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Original Article

Pre-eclampsia and nasal CPAP: Part 2. Hypertension during pregnancy, chronic snoring, and early nasal CPAP intervention

Dalva Poyares [a,b], Christian Guilleminault [b,*], Helena Hachul [a], Luciane Fujita [a] Shanon Takaoka [b], Sergio Tufik [a], Nelson Sass [a]

[a] *Federal University of Sao Paulo Sleep Disorders Center, Brazil*
[b] *Stanford University Sleep Medicine Program, 401 Quarry Road, Suite 3301, Stanford, CA 94305, USA*

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Abstract

Objectives: To evaluate the potential benefit of nasal continuous positive airway pressure (CPAP) administration in pregnant women recognized with hypertension early in pregnancy.
Methods: This is a randomized study comparing the addition of nasal CPAP treatment to standard prenatal care to standard prenatal care alone in hypertensive women treated with alpha-methyl dopa during early pregnancy. Pregnant women with hypertension were recruited by their obstetricians and completed baseline sleep questionnaires and visual analogue scales on snoring and sleepiness. Subjects were then randomized to receive either CPAP with standard prenatal care (treatment group) or standard prenatal care alone (control group) with routine obstetric follow-up. Nocturnal polysomnography was performed in all patients randomized to the treatment group for initial CPAP titration. Periodic assessment of blood pressure control and CPAP compliance was performed by the same specialist at each scheduled follow-up visit.
Results: In the control group ($n = 9$), a progressive rise in blood pressure with a corresponding increase in alpha-methyl dopa doses was observed, beginning at the sixth month of pregnancy. There was also an increase in the number of non-scheduled post-natal visits during the first postpartum month. Pre-eclampsia occurred in one subject; the remaining eight patients had normal pregnancies and infant deliveries. In the treatment group ($n = 7$), blood pressure was noted to decrease significantly as compared to the control group with associated decreases in doses of antihypertensive medications at six-months of gestation. All treated patients experienced uncomplicated pregnancies and delivered infants with higher APGAR scores at one minute post-delivery compared to those of controls.
Conclusion: In pregnant women with hypertension and chronic snoring, nasal CPAP use during the first eight weeks of pregnancy combined with standard prenatal care is associated with better blood pressure control and improved pregnancy outcomes.

Keywords: Pregnancy; Hypertension; Pre-eclampsia; Nasal CPAP; Prevention; Snoring

1. Introduction

Hypertension complicates 1222% of all pregnancies and occurs as a spectrum of related disorders, including chronic (pre-existing) hypertension, gestational hypertension, and pre-eclampsia. Chronic hypertension is a known risk factor for pre-eclampsia and has been associated with significant maternal–fetal morbidity and mortality. It has been shown that pregnancies complicated by pre-eclampsia are characterized by an increase in systolic blood pressure (BP) by 95% and in diastolic

* Corresponding author. Fax: +1 650 725 8910.
E-mail address: cguil@stanford.edu (C. Guilleminault).

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BP by 13% between mid-gestation and delivery. Additionally, systolic (but not diastolic) BP may be slightly elevated during the first half of pregnancy in women who develop pre-eclampsia compared to those with gestational hypertension [1]. The circadian pattern of BP may also be a valuable disease predictor as significant changes in the circadian rhythm-adjusted mean of both systolic and diastolic BP and elevation in the 24-h mean pulse pressure have been reported in women who develop pre-eclampsia [2,3]. Ultimately, these BP abnormalities may have significant clinical consequences as data from the Nationwide In Patient Sample (19932002) showed that women with pre-existing hypertension, gestational hypertension, and chronic hypertension with superimposed pre-eclampsia had an increased risk of intracerebral hemorrhage in pregnancy, with respective odds ratios of 2.61 (95% CI: 1.34–5.07), 2.41 (95% CI: 1.62–3.59), and 9.23 (95% CI: 8.32–12.98) [4].

It has been also shown in a retrospective, cross-sectional, consecutive case series of 502 women with singleton pregnancy that snoring was reported in 23% of the women during the last week of pregnancy. Hypertension developed in 14% of the snorers versus 6% of the non-snorers, and pre-eclampsia occurred in 10% of the snorers and only 4% of the non-snorers [5]. Investigations of nasal continuous positive airway pressure (CPAP) administration in women with pre-eclampsia admitted to the antenatal ward have shown a significant decrease in BP and improvement in cardiac output with use of CPAP compared to no therapy [6,7]. Furthermore, a preliminary study in women with known risk factors for pre-eclampsia and concurrent snoring or airflow limitation on polysomnography assessed the effect of nasal CPAP treatment in early pregnancy. Although this intervention did not prevent pre-eclampsia in all subjects, in those with pre-existing hypertension we observed that a small group of women normalized BP without change in antihypertensive medications, tolerated CPAP without difficulty, and had normal pregnancy outcomes.

Based on these preliminary results, this randomized, controlled study was designed to investigate the effect of nasal CPAP on pregnant women with pre-existing hypertension controlled by antihypertensive medication and chronic snoring. Major outcomes of interest included BP patterns during pregnancy and newborn outcomes.

2. Materials and methods

2.1. Subjects

This study was performed in an obstetrics department responsible for providing perinatal care to high-risk women primarily from the lower and middle class in Sao Paulo, Brazil. Due to these socioeconomic factors and limited access to prenatal care in this population, a high rate of pregnancy-related complications (i.e., pre-eclampsia) has been observed. Women presenting to this obstetric clinic during the first weeks of pregnancy with pre-existing hypertension treated with medications and chronic snoring were considered for the study. Hypertension was defined as BP $\geqslant$140/90 mm Hg (measured after 15 min of rest confirmed by two subsequent readings at five-minute intervals) or use of antihypertensive medications for at least three months. Informed consent was obtained from all participants by their primary obstetricians. No exclusion criteria were specified.

A randomization table based on an anticipated total of 20 consecutive subjects was used to assign patients to control or treatment groups at the time of first consultation. Only 16 patients were eligible for study participation at the conclusion of the specified enrollment period which resulted in a slight difference in the number of patients assigned to each group. As such, seven women were randomized to receive standard prenatal care with CPAP (treatment group) versus nine patients who would receive standard care alone (control group). Fifteen of the subjects had known hypertension prior to pregnancy, and one patient developed hypertension with pregnancy onset. Following treatment with alpha-methyl dopa for one week, mean systolic BP was 123.6 mm Hg, and mean diastolic pressure was 80.9 mm Hg. None of the subjects were obese (mean body mass index 24.2 ± 1.8 kg/m^2, median 23.8 kg/m^2) or had any history of associated metabolic disorders (Table 1).

2.2. Study protocol

The study was approved by the Internal Review Boards of each investigator. After the women who provided informed consent were contacted by the research team, they underwent complete sleep evaluations, including specific questions regarding regular snoring during sleep. Subjects with pre-existing hypertension treated with medications and evidence of chronic snoring were randomized as above to nasal CPAP or no treatment. Both groups continued to receive standard prenatal care with regularly scheduled follow-up visits for medication adjustments and routine obstetric monitoring by the treating obstetrician.

Women in the treatment arm underwent a split night sleep study for baseline assessment of sleep-related breathing and nasal CPAP titration. Four-channel electroencephalography (EEG), right/left eye electrooculography (EOG), submental and bilateral leg electromyography (EMG), modified V2-lead electrocardiography (ECG), nasal flow by nasal cannula-pressure transducer, mouth thermistor, thoracic and abdominal piezzo-electric bands, finger oximetry, neck

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Table 1
Subject characteristics

Variables	CPAP treated, $N = 7$	Controls, $N = 9$	
Age (years)	32.8 ± 7.0	30.8 ± 7.6	ns
Body mass index (kg/m2)	24.3 ± 1.7	24.1 ± 2.0	ns
Parity	1st $n = 1$ (14%)	$n = 1$ (11%)	ns
	2nd $n = 4$ (57%)	$n = 5$ (55.5%)	
	3rd $n = 2$ (28.5%)	$n = 3$ (33.3%)	
Vaginal delivery	$N = 7$	$N = 8$	ns
Birth weight	2928.8±796.9 g	2860 ± 757.9 g	ns
Apgar 1 min	9.1 ± 0.41	8.1 ± 0.7	$P = 0.04$
Postpartum visits	7	25	$P = 0.05$
Hypertensive prior pregnancy	$N = 6$	$N = 9$	
Hypertension with pregnancy	$N = 1$	$N = 0$	
Prior pregnancy with hypertension	$N = 6$	$N = 7$	
History of pre-eclampsia	$N = 0$	$N = 0$	
Hypertensive treatment at time of pregnancy	$N = 6$	$N = 9$	
Presence of some degree of snoring at time of pregnancy	$N = 6$	$N = 7$	
Associated metabolic disorders.	$N = 0$	$N = 0$	

microphone, and position sensor were all systematically monitored during the first two hours of sleep. Thereafter, nasal CPAP was instituted and upwardly titrated during the remainder of the study to alleviate snoring. Subjects were subsequently treated with nasal CPAP at optimal pressures determined at the end of nocturnal titration. Women in the control group were asked to complete sleep questionnaires and visual analogue scales on sleep, daytime sleepiness, and snoring. Optional nocturnal polysomnograms were offered, but none accepted due to lack of perceived benefit and inconvenience in the setting of socioeconomic hardship.

Clinical follow-up was scheduled every four weeks initially; frequency of visits increased after 32 weeks of gestation. The following data were routinely collected at each visit: height and weight of subject, general medical evaluation, obstetric variables, and results of blood and urine analyses. Women were evaluated within the same four-hour period at each follow-up visit, and blood pressure was systematically measured after 15 min of rest, seated, using a conventional manual sphygmomanometer. Per recent World Health Organization recommendations, three BP measurements were obtained at five-minute intervals. All women were treated for hypertension with alpha-methyl dopa, an antihypertensive recommended in pregnancy [11] and approved for treatment in governmental social security clinics. Dosage of alpha-methyl dopa was adjusted based on clinical findings at routine follow-up; no other drugs were added to the medical regimen.

Also evaluated at each visit was the degree of snoring reported by bed-partners, other sleep-related information (i.e., degree of sleep disruption, presence of daytime sleepiness), nasal CPAP tolerance, and compliance based on data downloaded from the CPAP device. At the time of delivery, several clinical obstetric variables were noted, including type of delivery and placental aspect/weight. Infant variables, including APGAR score, neonatal status at birth, and birth weight were also recorded. Change in infant status during the first 24 h, clinical and neurological evaluations at the time of maternal and child discharges, and frequency of return for any reason to the neonatal clinic during the first month of life were also noted.

2.3. Data analysis

During polysomnography, sleep/wake periods and respiratory events (e.g., episodes of apnea, hypopnea, oxygen desaturation) were scored using the standardized international criteria [8–10]. Unpaired *t*-testing, one-way analysis of variance (ANOVA) for repeated measures, and group-by time interaction were used to evaluate changes in BP and other clinical variables. χ^2 tests were performed to analyze any data given as percentages.

3. Results

3.1. Snoring and sleep

Interviews with subjects and their bed-partners at study entry indicated the presence of snoring in all women; however, it was never reported as "loud" or "disruptive" by either group of respondents. Furthermore, snoring occurred for more than 30% of the total sleep time in all cases during the initial two-hour period of diagnostic polysomnography (mean $34\% \pm 2.5\%$, range 31–37%). Despite this finding, the apnea–hypopnea index (AHI: number of abnormal breathing events per hour of sleep) was less than five events/hour in all CPAP-treated patients: mean AHI was 3.1 ± 1 events with an average minimum oxygen saturation of $92\% \pm 1\%$.

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3.2. Blood pressure (BP)

All hypertensive women were treated with alpha-methyl dopa, with emphasis on antihypertensive compliance to prevent complications during pregnancy. If they were previously treated with other antihypertensive drugs, they were transitioned to this medication by the treating obstetrician. One week after initiation of medical therapy, BP measurements were obtained in all women to establish a baseline. The treatment group had a mean BP of 126.3 ± 2.29 mm Hg/83.4 ± 1.51 mm Hg, and the control group had a lower mean BP of 121.55 ± 1.74 mm Hg/78.9 ± 1.51 mm Hg (systolic: $p = 0.015$, diastolic: $p = 0.03$) at study entry. As illustrated in Fig. 1, BP measurements were similarly stable in both groups until the sixth month of pregnancy. At this point, there was a progressive increase in systolic and diastolic BP in the control group, while the CPAP-treated group (with higher mean BP initially) showed a continuous decrease in both systolic and diastolic BP. Heart rate measured at the same visit was not significantly different between groups due to large standard deviation.

Based on these clinical measurements, doses of alpha-methyl dopa were increased in the control subjects, while the medication dosage remained constant or decreased starting at gestational week 30 in the treatment group. Mean methyl-dopa dosage was 750 mg in the nasal CPAP group at the last measurement while the mean dose was 2000 mg in the control group. Despite the much higher mean dose of alpha-methyl dopa in the non-CPAP subjects, BP was significantly higher at gestational week 32, with a significant change between groups in diastolic BP (interaction: $p = 0.0003$) and a significant increase in systolic BP (interaction: $p = 0.001$) at 35 weeks of gestation (Fig. 1). This last measurement included only 15 women as one subject had been hospitalized for symptoms of pre-eclampsia.

3.3. Nasal CPAP

Nasal CPAP pressures were determined during nocturnal polysomnography ([mean ± standard deviation] all night total sleep time = 397 ± 16 min; mean % rapid eye movement (REM) sleep = 18.6 ± 0.7; mean % stage 3 and 4 non-REM (NREM) sleep = 18.2 ± 1.1; mean % stage 2 NREM sleep = 53.6 ± 3.7). Nasal CPAP was delivered at fixed pressures using the Meditron Electromedicina AS 800™ (the Brazilian national nasal CPAP brand). The mean duration of equipment usage was six hours, and it was used seven days a week by all patients during the first month. Over the subsequent months, patient adherence to therapy remained high despite rare nights of missed CPAP due to travel or specific family-related issues. Of note, this occasional absence of CPAP usage was also associated with the complete lack of sleep or significantly reduced sleep on those nights for the same previously mentioned reasons. Overall, such events occurred less than once per month for the entire group. During the latter stages of pregnancy, patients reported more disturbed sleep but continued to use nasal CPAP nightly for at least five hours per night. Occasional nap-taking was reported during this period, but nasal CPAP was never used during these daytime naps which lasted up to 20 min at a time.

3.4. Pregnancy outcomes

One woman in the control group was hospitalized with uncontrolled hypertension at 33.5 weeks of gestation. Despite appropriate treatment, symptoms of pre-eclampsia developed. Based on the status of both mother and fetus, delivery was induced 30 h following hospital admission. The infant was premature and required immediate intubation following delivery. The remaining eight women in the control group had normal spontaneous vaginal deliveries at full term with no notable complications, despite significantly higher systolic and diastolic BPs during pregnancy and need for higher doses of alpha-methyl dopa as compared to the CPAP group. All seven women in the treatment arm had normal, full-term vaginal deliveries (Table 1).

There was no significant difference in the birth weights of the 15 full-term infants: those born to the CPAP-treated women weighed 2928.8 ± 796.9 g versus a mean newborn weight in the non-treated group of 2860 ± 757.0 g. Neonatal APGAR scores were, however, higher in the CPAP group at one minute post-delivery (9.1 ± 0.41 vs. 8.1 ± 0.7 in non-CPAP group, $p = 0.04$). One infant in the control group was born with skeletal malformations and had an APGAR score of 4 at one minute, then 9 at five minutes. However, there was no significant difference at five minutes across the entire group. All infants in the treatment group were discharged home after 24 h, while two infants from the control group (including the infant with skeletal malformation and another with borderline hyperbilirubinemia) remained in the hospital for more than seven days (Table 1).

The frequency of spontaneous return visits to the neonatology-pediatric clinic during the first post-partum month was significantly higher for all of the subjects who were not treated with CPAP ($n = 7$ versus $n = 25$). However, none of these visits resulted in re-hospitalization of mother or infant. Patients from the CPAP-treated group returned to the clinic only for their regularly scheduled clinic visits (Table 1).

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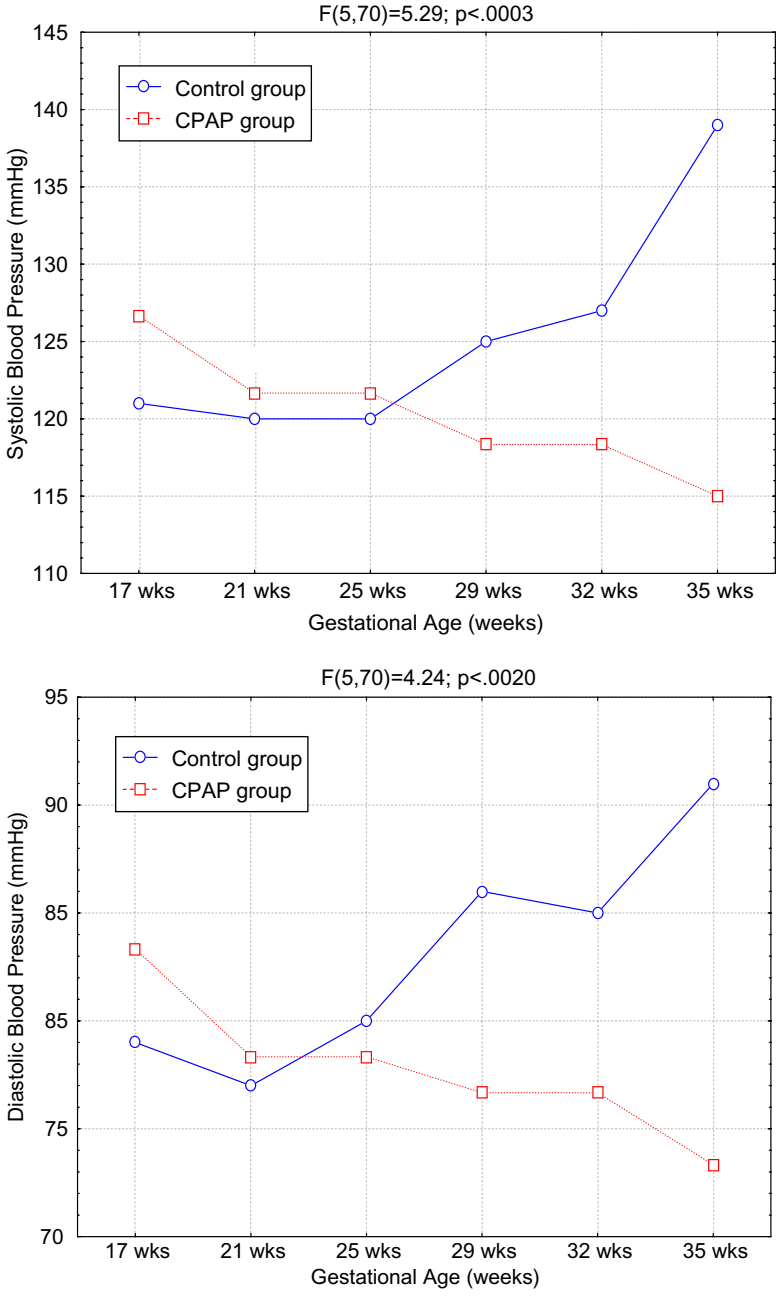

Fig. 1. Longitudinal blood pressure measurements.

4. Discussion

Chronic snoring in pregnancy has been associated with an increased rate of pre-eclampsia [5] and intrauterine growth retardation in women with hypertension during early pregnancy. Likewise, inspiratory flow limitation has been observed more frequently in women with pre-eclampsia as compared to normal gravida [12]. Upper airway dimensions, measured with the acoustic reflection technique, indicate that pre-eclamptic women have a smaller upper airway than women with normal pregnancy [13]. The presence of abnormal upper airway resistance, particularly during sleep [14], may be an additional factor that contributes to further BP alterations and increases the risk of abnormal pregnancy and pre-eclampsia.

This randomized, controlled trial was based on the prior observation that in women with risk factors for pre-eclampsia, normalization of BP could be achieved with the use of nasal CPAP during early pregnancy. Because snoring has also been implicated as a risk factor for poor pregnancy outcomes, this study attempted to control mild to moderate snoring using nasal CPAP and thus improve maternal-fetal outcomes. This study

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was performed at a center that served as a referral center for low-income patients with high-risk pregnancies complicated by chronic hypertension or pre-eclampsia. It was inferred that the subjects exhibited signs of abnormal upper airway resistance based on history of chronic snoring in the setting of AHI <5 apnea–hypopnea per hour of sleep. In this first-ever study performed to assess the effect of nasal CPAP on women at risk for developing pre-eclampsia, scoring of these respiratory events was based solely on the well-established international scoring criteria previously described [10]. It is possible that some of these patients may have presented with other abnormal breathing patterns not currently described by the international rules, including flow limitation. However, the scoring team was not trained to recognize such events and adhered strictly to the accepted international criteria for apnea and hypopnea.

Other limitations of this preliminary study were the small number of patients enrolled, as well as the refusal of all control group patients to undergo nocturnal polysomnography. The small number of patients may lead to a type II error due to lack of statistical power to detect group differences for some of important outcome variables, but we had at least significant difference on one major variable: blood pressure. The study protocol was explained by the obstetricians prior to referral to the research team, and the women understood the need for nasal CPAP titration as well as the rationale and anticipated benefits of therapy. However, polysomnography alone was considered lacking in any positive impact on pregnancy by the control group. Furthermore, these subjects came from lower socioeconomic backgrounds such that an overnight polysomnogram performed only for research purposes and without any perceived benefit was a significant imposition on an already difficult daily life. The choice to defer polysomnography may have also reflected the position of the treating physicians who initially evaluated the patients, explained the study purpose and protocol, and obtained informed consent.

Randomization of the subjects was performed prior beginning of study and was performed using a randomization table subdividing an anticipated study population of 20 patients. As this was the first study, the speed of recruitment, support from treating obstetricians, and the difficulty of placing a research team focused on sleep disorders in an obstetrical clinic for disadvantaged patients were unknown factors. At the end of the enrollment period, authorized by the Internal Review Board, only 16 women had been recruited and randomized (using the table constructed for 20 patients as described above), resulting in a slight difference in subject numbers between the two groups (7 vs. 9).

All subjects at the start of the study had documented hypertension, and all were treated with the same recommended agent for BP control in pregnancy (alpha-methyl dopa). Despite their poor socioeconomic status, all subjects carefully followed the advice of their treating obstetricians and appropriately attended all regularly scheduled follow-up visits. Medication compliance was not subjectively felt to be problematic, and BP was well controlled during the first months of pregnancy. Treatment subjects were also very compliant with nasal CPAP usage during sleep, as discussed previously, with no significant side effects documented. Mask and pressure adjustments were occasionally required, and systematic humidification was eventually used (particularly after the fifth gestational month) for the known nasal turbinate enlargement related to placental hormonal activity.

In this small series of pregnant women with hypertension and chronic snoring, nasal CPAP added to standard prenatal care appeared to decrease the occurrence of complications during pregnancy as well as improve BP control without the need for escalated doses of antihypertensive medication. Without the use of CPAP, BP control remained poor despite the use of higher alpha-methyl dopa doses. Although infant outcomes appeared to be similar in both groups, there was a trend toward shorter hospital stays and less frequent neonatal clinic visits during the first postpartum month in infants born to women treated with CPAP. The significant difference in infant APGAR scores at one minute between the two subject groups is difficult to interpret, particularly considering that the mean difference was only one point. While this observation was statistically significant, the clinical relevance is unclear particularly as there was no appreciable difference in APGAR scores at five minutes.

Although this preliminary study was small due to absence of funding, it demonstrates the feasibility of similar investigation on a larger scale. Many other issues need to be addressed, including identification of the best candidates for such therapy. Despite the limitations, these preliminary data support further study of the role of nasal CPAP as a safe, non-invasive, preventative therapy in pregnant women with hypertension, with an ultimate goal of improving maternal-fetal outcomes in high-risk populations.

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