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Sleep disordered breathing controlled by CPAP and sFlt-1 in a pregnant patient with chronic hypertension: Case report and literature review

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Abstract

Background: There is recent interest exploring the possible impact of sleep disordered breathing on the mechanisms of preeclampsia. A biomarker of preeclampsia, soluble fms-like tyrosine kinase-1, has come to prominence in recent years. The aim of this study was to investigate the relationship between continuous positive airway pressure treatment, sleep disordered breathing and soluble fms-like tyrosine kinase-1 concentrations during pregnancy.

Methods: A 38-year-old G1P0 presented at 20 + 5 weeks. She had a history of chronic hypertension. Sleep studies revealed she had sleep disordered breathing with an AHI of 7.3/h. She was commenced on continuous positive airway pressure. Soluble fms-like tyrosine kinase-1 concentrations and blood pressure recordings were taken at various points during her pregnancy.

Results: She did not develop preeclampsia or require an escalation in her antihypertensives. Soluble fms-like tyrosine kinase-1 concentrations rose 16% from a low baseline. She remained compliant with her continuous positive airway pressure. She progressed to birth a well, live, term baby.

Conclusion: Continuous positive airway pressure treatment controlled sleep disordered breathing in a high risk pregnant woman with chronic hypertension with no increase in soluble fms-like tyrosine kinase-1 concentrations.

Keywords

Hypertension, sleep medicine

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Background

Preeclampsia complicates 3–5% of all pregnancies and is recognised as one of the leading causes of perinatal morbidity and mortality.[1] The initiating event is thought to be abnormal trophoblast invasion resulting in placental hypoperfusion.[2] There is increased expression of soluble fms-like tyrosine kinase-1 (sFlt-1), an alternate form of splicing of vascular endothelial growth factor receptor 1 (FLT1), which is postulated to induce endothelial dysfunction and vasoconstriction.[2,3] sFlt-1 may be driven by a hypoxic mechanism.[3] It may provide the link between hypoxia, placental dysfunction and endothelial dysfunction in preeclamptic pathogenesis.[3,4]

As a result of the factors released by the placenta, there is direct or indirect endothelial damage, resulting in hypertension and the other clinical manifestations of preeclampsia.[4] The proposed sequelae of placental hypoperfusion is systemic endothelial dysfunction via the release of anti-angiogenic agents, such as sFlt-1.[3]

Elevated sFlt-1 concentrations precede the presentation of preeclampsia by six to eight weeks gestation, and the higher the concentrations, the stronger the predictive value of preeclampsia and the more severe the disease.[3,5–8]

There has been recent interest in the past decade exploring the link between sleep disordered breathing and preeclampsia.[9–12] SDB encompasses a range of sleep disorders from snoring to severe obstructive sleep apnoea (OSA). Sleep disordered breathing (SDB) can have serious cardiovascular consequences; it has been identified as a risk factor for hypertension in the general population.[9] The exact prevalence of OSA in the pregnant population is unknown but has been reported to be as high as 25%.[13] Similarly, snoring is reported to be higher in the pregnant population than their non-pregnant premenopausal counterparts, with rates reported at 14–48% in the third trimester.[9] Pregnant women are more at risk of SDB due to rhinitis, weight gain, increased neck circumference, reduction in airway size and an increased propensity for the airway to collapse.[9,10,14] Effective treatment with continuous positive airway pressure (CPAP) of OSA in non-pregnant patients with hypertension can result in a significant reduction in blood pressure.[1] However, several studies exist to support the use of CPAP for SDB in pregnancy in an effort to decrease the risk of preeclampsia.[9,15–18] To date, there are no published studies reviewing the effect of CPAP treatment on sFlt-1 concentrations in pregnancy.

Case report

A 38-year-old gravida 1, para 0, woman presented at 20 + 5 weeks gestation with a history of chronic hypertension. Her pre-pregnancy BMI was 41 kg/m^2 and her body mass index (BMI) at the time of presentation was 42.7 kg/m$^{2.}$ Her medical history included type II insulin-dependent diabetes mellitus which was well controlled with insulin. Medication included alpha-methyldopa and acetyl salicylic acid. Her antenatal blood pressure was 130/70 mmHg and she reported a history of snoring prior to pregnancy.

As part of an incidental trial, at the same time point, a formal sleep study (using polysomnography with a standard montage of electroencephalogram, electrooculogram, pulse oximetry and airflow

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detectors, along with a portable ambulatory blood pressure monitor) revealed she snored 33% of her sleep time and had an apnoea/hypopnea index (AHI) of 7.3 events/h. This represents 7.3 episodes of either an apnoea (a cessation of breathing during sleep lasting for > 10 s) or hypopnea (a 50% or greater reduction in airflow lasting > 10 s) in an hour, and is considered mild in severity (range <5 events/h normal and >15 events/h as severe). Her mean oxygen saturation during sleep was 96% SaO_2 and her minimum was 87% SaO_2. Mean overnight blood pressure was 200/95 mmHg and her maximum was 221/122 mmHg. A referral was made to a respiratory physician and CPAP treatment was commenced 8 days later, at 22 weeks. Her therapeutic level was 11 cm H_2O. This titrated pressure reflects the pressure of air at which hypopneas and apnoeas have been prevented, measured in cm of water. After a fortnight of treatment, her overnight blood pressures were reassessed, with a new overnight average of 136/78 mmHg and a maximum of 140/81 mmHg. Daytime blood pressures were monitored and remained relatively constant, and blood samples were taken at each blood pressure monitoring. Her compliance to CPAP was reasonable, with an average of 4 h of treatment per night.

Initial concentrations of sFlt-1 were 370 pg/mL at 20 + 5 weeks. At 21 + 5 weeks, the concentration was 434 pg/mL. CPAP treatment was commenced and a concentration of 376 pg/mL was taken two nights later. The concentration then increased to 522 pg/mL at 24 + 1 weeks gestation, but then decreased to 431 pg/mL at 27 + 1 weeks. Overall this represented a percentage increase of 16% from a relatively low baseline. No further samples were taken due to time constraints.

The woman continued on throughout her pregnancy without any suggestion of preeclampsia throughout her pregnancy. She did not develop proteinuria. She had a caesarean section at 39 + 6 weeks after a failed induction of labour. She had a live birth of a baby boy, weighing 3645 g, with APGARS of 9 at both 1 and 5 min. The baby was admitted to special care nursery due to maternal diabetic status but was otherwise well. The mother was maintained on the same dose of alpha-methyldopa and post-partum, while breastfeedingand was normotensive at the time of discharge on this medication. Her CPAP treatment was continued at 11 cm H_2O.

Discussion

This is the first case study to examine sFlt-1 in a pregnant woman with SDB and the impact CPAP can have on SDB and potentially this marker. Control of SDB with CPAP was associated with a low level of sFlt-1 between 20 and 27 weeks gestation. This patient did not exhibit a significant change in her sFlt-1 concentrations during a critical period, defined by Levine[19] as between 21 and 24 weeks gestation, where women who would go onto develop preeclampsia would have a significant increase in their sFlt-1 concentrations. This patient did not develop preeclampsia, despite her high risk status due to being primiparous, having a high BMI and having pre-existing hypertension. The nocturnal hypertension identified in this case would also be considered to be a strong risk factor for further placental dysfunction. This case is supportive of the hypothesis that CPAP control of SDB may have a beneficial effect on preventing a rise in sFlt-1 concentrations and potentially limit the progression of preeclampsia in a patient at high risk.

In the context of the general population, OSA is widely regarded as a strong risk factor for hypertension, especially nocturnal hypertension, through a mechanism involving oxidative stress and cytokine release, resulting in endothelial dysfunction.[20–22] Sleep disordered breathing results in an inflammatory response in pregnancy, indicated by increased cytokine release.[10] Subsequently, these cytokines have been implicated in dysregulation of trophoblast invasion.[10] Furthermore, the sympathetic nervous system activation, which is also a hallmark of preeclampsia, seen also in OSA, can lead to cytokine release.[6,10,11,14,18] Cytokines are known to activate endothelial cells, resulting in endothelial dysfunction, a characteristic of preeclampsia which leads to vasoconstriction and organ hypoperfusion.[12,13]

In addition, the intermittent hypoxia that occurs in SDB may augment placental ischemia.[23] It is now widely regarded that placental hypoperfusion is an important mechanism for the development of preeclampsia and causes the release of sFlt-1 from the placenta.[8,9] Indeed, sFlt-1 is elevated in non-pregnant subjects with hypertension and OSA.[21,22] Thus, it is reasonable to suggest that sFlt-1 concentrations will be increased in pregnant women with SDB and increase their risk of preeclampsia. Recently, Bourjeily[4] et al. demonstrated that sFlt-1 was significantly higher in pregnant women with OSA compared to pregnant controls.

The intervention of CPAP treatment in non-pregnant populations has been reported to decrease inflammatory cytokines and reduce blood pressure.[6,15–18] In pregnancy, Guilleminault[7] used CPAP on chronic hypertensive women with risk factors for preeclampsia and showed blood pressure was maintained, while Poyares[8] employed CPAP on chronic snorers with hypertension in pregnancy and demonstrated a reduction in blood pressure, compared to an increase in blood pressure in those not treated with CPAP. Edwards[9] demonstrated a reduction in blood pressure in preeclamptic women with CPAP treatment. Recently, Blyton et al.[18] used CPAP on preeclamptic patients with SDB and revealed a reversal of low foetal activity levels. They did not, however, investigate any mechanism of placental dysfunction or hypoxia. By eliminating the intermittent hypoxia of SDB with CPAP, the postulated augmentation to placental hypoperfusion may be avoided, potentially evidenced by lower concentrations of sFLt-1 and the apparent attenuation of the rise of sFLt-1. Control of nocturnal hypertension may also be a postulated mechanism. Further work is needed to elucidate the exact mechanism of causality.

Conclusion

This case study suggests that sFlt-1 is a possible marker of disease control in hypertensive disorders of pregnancy (HDP) especially in women being monitored for progression due to known risk factors for preeclampsia.

The salient finding of this study is that CPAP treatment, when used in the setting of a pregnant woman with SDB and chronic hypertension, appeared to control the SDB and may potentially attenuate the increase of sFlt-1 during pregnancy. Therefore, this study supports the hypothesis that CPAP may have a potentially beneficial effect in pregnant women with SDB via possibly attenuating the rise of sFlt-1, but further large scale studies are required to fully substantiate this.

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Declaration of conflicting interests

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Ethical approval

This research was approved by NHMRC, project approval for 0711-215M: Sleep Disordered Breathing in Pregnancy: frequency and impact.

Guarantor

AD

Contributorship

Case report and literature review performed by AD. AM and AH provided clinical care and contributed to editing. All other authors provided data analysis and contributed to editing.

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