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

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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 (6-16wks), late pregnancy (27-33wks), and at 3 months postpartum (between 8 and 12 weeks postpartum). Subjects with an apnea hypopnea index (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 continuous positive airway pressure (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 WATCHPAT sleep study), were currently taking alpha blockers or nitrates (interfere with WATCHPAT 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 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 dthat 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.