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SCIENTIFIC INVESTIGATIONS

Impact of nasal dilator strips on measures of sleep-disordered breathing in pregnancy

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Study Objectives: Women with sleep-disordered breathing (SDB) in pregnancy are at a greater risk of developing serious adverse perinatal outcomes. However, the pathogenesis of SDB in pregnancy is poorly understood. As nasal congestion is common in pregnancy, nasal obstruction may contribute to SDB in this population. This study aims to assess the impact of nasal dilator strips (NDS) on measures of SDB and their potential for use as a placebo condition.

Methods: Pregnant women ≥ 18 years old, body mass index ≥ 27 kg/m^2, and habitual snoring were enrolled. Participants completed 2 consecutive level III home sleep apnea tests and used NDS during the second test. Objective measures including respiratory event index and pulse transit time drop index, a measure of increased arterial stiffness, were compared across tests. Subjective assessments of participants' perceived impact of NDS use was also obtained.

Results: 54 women, 59% White, 60% in the third trimester were enrolled. Median time between the 2 studies was 1 day (interquartile range [IQR] 4). There was no significant change between the night without NDS use and the night with NDS use in respiratory event index (5.30 [IQR 6.20] vs 4.80 [IQR 6.78], $P = .8$) or pulse transit time drop index (6.8 [IQR 13.3] vs 6.6 [IQR 15.8], $P = .360$). Subjective measures of sleep did not differ between the 2 nights.

Conclusions: Despite the high prevalence of pregnancy-associated rhinitis, NDS do not have a significant impact on measures of SDB. Results from this study support the use of NDS as an appropriate placebo in prenatal clinical trials.

Keywords: sleep-disordered breathing, obstructive sleep apnea, nasal dilator strips, placebo, sleep, pregnancy, pulse transit time, respiratory event index

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The pathogenesis of sleep-disordered breathing in pregnancy is poorly understood, despite its serious adverse pregnancy-related outcomes, including gestational diabetes and hypertensive disorders. Our study aims to examine the impact of nasal dilator strips on measures of sleep-disordered breathing, as it is hypothesized that nasal obstruction may contribute to its development in this population.

Study Impact: The results of this study demonstrate no significant differences in objective measures of sleep-disordered breathing. This study is also one of the first, to our knowledge, to offer insight into the use of a noninvasive placebo in prenatal studies investigating sleep-disordered breathing.

INTRODUCTION

Sleep-disordered breathing (SDB) encompasses a spectrum of breathing abnormalities, including snoring, sleep-related hypoventilation, central sleep apnea, and obstructive sleep apnea (OSA).[1] While SDB is a relatively common condition in the nonpregnant population, it is significantly more common in pregnancy.[2] Furthermore, the number of women with SDB in pregnancy is increasing, as the prevalence of some of its risk factors, including obesity and advanced maternal age, rises. In the United States, over 30% of women of reproductive age have obesity and a growing proportion of women are postponing pregnancy.[3,4] Large studies report that habitual snoring affects one-third of all pregnant women during the course of their pregnancy,[2,5] and that OSA affects nearly 9% of low-risk pregnant patients.[6] The prevalence of OSA in women with complicated pregnancies is significantly higher.[7–9]

SDB in pregnancy has also gained more attention in recent years as numerous studies have demonstrated its strong association with a number of adverse maternal and fetal outcomes. Even when controlling for obesity, OSA in pregnancy has been shown to increase the likelihood of preeclampsia, eclampsia, gestational diabetes, and severe maternal morbidity.[6,10,11] The impact of these complications extends well beyond pregnancy, affecting the long-term cardiometabolic health of women.[12] Rates of adverse neonatal outcomes, including congenital anomalies and neonatal intensive care unit admissions, have also been shown to be significantly higher in newborns born to mothers with OSA.[11]

Despite the many studies demonstrating the adverse outcomes of SDB in pregnancy, the pathogenesis remains unclear, as it is likely different from that of the general population. There are a number of physiologic changes that happen during pregnancy that may alter the patency of the upper airway,

particularly at the level of the nasal passages. Rising levels of sex hormones, including estrogen and progesterone, are implicated in the altered nasal physiology of pregnancy, as the nasal mucosa contains estrogen receptors.[13] These hormones also increase the expression of histamine receptors in the nasal mucosa, exacerbating nasal hyperreactivity in pregnancy.[14] Additionally, increases in circulating blood volume seen in pregnancy may contribute to nasal obstruction.[15] Given these changes and the high percentage of women (40%) who report new-onset nasal congestion in pregnancy, known as pregnancy-related rhinitis, nasal obstruction may play a significant role in the development of SDB in this population.[16]

Nasal dilator strips (NDS) are designed to resist collapse of the nasal vestibule by mechanically pulling on the nasal walls superior to the alar cartilage. In theory, this should reduce resistance at the nasal passages and improve ease of breathing.[17] While 12 of 14 studies examining the effect of NDS on the apnea-hypopnea index in nonpregnant patients with OSA showed no significant impact, it is unclear whether NDS may impact SDB in pregnancy given the aforementioned physiologic changes that occur.[18] Investigation of the effects of NDS on SDB will offer insight into the role that nasal obstruction plays in the pathogenesis during pregnancy. It may also offer further insight into possible adjunctive therapy or whether NDS are an appropriate placebo in trials needed to examine the impact of therapy on pregnancy outcomes. We hypothesized that nasal dilator strips may improve self-reported nasal symptoms but would not impact objective breathing measures during sleep. To test this hypothesis, we recruited pregnant women with suspected SDB and compared their in-home sleep study data with and without the use of NDS, along with self-reported assessments.

METHODS

Participants

This study was approved by the Institutional Review Board of Lifespan Health System. Patients were recruited from community and hospital-based obstetric practices at the time of clinical visits. Pregnant women over the age of 18 years with a singleton pregnancy and risk factors for sleep-disordered breathing, including a body mass index ≥ 27 kg/m^2 and significant habitual snoring (≥ 3 nights/week), were enrolled in the study in either their first or third trimester of pregnancy.

Participants with overweight or obesity and habitual snoring who were previously enrolled in 2 prospective studies were invited to participate in this study. The first study, Positive Airway Pressure for Sleep Apnea in Pregnancy (PAPSAP), enrolled participants suspected of SDB and randomized those with SDB to positive airway pressure and NDS or NDS alone. Prior to receiving their assigned intervention, participants were provided with the option to repeat the sleep study with NDS and answer questionnaires. The PAPSAP study provided only first trimester participants due to design. The second study, De-novo development of obstructive Sleep Apnea in Pregnancy (DeSAP), enrolled women in early pregnancy and screened them for sleep apnea using the same methodology as PAPSAP (see below) in early pregnancy. Participants without sleep apnea in early pregnancy had repeat home sleep apnea testing in the third trimester. At the completion of participation in the DeSAP study, participants were invited to participate in the present study. Finally, to enrich the third trimester sample, given that nasal pathology is likely most prevalent and most severe in later stages of pregnancy, additional patients in their third trimester of pregnancy who were not enrolled in either study were also invited to participate.

All women provided written informed consent prior to data collection. Demographic information, a basic medical and social history, and baseline sleep surveys were collected at the initial visit.

Home sleep apnea monitoring

Participants were instructed to complete 2 consecutive home sleep apnea tests (HSATs) using an in-home level-III recording device, NoxT3 (Nox Medical, Suwanee, GA). The device features allow for recording of snoring, nasal pressure, sleep position, respiratory effort, and electrocardiography. In addition, pulse oximeters were paired via Bluetooth with the NoxT3 during recording for collection of peripheral capillary oxygen saturation data. An autoscore-derived apnea-hypopnea index strongly relates to apnea-hypopnea index derived from in-laboratory polysomnography ($r = .93$).[19] However, for the purposes of this study, all studies were scored by an experienced certified polysomnography technician. Hypopneas were defined using the recommended rule (3% desaturation rule) by the American Academy of Sleep Medicine guidelines.[20]

Following 1 night of baseline recording without NDS, participants were instructed to complete a second HSAT recording while wearing a standard NDS for the duration of their sleep. Participants were given written instructions on the application of the NDS to the external surface of their nose prior to sleep following manufacturer's instructions. Participants with recordings with poor data quality or without a minimum of 4 hours of sleep recorded were asked to repeat the study. Upon return of the sleep device, a member of the research team confirmed the use of NDS on the second night of the study.

Pulse transit time measurements

Pulse transit time (PTT) is the length of time it takes a pulse pressure to travel from the left ventricle to a peripheral arterial site (the fingertip in this case). This length of time is inversely proportional to arterial stiffness. PTT is measured between the R wave on electrocardiography and a constant on the plethysmography tracing of oxygen saturation. PTT measures the change in arterial stiffness caused by sympathetic activation[21] and is associated with arousals that occur during sleep.[22,23] PTT has been proposed as an alternative to esophageal pressure monitoring.[24,25] This measure has been validated in children and adults.[25,26] PTT drop index represents the number of drops in PTT per hour and was defined as a drop of at least 15 ms in PTT from the average PTT in the 60 s immediately prior that lasts for a minimum of 5 s. We previously described this measure in a pregnant cohort and demonstrated significantly more PTT drops than apneas and hypopneas, as defined by the

American Academy of Sleep Medicine, making it a potentially more sensitive measure of SDB.[20,27]

Questionnaire data

All participants completed the Berlin Questionnaire, which includes questions about risk factors predictive of SDB, to assess their baseline OSA risk category.[28] Participants were also asked to complete the Nasal Obstruction Symptom Evaluation (NOSE) scale after their sleep recording without NDS and after their recording with NDS use.[29] Participants self-rate each of the 5 individual items on a scale of 0 to 4, with 4 being the most severe degree of obstructive symptoms. The final score is the sum of these items multiplied by 5, with a final score ranging from 0 to 100. Scores greater than 30 are considered elevated, correlating with more severe nasal obstruction.[30] The NOSE questionnaire was modified to be in reference to each night of recording, and item 5 was modified to say, "Unable to get enough air through my nose," without relation to exercise or exertion. In addition, participants were asked about their adherence to the use of NDS on the second night of recording, potential side effects from the use of NDS, and whether they perceived their sleep quality to have improved, worsened, or stayed the same with the use of NDS.

Statistical analysis

A power analysis for a paired *t*-test estimating an effect size of 0.5 was performed using Stata SE 15.0 to calculate required sample size of 54. Descriptive statistics were used to calculate the mean, median, standard deviation, interquartile range, and percentages. Wilcoxon signed-rank test was utilized to analyze the significance of differences in respiratory event index (REI) in participants with and without the use of NDS given the nonnormal distribution. Paired *t*-tests were also performed to analyze NOSE scores and the additional objective sleep parameters, including oxygen desaturation index, SpO_2 minimum, and snore index. Wilcoxon rank-sum test was utilized to compare the change in objective measures with the use of NDS in the first and third trimester participant subgroups. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

Participant characteristics

A total of 54 pregnant participants were recruited for the study, with no participants withdrawing before completion of the sleep recordings. Demographics of the study population are reported in **Table 1**. Maternal race and ethnicity are based on participants' self-report through the administered demographics surveys and show a wide racial and ethnic distribution. Twenty-two participants were in their first trimester, with a mean gestational age of 12.1 ± 2.2 weeks, and 32 participants were in their third trimester, with a mean gestational age of 31.8 ± 1.9 weeks at the time of the baseline HSAT recording without NDS. The sample was comprised of 13 participants who were primigravida, and the mean number of previous pregnancies of 2.67 ± 2.19. Mean body mass index at time of recording without NDS was 37.9 ± 7.4 kg/m^2. Thirty women (55.6%) had an REI of ≥ 5 events/h of sleep on their recordings without NDS. The median number of days between HSAT recording without NDS and HSAT recordings with NDS was 1, with an IQR of 4 days. Of the 41 participants with available birth records by the time of study completion, 22.0% were diagnosed with gestational diabetes mellitus, and 29.3% were diagnosed with gestational hypertensive disorders.

Table 1—Demographic and medical characteristics of study population (n = 54).

	Values
Age, y	32.6 ± 5.3
BMI, kg/m^2	37.9 ± 7.4
Maternal race and ethnicity, n (%)	
White	32 (59.3)
Black	8 (14.8)
Asian	2 (3.7)
American Indian/Alaska Native	1 (1.9)
Native Hawaiian/Pacific Islander	0
More than one race	6 (11.1)
Other	5 (9.3)
EGA, wk	23.8 ± 10.0
Trimester 1	12.1 ± 2.2
Trimester 3	31.8 ± 1.9
Primigravida, n (%)	13 (24)
Prepregnancy hypertension, n (%)	8 (14.8)
Prepregnancy diabetes, n (%)	2 (3.7)

Data are presented as mean ± standard deviation and n (%). Maternal race and ethnicity are self-reported by participants. BMI = body mass index, EGA = estimated gestational age.

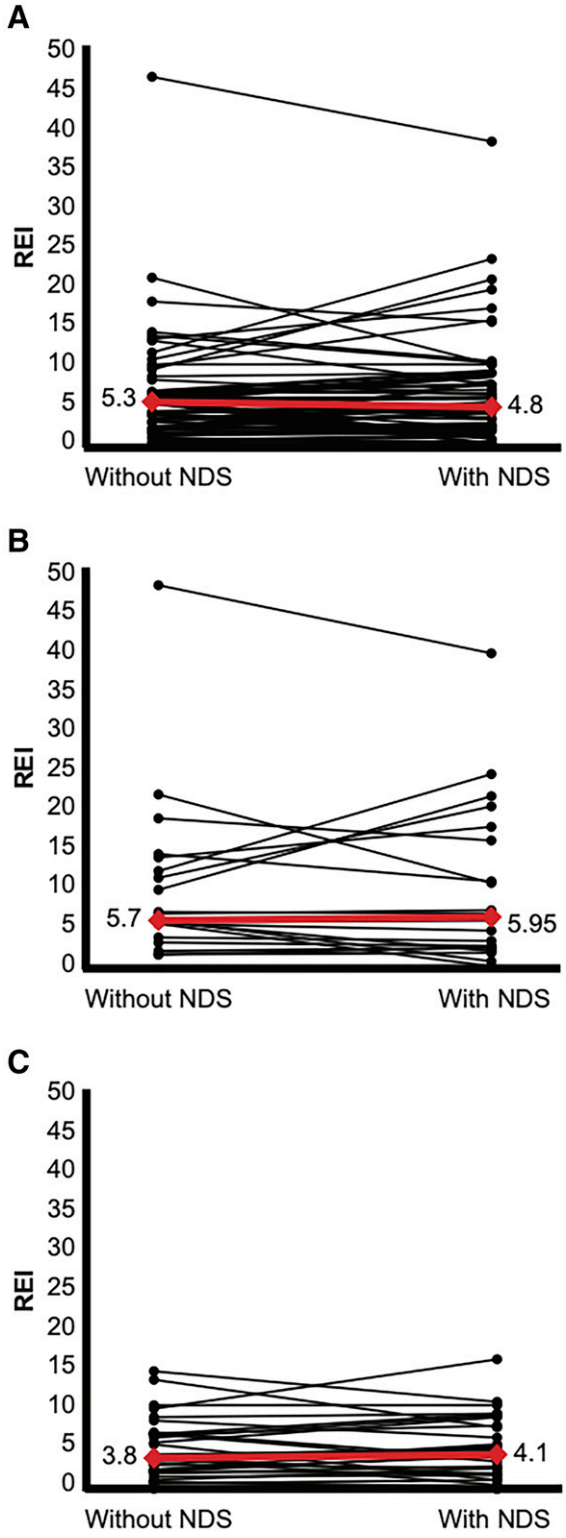
Objective measures of SDB

The percent of time spent supine in recordings with NDS was similar (36.18% ± 23.22%) to the percent of time spent supine in the NDS condition (36.51% ± 27.06%). Analysis of the data by Wilcoxon signed rank test (*P* = .80) showed no statistically significant difference in REI between recordings without NDS and recordings with NDS. Median REI without NDS was 5.30 events/h, with an IQR of 6.20 vs a median of 4.80 events/h and IQR of 6.78 with NDS, as seen in **Figure 1**. The NDS also did not significantly impact other polysomnography parameters, including snore index, oxygen desaturation index, and oxygen saturation minimum (**Table 2**).

When the subgroup of participants with REI ≥ 5 events/h (n = 30) was analyzed separately, there were also no significant differences in median REI between the night without NDS use and the NDS night (6.65 events/h [IQR 5.57] vs 8.05 events/h [IQR 4.62], *P* = .22).

When participants were analyzed by trimester subgroup, participants had no significant difference in the REI in the first

Figure 1—AHI without NDS use vs with NDS use.



AHI without NDS use vs with NDS use for all participants **(A)**, participants in their first trimester **(B)**, and participants in their third trimester **(C)**. Labeled data points with red markers indicate median values for each set of data. NDS = nasal dilator strips, REI = respiratory event index.

trimester ($P = .95$) or in the third trimester ($P = .97$), oxygen desaturation index in the first ($P = .57$) and third trimester ($P = .93$), snore index in the first ($P = .65$) and third trimester ($P = .78$) with the use of NDS vs without the use of NDS. SpO_2 nadir was also not significantly impacted by NDS use when analyzing the first trimester ($P = .09$) and third trimester ($P = .88$) subgroups separately.

Measurements of PTT were compared without and with NDS use. There were no significant differences in PTT drop index comparing the night without and the night with NDS (6.8 events/h [IQR 13.3] vs 6.6 events/h [IQR 15.8], $P = .360$) (**Figure 2**).

Subjective measures

Forty-four participants fell into the high-risk category for sleep apnea, while 10 participants met low-risk criteria, on the basis of the Berlin Questionnaire at study outset (**Table 3**). Of these, 96% of participants reported snoring on the questionnaire. All participants reported wearing the NDS on the second night of recording when assessed at follow-up. Two-thirds of participants reported no change in their sleep quality with NDS (**Table 3**). Two participants reported side effects associated with the NDS, which included skin irritation, sleep disturbance, and rhinorrhea. Twenty-five participants completed the NOSE scale following each recording, with no significant difference ($P = .81$) between the NOSE score reported at baseline without NDS (17.81 ± 20.24) vs with NDS use (16.88 ± 21.17).

DISCUSSION

This study is the first, to our knowledge, to test the effect of NDS on measures of SDB in pregnant women. We did not demonstrate any significant change in objective measures of SDB following the use of NDS. Additional measures of SDB, such as the snore index, oxygen desaturation index, and oxygen saturation minimum, were also not significantly different across the 2 conditions. Furthermore, there were no significant differences in PTT drop indexes, which serve as a measure of arterial stiffness. Nearly 30% of participants who completed the questionnaires reported an improvement in their sleep quality with NDS, whereas roughly 67% reported no change in their sleep when answering that question assessing sleep quality.

While there are existing studies demonstrating a perceived improvement in pregnancy-related nocturnal nasal obstruction with NDS in women who reported symptoms of nocturnal nasal congestion, there are no studies examining the impact of NDS on objective measures of SDB in pregnancy. However, the findings in our study are consistent with similar studies performed in nonpregnant participants. Camacho and colleagues'[18] meta-analysis demonstrated that external NDS had no impact on OSA measures. An additional study conducted by Yagihara et al[31] supported these findings by showing that NDS had no significant impact on polysomnographic parameters in 26 patients with OSA. This study also evaluated self-reported parameters of sleep quality and found that participants reported improvement in depressive symptoms and sleepiness with the

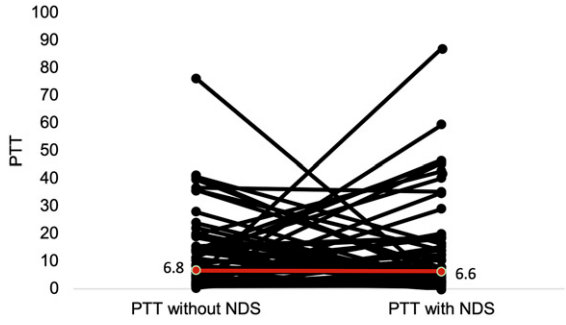
Table 2—Breathing parameters during sleep data (n = 54).

	Without NDS	With NDS	*P*
REI, events/h	5.30 ± 6.20	4.80 ± 7.78	.80
Snore index, %	18.02 ± 18.70	17.93 ± 15.35	.96
ODI	7.24 ± 8.52	6.86 ± 7.65	.60
SpO_2 minimum, %	87.35 ± 3.98	87.72 ± 4.13	.40
% of time supine	36.18 ± 23.22	36.51 ± 27.06	.91

Values are listed as mean ± standard deviation. Snore index is measured as the total duration of snore episodes as a percentage of time in bed. NDS = nasal dilator strips, REI = respiratory event index, ODI = oxygen desaturation index, SpO_2 = oxygen saturation.

NDS, prompting the conclusion that NDS may be used as a placebo intervention. Amaro et al[32] also reported a perceived improvement in sleep parameters, although modest, without any objective improvement in OSA. Their data supported the use of NDS as a placebo condition in studies investigating continuous positive airway pressure (CPAP) in patients with OSA.

Figure 2—PTT without and with NDS.



Red data labels indicate median values for each condition. NDS = nasal dilator strips, PTT = pulse transit time.

Table 3—Subjective data (n = 39).

Berlin Risk Category at Baseline	Values
High risk	81.48 (44)
Low risk	18.52 (10)
Participant's sleep quality	
Improved	28.21 (11)
No change	66.67 (26)
Worsened	5.13 (2)
NOSE scale results	
Without NDS	17.81 ± 20.24 (25)
With NDS use	16.88 ± 21.17 (25)

Values are listed as % (n) and mean ± standard deviation (n). Fifteen participants did not complete the questionnaire assessing the perceived impact of the NDS. NDS = nasal dilator strips, NOSE = Nasal Obstruction Symptom Evaluation.

There is an absence of robust literature supporting the use of NDS as a placebo condition for CPAP in studies investigating SDB in pregnancy. When implemented in some studies examining the efficacy of CPAP in pregnancy-related SDB, NDS have been used for their hypothesized effects in conjunction with other devices, such as mandibular advancement devices.[33] However, most studies investigating interventions in pregnancy lack the application of a placebo device altogether.[34–37] Given the limited number, as well as design limitations, of existing studies evaluating the treatment of SDB with CPAP on maternal-fetal outcomes, this treatment modality requires further investigation.[38] Additionally, the nature of CPAP as a device that is manually applied warrants the use of an appropriate placebo that must also be physically applied.

Our results suggest that NDS may be useful as a placebo condition in future studies examining objective polysomnography parameters in pregnant women with risk factors for SDB. In the context of clinical trials, a placebo is administered to the control group to eliminate effects of the process of substance administration. The placebo should have no objective medical effects on those who receive it, whether the effect is positive or negative.[39] The absence of any significant impact of the NDS on objective sleep measures, such as REI and PTT drop index, in our study demonstrates that they meet these criteria. Our study data also indicate that NDS were safe, with minimal side effects, and the majority of participants did not feel that the NDS worsened their quality of sleep, making NDS a well-tolerated intervention.

The examination of the impact of NDS in pregnancy is necessary, given that the pathogenesis and pathobiology of SDB and the site of obstruction may differ in this population. Our data contribute to the scarcity of knowledge around the pathogenesis of SDB in pregnancy.[40] While the failure of NDS to improve REI in this study does not support the hypothesis that the nasal airway is a key level of obstruction in this population, it supports alternative theories of a complex pathogenesis. Dimensions of the upper airway, defined as the oropharyngeal junction to the glottis, are significantly smaller in the third trimester of pregnancy when compared to postpartum dimensions.[41] Similarly, Mallampati grades have been shown to increase in later trimesters, further supporting that narrowing of the pharyngeal airways is implicated in the development of SDB.[42] There also appears to be an interaction between Mallampati grade and neck circumference measurements in the

prediction of SDB in early pregnancy, with a nearly 3-fold increase in the risk of SDB with each unit increase in neck circumference in patients with Mallampati grade I.[40]

Sex hormones may also play a role in SDB outside of the nasal passageways. Elevated progesterone acts on central chemoreceptors to stimulate the ventilatory drive, which in turn increases the negative pressures generated by the diaphragm. This effect has the potential to intensify the inward force on the upper airway, promoting collapse.[15] It is also possible that different levels of obstruction play a role at different points during gestation, as the airway changes are dynamic. Our study enrolled women in early and late gestation and showed no differences in REI without and with NDS at either stage. Hence, NDS are not an effective treatment for SDB despite physiologic changes of pregnancy and the higher prevalence of nasal congestion.

Further studies are needed to examine the pathogenesis of SDB in pregnancy across the trimesters of pregnancy. In addition, the use of NDS could be compared to alternative potential placebo interventions such as sham-positive airway pressure or care as usual.

Strengths of this study include the objective measurement of SDB, the recruitment of women in early and late pregnancy from a diverse racial and ethnic background, and the reported adherence of all participants with the NDS. The study also recruited a relatively large sample size in comparison to previous studies examining the effects of NDS.[32,43,44] Given potential limitations of REI in general and in the pregnant population, the study also utilized an alternative measure, PTT.

A limitation of the study is the use of level III in-home sleep studies, rather than the use of in-laboratory sleep studies. In-home sleep studies lack electroencephalogram recording capacity, which may limit the detection of hypopneas. However, level III devices have been validated for use in pregnant women and show strong correlations to objective measures recorded with in-laboratory polysomnography.[45] Additionally, all sleep studies were scored by an experienced polysomnography technician in our sample. Another limitation of this study was the failure of all participants to complete all self-reported assessments associated with the study, which limited our ability to assess for statistical significance of perceived impact. Lastly, participants were enrolled in the first and third trimester, and none were in the second trimester of pregnancy. However, it is unlikely that the impact of NDS in the second trimester would differ from current findings.

CONCLUSIONS

Despite the high prevalence of pregnancy rhinitis and the physiologic changes in pregnancy that exacerbate nasal hyperreactivity, results from this study suggest that NDS do not have a significant impact on the objective measures of pregnancy related SDB and are not an effective treatment. In contrast, the results of this study support the use of NDS as a placebo condition in clinical trials examining SDB in pregnancy in participants with risk factors.

ABBREVIATIONS

CPAP, continuous positive airway pressure
HSAT, home sleep apnea test
IQR, interquartile range
NDS, nasal dilator strip(s)
NOSE, Nasal Obstruction Symptom Evaluation scale
OSA, obstructive sleep apnea
PTT, pulse transit time
REI, respiratory event index
SDB, sleep-disordered breathing

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