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Snoring and markers of fetal and placental wellbeing

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ABSTRACT

Introduction: Snoring, the symptom of partial airway obstruction during sleep, is a common complaint during pregnancy and is associated with adverse perinatal outcomes. Mechanisms underlying this association have not been studied. We investigated the relationship between snoring in pregnancy and maternal serum markers of feto-placental wellbeing.

Methods: We conducted a secondary analysis of a cross sectional study designed to investigate perinatal outcomes of sleep-disordered breathing. Women admitted for delivery were systematically selected and answered a questionnaire about snoring using the Multivariable Apnea Prediction Index. Participants who had screening markers measured were included and divided into snorers and non -snorers. Markers measured included first and second trimester Down syndrome screening markers, reported as multiples of the median (MoM). An additional analysis was performed with snorers categorized as acute or chronic snorers based on duration of snoring in relation to pregnancy.

Results: While significant differences were noted in co-morbid maternal medical conditions between snorers and non-snorers, there were no significant differences in the neonatal outcomes assessed between the two groups. No significant differences were noted in any of the first trimester (PAPP-A) or second trimester (AFP, uE3, hCG, inhibin-A) markers between snorers and non-snorers, $p > 0.25$. In addition, no significant differences in marker levels were noted between acute and chronic snorers.

Conclusion: Snoring is not associated with alterations in the markers of fetal or placental wellbeing tested here and suggests that there are alternative mechanisms underlying the association between snoring and adverse perinatal outcomes.

1. Introduction

Snoring, the symptom of partial airway obstruction during sleep, is a common complaint among pregnant women. Snoring falls within the spectrum of sleep disordered breathing (SDB), which encompasses disturbances from snoring to obstructive sleep apnea (OSA). In contrast to isolated snoring, OSA includes recurrent oxygen desaturations and arousals during sleep as well as a significant degree of airflow limitation. Though snoring is often a symptom of OSA, it may also be present in the absence of a polysomnographic diagnosis of OSA. SDB is significantly more common in the pregnant than the non-pregnant population (35% versus 9%) [1], though the prevalence of snoring during pregnancy has been variously reported to range from 12% to 45% [2–4]. The overall increased frequency of SDB during this time can be attributed to the physiologic changes of pregnancy, including reduced upper airway size [5] and increased mucosal edema and friability, with higher Mallampati scores [6], as well as a decreased functional residual capacity. Functional residual capacity is reduced approximately by 20% at term due to the gravid uterus causing diaphragmatic elevation. A reduced FRC may result in less caudal traction of the trachea and pharynx, potentially leading to increased airway collapsibility and an increased risk of SDB [7, 8].

Importantly, SDB has been consistently associated with adverse pregnancy outcomes such as a two to three fold increase in the risk of hypertensive disorders of pregnancy and a threefold increase in the risk of gestational diabetes [1, 4, 9], as well as adverse neonatal outcomes [10, 11] such as growth restriction and preterm birth [12].

The placenta may play an important role in explaining the

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relationship between SDB and adverse pregnancy outcomes. However, mechanistic pathways linking SDB to diseases such as preeclampsia have not been well established. Plausible pathophysiologic explanations involve the role of intermittent hypoxia, airflow limitation, and/or repeated arousals in pregnant women with SDB, ultimately leading to sympathetic stimulation, oxidative stress, inflammation, and endothelial dysfunction, impacting placental function [9]. Intermittent hypoxia in OSA may cause feto-placental hypoxia, as suggested by fetal normoblastemia and increased expression of tissue hypoxia marker carbonic anhydrase IX [13]. It is plausible that placental hypoxia may then to lead to subsequent endothelial dysfunction and angiogenic-antiangiogenic disequilibrium, changes that have been linked to the development of preeclampsia [1, 14, 15]. In addition, alterations in prenatal screening markers have also been linked to the development of preeclampsia [16]. Initial studies of feto-placental markers among pregnant women with OSA have yielded some insight into the placental dysfunction that interfaces between OSA and placenta-mediated diseases such as preeclampsia. In previous studies by the investigators, well-established markers of feto-placental wellbeing, some linked to later development of preeclampsia [12, 16] such as unconjugated estriol (uE3), α-fetoprotein (AFP), pregnancy-associated plasma protein-A (PAPP-A) and inhibin A were studied. Pregnant women with OSA had significantly decreased levels of uE3 [12] and PAPP-A [16], persisting after adjusting for body habitus. Additionally, the investigators have previously reported an imbalance between angiogenic and anti-angiogenic markers among pregnant women with OSA, similar to that observed in preeclampsia [16].

Though snoring has been associated with hypertensive disorders of pregnancy [1, 17] and preliminary data suggest improved hemodynamics in women at risk for preeclampsia [18] and women with preeclampsia who are treated with positive airway pressure [18, 19], the gold standard treatment of OSA, mechanisms linking snoring to these outcomes remains to be studied.

We aimed to investigate the relationship between snoring in pregnancy and maternal serum markers of feto-placental wellbeing, namely AFP, uE3, hCG, inhibin A, and PAPP-A. A positive finding would suggest that airflow limitation associated with snoring may be sufficient to impact placental function. A negative finding would suggest that alterations in feto-placental markers are specific to OSA in pregnancy, rather than related more broadly to snoring, and may also involve other pathophysiologic mechanisms such as intermittent hypoxia or recurrent arousals.

2. Material and methods

2.1. Methods

This study represents a secondary analysis of a convenience sample that resulted from a cross sectional study designed primarily to investigate maternal and fetal outcomes of sleep disordered breathing in pregnancy. It was conducted at a large tertiary care teaching hospital, with approval from the Institutional Review Board (Women and Infants' Hospital, Providence, RI).

2.2. Participant selection

Initially, 1000 women admitted for delivery were randomly selected for screening for SDB, over the course of an 18-month period. Subjects were English speaking and ≥ 18 years of age. Women with fetal or neonatal demise were excluded. Informed consent was obtained from all participants. A questionnaire was administered to participants by trained study personnel, eliciting information about patient demographics, medical history and sleep habits. More detailed methods of this survey-based study protocol have been previously published [1]. In brief, symptoms of sleep disordered breathing were assessed using the Multivariable Apnea Prediction Index [20]. Participants were asked the following questions: “In the last 3 months of your pregnancy, how often have you experienced (or were you told about) the following symptoms? A) You snored loudly; B) You snorted or gasped; C) Your breathing stopped, you choked or you struggled for breath.” Reponses were categorized in the following point system: “0) Never; 1) Rarely (less than once a week); 2) Sometimes (1–2 times a week); 3) Frequently (3–4 times a week); 4) Always (5–7 times a week).” Women who responded that they “snored loudly” either frequently (3–4 times a week) or always (5–7 times a week) were designated as cases (snorers) for this study. Women who denied all three symptoms, responding “never” to snoring, snorting/gasping and witnessed apneas, were designated as controls (non-snorers). Of these cases and controls, women that had first trimester or second trimester screening markers available in their records were ultimately included in this study. None of the women had a prior history of sleep apnea. The large study -from which this subset was drawn- examined perinatal outcomes and showed an increased risk for gestational hypertensive disorders, gestational diabetes and cesarean delivery after adjusting for age, body mass index, diabetes mellitus, chronic hypertension, multifetal gestation, renal disease and cigarette smoking. Though there was no significant association with growth restriction, the risk for preterm birth was significantly elevated even after adjusting for age, smoking, and multifetal pregnancies [1].

2.3. Screening markers

Maternal serum screening biomarkers were originally obtained for Down syndrome screening in the first (1T) and/or second trimester (2T) of pregnancy. Screening markers included alpha fetoprotein (AFP) (2T), unconjugated estriol (uE3) (2T), pregnancy-associated plasma protein A (PAPP-A) (1T), inhibin A (2T), and human chorionic gonadotropin (HCG) (2T). Marker levels were determined using automated chemiluminescent methods on the DxI instrument (Beckman Coulter), except for PAPP-A which was measured using a manual ELISA (Ansh Labs). Marker levels were reported as multiples of the median (MoM) to correct for gestational age and maternal weight, as described below in statistical analysis.

2.4. Neonatal characteristics

Neonatal characteristics collected included placental weight, birth weight, gestational age, weight for gestational age, APGAR score at 1 min and APGAR score at 5 min. Small for gestational age was defined as less than 10th percentile for gestational age, and large for gestational age was defined as greater than 90th percentile for gestational age.

2.5. Statistical analysis

All analyses were performed using BMDP Statistical Software, Inc. Descriptive statistics included means, medians, and standard deviations as appropriate. Levene's test for equal variances was performed prior to using either a pooled or separate Student's *t*-test to examine the difference between levels found in women who did not snore versus those that did. Some markers (e.g., BMI, serum markers) were subject to a logarithmic transformation prior to analysis.

Down syndrome screening marker levels were expressed as multiples of the median (MoM). Normal median levels of each marker are established in relation to gestational age and each patient result is then expressed as a multiple of the median for a given decimal gestational age [21]. The MoM value is further corrected for effects of maternal weight, African American (Black) race, cigarette smoking, insulin dependent diabetes and pregnancy conceived by in vitro fertilization. *P*-values were two-sided and statistical significance was considered at < 0.05.

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