Sleep-disordered breathing and preeclampsia

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REVIEW ARTICLE

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Abstract

Preeclampsia is a common cause of maternal and fetal morbidity. Endothelial dysfunction (ED) is the most important pathophysiologic mechanism for preeclampsia. Sleep-disordered breathing (SDB) is an important underlying mechanism in cardiovascular complications such as hypertension and ischemic heart disease with ED. Physiological changes during pregnancy predispose women to increased prevalence of SDB during the third trimester of pregnancy. SDB is seen more often in preeclampsia and ED is seen in preeclampsia and SDB. ED in preeclampsia may be potentiated by SDB. SDB appears to contribute significantly to the severity of ED in preeclampsia leading to more severe maternal and fetal outcomes. Continuous positive airway pressure (CPAP) treatment has shown benefit in reducing the severity of preeclampsia and improving the maternal and fetal outcomes in some studies. Further research is warranted in this area, especially to study the impact of CPAP on the severity of preeclampsia.

Keywords: Gestational hypertension, Preeclampsia, Sleep Disordered Breathing, Maternal outcome, Fetal outcome

Preeclampsia is a hypertensive disorder unique to pregnancy, which is characterized by hypertension, proteinuria, and edema. It affects about 7%-10% of all pregnant women and has a predilection for primigravidas. It is diagnosed by a new-onset hypertension of >140/90 mm Hg after 20 weeks of gestation, along with proteinuria of 0.3 g in a 24 h urine specimen or a dipstick value of >1+ if quantitative measurement is not available. In patients with new-onset hypertension without proteinuria, the new onset of the following features is also diagnostic of preeclampsia: platelet count <1 lac/ml, serum creatinine >1.1 mg/dl, liver transaminases more than double the normal, pulmonary edema, and cerebral or visual symptoms. Gestational hypertension, but without proteinuria, is also a new-onset hypertensive disorder of pregnancy that can develop into preeclampsia during the course of pregnancy.

Preeclampsia is one of the leading causes of maternal morbidity and mortality, ICU admissions, and neonatal morbidity. The adverse maternal outcomes include placental abruption, seizures, stroke, renal failure, liver dysfunction, cardiac dysfunction, and pulmonary edema. Patients with preeclampsia are also at risk of developing coronary artery disease and stroke later in life. The notable adverse fetal outcomes include preterm birth, intrauterine growth restriction, still birth, low APGAR.
at birth, and prolonged nursery stay\textsuperscript{5,6}.

The exact pathogenesis of the hypertensive disorders is not certain; however most research points toward the central role of placenta, as placenta is necessary for the development of preeclampsia and not the fetus. Besides, the definitive treatment of preeclampsia is delivery. It is postulated that defective trophoblastic invasion or differentiation results in production of reactive oxygen species and other inflammatory mediators, which ultimately leads to endothelial dysfunction (ED) affecting all the systems of the body\textsuperscript{7} (Fig 1).

Sleep-disordered breathing (SDB) is a spectrum of disorders ranging from the mildest form of upper airway resistance syndrome to the most severe form of obesity hypoventilation syndrome\textsuperscript{8}. The pathogenesis of SDB may be related to anatomical factors, such as craniofacial abnormalities or mechanical obstruction of the airway, leading to small pharyngeal airway or a central ventilatory control disorder\textsuperscript{9}.

SDB is associated with several cardiovascular manifestations including hypertension\textsuperscript{10–14}. The breathing disturbances are characterized by repeated episodes of partial or complete upper airway obstruction during sleep, which can result in disturbance of normal ventilation, intermittent hypoxemia, and repeated arousals from sleep, leading to increased sympathetic activity even in wakefulstate\textsuperscript{15}. These episodes are also associated with oxidative stress, inflammation, and reductions in antioxidant levels. During intermittent hypoxia, the initial response is an increase in the generation of reactive oxygen species. When the generation of reactive oxygen species exceeds antioxidant capacity, oxidative stress can result in ED\textsuperscript{16}. The causation of hypertension in SDB is hence postulated to be due to a combination of increased sympathetic activity and ED (Fig 2).

The physiological and anatomical changes during pregnancy that make a gravid woman more prone to SDB are nasal congestion and rhinitis\textsuperscript{17} (estrogenic effect), edema of the airways (progestogenic effect)\textsuperscript{17}, increase in Mallampatiscores\textsuperscript{18}, gestational weight gain\textsuperscript{19}, and decreased functional residual capacity\textsuperscript{19}. Changes in the upper airway patency may also be related to the fluid shifts from the lower limbs to the neck area, as a result of prolonged sitting and recumbency, which is often a feature of pregnancy\textsuperscript{20}. The 40% increase in the blood volume, which occurs in normal pregnancy, makes the fluid shift more remarkable. Some of these changes, such as the edema of the airways, are even more pronounced in preeclampsia\textsuperscript{21}.

Symptoms of SDB are much more common in pregnant population. Estimates from European and North American studies suggest loud snoring in 14%–46% pregnant women\textsuperscript{22}. In a study conducted by Suri and colleagues\textsuperscript{23}, it was found that snoring occurred in 27.5% of the 120 pregnant women compared to 7% of the 100 nonpregnant women ($p=0.00$). The occurrence of SDB

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\caption{Model for pathogenesis of preeclampsia}
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Mechanism of cardiovascular disease in obstructive sleep apnea}
\end{figure}
in the same group of women was 10.8% and 1%, respectively \( (p = 0.146) \). In another study conducted by the authors, the prevalence of SDB in pregnant women was 9.5% against the prevalence of 2% in nonpregnant women \( (p = 0.05) \). Another interesting observation in this study was that the occurrence of SDB increased with gestational age \( (p = 0.04) \). Izci et al. \(^{17} \) and Facco et al. \(^{19} \) also observed an increase in the prevalence of snoring from the first trimester to the third trimester. In a prospective study on 105 pregnant women who underwent polysomnography (PSG) in the first and third trimesters, it was found that the overall prevalence of SDB was 8.4% and 19.7% in the first and third trimesters, respectively \(^{23} \). The possible association for this increase in snoring and SDB with the gestational age can be explained by the fact that the levels of estrogen and progesterone increase with increasing gestation, the physiological changes such as nasal congestion and edema of the airway can get exaggerated, compromising the caliber and patency of the upper airway. Besides this, the mechanical effect of the growing uterus which elevates the diaphragm also plays an important role.

It is possible that, among pregnant women with SDB, intermittent hypoxia leading to abnormal sympathovagal balance and ED may contribute to the development of new-onset hypertension, that is, preeclampsia, which is also known to be the pathogenic mechanism for preeclampsia, as discussed earlier. Thus, this common possible pathway of the two conditions can explain the strong association of snoring and SDB with pregnancy-induced hypertension demonstrated by a growing body of evidence \(^{25} \). Both conditions are associated with similar long-term cardiovascular and metabolic consequences. Moreover, both preeclampsia and SDB are more often seen in the third trimester and are associated with poor fetal and maternal outcomes.

Several researchers have corroborated this close association of preeclampsia and SDB. Preeclampsia was seen in 18% (OR 2.3, CI 1.4–4) of people with snoring and 23% of those with SDB (OR 2.1, CI 1.1–3.9) by Bourjeily et al. \(^{21} \). We too observed that preeclampsia occurred in 30% patients with snoring compared to 9% without snoring \( (p = 0.004) \). In a recently published study, Louis et al. \(^{21} \) observed that obstructive sleep apnea (OSA) was associated with increased odds of pregnancy-related morbidities including preeclampsia (OR 2.5, 95% CI 2.2–2.9) and eclampsia (OR 5.4, 95% CI 3.3-8.9).

In a study conducted to determine the relationship between snoring, pregnancy-induced hypertension, and intrauterine growth restriction, 502 women completed a questionnaire about snoring and day-time sleepiness and witnessed sleep apnea on the day of delivery. It was found that habitual snoring was independently predictive of hypertension \( (OR2.0, p<0.05) \) and intrauterine growth restriction \( (OR3.45, p<0.01) \), in a logistic regression analysis, controlling for weight, age, and smoking. \(^{26} \)

A meta-analysis of five studies published in 2014 found that in women with SDB the risk of preeclampsia increased by twofold (adjusted OR 2.34, 95% CI 1.60–3.09). In these studies, the diagnosis of preeclampsia was made by questionnaires in three and by PSG in the remaining two \(^{21} \). In a largest cohort study with PSG-confirmed SDB \((n=791)\), it was observed that women with SDB had an increased risk of developing preeclampsia (OR 1.6, 95% CI 2.16-1.12) \(^{27} \). This study however did not include the body mass index data and the role of obesity in the findings could not be determined. Louis et al. \(^{21} \) in a cohort of 57 women found a significantly higher rate of preeclampsia in SDB compared to normal-weight controls, but the difference ceased to be significant when obese controls were used, defining the independent role of obesity.

The next important point of consideration is that since both SDB and preeclampsia are linked with ED, does SDB contribute to ED seen in preeclampsia. In a study conducted by Yinon et al. \(^{25} \), in 17 women with preeclampsia and 25 controls with normal pregnancy who underwent ambulatory sleep study and reactive hyperemia test using Endo_Pat, it was seen that the women with preeclampsia had a significantly higher respiratory distress index \( (RDI; 18.8\pm8.4 \text{ vs. } 8.3\pm1.3) \) and significantly lower endothelial function index \( (EFI; 1.5\pm0.1 \text{ vs. } 1.8\pm0.1) \), signifying ED. EFI correlated with RDI and respiratory disturbances contributed to functional abnormality of blood vessels in preeclampsia. More studies are required in this area to determine the role of ED in SDB in the causation of pregnancy-induced hypertension.

Even though there is some evidence regarding the poor maternal and fetal outcomes of SDB during pregnancy, the outcomes of SDB in women with preeclampsia have not been studied extensively. However, preliminary evidence shows a worsening of hypertension as the severity of SDB increases. Yinon et al. \(^{25} \), in a study on 17 women with preeclampsia and 25 controls observed that there was a significant correlation between RDI and mean BP \( (r = 0.41, p<0.05) \). Also,
the birthweight of the neonates correlated negatively with RDI ($r = 0.19, p<0.2$).

The standard treatment for OSA is the use of nasal continuous-positive airway pressure (CPAP). In a study conducted by Edwards et al. who recruited patients with severe pre-eclampsia and did a baseline PSG with continuous BP measurements and repeated the PSG with CPAP, it was observed that there was a significant drop in both the systolic ($p<0.006$) and diastolic ($p<0.004$) blood pressure during treatment with CPAP. In another study on 24 patients with preeclampsia and 15 controls at 34 weeks’ gestation, patients with preeclampsia were randomized to CPAP or no-CPAP and baseline night and intervention night PSG was carried out. Beat-to-beat continuous BP measurements and repeated the PSG with CPAP, it was observed that there was a significant drop in both the systolic ($p<0.006$) and diastolic ($p<0.002$) in both the systolic ($p<0.006$) and diastolic ($p<0.004$) blood pressure during treatment with CPAP. In another study on 24 patients with preeclampsia and 15 controls at 34 weeks’ gestation, patients with preeclampsia were randomized to CPAP or no-CPAP, and baseline night and intervention night PSG was carried out. Beat-to-beat continuous BP measurements and repeated the PSG with CPAP, it was observed that there was a significant drop in both the systolic ($p<0.006$) and diastolic ($p<0.002$) in both the systolic ($p<0.006$) and diastolic ($p<0.002$) in both the systolic ($p<0.006$) and diastolic ($p<0.002$) in both the systolic ($p<0.006$) and diastolic ($p<0.002$).

It is concluded therefore that there is a strong association between preeclampsia and SDB; however, the exact causal relationship is yet to be determined. In favor of SDB leading to preeclampsia, it can be said that SDB has many metabolic and cardiovascular outcomes with similar risk factors as preeclampsia. However, the points in favor of preeclampsia leading to SDB are the physiological changes in the upper airway, which are specially pronounced in preeclampsia. More interventional studies with larger number of patients will help in determining the directionality of the association and are urgently warranted.

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