AWARD NUMBER: DM150091

TITLE: Randomized Controlled Trial of a Sleep Study + Targeted CPAP Therapy for Obstructive Sleep Apnea to Reduce the Incidence of Adverse Pregnancy Outcomes

PRINCIPAL INVESTIGATOR: CAPT Dennis L. Spence, NC, USN, PhD, CRNA

CONTRACTING ORGANIZATION: Naval Medical Center San Diego,
San Diego, CA 92134

REPORT DATE: Jan 2020

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland, 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Jan 2020	Final	**03/07/2016 - 09/06/2019**

4. TITLE AND SUBTITLE

Randomized Controlled Trial of a Sleep Study + Targeted CPAP Therapy for Obstructive Sleep Apnea to Reduce the Incidence of Adverse Pregnancy Outcomes

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DM150091

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
PRINCIPAL INVESTIGATOR: CAPT Dennis L. Spence, NC, USN, PhD, CRNA
CO-INVESTIGATOR(s): CDR Monica Ann Lutgendorf, MC, USN; CAPT (ret)Tony Han, NC, USN
SITE PM: Mitchell Dukovich, PhD, Scientific Director, Naval Medical Center, San Diego, 619-532-5524
Email: dennis.l.spence.mil@mail.mil

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Naval Medical Center, San Diego
34800 Bob Wilson Drive
San Diego, CA 92134-1005

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this study was to determine if parturients identified as high risk for OSA who are randomized to receive an unattended sleep study during early and late pregnancy (early = between 6 and 16 weeks; late = between 27 and 33 weeks) plus initiation of CPAP therapy if the AHI ≥5 events/hour with standard prenatal care have a decreased incidence of adverse pregnancy outcomes (APOs) at the time of delivery when compared to a group who receives standard prenatal care only (APOs defined as a composite variable which includes gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, or stillbirth). **Methods:** Randomized controlled trial. **Results**: There were N = 187 subjects analyzed (treatment group n = 97 and control group n = 93). No significant differences were found in composite APOs (46.4% vs. 43.3%, *P* = .77), individual APOs (*P* > .05), and hospital costs (*P* = .76). Only 4 subjects required CPAP and compliance was poor. The overall rate of OSA was 4.3% (n = 4) in early pregnancy, 12% (n = 11) in late pregnancy, and 19% (n =17) at 3 months postpartum. Most OSA cases were mild (early = 3.2%, late = 12%, 3 months postpartum = 11.3%). **Conclusion:** The study was underpowered to detect a difference in the effect of CPAP on APOs. Results of this study should be used to design large, multi-center clinical trials.

15. SUBJECT TERMS
parturients, adverse pregnancy outcomes, obstructive sleep apnea, continuous positive airway pressure (CPAP) therapy, apnea hypopnea index, gestational hypertension, preeclampsia, gestational diabetes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	26	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

1. Introduction.

The purpose of this randomized controlled trial was to determine if parturients identified as high risk for OSA (defined as an AHI ≥5 events/hour; *risk factors*: pre-pregnancy BMI≥30 kg/m^2, chronic hypertension, pre-gestational diabetes [type 1 or type 2], history of prior preeclampsia, and/or a twin gestation) who are randomized to receive an unattended sleep study during early and late pregnancy (early = between 6 and 16 weeks; late = between 27 and 33 weeks) *plus* initiation of CPAP therapy if the AHI ≥5 events/hour with standard prenatal care have a decreased incidence of adverse pregnancy outcomes (APOs) at the time of delivery when compared to a group who receives standard prenatal care only (APOs defined as a composite variable which includes gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, or stillbirth). Secondary outcomes included describing incidence and severity of OSA at early and late pregnancy, and at 3 months postpartum (8-12 weeks postpartum), and to compare total hospital costs at time of delivery. An exploratory aim was to compare differences in rates of adverse pregnancy outcomes between parturients at high risk for OSA started on CPAP therapy in either early or late pregnancy.

2. Keywords: Parturients, Adverse Pregnancy Outcomes, Obstructive Sleep Apnea, Continuous Positive Airway Pressure (CPAP) Therapy, Apnea Hypopnea Index, gestational hypertension, pre-eclampsia, gestational diabetes

3. Accomplishments

The major goals of this project are presented as stated in the approved Statement of Work. All major tasks have been completed, except for submitting for scientific presentation and peer reviewed journal articles which are underway. A summary of findings is listed below:

Introduction. Pregnant women with diagnosed obstructive sleep apnea (OSA) have been found to have significantly higher rates of APOs such as gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, stillbirth, cesarean delivery, and higher total costs of care. The gold standard for OSA treatment is continuous positive airway pressure (CPAP). Unfortunately, there are no published studies examining the effect of CPAP on APOs in parturients who are high-risk for OSA.

Purpose. The purpose of this prospective, randomized controlled clinical trial was to determine if parturients identified as high risk for OSA who are randomized to receive an unattended sleep study during early and late pregnancy plus referral for possible CPAP therapy if the AHI ≥5 events/hour and with standard prenatal care have a decreased incidence of APOs at the time of delivery when compared to a group who receives standard prenatal care only. Secondary outcomes included examining the OSA incidence and severity from early to 3 months postpartum (8-12 weeks postpartum), and to compare total hospital costs at time of delivery.

Methods. Prospective, randomized controlled clinical trial of N = 193 parturients at high-risk for OSA (1 or more of the following risk factors: pre-pregnancy BMI ≥30 kg/m^2, chronic hypertension, pre-gestational diabetes [type 1 or type 2], history of prior preeclampsia, and/or a twin gestation). Patients in the treatment group completed a sleep study in early (6-16 weeks gestation), late pregnancy (27- and 33-weeks gestation), and at approximately 3 months (8-12 weeks) postpartum. Subjects were referred for possible CPAP therapy if their AHI ≥5 events/hour. The control group received standard prenatal care and completed a sleep study at 3 months postpartum. Descriptive and inferential statistics were used to analyze the results. A $P <$ .05 was significant.

Results. There were N = 187 subjects analyzed (treatment group n = 97 and control group n = 93). No significant differences were found in composite (46.4 vs. 43.3, P = .77) and individual APOs between the groups (P >.05), and hospital costs (mean [95% CI]: $12,185 [$11,155 to 13,215] vs. $12,607 [$11,210 to 14,004], P = .76). Only 4 subjects required CPAP and compliance was poor. The overall rate of OSA was 4.3% (n = 4) in early pregnancy, 12% (n = 11) in late pregnancy, and 19% (n =17) at 3 months postpartum. The AHI increased during the course of pregnancy and peaked at 3 months postpartum (P < .05). Most OSA cases were mild (early = 3.2%, late = 12%, 3 months postpartum = 11.3%).

Conclusion. The incidence and severity of OSA worsens over the course of pregnancy and appears to peak at 3 months postpartum in parturients at high-risk for OSA. This study was underpowered to detect an effect of CPAP therapy on the incidence of APOs. Investigators should consider using results from this study to design future large, prospective, multi-center clinical trials.

Specific Task(s)
Major Task 1: Preparation for Team Performance Research (Milestone 1)
Subtask 1.1: Submission and approval of research plan to NMCSD IRB
Subtask 1.2: Submission of research study to USAMRRC HRO for Approval
Subtask 1.3: Create and print recruitment materials (flyers and brochures)
Subtask 1.4: Execute study contracts for Research Coordinator and Other Direct Costs for Durable Medical Equipment (CPAP), and Itamar sleep study consumable materials.
Subtask 1.5: Periodic Investigator meetings/trainings
Milestone 1 Goal: All requirements to begin study with subtasks completed
Major Task 2: Enrollment/Data Collection/Data Analysis
Subtask 2.1: Recruitment and Enrollment
Subtask 2.2: Data quality checks, data cleaning and locking of final data set
Milestone 2 Goal: Projected numbers of subjects attained; data collected as indicated for study.
Major Task 3: Data Analysis/Dissemination
Subtask 3.1: Data Analysis
Subtask 3.2: Presentation of results and compilation of findings for Scientific Review, Publication, and/or Presentation and final reports
Milestone 3 Goal: Projected numbers of subjects attained, data collected as indicated for study, data analysis, and conclusions completed. Scientific presentation and publications completed.

What was accomplished under these goals?

As requested, we describe the: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements in the pages that follow. We have included discussions of stated goals not met. We provide pertinent data and graphs in sufficient detail to explain significant findings. A description of the methodology is also provided.

Major Task 1: Preparation for Team Performance Research

All requirements to begin study with subjects completed as described in Milestone 1.

Major Task 2: Enrollment/Data Collection/Data Analysis

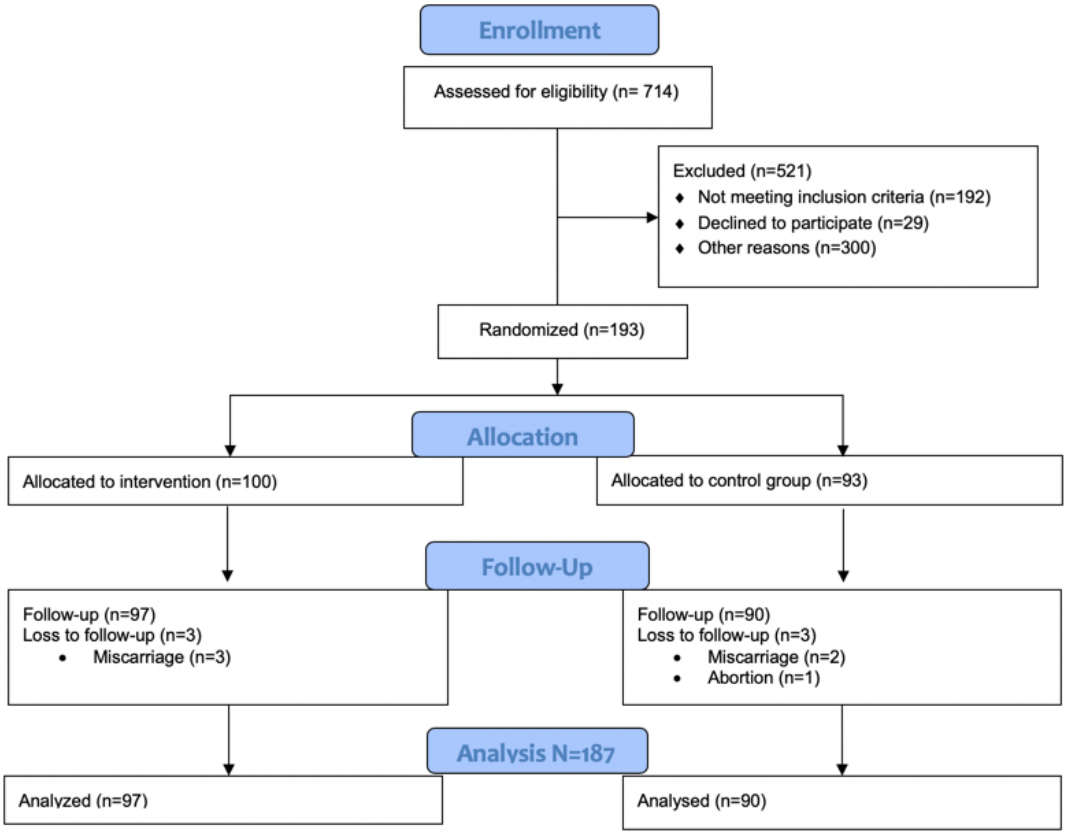
Subtask 2.1: Recruitment and Enrollment

Enrollment. There were 714 women assessed for eligibility with N = 193 meeting inclusion criteria and consenting to participate (27% enrollment rate). We ended recruitment in January 2019 with n = 100 randomized to the treatment and n = 93 to the control group. Three subjects in each group were loss to follow-up due to miscarriage or abortion (Figure 1). Data collection was completed in July 2019.

We originally estimated we could enroll 252 to 288 subjects (126 to 144 per group). Enrollment was less than expected because of decreased number of deliveries at Naval Medical Center San Diego (NMCSD) and lower number of patients meeting inclusion criteria. Having a research coordinator drive to the subjects' home to set-up and pick up the WATCH-PAT devices as well as providing subjects with a $150 gift card to Target upon completion of the 3-month postpartum sleep study helped improve subject enrollment and retention.

Enrollment results are presented in Figure 1.

Figure 1. Consort Flow Diagram



Subtask 2.2: Data quality checks, data cleaning and locking of final data set

Data collection, quality checks, cleaning and locking of final data set was completed September 12, 2019.

Milestone 2 Goal was partially achieved: data was collected as indicated for study. However, the projected numbers of subjects attained was not obtained (see Subtask 2.1 results).

Major Task 3: Data Analysis/Dissemination

Subtask 3.1: Data Analysis

Data analysis was completed September 15, 2019.

Subtask 3.2: Presentation of results and compilation of findings for Scientific Review, Publication, and/or Presentation and final reports

A summary of the study background, methods, results, discussion, and conclusion are presented below.

Milestone 3 Goal was partially achieved. Results are compiled below, and we are in the process of preparing manuscripts and disseminating results to stakeholders at NMCSD.

Background and Significance

OSA is characterized by chronic, frequent obstructions of the airway during sleep. Obstructive sleep apnea (OSA) is underdiagnosed during pregnancy, and the severity has been found to worsen over the course of pregnancy due to the physiological changes of pregnancy.[1-3] Over time, these effects are associated with significant morbidity and mortality in non-obstetrical[4] and obstetrical patients.[3] Pregnant women with diagnosed OSA have been found to have significantly higher rates of adverse pregnancy outcomes (APOs) such as gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, stillbirth, cesarean delivery, and higher total costs of care.[3,5] Diagnosed OSA is associated with a higher odds of cesarean delivery (AOR,1.60; 95% CI, 1.06-2.40), gestational hypertension, (AOR, 2.46; 95% CI, 1.30-4.68), preeclampsia (AOR, 2.42; 95% CI, 1.43-4.09), and preterm delivery (AOR, 1.90; 95% CI, 1.09-3.30).[5]

The prevalence of diagnosed OSA in parturients has increased from 0.7 per 10,000 in 1998 to 7.3 per 10,000 in 2009[3] Spence et al[5] examined 305,000 deliveries in the Military Health System and found an overall rate of 8.7 per 10,000, with the rate increasing from 6.4 to 9.9 per 10,000 from 2009 to 2013. These increases correlate with the increasing obesity epidemic seen in the United States. It is likely that this rate underestimates the true incidence of OSA during pregnancy since most parturients are never screened for OSA symptoms. A cohort study of 1,509 parturients of all gestational ages found an OSA prevalence rate of 4.9%.[6]

In the general obstetrical population the rate of sleep disordered breathing (which ranges from snoring to OSA) has been reported to increase from 3.6% in early pregnancy (6-15 weeks gestation) to 8.3% in mid-pregnancy (22-31 weeks of gestation).[7] However, higher rates are reported in patients at high-risk for OSA (i.e., body mass index [BMI] $\geq$ 30 mg/kg^2 , advanced maternal age, chronic hypertension, gestational diabetes, prior history or preeclampsia and/or twin gestation). In a high-risk cohort, in early pregnancy (6-20 weeks) 21% had mild OSA, and 9% of patients had moderate-to-severe (AHI $\geq$15); in late pregnancy the severity increased, with 35% having mild OSA and 12% having moderate-to-severe OSA; however, this study used a more liberal diagnostic criteria: an AHI that included all apneas, plus hypopneas with $\geq$3%

oxygen desaturation, with an AHI ≥5 used to define OSA.[8] The Centers for Medicare and Medicaid require diagnosis to only score hypopneas with ≥4% oxygen desaturation.

Only one study has examined if OSA symptoms resolve in the postpartum period.[9] Investigators examined changes in OSA severity in a cohort study of 18 parturients (n = 11 with gestational hypertension and n = 7 healthy controls) who completed a polysomnography in the third trimester (gestational age >32 weeks) and again 10-23 months after delivery. In parturients with gestational hypertension AHI decreased from 4.6 ± 9.3 to 2.6 ± 2.7 (P =.77); and in healthy controls the AHI was similar (0.9 ± 2.4 vs. 1.1 ± 2, P = 0.31). The researchers speculated that pregnancy-related factors, and not just obesity, may have contributed to OSA symptoms during pregnancy, and resolved after the resolution of the physiological changes of pregnancy. Unfortunately, it is unknown if OSA severity continues to be elevated in the early postpartum period (3 months postpartum).

The gold standard for OSA treatment is continuous positive airway pressure (CPAP), which helps stent the airways open during sleep.[10] CPAP therapy has been shown to reduce the rate of cardiovascular and metabolic complications in non-pregnant patients;[4,10] however, no randomized controlled trials have been published examining its effect on decreasing APOs in pregnant women at high-risk for OSA.[11] There are three published case reports suggesting starting CPAP treatment during pregnancy may prevent or reduce the severity of APOs (i.e., preeclampsia).[12-14] However, one case series of 12 pregnant women with risk factors for preeclampsia reported initiation and active CPAP management during pregnancy improved blood pressure control but had no effect on APOs.[15] One clinical trial is actively recruiting pregnant at women at high-risk for adverse pregnancy outcomes in a CPAP trial in Thailand.[16] One group of researchers in Canada are currently conducting a pilot randomized controlled trial examining the feasibility and CPAP compliance, and the effect on glycemic control in pregnant women with gestational diabetes.[17]

SPECIFIC OBJECTIVE:
The purpose of this study was to determine if parturients identified as high-risk for OSA (*risk factors*: pre-pregnancy BMI≥30 kg/m^2, chronic hypertension, pre-gestational diabetes [type 1 or type 2], history of prior preeclampsia/eclampsia or intrauterine growth restriction, and/or a twin gestation) who are randomized to receive an unattended sleep study during early and late pregnancy (early = between 6 and 16 weeks; late = between 27 and 33 weeks) *plus* initiation of CPAP therapy if the AHI ≥5 events/hour with standard prenatal care have a decreased incidence of APOs at the time of delivery when compared to a group who receives standard prenatal care only (APOs defined as a composite variable which includes gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, or stillbirth).

<u>Specific Aims</u>

Primary Aim:
1. Determine if the rate of a composite of APOs (which includes gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm delivery, low birth weight, or stillbirth) is decreased in parturients at high-risk for OSA who develop OSA (AHI ≥5) in

early or late pregnancy and are started on CPAP therapy during pregnancy when compared to a group who receive standard prenatal care.

Hypothesis:

1. We hypothesize that the identification, using an unattended sleep study, and treatment of OSA with CPAP when clinically indicated (when the AHI ≥5) during early or late pregnancy will significantly decrease the incidence of APOs pregnancy in parturients identified as being high risk for OSA when compared to a group of parturients who do not complete an unattended sleep study in early and late pregnancy.

Secondary Aim:

2. Calculate the rate and trends for mild (AHI ≥5-14), moderate (AHI 15-29), and severe OSA (AHI ≥30) in early and late pregnancy, and at 3 months after delivery in parturients randomized to the sleep study + CPAP group.

Hypothesis:

2. We hypothesize that the rate and severity of OSA will be significantly greater in late pregnancy compared to early pregnancy and at 3 months post-delivery.

Secondary Aim:

3. Compare differences in total hospital costs at the time of delivery between the sleep study + CPAP group and the group who receive standard prenatal care.

Hypothesis

3. We hypothesize that total hospital costs at the time of delivery will be significantly less in parturients randomized to the sleep study + CPAP group as compared to those receiving standard prenatal care.

Exploratory Aim:

Compare differences in rates of adverse pregnancy outcomes between parturients at high risk for OSA started on CPAP therapy in either early or late pregnancy**.**

Research Design and Methodology

A prospective, randomized, parallel group, clinical trial design was used. The treatment group was randomized to receive an unattended WatchPAT-200[18] sleep study in early (6-16 weeks gestation), late pregnancy (27-33 weeks gestation), and at 3 months postpartum (between 8 and 12 weeks postpartum). Subjects with an AHI ≥5 were referred to a sleep medicine physician at Naval Medical Center San Diego (NMCSD) for evaluation, education on OSA, and possible initiation of CPAP (auto-titrated CPAP). Subjects randomized to the control group received usual standard prenatal care. Control group subjects completed an unattended sleep study at 3 months postpartum.

Inclusion criteria were at least one of the following risk factors for OSA: pre-pregnancy BMI ≥ 30kg/m^2, chronic hypertension, pregestational diabetes, twin gestation, or a history of prior pregnancy affected by: preeclampsia, eclampsia or fetal growth restriction. Between 6- and 16-

weeks gestation at time of enrollment. Subjects were excluded if they had a current diagnosis and treatment of OSA, refused to be randomized, had a permanent pacemaker (interfere with Watch-PAT sleep study), were currently taking alpha blockers or nitrates (interfere with Watch-PAT sleep study), had coronary artery disease or congestive heart failure or cardiomyopathy, not delivering and completing their postpartum visit at NMCSD, inability to read or understand the consent, and <18 years of age.

Each subject completed a baseline questionnaire which obtained demographics, past medical, obstetrical, and surgical history, and snoring frequency. Subjects in the control group received usual prenatal care and at 3 months postpartum they completed an unattended Watch-PAT-200 sleep study.

Subjects in the treatment group completed an OSA pregnancy screening questionnaire[18] at each time point. The questionnaire collects information on general work and sleep patterns, sleep habits, snoring and sleep apnea symptoms, and STOP-BANG score.[19,20] A research coordinator drove to the patient's home to set-up the unattended sleep study at each time point with the Watch-PAT-200 devices. The next day the research coordinator picked-up the device. Watch-PAT data was downloaded on a password-protected password and analyzed with the WatchPat zzzPAT proprietary software which automatically scored the results. If there was a technical error with the sleep study the research coordinator attempted to reschedule completion of the sleep study.

The Watch-PAT-200 is an FDA-approved portable diagnostic device (6 channels: peripheral artery tone, pulse rate, oxygen saturation, actigraphy [to calculate sleep stages], body position, & snoring) used for screening, detection, and the follow-up treatment of OSA. It uses peripheral artery tonometry (PAT) finger plethysmography and standard oxygen saturation (SPO_2) probe, which allows for recording of the PAT signal, heart rate, and SPO_2. Sleep time is estimated with actigraphy. Specific data obtained included: sleep stages, pRDI, pAHI, pODI (peripheral artery tonometry respiratory disturbance index [pRDI], apnea hypopnea index [pAHI], and oxygen desaturation index [pODI]), mean and lowest oxygen saturation, percent sleep time with SPO_2 <90%, <88%, <85%, <80%, and <70%, percent rapid eye movement of sleep time (% of sleep in REM), and the mean, minimum, and maximum heart rate.

Subjects with an AHI ≥5 were referred to the sleep medicine department for evaluation and possible treatment with CPAP. Those subjects referred for to sleep medicine received education on OSA and treatment options. If CPAP was ordered a contracted durable medical equipment company representative contacted the subject and coordinated delivery and set-up of the CPAP device. Devices used were the AirSense 10 AutoSet with auto-titrated pressure ranging from 5 to 15 cm H_2O. CPAP compliance data was obtained from the durable medical equipment contractor. CPAP compliance defined as >4 hours/night for 70% of nights.

The primary outcome was the difference in APOs between the two groups. After delivery the research coordinator reviewed the medical records and recorded the rate of individual and composite APOs in both groups (defined as a composite variable which included gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, or stillbirth). Results were confirmed with a co-investigator who was a Maternal Fetal Medicine Obstetrician. Secondarily, we examined the rate and trends in OSA in early and late pregnancy,

and at 3 months postpartum (between 8 and 12 weeks), and differences in hospital costs at the time of delivery. An exploratory aim was to compare differences in APOs between subjects at high risk for OSA started on CPAP therapy in either early or late pregnancy.

Upon completion of the 3-month postpartum sleep study subjects were given a $150 Target gift card.

Statistical Analysis. Descriptive and inferential statistics were used to analyze the results. A Fisher's Exact test was used to compare differences in APOs between the treatment and control group. If significant differences are found in APOs a multiple logistic regression control for significant covariates and CPAP usage. Because sleep study results were not normally distributed a Friedman's test was used to analyze differences in sleep study results at the three time points. If significant differences are found in sleep study results a post hoc Wilcoxon Ranked Sign test will be used to compare differences at individual time points. Differences in hospital costs at the time of delivery were analyzed with a *t*-test. A $P < .05$ was considered significant.

Sample Size Estimate. Accurate effect sizes are difficult to determine given the limited research on the effect of CPAP on APOs. We estimate that initiation of CPAP in the treatment group will reduce their risk of APOs by 20%. Using G*Power 3.1.9.2 and a one-sided Fisher's exact test with an alpha of 0.05 and power of 80%, and a 2 to 1 allocation of control: treatment group, we would need 55 subjects in the treatment group and 110 in the control group (N = 165). Over a 36-month data collection period we originally estimated we could enroll up to 30 subjects per quarter for a total of N = 360 by the end of data collection (N = 180 in each group). Subjects will be randomized to one of the two groups in a 1:1 ratio. Assuming 30% of subjects in the treatment group require CPAP initiation during their pregnancy this will give us at approximately N = 55 subjects who received CPAP during pregnancy and up to N = 180 control subjects. These enrollment estimates thus meet our sample size calculation and approximate 2:1 allocation plan for analysis.

The sample size estimate of was revised 18 January 2018 and approved by CDR Mosquera. Our new sample size estimate was based on a 20% difference in adverse pregnancy events would be N = 180 (144 in control group and 36 in treatment [CPAP group]). The plan was to continue enrollment until January 2019. The reason for stopping in January is because of the 9-month follow-up period, which would take us to September 2019. We estimated that we could enroll between 11-14 patients per month which would give us an estimated sample size at the end of active recruitment of N = 252 to 288 subjects (126 to 144 per group). If we assume 25% in the treatment group have OSA, then we estimate we will have 32 to 36 subjects in the treatment group who will require CPAP therapy, meeting our target sample size.

Results

Demographics. Enrollment results are described in Subtask 2.1 and Figure 1. There were N = 193 subjects enrolled to either a treatment group (n = 100) or control group (n = 93). No significant differences were found in baseline demographics and clinical characteristics between the groups ($P > .05$; Table 1). After exclusion of subjects who had a miscarriage or abortion there

were N = 187 subjects who had complete data for analysis. In the treatment group there were 51 (53.1%) vaginal deliveries and 45 (46.9%) cesarean deliveries. In the control group there were 63 (70%) vaginal deliveries and 27 (30%) cesarean deliveries.

Table 1. Baseline characteristics

n (%) or mean ± SD	Overall (n =193)	Treatment Group (n = 100)	Control Group (n = 93)	*P*-value
Maternal age	29.0 ± 5.0	29.1 ± 4.8	28.8 ± 5.2	.76
Ethnicity				.91
White	89 (47.1)	43 (43.9)	46 (50.5)	
African-American	37 (19.6)	21 (21.4)	16 (17.6)	
Hispanic	36 (19.0)	20 (20.4)	16 (17.6)	
Asian	10 (5.3)	5 (5.1)	5 (5.5)	
Other	17 (9.0)	9 (9.2)	8 (8.8)	
Pre-pregnancy BMI	33.9 ± 7.0	34.5 ± 7.0	33.3 ± 6.8	.24
Pre-pregnancy BMI				.92
<25	7 (3.6)	4 (4.0)	3 (3.2)	
25-29	19 (9.8)	9 (9.0)	10 (10.8)	
30-34	101 (52.3)	50 (50.0)	51 (54.8)	
35-39	42 (21.8)	24 (24.0)	18 (19.4)	
40+	24 (12.4)	13 (13.0)	11 (11.8)	
Prior cesarean delivery	29 (29.9)	26 (28.9)	55 (29.4)	.50
Chronic hypertension	22 (11.4)	13 (13.0)	9 (9.7)	.47
Pre-gestational diabetes	9 (4.7)	6 (6.0)	3 (3.2)	.36
History of preeclampsia	31 (16.1)	19 (19.0)	12 (12.9)	.25
Multiple gestation	2 (1.0)	2 (2.0)	0 (0)	.17
Nulliparous	45 (24.6)	2 (22.0)	25 (27.2)	.41
Neck circumference				.24
<34 cm	31 (16.4)	14 (14.1)	17 (18.9)	
34-36.5 cm	79 (41.8)	38 (38.4)	41 (45.6)	
>36.5 cm	79 (41.8)	47 (47.5)	32 (35.6)	
STOP-BANG score[a]	1.8 ± 1.0	1.8 ± 1.1	1.7 ± 0.9	.42
STOP-BANG category[a]				.61
Low (0-2)	152 (80.4)	77 (77.8)	75 (83.3)	
Intermediate (3-4)	35 (18.5)	21 (21.2)	14 (15.6)	
High (≥5)	2 (1.1)	1 (1.0)	1 (1.1)	
Snoring bother	33 (17.1)	18 (18.0)	15 (16.1)	.73
Tired during day	173 (89.6)	86 (86.0)	87 (93.5)	.09
Observed apnea	21 (10.9)	11 (11.0)	10 (10.8)	.96
Tx HTN	26 (13.5)	15 (15.0)	11 (11.8)	.52
BMI > 35	72 (37.3)	43 (43.0)	29 (31.2)	.09
Neck > 40cm	11 (5.8)	7 (7.1)	4 (4.4)	.44

Abbreviations: BMI = Body mass index; Tx = treated; HTN = hypertension

[a]STOP-BANG category excludes age over 50 and male gender from calculation.[19,20]

Sleep Studies. In the treatment group (n = 97) the number of valid sleep studies were 93 in early pregnancy, 92 in late pregnancy, and 89 at 3 months postpartum in the treatment group. In the treatment group technical difficulties with the WATCH-PAT or missing data resulted in 4 (4.1%), 5 (5.2%), and 8 (8.2%) subjects who did not have a valid sleep study in early, late, and 3-months postpartum, respectively. In the control group 80 out of 90 subjects completed a sleep study at 3 months postpartum.

A research coordinator drove to the subjects' home to set-up and pick up the Watch-PAT devices and the following day downloaded the sleep study data. If the Watch-PAT report indicated an error in the sleep study the research coordinator attempted to contact and reschedule the sleep study. This process helped ensure accurate sleep study reports and minimized missing data. Additionally, providing subjects with a $150 gift card to Target upon completion of the 3-month postpartum sleep study minimized attrition and reduced the number of missing sleep studies.

Incidence of OSA. In the treatment group the overall rate of OSA was 4.3% (n = 4) in early pregnancy, 12% (n = 11) in late pregnancy, and 19% (n =17) at 3 months postpartum (Figure 2) The rate of OSA increased during the course of pregnancy and peaked at 3 months postpartum**.** There were 3 (4.3%) patients who had a new diagnosis in early pregnancy, 10 (10.8%) in late pregnancy, and 11 (12.3%) postpartum (Figure 3). There was one subject who tested positive for OSA only in early pregnancy and 3 months postpartum. There was 1 subject who tested positive for OSA in early pregnancy who was loss to follow-up.

Severity of OSA. The majority of subjects who were diagnosed had mild OSA (Table 2). One subject had severe OSA in early pregnancy, and 2 subjects had moderate OSA and 1 subject had severe OSA at 3 months postpartum. In the control group 9 subjects had mild OSA and 2 had moderate OSA at 3 months postpartum. The rate of mild OSA increased from 3.2% in early pregnancy to 11% in late pregnancy and peaked at 15.7% at 3 months postpartum.

Sleep study results listed in Table 3 demonstrate that the frequency and severity of OSA symptoms (oxygen desaturations and apnea/hypopneas) worsened during the course of pregnancy and peaked at 3 months postpartum. The pODI increased from a median (min. max) of 0.4 (0, 75) in early pregnancy to 0.75 (0,11.9) in late pregnancy and peaked at 1.45 (0,40) at 3 months postpartum (P <.001). Similarly, pAHI significantly increased over from 0.35 (0, 76) in early and 0.9 (0, 12.1) in late pregnancy and peaked at 1.55 at 3-months postpartum (P <.001).

Figure 2. Overall OSA rate by time point in treatment group

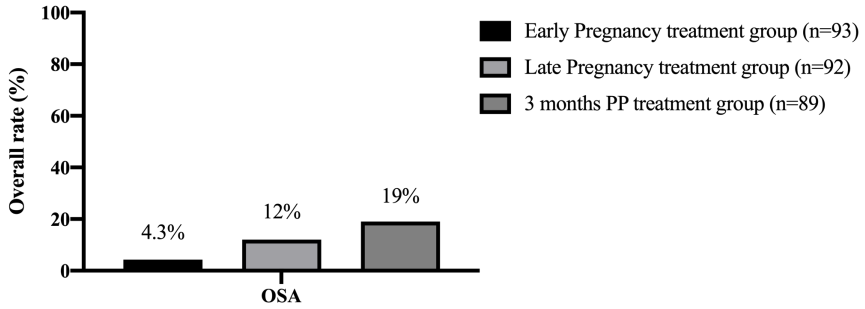


Figure 3. New OSA Diagnosis

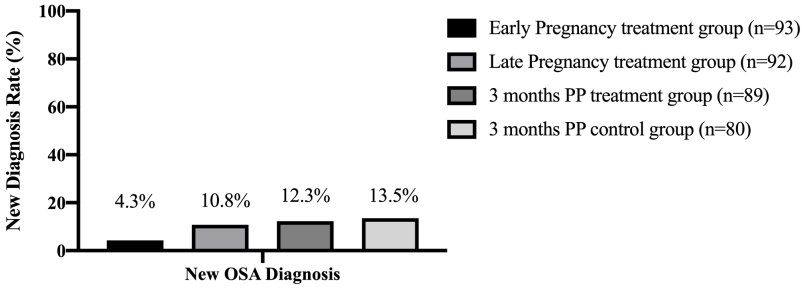


Table 2. OSA severity

OSA Severity[a,b] n (%)	Early Pregnancy[c] Treatment Group (n = 93)	Late Pregnancy Treatment Group (n = 92)	3-Months PP Treatment Group (n = 89)	3 Months Control group (n = 80)
No OSA	89 (95.7)	81 (88)	72 (80.9)	69 (86.3)
Mild (AHI 5-14)	3 (3.2)	11 (12)	14 (15.7)	9 (11.3)
Moderate (AHI 6-29)	0 (0)	0 (0)	2 (2.2)	2 (2.2)
Severe (AHI ≥30)	1 (1.1)	0 (0)	1 (1.1)	0

Abbreviations: PP = postpartum. AHI = apnea/hypopnea index.

[a]Results exclude subjects that had a miscarriage or abortion.

[b]Obstructive apnea was defined as a cessation or decreased airflow of ≥90% of baseline for ≥10 seconds and is associated with continued or increased inspiratory effort; hypopnea was defined as decreased airflow of ≥30% that is associated with oxygen desaturation of ≥4% compared to baseline.

[c]There was n = 1 who was OSA (+) only in early and 3 months postpartum; there was n = 1 who was OSA (+) in early pregnancy who was lost to follow-up.

Table 3. Sleep Study Results in Treatment Group[a,b]

Median (min, max)	Early Pregnancy (6-16 weeks)	Late Pregnancy (27-33 weeks)	3-Months PP	n	X^2	*P*-value
O2 Saturation, Mean	96.5 (89, 98)[c]	96.0 (93, 98)[d]	96.0 (88, 99)	84	22.39	<.001
O2 Saturation, Minimum	92.0 (57, 96)[c]	91.5 (73, 96)[d]	90.0 (61, 97)	84	18.41	<.001
O2 Desat, %: 4-9	2 (0, 44.0)[c]	7 (0, 100.0)[d]	9 (0, 194.0)	85	44.56	<.001
O2 Desat, %: 10-20	0 (0, 75.7)[c]	0 (0, 37.0)[d]	0 (0, 48.0)	85	9.03	.011
O2 Desat, %: >20	0 (0, 1.7)	0 (0, 0)	0 (0, 1.0)	85	2.00	.368
O2 Saturation <90%	0 (0, 141.4)[c]	0 (0, 11.0)[d]	0 (0, 159.2)	85	16.70	<.001
O2 Saturation <88%	0 (0, 108.2)[c]	0 (0, 8.0)[d]	0 (0, 126.3)	85	8.92	.012
O2 Saturation <85%	0 (0, 67.0)	0 (0, 4.5)	0 (0, 80.2)	85	5.84	.054
O2 Saturation <80%	0 (0, 28.7)	0 (0, 1.2)	0 (0, 31.4)	85	5.30	.070
O2 Saturation <70%	0 (0, 5.3)	0 (0, 0)	0 (0, 0.5)	85	3.20	.202
pRDI all night	6.8 (1.2 ,76.8)	5.9 (0, 27.4)[d]	10.05 (0.8, 50.7)[e]	84	40.68	<.001
pAHI all night	0.35 (0, 76.0)[c]	0.90 (0, 12.1)[d]	1.55 (0, 48.2)[e]	84	54.66	<.001
pODI all night	0.4 (0, 75.0)[c]	0.75 (0, 11.9)[d]	1.45 (0, 40.0)[e]	84	50.60	<.001
% of sleep in REM	18.4 (1.9, 33.4)	16.8 (0, 38.7)	19.1 (2.0, 34.1)	83	5.86	.054

Abbreviations: pRDI: PAT Respiratory disturbance index; pAHI: PAT apnea hypopnea index; pODI: PAT oxygen desaturation index; REM = rapid eye movement; PP = postpartum.

Definitions: O2 Desat, %: number of oxygen desaturations of 4-9%, 10-20%, and >20%; O2 Saturation: total time in minutes with oxygen saturation <90%, <88%, <85%, <80%, and <70%.

[a]Analyzed using a Friedman test with Wilcoxon Ranked Sign test for post hoc analysis since data were not normally distributed.

[b]Results are for subjects who had valid sleep study at each time point and no technical problems with Watch-PAT.

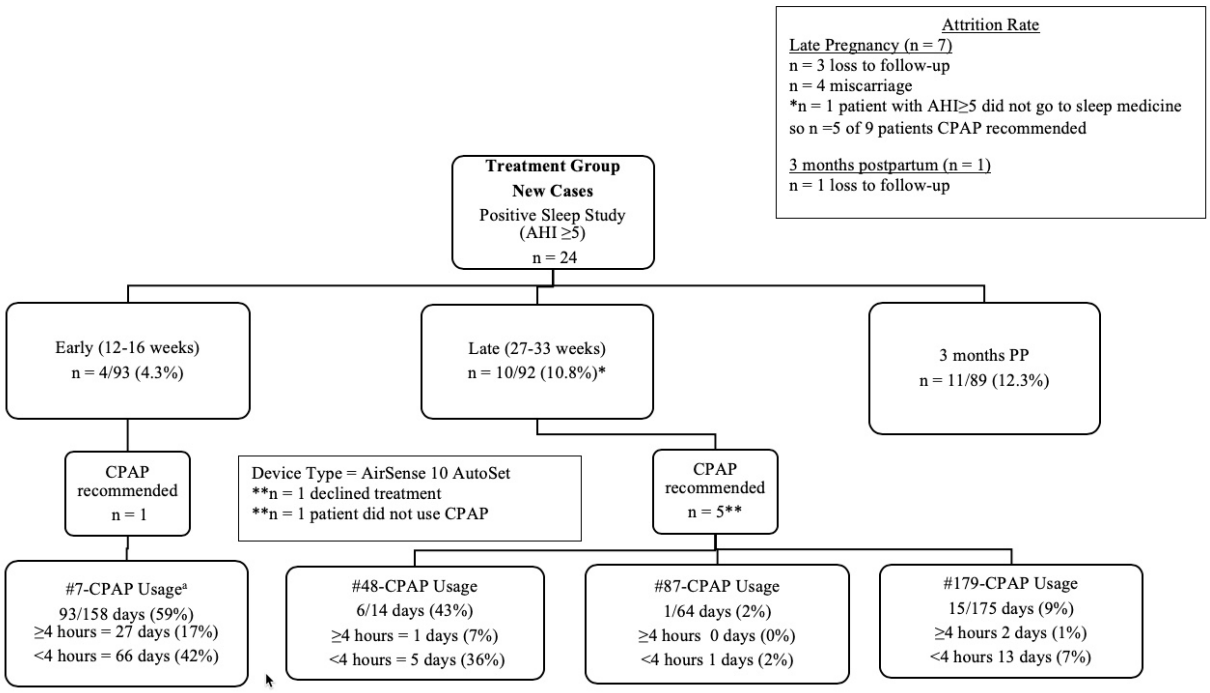
[c]*P* <.05 early vs. late pregnancy

[d]*P* <.05 early vs. 3 months postpartum

[e]*P* <.05 late vs. 3 months postpartum

CPAP Compliance. There were 24 subjects who had a new diagnosis of OSA, with 6 in whom CPAP was prescribed. In early pregnancy 1 subject and 5 subjects in late pregnancy had CPAP prescribed. Compliance with CPAP therapy was poor (CPAP compliance defined as ≥4 hours/night for 70% of nights); the subject in early pregnancy used it for 93/158 days (59% usage) and only 17% of nights for ≥4 hours. Of the 5 subjects prescribed CPAP in late pregnancy, only 3 used CPAP. There compliance rates were poor with usage rates ranging from 2% (1 of 64 days) to 43% (6 of 14 days). One subject used CPAP for 15 of 175 days (9%), but only used it ≥4 hours for 2 nights (Figure 4).

Figure 4. CPAP usage and compliance data



[a]CPAP compliance defined as ≥4 hours/night for 70% of nights.

Incidence of Adverse Pregnancy Outcomes. No significant differences were found in the rate of composite APOs (46.4% vs. 43.3%, *P* = .77) and individual APOs (*P* > .05) between the experimental and control groups (Table 4). Hospital costs at the time of delivery were similar between the two groups.

A post hoc analysis revealed that subjects in the treatment group who tested positive for OSA in late pregnancy (n = 11) had a significantly higher rate of APOs when compared to those who did not test positive (n = 82) for OSA (81.8% vs. 43.9%, *P* = .024). Groups were similar on baseline demographics and pregnancy history (*P* > .05). Rates of APOs were similar if OSA was diagnosed in early pregnancy (n = 4) as compared to those who did not (n =83) test positive (75% vs. 44%, *P* = .32). In those with OSA in late pregnancy the rates of preeclampsia (36.4% vs. 11%, *P* = .044) and gestational diabetes (45.5% vs.17.1%, *P* = .044) were significantly higher when compared to those without OSA. Total hospital costs were also significantly higher in those with OSA diagnosed in late pregnancy ($16,150 vs $11,734, *P* = 006; Table 5).

Exploratory aim. Due to the limited number of subjects requiring CPAP in early (n = 1) and late (n =3) pregnancy we were unable to compare differences in outcomes.

Table 4. Comparison of Adverse Pregnancy Outcomes and Hospital Costs by Group

Outcome, n (%)	Experimental Group n = 97	Control Group n = 90	*P*-value
Gestational HTN	10 (9.3)	16 (17.8)	.13
Preeclampsia	13 (13.4)	12 (13.3)	1.0
Eclampsia	0 (0.0)	1 (1.1)	.48
Gestational Diabetes	19 (19.6)	12 (13.3)	.33
Pre-term Birth	13 (13.4)	9 (10)	.50
Low Birth Weight	5 (5.2)	6 (6.7)	.76
Stillbirth	1 (1.0)	0 (0.0)	1.0
1 or more APO[1]	45 (46.4)	39 (43.3)	.77
Hospital Costs[2] Mean (95% CI)	$12,185 (11,155 to 13,215)	$12,607 (11,210 to 14,004)	.76

Abbreviations: HTN = hypertension; APO = adverse pregnancy outcome.
[1]APO = 1 or more adverse pregnancy outcome (APO). APO is a composite of the adverse outcomes listed above.
[2]Hospital costs calculated at time of delivery.
Subjects who had miscarriage were excluded from the analysis.

Table 5. Comparison of Adverse Pregnancy Outcomes and Hospital Costs by OSA Diagnosis in Late Pregnancy

Outcome, n (%)	OSA n = 11	No OSA n = 82	*P*-value
Gestational HTN	9 (11)	9 (11)	1.0
Preeclampsia	4 (36.4)	9 (11)	.04
Eclampsia	0 (0.0)	0 (0)	
Gestational Diabetes	5 (45.5)	14 (17.1)	.04
Pre-term Birth	2 (18.2)	10 (12.2)	.63

Low Birth Weight	2 (18.2)	3 (3.7)	.11
Stillbirth	0 (0)	0 (0.0)	
1 or more APO[1]	9 (81.8)	36 (43.9)	.02
Hospital Costs[2] Mean (95% CI)	$16,150 (12,481 to 19,819)	$11,734 (10,682 to 12,786)	.006

Abbreviations: HTN = hypertension; APO = adverse pregnancy outcome.
[1]APO = 1 or more adverse pregnancy outcome (APO). APO is a composite of the adverse outcomes listed above.
[2]Hospital costs calculated at time of delivery.
Subjects who had miscarriage were excluded from the analysis.

Discussion

This is one of the few clinical trials to examine if the rate of APOs can be reduced with implementation of an OSA screening program including overnight sleep studies and treatment with CPAP as needed. It was hypothesized that the identification, using an unattended sleep study, and treatment of OSA with CPAP when clinically indicated (when the AHI ≥5) during early or late pregnancy will significantly decrease the incidence of APOs pregnancy in parturients identified as being high risk for OSA when compared to a group of parturients who do not complete an unattended sleep study in early and late pregnancy. We found no significant differences in the rate of APOs or in total hospital costs between the groups; however, the study is underpowered given the low incidence and severity of OSA and need for CPAP in the treatment group (6 out of 97 = 6.2%). Only 6 out of 24 subjects with a new diagnosis of OSA were recommended CPAP therapy (CPAP recommendation rate = 25%). Within these subjects CPAP compliance was poor. We estimated we would need 32 and 36 subjects to require CPAP to be able to detect a 20% difference in APOs. Therefore, future studies may need to enroll over 400 subjects per group to determine if implementation this screening program would be effective in decreasing APOs.

We did find those subjects diagnosed with OSA in late pregnancy had significantly higher rates of APOs and hospital costs when compared to those who did not test positive for OSA. This was mainly due to significantly higher rates of preeclampsia and gestational diabetes. These results are consistent with previous investigations and confirms OSA is associated with APOs and higher hospital costs at the time of delivery.[5,7]

Future CPAP trials investigations should consider limiting inclusion criteria to those subjects who are at most risk for OSA to stratify sampling based on risk factors to ensure adequate power to detect a treatment effect. For example, patients with a prepregnancy BMI≥30 kg/m^2 are considered at high risk for undiagnosed OSA.[2] Use of valid and reliable screening instruments for undiagnosed OSA during pregnancy should be used.[21] Facco et al[21] recently published a report on the development of a OSA prediction model which includes age, frequent snoring, and BMI.

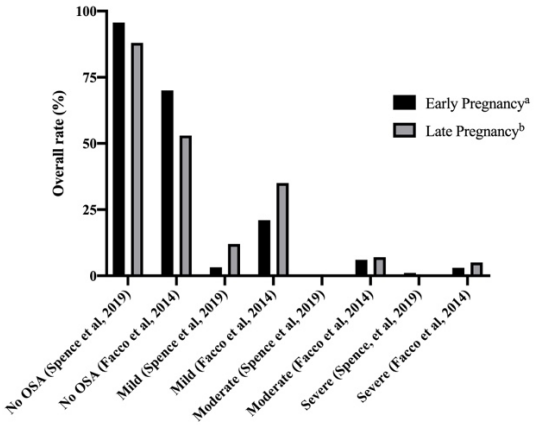
These results should be considered preliminary pilot data which investigators can use in the design of future clinical trials. Given that only 4 subjects used CPAP (1 in early and 3 in late pregnancy) we were unable to compare differences in APOs between subjects who were started on CPAP in early or late pregnancy. Most patients will be diagnosed in late pregnancy, and it is unknown if there is enough time between initiation of CPAP treatment and delivery to be

effective in decreasing APOs.[11,17] Interventions should be put in place to improve adherence with CPAP during pregnancy, and investigators should determine if there are any modifiable factors to improve compliance with CPAP, especially in late pregnancy.

It was hypothesized that the rate and severity of OSA would be significantly greater in late pregnancy compared to early pregnancy and at 3 months post-delivery (between 8 and 12 weeks). Our results indicate that OSA severity (based on AHI) increases in late pregnancy but is highest at 3 months postpartum rather than in late pregnancy. This may be due to poor sleep quality and may be associated with feeding and caring for a newborn. This is the first study to examine the trajectory of OSA severity in pregnant women at high-risk for OSA from early pregnancy to the early postpartum period. One small cohort study of 11 patients found the AHI decreased from AHI decreased from 4.6 ± 9.3 at 32 weeks to 2.6 ± 2.7 at 11 to 23 months postpartum (P =.77).[9] Future studies are needed to determine when or if OSA symptoms and severity resolve after delivery.

The incidence and severity of OSA in this study was lower than previously published by Facco et al (Figure 5).[22] There are three possible reasons for this difference- differences in population, timing of sleep studies, and the criteria for an AHI event. Subjects in this study were Military Health Service beneficiaries delivering at a Military Treatment Facility, whereas those in the Facco et al.[22] study delivered at a University hospital who had public and private insurance. In this study early sleep studies were conducted between 6 and 16 weeks and again between 27 and 33 weeks as compared to between 6 in 20 and 28 to 37 weeks in the Facco et al study.[22] In the Facco et al study a ≥3% oxygen desaturation was used for hypopnea events as compared to a ≥4% oxygen desaturation in this current study.

Figure 5 Comparison of OSA rates across pregnancy



[a]Early Pregnancy: Spence et al. (2019) = 6 to 16 weeks
[a]Early Pregnancy: Facco et al. (2014) = 6 to 20 weeks[22]
[b]Late Pregnancy: Spence et al. (2019) = 27 to 33 weeks
[b]Late Pregnancy: Facco et al. (2014) = 28 to 37 weeks

There are several limitations of this study. As was previously mentioned, given the low CPAP rate and poor compliance our study is underpowered to detect differences in rates of APOs between the groups. Delays in between prescription and setting up the CPAP in the subject's home may have impacted CPAP use and compliance. Furthermore, we initially planned to contact subjects on CPAP monthly to monitor compliance and address any issues. However, due to the low numbers and logistical issues were unable to do this. Most subjects required CPAP in late pregnancy and there may not have been enough time between CPAP initiation and delivery to have an effect on APOs. However, our results are pragmatic in that they reflect the challenges and issues clinicians may face when prescribing CPAP to pregnant patients with OSA. Clinicians and patients were not blinded to group assignment. We provided an informational brief to the Obstetrics department prior to subject enrollment, and a recorded advertisement for subject recruitment was played when patients called into the hospital for an appointment. It is possible that clinicians modified their treatment plan and subjects modified their behavior and that this may have impacted our results.

Conclusion

In conclusion, results of this study confirm that the incidence and severity of OSA worsens over the course of pregnancy and appears to peak at 3 months postpartum in parturients at high-risk for OSA. Most cases were mild and did not require treatment. This study was underpowered to detect a difference in hospital costs at the time of delivery and composite APOs. Given the low OSA incidence and CPAP requirement we identified in this study, future studies may need to enroll over 400 subjects per group to determine if an OSA screening and CPAP treatment program would be effective in decreasing APOs. Investigators should consider using results from this study to design future large, prospective, multi-center clinical trials. Methods should be put in place to increase CPAP adherence.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

We are in the process of preparing manuscripts and abstracts for presentation at national conferences. Results were shared with stakeholders in the obstetrical department at NMCSCD and with other researchers in this field who may use the results to design large, prospective randomized controlled trials.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

The impact of these results on scientific knowledge is that they confirm that in pregnant women at high-risk for OSA (defined as an AHI ≥5 events/hour; *risk factors*: pre-pregnancy BMI≥30 kg/m^2, chronic hypertension, pre-gestational diabetes [type 1 or type 2], history of prior preeclampsia, and/or a twin gestation) that the rate and severity of OSA worsens over the course of pregnancy, and peaks at 3 months postpartum (8-12 weeks). This latter finding has not previously been reported. Most patients had mild OSA and did not require CPAP treatment. Because of the low CPAP requirement, the study did not have enough patients enrolled to detect a difference in APOs between patients in the treatment group and control group. Future investigations may need very large sample sizes to determine if CPAP is effective in decreasing APOs in pregnant women at high-risk for OSA. Investigators may want to limit inclusion criteria to patients at most risk for undiagnosed OSA (i.e., obese parturients) and consider using screening tools for OSA to select high-risk patients.[21]

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. Changes/Problems

Changes in approach and reasons for change.

The sample size estimate of was revised 18 January 2018 and approved by CDR Mosquera.

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects
Nothing to report.

Significant changes in use or care of vertebrate animals.
N/A

Significant changes in use of biohazards and/or select agents
N/A.

6. Products

We are currently preparing manuscripts for publication.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

No funds were used to pay personnel on this study. All personnel are active duty or GS, with the exception of contract personnel.

Personnel	Role	Percent Effort
Ted Morrison, PhD	Contractor – Research Coordinator	100
Patrick Nardulli	Contractor – Research Associate	25
CAPT Dennis Spence, NC, USN, PhD CRNA	PI	30
CAPT Tony Han (ret), MC, USN (Sleep Medicine)	AI	5
CDR Monica A. Lutgendorf, MC, USN (Maternal Infant Medicine)	AI	5

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report.

What other organizations were involved as partners?
LEIDOS – contracting of non-personnel services; there was, however, no Cooperative Research and Development Agreement (CRADA) for this study.

8. Special Reporting Requirements- Quad Chart

Randomized Controlled Trial of a Sleep Study + Targeted CPAP Therapy for Obstructive Sleep Apnea to Reduce the Incidence of Adverse Pregnancy Outcomes (DM150091)

PI: CAPT Dennis Spence, NC, USN, PhD, CRNA

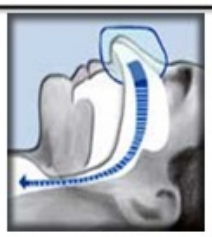
Org: Naval Medical Center San Diego **Award Amount: $ 998,787.00** (All funding for this project have been executed)

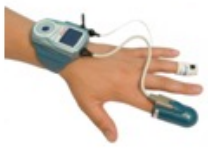
Study Aims

- Determine if the rate of a composite of adverse pregnancy outcomes (gestational hypertension, preeclampsia, eclampsia, gestational diabetes, preterm birth, low birth weight, or stillbirth) is decreased in pregnant women at high risk for OSA who develop OSA (AHI ≥5) in early or late pregnancy and are started on CPAP therapy when compared to standard prenatal care.
- Calculate the rate and trends for mild, moderate, and severe OSA in early and late pregnancy, and at 3 months after delivery.
- Compare differences in total hospital costs at the time of delivery between the sleep study + CPAP group and the standard prenatal care group.

Approach

- Randomized controlled trial (n = 180 each group)
- Treatment group: WatchPAT-200 sleep study at early (6-16wks), late (27-33wks), and 3 months postpartum. CPAP started if AHI ≥5.
- Comparison group: standard prenatal care





Activities CY	16	17	18	19
IRB approval, Hire Staff, prepare for data collection				
Recruitment and Data Collection				
Recruitment and Data Collection				
Analysis and Dissemination				
Estimated Awarded Budget ($K)	**370**	**314**	**314**	**EWC**
Obligated Funding ($K)	**365**	**314**	**314**	

Updated: *(09/21/2019); EWC = extension w/o cost*

Goals/Milestones

CY15 - 16 Goal (4th and 1st Quarter, respectively)

- Preparation for Team Performance Research (goal met)

CY16 Goals (2nd – 4th)

- Recruitment & Data collection (goal met)

CY17 Goals (1st - 4th)

- Recruitment & Data collection (goal met)

CY18/19 Goals (1st – 4th)

- Recruitment & Data collection (goal partially met)
- Data cleaning, database lock (goal met)
- Data Analysis, manuscript & technical report preparation (goal met).
- Dissemination of results (in progress).

9. Appendices

References

1. Pamidi S, Pinto LM, Marc I, Benedetti A, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2014;210(1):52 e51-52 e14.
2. Louis J, Auckley D, Miladinovic B, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. *Obstet Gynecol.* 2012;120(5):1085-1092.
3. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. *Sleep.* 2014;37(5):843-849.
4. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin Sleep Cohort. *Sleep.* 2008;31(8):1071-1078.
5. Spence DL, Allen RC, Lutgendorf MA, Gary VR, Richard JD, Gonzalez SC. Association of obstructive sleep apnea with adverse pregnancy-related outcomes in military hospitals. *Eur J Obstet Gynecol Reprod Biol.* 2016;210:166-172.
6. Antony KM, Agrawal A, Arndt ME, et al. Obstructive sleep apnea in pregnancy: reliability of prevalence and prediction estimates. *J Perinatol.* 2014;34(8):587-593.
7. Facco FL, Parker CB, Reddy UM, et al. Association Between Sleep-Disordered Breathing and Hypertensive Disorders of Pregnancy and Gestational Diabetes Mellitus. *Obstet Gynecol.* 2017;129(1):31-41.
8. Facco FL, Ouyang DW, Zee PC, et al. Implications of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol.* 2014;210(6):559.e551-556.
9. Reid J, Glew RA, Skomro R, et al. Sleep disordered breathing and gestational hypertension: postpartum follow-up study. *Sleep.* 2013;36(5):717-721b.
10. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2019;15(2):335-343.
11. Facco F. Sleep-disordered breathing in pregnancy: a brief summary of current knowledge. *BJOG.* 2014;121(13):1694.
12. Gruca-Stryjak K, Cofta S, Wysocka E, Banaszewski J, Breborowicz G. [Is there a relationship between pregnancy induced hypertension and obstructive sleep apnea? Case report]. *Pneumonol Alergol Pol.* 2014;82(2):156-162.
13. Daly A, Robertson A, Bobek G, Middleton S, Sullivan C, Hennessy A. Sleep disordered breathing controlled by CPAP and sFlt-1 in a pregnant patient with chronic hypertension: Case report and literature review. *Obstet Med.* 2018;11(1):32-34.
14. Whitehead C, Tong S, Wilson D, Howard M, Walker SP. Treatment of early-onset preeclampsia with continuous positive airway pressure. *Obstet Gynecol.* 2015;125(5):1106-1109.
15. Guilleminault C, Palombini L, Poyares D, Takaoka S, Huynh NT, El-Sayed Y. Pre-eclampsia and nasal CPAP: part 1. Early intervention with nasal CPAP in pregnant women with risk-factors for pre-eclampsia: preliminary findings. *Sleep Med.* 2007;9(1):9-14.
16. Screening and treatment of obstructive sleep apnea in high-risk pregnancy. Clinical Trials.gov. https://ClinicalTrials.gov/show/NCT03356106. Updated 17 September 2019. Accessed September 18, 2019.
17. Pamidi S, Meltzer SJ, Garfield N, et al. A Pilot Randomized-Controlled Trial on the Effect of CPAP Treatment on Glycemic Control in Gestational Diabetes: Study Design and Methods. *Front Endocrinol (Lausanne).* 2018;9:659.
18. Facco FL, Ouyang DW, Zee PC, Grobman WA. Development of a pregnancy-specific screening tool for sleep apnea. *J Clin Sleep Med.* 2012;8(4):389-394.
19. Tantrakul V, Sirijanchune P, Panburana P, et al. Screening of obstructive sleep apnea during pregnancy: differences in predictive values of questionnaires across trimesters. *J Clin Sleep Med.* 2015;11(2):157-163.
20. Pearson F, Batterham AM, Cope S. The STOP-Bang Questionnaire as a Screening Tool for Obstructive Sleep Apnea in Pregnancy. *J Clin Sleep Med.* 2019;15(5):705-710.

21. Louis JM, Koch MA, Reddy UM, et al. Predictors of sleep-disordered breathing in pregnancy. *Am J Obstet Gynecol.* 2018;218(5):521.e521-521.e512.
22. Facco FL, Ouyang DW, Zee PC, Grobman WA. Sleep disordered breathing in a high-risk cohort prevalence and severity across pregnancy. *Am J Perinatol.* 2014;31(10):899-904.