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SCIENTIFIC INVESTIGATIONS

Obstructive Sleep Apnea in Gestational Diabetes: A Pilot Study of the Role of the Hypothalamic-Pituitary-Adrenal Axis

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Study Objectives: Obstructive sleep apnea (OSA) in pregnancy is associated with gestational diabetes mellitus (GDM). This propensity toward heightened insulin resistance in OSA patients has not been well characterized and may be related to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The aim of this study was to (1) assess the prevalence of OSA in pregnant women with GDM, (2) evaluate whether HPA axis dysregulation relates to OSA, and (3) investigate the relation between insulin resistance and OSA. We hypothesized that OSA is prevalent among pregnant women with GDM and that women with OSA will have higher levels of insulin resistance and dysregulation of the HPA axis.

Methods: Twenty-five pregnant women in whom GDM was diagnosed were enrolled. Subjects answered sleep questionnaires and underwent in-home sleep studies using a level III device. The presence of OSA was defined by apnea-hypopnea index ≥ 5 events/h. Homeostasis Model Assessment of insulin resistance was derived from measurements of fasting glucose and C-peptide levels. Three salivary cortisol levels were obtained across 1 day to assess circadian variation. Multivariable linear regression analyses were used to assess associations between variables.

Results: The sample consisted of 54% Caucasian pregnant women with a median body mass index of 36.1 and interquartile ratio of 10.6 kg/m^2. OSA was diagnosed in 17% of participants. Circadian variation of cortisol was preserved in women with OSA. Women with OSA displayed blunted cortisol awakening responses.

Conclusions: OSA is prevalent in women with GDM. OSA is associated with preserved circadian variation and blunted cortisol awakening responses.

Keywords: cortisol, diabetes, gestational diabetes, hypothalamic-pituitary-adrenal axis, insulin resistance, obstructive sleep apnea

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The prevalence of obstructive sleep apnea (OSA) in women with gestational diabetes mellitus (GDM), and the mechanisms underlying heightened insulin resistance among women with sleep-disordered breathing have not been well characterized. OSA and GDM may be related due to intermittent hypoxia and sympathetic activation, possibly leading to dysregulation of the hypothalamic-pituitary-adrenal axis.

Study Impact: This study adds to the understanding of the effect of OSA on the hypothalamic-pituitary-adrenal axis in women with GDM. Though hypoxemia burden appears to correlate with flattening of the cortisol awakening response, this effect is not likely to explain the association of OSA with GDM.

INTRODUCTION

Sleep-disordered breathing and obstructive sleep apnea (OSA) have been associated with abnormal glucose metabolism and type 2 diabetes mellitus in experimental human[1,2] and animal[3,4] models, small cohort studies[5] and in larger population studies.[6–8] Recent years have witnessed the emergence of data showing the associations of sleep-disordered breathing with gestational diabetes mellitus (GDM), a precursor of type 2 diabetes mellitus, which occurs in a population younger than the average population with sleep-disordered breathing.

Pregnancy accounts for numerous physiologic changes that may predispose women to the development of OSA.[9] Both OSA[10–12] and sleep-disordered breathing[13,14] are associated with an increased risk of GDM. The prevalence of OSA in women with GDM has not been as well characterized. A study by Reutrakul et al. has found that the prevalence of OSA in a sample of mainly African-American women with GDM was 73%.[15] Because OSA appears to be more common in certain races,[16,17] it is not clear whether this same prevalence would be applicable in cohorts with a different racial and geographic representation. The first aim of the current study was to examine the prevalence of OSA within a sample of pregnant women with OSA.

Mechanisms underlying heightened insulin resistance among women with sleep-disordered breathing have not been well characterized and may be related to intermittent hypoxia and sympathetic activation possibly leading to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and oxidative stress.[18] As cortisol secretion undergoes significant circadian variations and may be affected by nocturnal arousals similar

to those seen in OSA, it is possible that the HPA axis is influenced by OSA,[19] which may explain the association between OSA and abnormal glucose metabolism. The placenta, a key organ determining the health of pregnancy, has a significant secretory function. Human placental lactogen is secreted in large quantities with increasing levels with pregnancy progression. This hormone plays an important role in the physiologic insulin resistance that is typically observed in pregnancy. The placenta also secretes significant amounts of cortisol-releasing hormone, which is known to stimulate adrenal corticothyrotrophic hormone, resulting in significant physiologic changes in cortisol secretion.

Past studies examining the link between OSA and the HPA axis have reported no significant association[20,21] or even hypocortisolemia[22] in participants with OSA, and very few studies have reported increased HPA axis activity.[23] The second aim of the current study was to examine, in a cohort of women with GDM, circadian cortisol levels among pregnant women with and without OSA.

We hypothesized that the prevalence of OSA would be high, and that measures of OSA would be associated with higher levels of insulin resistance and activation of the HPA axis.

METHODS

Setting and Participants

Women in whom GDM was diagnosed based on the 3-hour glucose test were approached at the time of their first clinical visit to the diabetes nurse educator or the nutritionist at a large hospital-based practice, invited to participate, and asked to sign an informed consent. Women with a history of OSA or type 1 or type 2 diabetes mellitus, as well as shift workers, were excluded.

All anthropometric measures were obtained prior to sleep apnea testing. Weight and height were measured at the time of enrollment. Neck circumference was measured using a disposable medical measuring tape at the level of the hyoid bone in the seated position.

Respiratory Assessment During Sleep

The MediByte device (Medibyte, Braebon Inc., Kanata, Ontario, Canada) is a type III classification portable monitor for OSA and was used in this study. The device consists of two respiratory effort bands (chest and abdomen) equipped with respiratory inductive plethysmography technology, a nasal cannula pressure transducer for airflow detection, a finger pulse oximetry sensor (oxygen saturation and heart rate), and a body position sensor. The device is placed in the middle of the sternum for comfort and for body position detection and held in place via the chest effort band. The device operates on battery power (3.6 V) and has a sampling rate of 2,000 Hz.

Data from the portable monitoring device were downloaded into a chronologically readable format by using Pursuit software (Braebon Medical Corporation, Ontario, Canada) for review and manual scoring. The device has been validated against in-laboratory polysomnography.[24] All studies were scored by the same polysomnography technician with many years of experience based on the 2012 American Academy of Sleep Medicine guidelines.[25] Apneas were defined as > 90% flow limitation for at least 10 seconds. Hypopneas were defined if there was a 30% reduction in airflow for at least 10 seconds with 4% reduction in oxygen saturation. OSA was defined as an apnea-hypopnea index (AHI) > 5 events/h.

Laboratory Measurements

Fasting blood was obtained the morning after the sleep study and tested for glucose and C-peptide. Glucose testing consisted of blood collection in a heparinized tube via venipuncture following an 8-hour fast. The sample was spun for 10 minutes at 3,500 rpm and separated from cells within 3 hours of collection. The specimen was checked for acceptability and loaded onto the 5800 analyzer (Beckman Coulter, Inc., Brea, California, United States). Serum was also collected for C-peptide measurements, transported at room temperature for testing and processed via immunoassay.

The Homeostatic Model Assessment for Insulin Resistance was then calculated using the formula fasting insulin (microU/L) × fasting glucose (nmol/L) / 22.5.

Salivary cortisol samples were collected at 3 time points over a 24-hour period: bedtime of the night of the sleep study, wake, and 45 minutes after wake. Participants were given verbal as well as written instructions regarding the collection process, and dietary and lifestyle modifications required for this specific test. For instance, participants were asked to avoid brushing their teeth 1 hour before saliva collection, avoid acidic food or foods high in sugar, avoid large meals within an hour before collection, and avoid alcohol 12 hours before the test. Participants also recorded the time of day at each sample collection. The process was again reviewed with the participant upon sample drop-off.

The saliva was collected using the passive drool method into 5-mL polypropylene cryovials (Salimetrics, LLC, State College, Pennsylvania, United States). The subjects were instructed to let saliva collect in their mouth and gently push the saliva into a short section of a small straw into the cryovial. The samples were stored at −80°C until time of testing. Salivary cortisol measurements were performed in duplicate using an enzyme immunoassay by Salimetrics Laboratories (Carlsbad, California, United States; https://www.salimetrics.com/assets/documents/1-3002n.pdf). All reagents were then brought to room temperature. Wash buffer was prepared by diluting wash buffer concentrate with room temperature-deionized water at a ratio of 1:9. The enzyme conjugate is then diluted with assay diluent and incubated at room temperature for 60 minutes. After plates are washed with wash buffer, tetramethylbenzidine substrate solution is added and plates incubated for another 25 minutes in the dark. Stop solution is then added and reading performed via a plate reader at 450 nm within 10 minutes of adding the stop solution. The test has average intra-assay and interassay coefficients of variation of 3.5% and 5.1%, respectively.

Statistical Methods

Analyses were performed using SAS software, 9.3 (SAS Institute Inc., Cary, North Carolina, United States) and SPSS v.20

Table 1—Patient characteristics (n = 23).

Age, years, median (IQR)	30.5 (7.0)
BMI at diagnosis, kg/m^2, median (IQR)	36.1 (9.6)
BMI at antenatal, kg/m^2, median (IQR)	32.6 (8.6)
GA at enrollment, weeks, median (IQR)	28.0 (4.0)
Hypertension, n (%)	3.0 (13.0)
Race, n (%)	
Asian	1.0 (4.0)
African-American	4.0 (16.0)
Caucasian	13.0 (54.0)
Multiracial and other	6.0 (25.0)
Hispanic ethnicity, n (%)	2.0 (8.0)

BMI = body mass index, GA = gestational age, IQR = interquartile range.

Table 2—Respiratory parameters during sleep.

Participants with OSA as defined by AHI > 5, n (%)	4.0 (16.7)
AHI, events/h, median (IQR)	0.9 (2.3)
Oxygen saturation average, %, median (IQR)	95.5 (1.8)
Oxygen saturation nadir, %, median (IQR)	84.0 (8.5)
Time spent with oxygen saturation < 90%, %, median (IQR)	0.4 (4.7)
Central apnea index, events/h, median (IQR)	0.0 (0.05)
Obstructive apnea index, events/h, median (IQR)	0.1 (0.7)

AHI = apnea-hypopnea index, IQR = interquartile range, OSA = obstructive sleep apnea.

(IBM Corp., Armonk, New York, United States). Descriptive analyses were performed to report demographics and comorbidities. Median values and interquartile range (IQR) were then used to describe nonparametric variables. We calculated the cortisol awakening response by taking the difference between the values of rise in cortisol from wake to 45 minutes after wake. We examined evening cortisol levels separately from the awakening response. Linear regression analyses were performed to examine associations among measures of sleep-disordered breathing and cortisol. Models were adjusted for gestational age, time of saliva collection, Perceived Stress Scale score, and Patient Heath Questionnaire-9. As stress and depression are known confounders of cortisol measurements, these two validated questionnaires were collected at the time of enrollment to assess perceived stress[26] and depression[27] in these women. Similar analyses were performed to assess the association of measures of sleep-disordered breathing and insulin resistance, adjusted for body mass index (BMI) and gestational age. Fisher exact test was used to compare nominal variables.

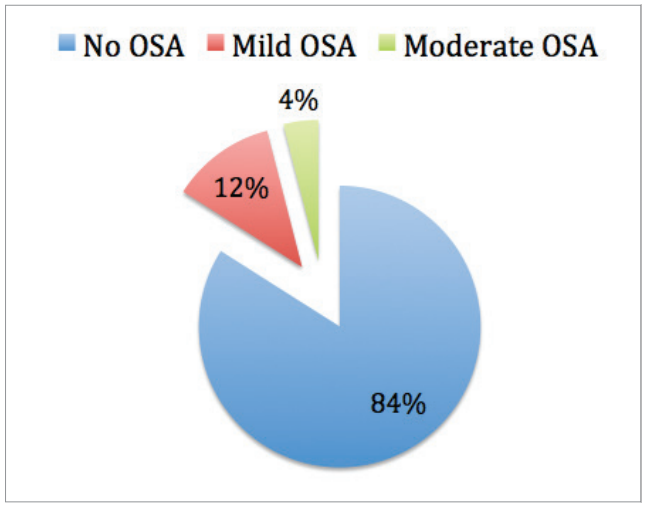
RESULTS

Sample Characteristics

A total of 31 participants consented for the study; 6 signed a consent form but failed to attend the enrollment visit. Twenty-five participants were enrolled and completed the study. Median age was 30.5 years (IQR 7) and median prenatal BMI was 32.6 (IQR 8.6) kg/m^2 (**Table 1**). Median BMI at the time of diagnosis of GDM was 36.1 (IQR 9.6) kg/m^2. The cohort was racially diverse and consisted of 54% Caucasian women, 16% African-American, and 4% Asian. Median gestational age at enrollment was 28 weeks. Most women were multigravida (65%) and multiparous (52%). Three women had chronic hypertension. BMI was significantly higher in women with OSA compared to those without (40.8 ± 8.5 versus 32.9 ± 6.2 kg/m^2, P = .01).

Neck and breast circumference were also significantly higher in women with OSA compared to those without OSA (41 ± 2.0 versus 36 ± 3.1 cm, P value = .02 and 125.5 ± 7.2 versus 111 ± 12.2 cm, P = .03, respectively). Four participants (16.6%) had OSA using the 4% desaturation criteria for hypopnea (**Table 2**). Three patients had mild OSA and one patient had moderate OSA (**Figure 1**). Median AHI was 0.9, IQR 2.3 events/h. Median nadir oxygen saturation was reduced at 84%, IQR 8.5.

Figure 1—Obstructive sleep apnea severity distribution.



OSA = obstructive sleep apnea.

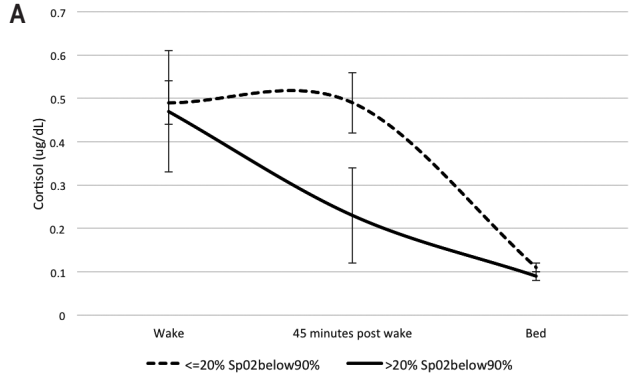
Cortisol Measurements

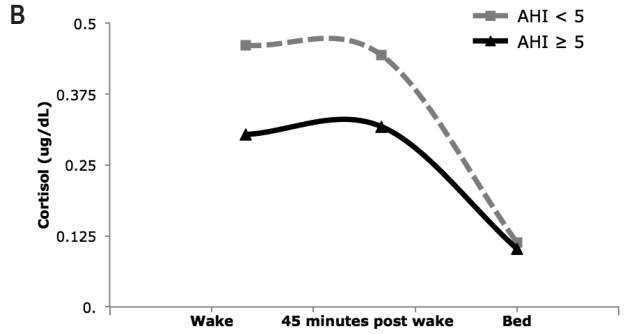
Results revealed a significant association between SpO_2 below 90% and cortisol awakening response (β = -.54, P = .02), such that women who spent greater time in < 90% oxygen saturation had lower awakening responses (**Figure 2A**). Cortisol awakening responses appear to be flattened when analyzed by AHI and the area under the curve is smaller; however, the difference did not reach statistical significance (**Figure 2B**). All other associations were nonsignificant (P > .24). We did not observe significant differences in awakening response or evening cortisol between OSA groups (P > .23).

Insulin Resistance

There were no significant differences in insulin resistance in women with and without OSA (t = −0.60, P = .56) (**Table 3**). The association of insulin resistance with cortisol awakening response and evening cortisol did not reach statistical significance. There were no significant associations among AHI or SpO_2 below 90% and insulin resistance (P > .47).

Figure 2—Breathing parameters during sleep predict cortisol awakening response.





(A) SpO_2 below 90% = percent time spent at blood oxygen saturation level below 90%, bed = bedtime. **(B)** AHI = apnea-hypopnea index.

Table 3—Participant anthropometric characteristics and cortisol values by OSA group.

	No OSA	OSA	*P*
Neck circumference, cm	36.00 (3.10)	41.00 (2.00)	.02
Breast circumference, cm	111.00 (12.20)	125.50 (7.20)	.03
Insulin resistance, HOMA-IR	11.42 (6.35)	13.64 (1.11)	.56
Cortisol awakening response, µg/dL	−0.02 (0.38)	−0.06 (0.23)	.88
Evening cortisol, µg/dL	0.10 (0.04)	0.15 (0.09)	.47

Values presented as mean (standard deviation). HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, OSA = obstructive sleep apnea.

DISCUSSION

This study shows a 17% prevalence of OSA in a cohort consisting mainly of multigravida, multiparous, Caucasian women with GDM. Women had mild or moderate OSA and none had evidence of central sleep apnea. More severe sleep-disordered breathing was associated with a flatter circadian cortisol pattern, demonstrated by lower cortisol awakening responses. There did not appear to be a significant relationship between OSA and insulin resistance.

The prevalence of OSA in this cohort appears to be similar to the prevalence of OSA in a high-risk pregnancy cohort with obesity.[28] However, a previous study that examined the prevalence of OSA in a sample of mainly African-American pregnant women with GDM reported OSA prevalence at 73%.[15] It is possible that our study may represent an underestimate of the true prevalence of OSA due to the technology used to make that diagnosis. Prevalence of polysomnography-diagnosed sleep-disordered breathing in pregnancy has varied significantly in the literature from 8% to 66%.[10,29] These differences are likely related to the definition of sleep-disordered breathing. Previous studies have shown that sleep-disordered breathing in pregnancy consisted of more subtle airflow limitations rather than significant desaturations.[30,31] Other factors that may affect the prevalence of sleep-disordered breathing include the device used to diagnose the condition, gestational age at enrollment, the type of population being studied in terms of its cardiometabolic risk profile, and the presence or absence of symptoms of sleep-disordered breathing. Level III devices have been validated in the evaluation of sleep-disordered breathing in pregnant women.[32] However, because these devices do not record sleep, total sleep time is likely overestimated, and hypopneas associated with arousals without desaturations of 4% are possibly missed, leading to an underestimate of the true prevalence of the disease. Level III devices also fail to detect REM-related sleep-disordered breathing, which is thought to be more prevalent in young women. REM-related sleep-disordered breathing has been associated with abnormalities in glucose control likely due to the high adrenergic state during REM sleep.[33] However, as REM sleep has been shown to be reduced in pregnancy,[34] it is unclear what the contribution of REM-related sleep-disordered breathing truly is in this population. It is also possible that racial differences in the samples of our study and Reutrakul et al.'s[15] could account for some of the differences, as their sample consisted of 80% African-American women. The diagnosis of OSA in pregnancy may also be complicated by the fact that polysomnographic criteria routinely used in the nonpregnant population may not be adequate in this population as sleep-disordered breathing in pregnant women may consist mostly of airflow limitation rather than oxygen desaturation.[31] These subtle airflow limitations may in fact be linked to negative outcomes[31,35] and are likely worthy of recognition.

The cross-sectional design of our study does not establish a temporal relationship between OSA and GDM to suggest causality and may have limited our ability to detect significant changes in cortisol measurements. Though the association between OSA and type 2 diabetes is likely bidirectional in the nonpregnant population,[36] it is unlikely that abnormal glucose metabolism of a short duration as seen in diabetes that is diagnosed in pregnancy would result in a similar ventilatory instability. Hence, it is more biologically plausible that the association of OSA with GDM is in fact unidirectional, with OSA leading to GDM.

We hypothesized that women with OSA and GDM would have HPA axis dysfunction compared to women with GDM but no OSA. In nonpregnant cohorts, there have been studies that have shown higher cortisol levels in patients with OSA.[23,37,38] Other studies have shown that OSA is associated with blunting of the cortisol awakening response[39,40] with reversal of

this effect with treatment with CPAP.[39] Our study showed that the circadian variation in cortisol secretion was preserved in pregnant women with OSA; however, women with disturbed breathing during sleep appear to have attenuated cortisol awakening responses and a smaller area under the curve for cortisol measurements. These data are consistent with previous studies in non-pregnant samples with OSA.[39,40] *Post hoc* power analysis showed that this study had 88% power to detect differences at a 0.05 level in awakening cortisol but was not powered enough to detect differences in other salivary cortisol measurements. It is therefore possible that the lack of an effect on non-wake cortisol measurements may be related to the fact that the study was underpowered to detect those differences. It is also possible that our results are influenced by the relative mild severity of OSA in our sample and the lack of measurements during the night that could detect changes in cortisol secretion in response to obstructive events.[19] These findings would need to be confirmed in larger future studies that include sampling of cortisol over a longer duration of time (multiple days) to avoid sampling bias. In addition, it would be important to understand whether women who start pregnancy with a diagnosis of OSA have a different HPA axis response than those in whom the condition develops during pregnancy.

Another possible explanation of our findings could be a potential role of the placenta in mediating associations of OSA with GDM. Corticotropin releasing hormone is a hypothalamic neuropeptide that is also exponentially produced and released by the placenta into both fetal and maternal compartments in human pregnancies.[41,42] Corticotropin-releasing hormone plays a central role in regulating the HPA axis. In previous studies, we have demonstrated an association of OSA with abnormal function of the placenta[43,44] as well as evidence of a hypoxic injury to the placenta in women with OSA compared to pregnant controls.[45] It is possible that OSA may affect cortisol secretion in pregnant women by affecting the placenta and effecting placental cortisol releasing hormone secretion. In another pregnant cohort, we demonstrated that poor sleep measured with the Pittsburgh Sleep Quality Index was associated with higher evening cortisol levels.[46] These findings suggest that the effect of OSA on the HPA axis is not related to poor sleep but rather to other characteristics of sleep apnea such as recurrent hypoxemia. Future studies examining placental cortisol-releasing hormone secretion in women with and without OSA may help to better answer this question.

Our study did not show a significant difference in insulin resistance in pregnant women with OSA and those without. This lack of an effect could be due to the fact that all women in this sample were insulin resistant—they all carried a diagnosis of GDM and were in the second half of their pregnancy. However, it may also be related to the low degree of severity of OSA in these women and to sample size. Cohorts of men with OSA have confirmed an association of moderate and severe OSA with insulin resistance diagnosed by the Homeostatic Model Assessment of Insulin Resistance.[40] In addition, that same study showed significant differences in the degree of insulin resistance in the severe OSA group, compared to the moderate OSA group. These data suggest that OSA severity plays an important role in the association of OSA with abnormalities in glucose metabolism. In addition, studies of children at risk for OSA showed that BMI was the strongest driver of insulin resistance but that AHI emerged as a contributor to higher degrees of insulin sensitivity in obese children.[47]

This study has many strengths. OSA was diagnosed using objective measures. This study is the first to examine cortisol secretion in relation to sleep apnea in pregnancy and included careful and standardized evaluation of circadian variation of cortisol secretion. Our study findings need to be interpreted in the context of some limitations such as sample size. Our study was not powered to detect changes in cortisol levels—other than wake cortisol—because of limited funding. Future studies are needed that include larger sample sizes and a comparison group of pregnant women without GDM to further understand relationships between GDM, OSA, and the HPA axis. In addition, cortisol and glucose levels were not measured during the night to detect immediate responses of glucose and cortisol to intermittent hypoxemia and recurrent arousals.

In conclusion, this study demonstrates a high prevalence of OSA in women with GDM, preserved circadian rhythm of cortisol, and blunting of cortisol awakening responses. Because higher cortisol levels would have possibly explained an association between OSA and insulin resistance, our findings suggest that the association may be mediated by pathways independent of the HPA axis, even in pregnancy.[48,49] However, future studies powered to examine cortisol circadian variations are needed.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
GA, gestational age
GDM, gestational diabetes mellitus
HOMA-IR, Homeostatic Model Assessment Of Insulin Resistance
HPA, hypothalamic-pituitary-adrenal
IQR, interquartile range
OSA, obstructive sleep apnea

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