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Effects of Maternal Obstructive Sleep Apnea on Fetal Growth: A Case-Control Study

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Abstract

Objective—To investigate whether maternal obstructive sleep apnea (OSA) is associated with changes in fetal growth trajectory.

Study Design—Retrospective review of pregnant women who underwent overnight polysomnography. Fetal growth was estimated using sonographic biometric measurements obtained during routine prenatal care. Customized estimated fetal weight and birth weight centiles were calculated and impaired fetal growth was defined as birth weight <10th centile or a slowing of fetal growth by >33% during the last trimester. Logistic regression models were used to determine the relationship between maternal OSA and altered fetal growth after adjusting for potential covariates.

Results—There were 48 women without and 31 women with OSA. There were no differences in the proportion of infants with birth weight <10th centile between women with and without OSA (23% vs. 25%, $p=1.0$). However, the presence of maternal OSA was predictive of impaired fetal growth (aOR 3.9, 95% CI 1.2–12.6). Logistic regression models were repeated using only a slowing of fetal growth in the 3rd trimester (excluding birth weight <10th centile) and OSA predicted a slowing in fetal growth across the 3rd trimester (aOR 3.6, 95% CI 1.4–9.4). Fourteen additional women were treated with positive airway pressure during pregnancy; fetal growth was not significantly different in these women compared to controls.

Conclusion—Obstructive sleep apnea is independently associated with altered fetal growth, which appears to be ameliorated with use of positive airway pressure.

Keywords

obstructive sleep apnea; fetal growth trajectory; growth restriction; customized growth curves; growth centile; positive airway pressure

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INTRODUCTION

Fetal growth restriction is a common complication of pregnancy with a wide range of etiologies that may be maternal, placental, or fetal in origin.¹ The diagnosis and management of fetal growth restriction remains a challenge in obstetric care because of varying diagnostic criteria, varying etiologies, and a lack of consensus regarding the optimal timing of delivery.² There are also implications for the long-term health of the individual. Because of this, the identification of treatable underlying etiologies for fetal growth restriction should be a priority in obstetric research.

One novel factor that has been associated with fetal growth restriction is maternal obstructive sleep apnea (OSA), a condition that occurs when the airway collapses during sleep, resulting in a temporary cessation of breathing. This can cause hypoxemia, hypercapnia, and activation of inflammatory pathways,³ all of which may possibly contribute to poor placental oxygen and nutrient exchange in the pregnant patient. It is plausible that maternal OSA may contribute to fetal growth restriction through these mechanisms. Indeed, several studies using both self-reported symptoms⁴⁻⁶ and overnight polysomnography^{7, 8} suggest that maternal OSA is associated with fetal growth restriction. Nonetheless, other studies fail to support this relationship.⁹⁻¹²

Of note, one study that did not find a relationship with growth restriction, defined as a birth weight <10th centile, did find a *slowing* in fetal growth in the last trimester, defined as a fall in centiles >33% between 32 weeks gestation and birth weight.¹³ Although the latter study used only one fetal growth measure, which may not be an accurate predictor of true birth weight,¹⁴ it suggests that the fetal growth trajectory should be considered rather than simply a classification of growth restriction from a given birth weight. The aim of our study, therefore, was to investigate the impact of maternal OSA on serial measures of fetal growth. Our hypothesis was that maternal OSA would be independently associated with a fall in fetal growth across the centiles during the last trimester.

MATERIALS AND METHODS

This was a retrospective review of fetal growth in pregnant women with singleton gestations who had undergone overnight sleep studies for research purposes between April 2010 and June 2015. No participant was receiving clinical care for sleep problems at initial enrollment and both snoring and non-snoring women were eligible. All women were at least 18 years old and were pregnant with a single fetus without a fetal anomaly. There were no other inclusion/exclusion criteria in the initial study for which all women provided informed consent. For the purposes of the present fetal growth study, at least three measures of fetal growth were required. This study was approved by the University of Michigan Institutional Review Board (HUM#00102196).

Polysomnography

All women underwent an overnight sleep study. Obstructive sleep apnea was considered present if the apnea/hypopnea index (AHI, number of respiratory events per hour) was at least 5.0 events per hour of sleep. Those women who had an AHI<5 comprised the control

group. Women who had OSA on polysomnography during pregnancy and who were treated with PAP were not included in the primary analysis, but were included as an additional comparison group that was analyzed separately.

Fetal Growth

Fetal growth data was collected from sonographic biometric measurements acquired during routine prenatal care beginning at the anatomic scan at approximately 20 weeks and at any time thereafter. Details regarding fetal growth parameters at each ultrasound assessment were extracted from the medical record including estimated fetal weight and any evidence of major fetal anomalies that could affect fetal growth. Fetuses with major anomalies were excluded from the analysis.

Customized estimated fetal weight centiles and customized infant birth centiles were calculated using the Gestation Related Optimal Weight (GROW) software,¹⁵ which is recommended by the Royal College of Obstetricians and Gynaecologists Guidelines.¹⁶ This software optimizes estimated fetal weight centile and birth centile based on maternal height, weight, ethnic origin, parity, infant gender, and gestational age and has been customized for use in the US population in a large National Institutes of Health- sponsored trial.¹⁷ Because these centiles are based on the growth potential of an individual fetus under ideal circumstances,¹⁸ they optimize the ability to differentiate between constitutional and pathologic smallness,¹⁹ to more accurately identify pregnancies at risk for adverse outcome than more commonly used national standards for fetal growth.²⁰ We defined impaired fetal growth as customized birth weight <10th centile or a slowing in customized estimated fetal weight centile by >33% in the third trimester.

Demographic Information

Demographic information and medical diagnoses were obtained from the medical record. This information included maternal age, gestational age at time of sonograms and sleep study, body mass index (BMI; kg/M²) both pre-pregnancy and again at the time of the sleep study, gravity, parity, medical comorbidities, and tobacco, alcohol, and drug use. Diagnoses of preeclampsia, gestational hypertension, or gestational diabetes as well as outcomes including birth weight, gestational age at delivery, and infant gender were abstracted from the patient medical record after delivery.

The primary exposure was presence of OSA. Our intention was to compare women with OSA to control (non-OSA) women. After identifying a sub-group of women who had been treated with PAP during pregnancy, a comparison of PAP-treated pregnant women was also undertaken. The outcome measure was evidence of impaired fetal growth, defined as customized birth weight <10th centile or a slowing in any customized estimated fetal weight centile by >33% in the third trimester.

Statistical Analysis

All data obtained were double-entered into a database to ensure accuracy and analyzed with software (SPSS, version 23.0, IBM Corp, Armonk, NY). Histograms, box plots, and descriptive methods were used to examine data for errors and outliers. Primary analyses

focused on comparison of OSA vs. non-OSA women using t-tests for continuous variables and χ^2 tests for dichotomous variables. Logistic regression was then used to determine associations between OSA and impaired fetal growth after adjusting for potential covariates (maternal age, BMI at time of sleep study, co-morbid hypertension, diabetes, anti-hypertensive medications, anti-diabetic medications, and smoking). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

Sample size

Sample size calculations were based on the findings of Fung et al¹³ that 43% of women with OSA had impaired fetal growth compared to 11% of women without OSA. For the primary outcome of impaired fetal growth a sample size of at least n=27 per group would have 80% power at the 0.05 (two-sided) significance level for the detection of the same difference between groups.

Although our goal was initially to compare OSA vs. non-OSA women, we identified a group of women who were treated with PAP therapy during pregnancy. These women were analyzed once our primary analyses, described above, were conducted. Users of PAP therapy were only included if they were adherent to therapy, defined as PAP use 4 hours per night on at least four nights per week. Non-adherent users were excluded. For this second-level analysis we conducted between-group comparisons of continuous variables with ANOVA and dichotomized variables were compared with χ^2 tests or Fisher's Exact Test where appropriate. Logistic regression was used to determine associations between exposure groups (no-OSA, OSA, and PAP groups) and fetal growth (impaired fetal growth vs. no growth problem) after adjusting for potential covariates (maternal age, BMI at time of sleep study, co-morbid hypertension, diabetes, anti-hypertensive medications, anti-diabetic medications, and smoking).

RESULTS

A total of n=107 snoring and non-snoring pregnant women were identified that had undergone overnight polysomnography. Of these women, n=101 were identified as having at least three fetal growth measures obtained in addition to birth weight. Eight women were excluded due to multifetal gestation (n=6) or fetal anomaly (n=2). Of the remaining n=93 women there were n=48 women without OSA, n=31 women with objective evidence of OSA (AHI ≥ 5), and n=14 women who were treated with (and adherent to) PAP during pregnancy. These latter women are reported as a second level analysis following the primary analysis of n=79 women (women with and without OSA). Demographics of the study sample are shown in Table 1.

Fetal growth in women with OSA vs. no-OSA

While there were no differences in the proportion of infants with birth weight <10th centile between women with and without OSA (23% vs. 25%, p=1.0), there were significant differences in the proportion with a slowing of fetal growth across the last trimester (61% vs. 29%, p=0.0095; Table 2). Overall, impaired fetal growth (either a birth weight <10th centile

OR a slowing in fetal growth) occurred in 61% of women with untreated OSA and 35% of women without OSA ($p=0.043$).

In an unadjusted logistic regression model with impaired fetal growth as the dependent variable (defined as a birth weight $<10^{\text{th}}$ centile or a slowing in growth $>33\%$ in the last trimester) and OSA status as the independent variable (non-OSA or OSA), the presence of OSA was independently predictive of impaired fetal growth; OR 2.9 (95%CI 1.1–7.3, $p=0.026$).

A logistic regression model that controlled for potential covariates (maternal age, BMI at the time of sleep study, smoking, chronic hypertension, preeclampsia at enrollment, Type II diabetes mellitus, gestational diabetes, anti-hypertensive medication use, and diabetic medication use) demonstrated that the presence of maternal OSA was independently predictive of impaired fetal growth, OR 3.9 95%CI 1.2–12.6, $p=0.021$.

Logistic regression models were repeated using only a slowing in fetal growth $>33\%$ in the third trimester (i.e., not including birth weight $<10^{\text{th}}$ centile). In the unadjusted model the presence of maternal OSA was associated with a slowing of fetal growth, OR 3.6, 95%CI 1.4–9.4, $p=0.008$.

In a regression model adjusting for the same covariates as listed above, maternal OSA was independently predictive of a slowing in fetal growth across the third trimester, OR 4.8, 95%CI 1.5–15.4, $p=0.008$.

Fetal growth in women with OSA, without OSA, and PAP therapy

Following the primary analysis of OSA and non-OSA groups, a second-level analysis was undertaken that included the $n=14$ women who were identified as using PAP therapy during pregnancy. Therapy usage was determined by a web-based system whereby data was downloaded automatically through a wireless modem and adherence was defined as PAP use for at least 4 hours per night on at least 4 nights per week. Analyses were repeated with comparisons made between three groups (OSA, non-OSA, and PAP therapy).

Overall there were 14% of infants with birth weight $<10^{\text{th}}$ centile in the PAP therapy group. This was not significantly different from either the OSA (23%, $p=0.7$) or the non-OSA group (25%; $p=0.5$).

However, there was a significant difference in the proportion of women with a slowing of fetal growth across the last trimester between the OSA group and PAP therapy group (61% vs. 14%, $p=0.004$; Table 2). In contrast, the non-OSA group and PAP therapy group were not statistically different (29% vs. 14%, $p=0.3$). Overall, impaired fetal growth (either a birth weight $<10^{\text{th}}$ centile OR a slowing in fetal growth) occurred in 29% of women using PAP. Compared to the OSA group, the frequency of impaired fetal growth in PAP users was lower and almost reached statistical significance (29% vs. 61%; $p=0.09$) but was not different compared to women without OSA (29% vs. 35%; $p=0.9$).

In an unadjusted logistic regression model with impaired fetal growth as the dependent variable (defined as a birth weight $<10^{\text{th}}$ centile or a slowing in growth $>33\%$ in the last

trimester) and OSA status as the independent variable (non-OSA, OSA, or PAP therapy), maternal OSA remained independently predictive of impaired fetal growth (OR 2.9, 95%CI 1.1–7.3, $p=0.026$) but PAP therapy was not associated with impaired fetal growth (OR 0.7, 95%CI 0.2–7.0, $p=0.6$). See Table 3.

A logistic regression model that controlled for the same potential covariates as described above (maternal age, BMI at the time of sleep study, smoking, chronic hypertension, preeclampsia at enrollment, Type II diabetes mellitus, gestational diabetes, anti-hypertensive medication use, and diabetic medication use) demonstrated that while the presence of maternal OSA remained independently predictive of impaired fetal growth, OR 3.4 95%CI 1.2–9.9, $p=0.025$, there was no association between use of PAP therapy and impaired fetal growth (OR 0.7, 95%CI 0.1–3.7, $p=0.7$). See Table 3.

Logistic regression models were repeated using only a slowing in fetal growth $>33\%$ in the third trimester (i.e., not including birth weight $<10^{\text{th}}$ centile). In the unadjusted model the presence of maternal OSA remained associated with a slowing of fetal growth (OR 3.6, 95%CI 1.4–9.4, $p=0.008$) but there was no association between PAP therapy and slowing of fetal growth (OR 0.4, 95%CI 0.1–1.9, $p=0.2$). See Table 3.

In a regression model adjusting for the same covariates as listed above, maternal OSA remained independently predictive of a slowing in fetal growth across the third trimester, OR 4.3, 95%CI 1.3–12.8, $p=0.008$, but the use of PAP therapy was not related to a slowing in fetal growth (OR 0.4, 95%CI 0.1–2.5, $p=0.3$). See Table 3.

DISCUSSION

The primary finding of this study demonstrates that maternal OSA is predictive of impaired fetal growth, particularly a slowing of fetal growth across the third trimester rather than a birth weight $<10^{\text{th}}$ centile. These data help to shed light on conflicting findings in the literature regarding the association between OSA and fetal growth restriction, typically defined using only birth weight. Moreover, a novel finding reported here for the first time is that, in contrast to women with OSA, there were no increased odds of impaired fetal growth in women who used PAP therapy during pregnancy.

There are a number of studies using habitual snoring as a proxy of OSA. While several studies have found an independent association between maternal snoring and fetal growth restriction/small-for-gestational-age,^{4–6} not all studies support this finding.^{21–24} However, in addition to differing study designs, comparison between studies is limited as several had only small sample sizes and/or a small number of growth restricted infants.^{23, 24} Moreover, we have previously shown that the timing of maternal snoring may impact fetal growth, as infants born to women with chronic habitual snoring had an increased odds of a customized birth weight $<10^{\text{th}}$ centile (aOR 1.65, 95%CI 1.02–2.66, $p=0.04$), but those born to women with pregnancy-onset habitual snoring did not.²⁵

Investigations utilizing overnight polysomnography are limited. Of the latter studies, most fail to find a relationship between maternal OSA and infant birth centile,^{10, 12, 13, 26, 27} although sample sizes were small, ranging from $n=44$ to $n=188$. Recently, Pamidi et al,⁸ in a

study of n=230 women (n=153 with OSA) have reported a 2–3 fold increase in the odds of SGA as the severity of OSA increases. Similarly, large epidemiological studies also have conflicting findings. A population-based Taiwanese study of >4700 pregnant women reported an increased odds of SGA in women with OSA (aOR 1.34, 95% CI 1.09–1.66),⁷ yet cross-sectional data from hospital discharges in both the USA²⁸ and Australia²⁹ found no association between a diagnosis of maternal OSA and growth restriction. While this could represent a real phenomena, epidemiological data from diagnostic codes should be interpreted with caution since the vast majority of women with OSA are not referred for a sleep study and thus remain undiagnosed³⁰ and therefore misclassification almost certainly occurs. Furthermore, none of the epidemiological studies report the proportion of women who were treated with PAP therapy; a major problem if PAP has a positive impact on fetal wellbeing.

Importantly, all but one study¹³ has reported fetal size at birth rather than true fetal growth. Although Fung et al¹³ did not find an association between maternal OSA and birth centile they did report that fetal growth fell across centiles between a measure obtained at 32 weeks' gestation and a measure obtained at birth, in fetuses of women with OSA. Our data support these findings and clearly demonstrate a slowing in fetal growth, using serial measures during the third trimester, regardless of whether infant size at birth was <10th centile.

Several case reports^{31–33} and small pilot studies^{34–39} have utilized PAP therapy in pregnancy and while none has specifically investigated fetal growth, PAP has been demonstrated to be a safe, non-pharmacological, and non-invasive treatment option that has a potential role in reduction of fetal morbidity in this population. Improvement in fetal movement has been observed when PAP therapy is used in women with pre-eclampsia and SDB.³⁹ Furthermore, improvement in both clinical and biochemical markers of pre-eclampsia were observed in a recent case report of a woman at 31-weeks gestational age when PAP was used to treat OSA. This resulted in a prolongation of pregnancy for an additional 30 days.³³

The strengths of our study include an adequately powered, relatively large sample of women with and without OSA, and with at least three serial fetal growth measures in the third trimester. Further, we have provided data on fetal growth trajectory rather than just a measure of birth weight. Although our original intent was to examine the impact of maternal OSA on fetal growth, the identification of women who initiated PAP therapy during pregnancy allowed for additional preliminary investigation. Nonetheless, a limitation is that the study was not specifically designed to prospectively investigate fetal growth in women randomized to OSA treatment or not and is thus limited to women who underwent serial fetal measures for a variety of clinical reasons. As such, our comparison group (no OSA) was a higher-risk cohort of women than a healthy control group would have been. Despite this, however, we still found a significant difference in fetal growth between groups. Another limitation is that since polysomnography occurred, on average, in later pregnancy, the temporal relationship between OSA and impaired fetal growth cannot be established. Of note, however, the vast majority of women with OSA reported that their symptoms of OSA had predated the pregnancy, which suggests that a temporal relationship is possible. Furthermore, the sample size of pregnant women who had received (and adhered) to PAP

therapy during pregnancy may be considered to be somewhat small and result in this exploratory analysis being underpowered. Despite this potential limitation, these data are the first to assess fetal growth in women using PAP therapy. That fetal growth did not appear to be impaired in these women is a highly novel finding that raises the intriguing possibility that PAP therapy could potentially minimize the negative impact to fetal growth. This suggests that OSA may play a causal role in impaired fetal growth and that PAP therapy has potential as a novel intervention to improve fetal health. Large randomized controlled clinical trials of PAP intervention undoubtedly merit urgent investigation.

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Table 1

Demographics of Participants at Enrollment

	No-OSA (n=48)	OSA (n=31)	PAP (n=14)
Maternal age (years)	30.7±6.2	32.0±6.5	36.0±3.9 ^{c,e}
African American (%)	19 (39.6%)	8 (25.8%)	5 (37.5%)
BMI at PSG (kg/m ²)	33.5±9.8	38.1±7.8	43.0±11.9 ^d
Gestational age at PSG (weeks)	31.0±7.1	33.2±4.9	28.7±6.7
AHI	1.9±1.4 ^a	16.0±18.5	31.5±46.0 ^d
Smoker (%)	3 (6.3%)	5 (16.1%)	0 (0%)
Chronic Hypertension (%)	9 (18.8%) ^b	12 (38.7%)	9 (64.3%) ^c
Pre-eclampsia (%)	1 (2.1%)	2 (6.5%)	0 (0%)
Anti-hypertensive medication use (%)	9 (18.8%)	8 (25.8%)	9 (57.1%) ^{c,e}
Diabetes (%)	2 (4.2%)	2 (6.5%)	3 (21.4%)
Gestational Diabetes (%)	4 (8.3%)	5 (16.1%)	3 (21.4%)
Diabetic medication use (%)	3 (6.3%)	5 (16.1%)	3 (21.4%)

OSA = obstructive sleep apnea; PAP = positive airway pressure; BMI = body mass index; PSG = polysomnography; AHI = apnea/hypopnea index

Primary analysis between non-OSA and OSA groups:

^a p<0.001;

^b p=0.089

Comparison between all three groups:

^c p<0.01 PAP vs. non-OSA;

^d p=0.08 PAP vs. non-OSA;

^e p 0.05 PAP vs. OSA

Table 2

Fetal growth

	No-OSA (n=48)	OSA (n=31)	PAP (n=14)
Birth weight <10 th centile (%)	12 (25%)	7 (23%)	2 (14%)
Fall in growth centile >33% (%)	14 (29%) ^a	19 (61%) ^b	2 (14%)
Impaired fetal growth (%) (either birth weight <10 th centile OR a fall in growth centile>33%)	17 (35%)	19 (61%) ^c	4 (29%)

^ap=0.0095 OSA vs. non-OSA

^bp=0.004 OSA vs. PAP

^cp=0.09 OSA vs. PAP

OSA=obstructive sleep apnea; PAP=Positive Airway Pressure

Table 3

Odds Ratio for Impaired Fetal Growth

	Impaired Fetal Growth (either birth weight <10th centile OR a fall in growth centile>33%)	
	Unadjusted OR (95%CI)	Adjusted* OR (95%CI)
No OSA	Reference	Reference
OSA	2.9 (1.1–7.3)	3.4 (1.2–9.9)
PAP	0.7 (0.2–7.0)	0.7 (0.1–3.7)
	Fall in growth centile>33% only	
	Unadjusted OR (95%CI)	Adjusted* OR (95%CI)
No OSA	Reference	Reference
OSA	3.6 (1.4–9.4)	4.3 (1.3–12.8)
PAP	0.4 (0.1–1.9)	0.4 (0.1–2.5)

* adjusted for maternal age, BMI at the time of sleep study, smoking, chronic hypertension, preeclampsia at enrollment, Type II diabetes mellitus, gestational diabetes, anti-hypertensive medication use, and diabetic medication use.

OSA=obstructive sleep apnea; PAP=Positive Airway Pressure