Obstructive Sleep Apnea in Pregnancy:

Development of a Pregnancy-Specific Screening Tool

NCT02383706

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This study was approved by the Duke University Medical System Institutional Review Board and registered in ClinicalTrials.gov (NCT02383706). We prospectively enrolled adult pregnant, nulliparous and multiparous subjects, between 24 and 35 weeks gestation from a university-affiliated prenatal clinic. Women were included if they had a BMI $\geq$ 40 $kg.m^{-2}$ at the time of enrollment and were 18 years or older. The World Health Organization classification of obesity was utilized to define class 3 (extreme) obesity.[1] Women with an established diagnosis of OSA or chronic opiate use, and subjects who did not speak English were excluded.

Following informed consent, demographic data was recorded (including pre-pregnancy BMI from chart review) and subjects completed three sleep disordered breathing screening questionnaires: the Berlin[2] (BQ) and STOP-BANG[3,4] questionnaires, and the American Society of Anesthesiologists' (ASA) checklist.[5] Subjects also completed the Epworth Sleepiness Scale (ESS) which is used to assess sleepiness that can be associated with OSA.[6] An OSA risk score was also calculated for each subject using the method proposed for use in pregnant women by Facco *et al*.[2]

$$\text{OSA risk score} = \text{Age} + \text{BMI}_{\text{pre-pregnancy}} + 15 \text{ (if frequent snoring)} + 15 \text{ (if chronic hypertension)}$$

The BQ, STOP-BANG, and ASA questionnaires, as well as the ESS were scored using published methods.[2,5-7] The BQ contains 10 items classified into three categories: Category 1 concerns snoring; Category 2 concerns daytime sleepiness; and Category 3 relates to BMI > 30 $kg.m^{-2}$ and chronic hypertension. The BQ is considered high risk for OSA if two of three categories were scored as positive.[2] Similarly, the ASA checklist contains 12-items in three categories: clinical signs and symptoms; history of apparent airway obstruction during sleep; and somnolence. If 2 or more of these categories are

endorsed, the patient is considered at high risk for OSA.[5] Each item on the STOP-BANG questionnaire receives one point, with the highest total possible score in this cohort equal to 6 (as male gender and age greater than 50 years do not apply to any of the subjects).[7,8] The ESS is considered concerning for excessive daytime sleepiness if scores are in the 11-24 range.[6]

Study data were entered into and managed using REDCap electronic data capture tools hosted at Duke University. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[9]

Vital signs were recorded, and subjects underwent a physical examination of the neck and upper airway by trained research assistants in the Department of Anesthesiology to measure neck circumference[4] and thyromental distance, and to assess retrognathia, tongue scalloping[10], Mallampati score (MMS)[11], modified MMS[12], tonsil size and lateral pharyngeal wall narrowing. MMS is a 1-4 numerical rating system commonly used to assess the airway and predict difficulty of intubation that is assessed by asking the subject to open their mouth as wide as possible with the tongue protruding. The modified Mallampati score leaves the tongue inside the mouth. Neck circumference was measured using a disposable measuring tape at the midpoint of the

neck just below the thyroid cartilage. Thyromental distance was measured using a disposable paper measuring tape from the mandible to the top of the thyroid cartilage. Retrognathia, tongue scalloping, MMS, modified MMS, tonsil size and lateral pharyngeal wall narrowing were rated using an illustrated numerical scoring tool.

Subjects received an unattended type III home sleep apnea test (ApneaLink Air™, ResMed, Poway, CA, USA), and instructions for wearing it during one night of sleep. The home sleep test consists of a pulse oximeter for recording of oxygen saturation and heart rate, a respiratory effort belt for measurement of respiratory effort, and a nasal sensor for detection of flow limitation, apnea hypopnea index (AHI) and snoring. The software on the device calculates AHI from the sum average number of apneas (80%-100% reduction in airflow with respiratory effort $\geq$ 10 seconds) and hypopneas (50%-80% reduction in airflow with respiratory effort $\geq$ 10 seconds) per hour during the recording time, based on the standard definitions of the American Academy of Sleep Medicine. The software also generates a report with details regarding variation in oxygen saturation during the study. Subjects with an AHI greater than 5 per hour on the home sleep test were referred to a sleep medicine physician for further evaluation.

Pregnancy outcomes were followed for all subjects, including maternal death, gestational diabetes, cerebrovascular accident, spontaneous labor, induction of labor, oxytocin administration during labor, cesarean delivery, estimated blood loss, neonatal weight, and composite outcomes of adverse maternal cardiovascular and peripartum events, and adverse fetal outcomes. A composite adverse maternal cardiovascular

outcome combined cases of: gestational hypertension; mild and severe preeclampsia; eclampsia; cardiomyopathy; and congestive heart failure. A composite adverse peripartum outcome included cases of: postpartum hemorrhage; maternal ICU admission; and post-operative wound infections. A composite adverse fetal outcome included cases of: neonatal intensive care unit admission; fetal growth restriction; preterm delivery (< 37 weeks gestation); and fetal demise.

Statistical analysis

OSA outcome was defined as AHI ≥ 5 events per hour among patients with at least 2 hours of nasal air flow time recorded. This measure was chosen to assess outcome because it represents the threshold for referral for in laboratory PSG and an OSA screening measure will need to be able to sensitively and specifically indicate when a referral for PSG is needed. We summarized the patient demographic, physical, and clinical characteristics as well as questionnaire responses in each outcome group via mean (SD) or median (Q1, Q3) for numeric variables and N (%) for categorical variables. We assessed univariate associations of patient characteristics and questionnaire responses with OSA outcome via t-test or Wilcoxon rank sum test for numeric variables, and chi-square or Fisher exact test for categorical variables.

We assessed the performance and agreement of the previously defined OSA risk scores via receiver operating curve (ROC) area under the curve (AUC) analysis, logistic regression, and Kendall Tau correlation for the numeric scores, and via sensitivity and

specificity, net reclassification indices (NRI) and Kappa statistics for the binary risk stratification.

We designed the study with an expectation of an OSA positive rate of 30-40% in our high-risk population.[1,2] A study of 80 patients (24-32 with OSA) with completed valid home sleep test, achieves 79% power in a logistic regression with two-sided alpha=0.05 to detect an odds ratio of 2.5 for a numeric risk score when the OSA rate is 35%. For the Kappa statistic used to assess agreement, with 80 subjects and an OSA rate of 35%, we will achieve 82% power at alpha = 0.05 to detect the difference between a kappa of 0.45 (fair agreement) and 0.75 (strong agreement). Power and sample size calculation were performed in NQuery (Statistical Solutions Ltd) software, statistical analysis was performed in SAS v9.4 (SAS Inc., Cary, NC), and significance was set at 0.05 level.

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