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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.

Keywords

Snoring; Fetoplacental markers; Sleep disordered breathing; Pregnancy

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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 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 fetoplacental 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 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 fetoplacental 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 fetoplacental 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 pre-eclampsia 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." Responses 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 .

3. Results

3.1. Maternal characteristics

A total of 313 participants were included in the study based on screening marker availability, consisting of 149 snorers and 164 non-snorers. Table 1 compares selected characteristics of the snorer and non-snorer participants. Snorers were found to be significantly older in age than non-snorers ($p = 0.0002$), at $30.7(\pm 5.9)$ y as compared to $28.1(\pm 6.2)$ y. Snorers also

had significantly higher BMI of $27.3(\pm 0.090)$ as compared to the non-snorers' BMI of $23.6(\pm 0.082)$ Kg/m² ($p < 0.0001$). There was no significant difference in race (non-black / black) ($p = 0.73$) between the 2 groups.

Significant differences were noted in co-morbid maternal medical conditions between snorers and non-snorers. Snorers had a significantly greater prevalence of chronic hypertension ($p = 0.0078$). However, the prevalence of type II diabetes was similar in both groups ($p = 0.48$). Maternal complications such as preeclampsia ($p = 0.013$) and gestational diabetes ($p = 0.0006$) occurred more frequently in snorers compared to non-snorers.

3.2. Neonatal characteristics

There were no significant differences in the neonatal outcomes assessed between snorers and non-snorers. No significant differences were found in gestational age at delivery ($p = 0.19$), or in birthweight ($p = 0.69$) between snorers and non-snorers. Infant APGAR scores at both 1 and 5 min after delivery were compared between snorers and non-snorers; there was no significant difference in APGAR score at either time point. Placental weight was evaluated in the partial sample of participants with available data, without significant difference between snorers and non-snorers. Table 1 also shows the prevalence of small for gestational age and large for gestational age neonates.

3.3. Fetoplacental markers

First trimester sampling was obtained at a mean gestational age of 11.9 weeks and second trimester sampling was obtained at a mean gestational age of 17.3 weeks. There was no significant difference in gestational age at sampling between snorers and non-snorers in either the first trimester or the second trimester. Table 2 shows markers in snorers ($n = 148$) and non-snorers ($n = 164$). 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.

Subsequently, we aimed to compare marker values based on chronicity of snoring in relation to pregnancy. A total of 99 women who snored answered the question explaining the chronicity of snoring. Women with loud snoring were then divided into 2 groups: acute snorers (AS) consisted of women who reported having started snoring during pregnancy ($n = 65$), while chronic snorers (CS) consisted of women who snored before pregnancy ($n = 34$). No significant differences were noted in any of the first trimester or second trimester markers when compared between AS and CS, CS and non-snorers (NS), or AS and NS. Results are shown in Table 3.

4. Discussion

This study demonstrated that as expected, pregnant women who snore have a significantly greater body weight and a significantly higher BMI than pregnant women who do not snore. Along corresponding lines, the snorer group was also found to have a significantly greater prevalence of gestational diabetes, chronic hypertension, and preeclampsia than the non-snorers group. There were no significant differences in levels of fetoplacental markers AFP, uE3, hCG, inhibin-A, or PAPP-A, when compared between snorers and non-snorers.

The lack of significant difference in the levels of maternal prenatal serum screening markers between pregnant women who snore and pregnant women who do not snore, as shown in this study, is in contrast to previous literature documenting significant alterations in the same markers among pregnant women with obstructive sleep apnea, as compared to control pregnant women at low risk for obstructive sleep apnea. Specifically, prior work by the investigators has shown that women with OSA have significantly decreased levels of uE3 and PAPP-A [12, 16]. Despite similar testing methods to our previously described studies, it appears that snoring does not impact placental function in the same way that obstructive sleep apnea does. As mentioned earlier, obstructive sleep apnea is characterized by not only snoring and airflow limitation, but also by recurrent arousals and intermittent hypoxemia and reoxygenation. Hoffstein et al. have suggested that non-apneic snorers were unlikely to have nocturnal oxygen desaturation [22]. Hence, it is likely that the airflow limitation and potential sympathetic activation associated with snoring is not sufficient as an independent mechanism to alter markers of fetal-placental wellbeing. Rather, the additional pathologic findings associated with obstructive sleep apnea, such as intermittent hypoxia and/or repeated arousals from sleep, may be required to cause the placental dysfunction that leads to altered levels of serum prenatal screening markers. The described association between snoring and adverse outcomes such as gestational hypertensive disorders and gestational diabetes, [1, 17] disorders mediated by the placenta, cannot be fully explained by alterations in the pathways leading to secretion of markers tested in this study. It is therefore possible that snoring may be associated with sympathetic activation through airflow limitation; this sympathetic activation is more likely to impact the placenta through different mechanisms than those tested in this study such as inflammation or activation of the renin-angiotensin system. Similarly, though some have argued that isolated snoring in pregnancy is unlikely to impact fetal oxygenation despite partial air flow limitation, in part due to potential protective mechanisms in place for the fetus, [23] others have shown evidence of fetal erythropoiesis in cord blood, a marker of fetal distress, in newborns born to women with a snoring history [24]. The latter findings suggest that snoring has significant bearing on fetal health.

Similarly, we aimed to examine whether markers differed by snoring duration. As previously described by O'Brien LM et al., perinatal outcomes have differed in some studies based on the duration of snoring in relation to pregnancy [25]. Pregnancy onset snoring was independently associated with gestational hypertension and pre-eclampsia [25] whereas pregnant women who were chronic snorers were more likely to have newborns who were small for gestational age [17]. These findings were not consistent in the literature as in another study by Tauman et al., newborns of snoring mothers without evidence of OSA were not shown to have evidence of growth restriction, regardless of the onset of snoring in pregnancy, compared to non-snoring mothers [26]. Nonetheless, our results did not show a difference in marker alteration by snoring duration, again, highlighting the specificity of the signal in these markers in women with obstructive sleep apnea compared to women with snoring only, and suggesting potential alternative pathways.

Findings from this study need to be interpreted in light of some limitations. Among women surveyed by questionnaire only those who had testing for serum markers were included in this study; however, the number of women excluded on the basis of unavailable serum markers was small (7 snorers and 2 non-snorers excluded), and it is unlikely that any

significant bias resulted from this exclusion. Given the retrospective nature of the study, and that participants were classified based on self-reported symptoms, it is possible that the snoring group may include a small number of participants who have undiagnosed sleep apnea - women with a known diagnosis of sleep apnea were not included in the study-. Inclusion of women with occult sleep apnea may have biased the results toward a positive effect, given that past studies have shown OSA to be associated with alterations in fetal-placental markers. However, given this study's negative results, we do not suspect this to be a major driver. In addition, our analysis of chronic and acute snorers was an attempt to address the temporal relationship of snoring and potential alterations in fetal and placenta-secreted serum markers; however, this reduced the sample size. The relationship between snoring, placental function, and preeclampsia may be bidirectional. It is possible that, through a systemic response related to airflow limitation, sympathetic activation, inflammation or other mechanism, sleep disordered breathing would result in a placental injury, which would impact placenta secreted markers and predispose to preeclampsia. On the other hand, a placental injury through non-SDB mechanisms may result in preeclampsia, inflammation, low oncotic pressure and upper airway changes which may lead to the development of snoring. The sensitivity analysis performed aims at differentiating between women whose snoring was present prior to pregnancy and those whose snoring started in pregnancy.

5. Conclusion

Contrary to obstructive sleep apnea, which is characterized by oxygen desaturation in addition to the isolated airflow limitation observed in snoring, snoring is not associated with alterations in the markers of fetal or placental wellbeing examined. The partial airflow limitation seen in snoring then, is unlikely to independently explain the association between sleep disordered breathing and placenta-mediated adverse outcomes such as hypertensive disorders of pregnancy. The mechanism linking snoring and such adverse pregnancy outcomes remains to be elucidated.

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Table 1

Selected characteristics of the study population, with stratification by snoring status.

Characteristic	All participants ^a (N = 313)	Non-snorers (N = 164)	Snorers (N = 149)	p-Value ^b
Demographics				
Age (years)	29.3 (6.2)	28.1 (6.2)	30.7 (5.9)	0.0002
Weight (pounds)	150 (38)	140 (30)	162 (42)	<0.0001
Height (cm)	185 (40)	173 (30)	198 (44)	<0.001
BMI (Kg/m ²) ^c	25.2 (0.092)	23.6 (0.082)	27.3 (0.090)	<0.0001
Race (N (%)Black)	38 (12.3%)	19 (11.7%)	19 (13.0%)	NS
Maternal preexisting conditions				
Pregestational DM II (N (%))	1 (0.32%)	0	1 (0.67%)	NS
Chronic HTN (N (%))	10 (3.19%)	1 (0.61%)	9 (6.04%)	0.0078
Pregnancy complications				
Gestational DM (N (%))	28 (8.95%)	6 (3.66%)	22 (14.8%)	0.0006
PEC (N (%))	18 (5.75%)	4 (2.43%)	14 (9.40%)	0.013
Neonatal outcomes				
Gestational age at delivery (weeks)	38.8 (2.1)	39.0 (2.0)	38.7 (2.1)	NS
Preterm Birth	7.3%	5.48%	9.4%	NS
Birthweight (grams)	3346 (604)	3333 (565)	3360 (646)	NS
Birth weight for GA				
SGA	9.9%	9.76%	10.07%	NS
LGA	10.5%	6.71%	14.77%	0.02
APGAR at 1 min	7.83 (1.23)	7.84 (1.29)	7.83 (1.17)	NS
APGAR at 5 min	8.90 (0.61)	8.95 (0.49)	8.85 (0.71)	NS
Laboratory investigations				
Gestational age at 1T sampling	11.9 (0.9)	11.9 (0.9)	11.9 (1.0)	NS
Gestational week at 2T sampling	17.3 (1.6)	17.4 (1.7)	17.2 (1.4)	NS
Placental weight (grams)				
Snorers N= 49, non-snorers N= 27	454 (134)	447 (153)	458 (123)	NS

Number of participants for 1st trimester GA = 209, 2nd trimester gestational age = 309.

^aReported as mean (SD) unless otherwise noted.^bComparing non-snorers and snorers.^cReported as median (log standard deviation).

Table 2

Prenatal serum screening marker levels in snorers and non-snorers.

Marker (N1, N2)	Non-snorers (N = 164)	Snorers (N = 148)	p-value
AFP	0.99 (0.15)	0.98 (0.15)	NS
uE3	1.03 (0.12)	1.00 (0.14)	NS
hCG	0.99 (0.22)	0.98 (0.24)	NS
Inh	1.04 (0.18)	1.08 (0.22)	NS
PAPP-A	0.96 (0.20) (N = 99)	0.96 (0.22) (N = 104)	NS

Marker levels are after conversion to an adjusted multiple of the median (MoM) and the median (logarithmic SD) are shown.

AFP: alpha-fetoprotein; uE3: unconjugated estriol; hCG: human chorionic gonadotropin; Inh: dimeric inhibin-A; PAPP-A: pregnancy associated plasma protein-A. The total sample for PAPP-A was smaller than the rest because PAPP-A was a first trimester marker, as fewer women had this done than second trimester markers.

Table 3

Serum screening marker levels comparison according to snoring chronicity.

Markers	Chronic snorers	Acute snorers	Non-snorers	p-Value
	<i>N</i> = 34	<i>N</i> = 65	<i>N</i> = 163	
	Mean (SD)	Mean (SD)	Mean (SD)	
AFP	0.01 (0.16)	−0.03 (0.14)	−0.004 (0.15)	NS
uE3	−0.01 (0.14)	−0.01 (0.11)	0.015 (0.12)	NS
hCG	0.01 (0.24)	−0.01 (0.23)	−0.002 (0.22)	NS
Inh	0.01 (0.21)	0.01 (0.22)	0.02 (0.18)	NS
PAPP-A	0.02 (0.21)	−0.03 (0.23)	−0.02 (0.19)	NS
	(<i>N</i> = 17)	<i>N</i> = 38	<i>N</i> = 108	

Marker levels are after conversion to an adjusted multiple of the median (MoM) compared between Chronic Snorers /Acute Snorers Chronic Snorers/non snorers and Acute Snorers/Chronic Snorers and the median (logarithmic SD) are shown.

AFP: alpha-fetoprotein; uE3: unconjugated estriol; hCG: human chorionic gonadotropin; Inh: dimeric inhibin-A; PAPP-A: pregnancy associated plasma protein-A. The total sample for PAPP-A was smaller than the rest because PAPP-A was a first trimester marker, as fewer women had this done than second trimester markers.