated with OSA have been well described. Chronic intermittent hypoxia and sleep fragmentation result in increased sympathetic traffic. Recurrent episodes of hypoxia and re-oxygenation activate neutrophils, and result in an increase in proinflammatory cytokines. These recurrent hypoxia and re-oxygenation cycles also generate oxidative stress.⁵⁹ Leptin, which is an adipokine responsible for a negative energy balance, is noted to be correlated with the AHI, indicating that worsening OSA is associated with leptin resistance. Adiponectin is another adipokine with insulin-sensitizing and anti-inflammatory properties. Adiponectin levels are lowered by OSA.^{60,61} These biochemical derangements are important as these mechanisms have also been implicated in the development of pre-eclampsia, gestational diabetes, and adverse pregnancy outcomes.^{62,63} Furthermore, in the absence of maternal disease, these molecular changes may impact the *in utero* environment and affect the future health of the neonate.

Summary

Among patients with OSA, there remains a large deficit of data to explain the mechanistic pathways by which OSA affects pregnancy outcomes. With that information, we would be able to direct treatment in order to improve outcome. Of particular importance is differentiating the impact of sleep duration independent of OSA. While there is some evidence to indicate that these women are impacted by glucose intolerance, the relationship would be more complex given the potential role of oxidative stress, cytokinemia, and sympathetic traffic. The *in utero* environment is important for fetal development, and programming for future health affects the future health of the neonate. Pregnancy may be an opportune time to intervene on behalf of future maternal and fetal health. However, we cannot achieve that goal unless we are able to delineate the most important pathophysiologic pathways impacting pregnancy outcome in these women. The investigations of these potential routes of intervention may benefit the greater of such a community as we aim to improve both maternal and fetal outcomes. ■

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