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Positive Airway Pressure as a Therapy for Preeclampsia?

Commentary on Blyton et al. Treatment of sleep disordered breathing reverses low fetal activity levels in preeclampsia. SLEEP 2013;36:15-21.

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In this issue of *SLEEP*, Blyton and colleagues[1] report a series of three small studies of fetal activity in women with and without preeclampsia. They found objective evidence of reduced fetal movements in women with preeclampsia, many of whom had sleep disordered breathing (SDB), and improvement in fetal movements following intervention with continuous positive airway pressure (CPAP). Although this study included only 20 women with preeclampsia and a further 10 who were studied during CPAP administration, it raises the possibility that a simple, noninvasive therapy for SDB may improve fetal well-being.

These findings are clinically important and very timely. There has been a marked rise in publications in recent years showing that the frequency of SDB is increased during pregnancy and is independently associated with gestational hypertension and preeclampsia.[2-7] In addition, a large proportion of pregnant women with gestational hypertension and preeclampsia appear to have unrecognized SDB.[8,9] Sleep disordered breathing is a known predictor of future hypertension in the non-pregnant population,[10-12] via mechanisms such as sympathetic overactivity, inflammation, oxidative stress, and endothelial dysfunction.[13] Notably, these mechanisms are remarkably similar to the biological pathways for preeclampsia. It is plausible that the normal maternal inflammatory response to pregnancy could be exacerbated by SDB, predisposing pregnant women to preeclampsia.[14,15]

Nonetheless, the impact of maternal SDB on the fetus is unclear. Case reports[16,17] and some studies[3,18] suggest that SDB is associated with growth restriction although this is not supported by other studies.[2,19] While maternal self-report of SDB is most often used to determine SDB status because of the logistical difficulty of polysomnography in pregnancy, the latter is clearly needed for physiological investigation. In a retrospective study of 57 women with a clinical diagnosis of SDB, all of whom underwent polysomnography either prior to or during pregnancy, Louis et al.[20] did not find an increased risk of growth restriction compared to women without a diagnosis, but they did find an increase in preterm birth. These findings cannot be directly compared to the present study,[1] since all women in the study by Louis et al. were recommended to use CPAP, but adherence was unknown, so its impact could not be determined.

One of the major limitations to the available literature on maternal SDB is that fetal activity has not been objectively examined; rather clinical outcome metrics (e.g., growth restriction, preterm birth, and Apgar score) have been used. These metrics are clearly important but require large studies to evaluate fully. Fetal activity is a marker of fetal well-being, and reduced fetal movements are a clinical sign that has been associated with growth restriction and stillbirth.[21,22] Nonetheless, reduced fetal movements have also been observed in non-pathological conditions.[23] The objective evidence from Blyton and colleagues[1] clearly demonstrates reduced fetal movements in women with preeclampsia. Remarkably, as the night progressed there was increased fetal movement in healthy pregnancies, yet movements reduced across the night in women with preeclampsia. The reasons for this are unknown but possibly due to fetal compensation to reduce energy secondary to placental insufficiency.[24]

Several investigators prior to Blyton et al.[1] have used fetal heart rate monitoring during maternal sleep rather than fetal movement.[25-29] Blyton et al. undertook a small validation study of fetal movement against ultrasound, which showed good agreement. Olivarez et al.,[28] in their study of one hundred third-trimester women (20 of whom had SDB), failed to find any association between maternal SDB and fetal heart rate, although fetal movements were not recorded. Only one woman with SDB in the latter study had preeclampsia, compared to all women in the study by Blyton et al.[1] This raises the question of whether the increased fetal movement noted with PAP in the study by Blyton and colleagues occurred via treatment of underlying SDB or due to an effect of PAP on the cardiovascular system independent of the presence of SDB. The current study cannot answer this question because all women had preeclampsia, and all of those who underwent CPAP had airflow limitation.

Limitations of the study of Blyton et al. are (1) the reporting of a series of small studies and (2) the fact that women treated with CPAP were a different group from those in whom fetal activity was well characterized across the night. Nine of the 20 preeclamptic subjects in study 2 had an AHI > 10 but data were not compared to non-preeclamptic controls. The mean AHI suggests SDB in both groups. It is also unclear in study 3 how many of those who underwent CPAP also had an AHI > 5; the mean AHI in study 3 was only 7/h, suggesting that most women likely had mild SDB. Regardless, the AHI threshold for morbidity is currently unknown in pregnant women and, as Blyton et al. point out, upper airway flow limitation is associated with elevations of systemic blood pressure, which has been shown to respond to low levels of CPAP.[30,31]

The findings of reduced hiccups and improvement with CPAP are intriguing. The purpose of fetal hiccups is poorly understood but may be a manifestation of a programmed isometric inspiratory muscle exercise in preparation for the postnatal respiratory function.[32] Maternal hypertension and preterm birth,

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both associated with SDB during pregnancy, increase the risk for SDB in childhood.[33-36] Despite its small size and the lack of infant outcome data in the present study,[1] the finding of reduced fetal hiccups in preeclampsia, with an increase during CPAP, suggests that this may be one mechanism that predisposes to upper airway dysfunction in the offspring. Future studies are needed to elucidate the independent role of maternal SDB relative to fetal and neonatal well-being.

In conclusion, the prospective study by Blyton et al.[1] emphasizes the need to understand the role of maternal SDB in both fetal health and the long-term well-being of the offspring. Maternal SDB represents a unique opportunity to study the effect of *in utero* exposures on postnatal development and future risk. This has major implications for public health.

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DISCLOSURE STATEMENT

Dr. O'Brien has received auto-PAP devices from Philips Respironics Inc. for research.

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