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Sleep disordered breathing in pregnancy: Food for thought

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Abstract

The last few years have witnessed a number of publications linking sleep disordered breathing to adverse pregnancy and neonatal outcomes in various populations. Associations with preeclampsia, gestational diabetes and growth restriction have been consistent across many studies. Though the manuscripts reviewed here consist mostly of preliminary data and need further confirmation, the studies have highlighted new directions in the assessment of the impact of sleep disordered breathing and pregnancy, and paved the way for new fields of research in this area.

Keywords

Sleep disordered breathing, hypertension, complications, neonatal medicine, aging, pregnancy

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Throughout the course of pregnancy, the respiratory system undergoes a significant number of physiologic changes. Some of the changes such as the reduction in functional residual capacity and upper airway patency, along with reduced oxygen reserve may predispose to sleep-disordered breathing (SDB). This spectrum of sleep-related breathing disorders ranges from uncomplicated snoring to obstructive sleep apnea (OSA) and obesity hypoventilation syndrome. Though central sleep apnea does not appear to be prevalent among pregnant women suspected of SDB,[1] obstructive disorders occur more frequently. Both snoring and OSA are common in pregnancy, and both are associated with adverse pregnancy outcomes such as preeclampsia,[2] gestational diabetes,[3] and reductions in birth weight.[4] The past few years have witnessed the emergence of a fair number of studies evaluating SDB in pregnancy, but the three studies published in 2015 and discussed here represent a new focus of this research and are certainly thought provoking.

Association between maternal symptoms of SDB and fetal telomere length

Data evaluating long-term outcomes in neonates born to mothers with SDB are lacking. The goal of this study[5] was to analyze the effects of maternal SDB on accelerated aging of the neonate, using fetal telomere length as a surrogate marker. Telomeres are the tips of chromosomes; they consist of protein complexes and non-coding DNA. Telomere shortening occurs with aging and constitutes a good marker because it is closely related to basic biological mechanisms, records the number of past cell divisions, is reproducible, and is associated with adverse lifestyle and other risk factors[6] such as obesity and smoking. Some limited data also link telomere length with sleep apnea in the non-pregnant population,[7] independently of cardiovascular and metabolic conditions. Emerging literature is suggesting an association between telomere length in adults and mortality. Thus, this study was conducted with the hypothesis that in-utero exposure to maternal SDB will be associated with shorter telomere length at birth.

The subjects enrolled in this study included 67 women; age 18–44 years old, mostly socioeconomically disadvantaged and ethnically diverse, who were delivering full-term live births and whose fetuses were not showing evidence of congenital or chromosomal anomalies. Sleep questionnaires including the Berlin Questionnaire, a screening tool for OSA, along with the Epworth Sleepiness Scale, a validated measure for daytime sleepiness, were used. Based on the responses to these questionnaires, subjects were divided into low risk and high risk for sleep apnea (positive responses on two categories or more of the Berlin questionnaire) and normal or abnormal daytime sleepiness ($\leq$10 or >10, respectively). In order to analyze telomere length, neonatal umbilical cord blood was obtained at birth and processed for genomic DNA. Relative telomere length in the DNA sample (telomere/single copy ratio or T/S ratio) was determined using the quantitative PCR method. Bootstrapping, a robust alternative to conventional statistical methods, was used as it provides more precise inferences when sample size is small.

There were no significant differences in socioeconomic and demographic variables in the groups at high versus low risk for sleep apnea or in the groups with normal versus abnormal sleepiness score. Though no significant differences were observed in birth weight or head circumference between the two groups, analysis of the neonatal cord blood T/S ratio using the bootstrapping technique revealed that the mean T/S ratio was significantly higher for subjects at low risk of sleep apnea versus compared to subjects at higher risk for sleep apnea. Similarly, mean T/S ratio was higher for subjects with normal sleepiness versus subjects with abnormal sleepiness according to the Epworth Sleepiness Scale; however, this difference was not statistically significant.

The robust statistical analysis employed in this study (bootstrapping technique) is certainly a strength. However, a major limitation of this study that was acknowledged by the authors was the lack of objective documentation of SDB with studies such as polysomnography. As shortened telomere length has been associated with age-related disorders such as cancer and cardiovascular disease, the findings from this study raise concern about the long-term impact of SDB on newborn babies. Future studies would need to include objective sleep measurements as well as long-term follow-up of the offspring exposed to SDB in-utero.

The effect of maternal SDB on the infant's neurodevelopment

This prospective study[8] aimed at observing a relationship between maternal SDB and infant neurodevelopment and social development. The study was structured to enroll mothers of uncomplicated, singleton

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pregnancies to complete a sleep survey in their second trimester and undergo a home sleep study between 33 and 36 weeks of gestation. Newborn general movements (GM) were evaluated by blinded clinicians who examined and scored videos of newborns at 48 h after birth and again at 8–11weeks and 14–16 weeks. There were consistent quality exclusion criteria in the videos used for assessment. At 12 months, the Brief Infant Sleep Questionnaire (BISQ) and infant developmental inventory questionnaires were given to parents for assessment of infant development. Statistical analysis used independent t tests for continuous variables and c2 analyses for categorical variables with adjustments for several confounders including gestational age, birth weight, sex, 5-min Apgar score, and socioeconomic status. Two-tailed P value was set at <0.05.

Of the 74 patients enrolled, 51 mother–infant pairs completed follow-up to one year. Approximately one quarter of women had SDB as defined by an apnea hypopnea index (AHI) of 5 events per hour or greater. Mean oxygen saturation was 94.7%, and mean nadir oxygen saturation was 89.6%. The corresponding GM assessment showed no significant difference at 48 h, 8–11 weeks or 14–16 weeks. In addition, neurodevelopment assessment by the validated survey BISQ showed no difference in all parameters other than infant snoring in which 5 of 12 (41.7%) mothers with SDB reported infant snoring as compared to 3 of 40 (7.5%) controls (p=0.004). At 12 months, the infant developmental inventory questionnaire showed a trend towards significantly lower mean social developmental scores in cases. When analyzing scores less than 100 in both groups, there was a significantly lower score for infants of SDB mothers as compared with controls (OR 16.7; P=0.036).

The innovation of this study was several fold; first in attempting to assess the association between maternal SDB and infant neurodevelopment, secondly to use a prospective approach, and thirdly in showing that infants of SDB mothers may suffer from an increased rate of snoring which has not previously been shown. In addition, though the authors did not in fact find neurodevelopmental delay as measured by a questionnaire among the cases and controls as they had hypothesized, they found an unexpected difference in social development.

Tauman et al.[8] correctly point out that this paper should be taken to represent preliminary data and call attention to the fact that neurodevelopment at one year was reported by parents and could be improved by an objective measurement by a provider. It is possible that this parameter was biased, as mothers who were diagnosed with SDB may have felt a sense of guilt or embarrassment as it related to any delay in their child's development, and therefore may not have accurately reported less than normal outcomes in the questionnaire. Additionally, mothers with SDB may be more sensitized to snoring and could have over-reported this phenomenon in their infants as compared with controls.

The GM scoring is an appropriate tool for the assessment neurodevelopmental delay.[9] The infant developmental inventory, however, is not a validated measure and future studies may benefit from using a different instrument. Interestingly, neural development in infants begins early in gestation, and thus it may have been useful to stratify mothers who suffered from SDB prior to pregnancy and those that had pregnancy-related SDB, as well as those with moderate OSA as per AHI>15 compared with those with mild OSA. This was complicated by loss to follow-up of several babies born to mothers with known history of SDB.

A more comprehensive set of variables such as maternal head and neck anatomy, siblings' and parents' contact with the child, vision and hearing development that affect infant social development may also be relevant for future studies.

Overall the strength of the trend seen in the influence of maternal SDB and social development of the infant would be more robust if the authors were able to follow a larger cohort of cases. While this sampling may truly reflect the prevalence of pregnancy-associated SDB and therefore, absolute outcomes in newborns, the study may not have had enough power for detect a true difference if present. Also, the biologic plausibility of SDB affecting neural development as outlined by the authors with reference to animal data[10,11] implicate hypoxia as the driving factor for offspring aberrancy in social behavior and neural development. However, as the absolute values of oxygen saturation in mothers are not clinically significantly different and cord blood samples not obtained, it is difficult to ascertain the underlying pathophysiological mechanism that would explain the findings. Airflow limitation leading to a heightened sympathetic drive may impact perfusion of the conception products and may also play an important role.

This study provides a strong basis for further investigation and though a difficult undertaking, possible prospective analysis of babies into childhood to assess for behavioral problems such as attention-deficit disorder (a manifestation of SDB in the pediatric population as the authors point out), which may potentially be a result of either infant snoring or maternal SDB effects.

Impact of overnight oximetry findings on cardiac autonomic modulation in women during second trimester of uncomplicated pregnancy

The role of SDB in pregnancy has been extensively investigated and in particular its possible implications with the development of gestational hypertension and pre-eclampsia.[12] Indeed, SDB and pregnancy do share several common factors as pregnant women exhibit an increase in body weight and fluid retention, which are two well-established risk factors for SDB.[13,14] However, not all pregnant women develop SDB such as OSA,[15] and screening all patients during pregnancy with a sleep test is somewhat cumbersome and time consuming. Therefore, understanding which patients are likely to develop SDB during pregnancy would be important to target patients at risk for the development of possible interventions that may prevent the development of adverse outcomes.

The paper by Watanabe et al.[16] tried to answer this question hypothesizing that autonomic modulations might be associated with (and possibly be a predictor of) SDB.

In their study, the authors enrolled 64 women in the second trimester of uncomplicated pregnancy. They excluded patients with other ongoing medical conditions, smokers, and alcohol drinkers.

All patients underwent both daytime heart rate variability (HRV) measurement by photoplethysmography, whilst resting in the supine position for 5–10 min and nocturnal pulse oximetry while awake, where mean and minimum oxygen saturation and 3% oxygen desaturation index were measured.

Baseline characteristics showed a cohort of young females (mean age 28.8 years) with a normal body mass index and office blood pressure. The mean Epworth Sleepiness Scale, an eight-item questionnaire that screens for daytime sleepiness in different day-to-day activities, was 5.4 points (normal <10) suggesting no relevant daytime sleepiness. Only 15.8% were habitual snorers. No relevant SDB was observed as the 3% oxygen desaturation index was between 0 and 4.4 events/h.

When comparing patients with minimum nocturnal oxygen saturation greater and lower than 90%, the authors found that the latter group had an increased heart rate and a decreased standard deviation of the R-R interval (SDNN), as well as the high-(H) and low-(L) frequency power.

A further multiple regression found that minimum oxygen saturation lower than 90% and age were significant predictors of SDNN and LF power, independently of the other covariates considered (gestational age, body mass index, employment, and parity).

This thought-provoking study, despite its limitations (small sample of patients and lack of patients with clinically relevant SDB), demonstrated that modulations of the autonomic nervous system (ANS) in pregnancy are associated with minimal nocturnal oxygen saturation and possibly with SDB. This is of interest it might help discriminate pregnant women at risk of preeclampsia regardless of typical symptoms of SDB such as excessive daytime sleepiness.

There are some aspects which need to be discussed.

Firstly, the authors have chosen HRV as a mean to measure ANS activity. This measure is quite complex: one of the most accurate ways involves microneurography, which allows visualizing and recording directly the traffic of nerve impulses that are conducted in peripheral nerves. However, this technique can be painful and unfeasible, particularly in the clinical setting. HRV analysis is an indirect technique, which allows measuring the variations of the sympathetic–parasympathetic balance simply by analyzing the changes in R-R intervals in the electrocardiographic tracing. Although this technique has been validated,[17] it does not allow for the direct measurement of the input of the two components of the ANS and provides a number of different parameters (time and frequency domain parameters) that must be interpreted to understand ANS activity.

Watanabe et al.[16] correctly analyzed LF and HF which reflect the combination of the sympathetic and the parasympathetic nervous system influences and vagal activity respectively; however, no data are available on very LF (measures rhythms between every 25 s and every 5 min) which is particularly exaggerated by SDB. Moreover, other sleep disturbances can influence the sympathetic–parasympathetic balance; sleep deprivation for instance is very common among pregnant women. It has been shown that people with <6 h sleep have higher heart rates and different ANS function (during awake, eyes-closed and open, in the resting condition) compared with people with >6 h of sleep.[18]

Thus, the data must be interpreted with caution mostly because daytime HRV measurements can be influenced by several other physiological and psychological factors. Furthermore, calculation of most HRV frequency domain requires a condition called "stationarity," (i.e. that the mean and variance of the signal do not change significantly at different points in the recording) because some frequency domain measures are less useful when the heart rate is changing rapidly.[19]

An interesting finding in this study is that HRV could capture the variations of the sympathetic–parasympathetic balance even if the severity of SDB in this cohort was very mild. Indeed, reductions in vagal tone have been demonstrated in patients with moderate to severe OSA, whilst this was less clear in patients with mild OSA.[20]

However, it should be noted that during pregnancy some ANS changes occur, and in particular a higher HF ratio in early pregnancy is observed, with a shift towards a higher sympathetic modulation in late pregnancy.[21]

To conclude, this study provides further insights on the ANS changes in pregnant patients and suggests a possible way to screen patients for OSA. This needs to be validated in larger prospective studies in order to establish whether HRV can become a tool to predict SDB and possibly prevent the development of gestational hypertension and preeclampsia.

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