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RESEARCH

Obstructive sleep apnoea in pregnancy and its association with pre-eclampsia

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Background: Obstructive sleep apnoea (OSA) in pregnancy is associated with an increased morbidity and mortality to both mother and foetus. In the South African setting the proportion of pregnant females suffering from OSA has not been well studied; nor has the association with pre-eclampsia. This study aimed to determine the prevalence of OSA in females before 35 weeks gestation using the STOP-BANG questionnaire and to determine the association with pre-eclampsia in a local South African setting.
Methods: A cross-sectional analytical study including 234 patients was conveniently sampled from Kalafong Hospital's antenatal ward, clinic and labour ward. Participants were of more than 20 weeks and less than 35 weeks gestation. All participants were interviewed with a modified STOP-BANG questionnaire. Patients were consecutively enrolled without prior knowledge of the presence of pre-eclampsia. At Kalafong hospital all pregnant patients are routinely screened and investigated for pre-eclampsia according to standard criteria.
Results: The median gestational age in this sample was 28 weeks; 80.3% (CI 74.62–85.2%) of pregnant females had a low risk for OSA, 15.4% (CI 11.01–20.65%) had an intermediate risk and 3% (CI 6.47–14.58%) had a high risk for OSA. A modified STOP-BANG questionnaire had a sensitivity of 62.5% and a specificity of 82.1% for pre-eclampsia when a score of 3 and more was scored. Females at high risk of OSA had an OR of 8.4 (CI 2.88–24.6) for having pre-eclampsia.
Conclusions: The authors report 15.4% of the study's pregnant population to be at intermediate risk and 3% at high risk of OSA. The association between the hypertensive disorders and OSA must be considered and screening implementation considered.

Keywords: anaesthesia, obstructive sleep apnoea, pre-eclampsia, STOP-BANG questionnaire

Introduction

Recently, interest has been shown in pregnant females suffering from obstructive sleep apnoea (OSA) because of the association with hypertensive disorders and an increased perinatal morbidity and mortality for mother and baby.[1–3] Continuous positive airway pressure (CPAP) treatment in patients with pre-eclampsia has been shown to decrease blood pressure and improve cardiac output in comparison with no treatment.[4]

In the USA the highest prevalence of OSA in pregnancy is among obese patients, with an increasing prevalence towards the second and third trimester. The South African prevalence has not been investigated; however, due to high rates of obesity, OSA is expected to be high. Surveys have shown that 90% of pregnant patients with OSA are unaware of their condition.[1]

The normal physiological changes during pregnancy predispose to snoring. The oropharyngeal diameter narrows and the Mallampati grade increases as the pregnancy progresses.[5,6] The nasal passages narrow from mucosal oedema and increased negative pharyngeal pressure is required with inspiration to overcome the increased upper airway resistance. Sleep decreases pharyngeal muscle tone further.[5,6] These changes lead to an increase in upper airway obstruction resulting in a spectrum of sleep-disordered breathing patterns. OSA leads to intermittent hypoxia associated with increases in blood pressure.[1]

The reference standard for diagnosing OSA is an overnight polysomnogram. This is expensive, time-consuming and not practical for the majority of the South African population. Screening questionnaires like the STOP-BANG have been validated to identify OSA in pregnancy.[4,7] Lockhart *et al.*[8] showed the STOP-BANG questionnaire to have the highest specificity (85%) and to have performed the best out of six screening tools. The STOP-BANG questionnaire takes common signs and symptoms of OSA into account and a score out of 8 is derived Each increase in the STOP-BANG score is associated with an increase in the probability of OSA and the severity of OSA.[4,9] A score of 0–2 indicates a low risk, a score of 3–4 indicates an intermediate risk and a score of ≥ 5 indicates a high risk for OSA.[10]

During pregnancy weight gain can be attributed to oedema, increase in blood volume, foetal tissue and amniotic fluid. A study done on parturients in the Metro West area of Cape Town showed a strong correlation between body mass index (BMI) and mid-upper arm circumference (MUAC) up to 30 weeks gestation.[11] In their study including 2912 pregnant females, Cooley *et al.*[12] also showed a correlation between BMI and MUAC that can be calculated as BMI = MUAC(cm) +/– 2 cm. MUAC is a much easier measurement to take as it does not necessitate using scales, height charts or calculations. Another advantage is that there is minimal change in MUAC during pregnancy, which is a good indicator of pre-pregnancy body fat and nutrition.[11] In this study we modified the STOP-BANG questionnaire using MUAC rather than BMI.

Pre-eclampsia is defined as new-onset hypertension and proteinuria or end organ damage after 20 weeks gestation.[13] New-onset snoring during pregnancy is a strong risk factor for gestational hypertension and pre-eclampsia. A correlation between a positive

score on the STOP-BANG and pre-eclampsia has also been proven.[14] In the USA, females diagnosed with OSA on polysomnogram have a 19.3% higher risk of having pre-eclampsia.[2]

The aim of this study was to determine the prevalence of OSA in females before 35 weeks gestation using a modified STOP-BANG questionnaire and to determine the association of OSA and pre-eclampsia in a local South African setting.

Methods

A cross-sectional analytical study was conducted. A convenience sample of patients was taken from patients admitted to the antenatal ward, labour ward or attending the antenatal clinic at Kalafong Hospital, without prior knowledge of the diagnosis or comorbidities. Each participant had to be 18 years or older, and be more than 20 weeks but less than 35 weeks pregnant. At Kalafong Hospital patients with pre-eclampsia are routinely delivered by 35 weeks, which determined our inclusion criteria.

Kalafong Hospital is a tertiary institution providing services to uninsured urban inhabitants of the south-western districts of the greater Tshwane. Patients are mostly from a lower socio-economic background and are predominantly African. The obstetric unit provides care to a large spectrum of patients from low-risk to high-risk pregnancies.

Recruitment was initiated from 11 February 2015 until 6 March 2015. Each participant was interviewed only once. Only one interviewer enrolled participants and assisted with the completion of a set questionnaire. The study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of Pretoria (Protocol approval nr: 5/2015). All participants approached for enrolment to the study were informed about all study procedures and what would be expected of them. Once participants indicated willingness to participate an informed consent document was signed. All patients attending the antenatal clinic, or those who were admitted to the ward, were approached for enrolment to the study. Demographic details such as age, race, parity, gravidity, and previous abortions were recorded. Other comorbidities like asthma, diabetes, smoking, other renal disease, pre-eclampsia and HIV status according to the patient if known were recorded.

The STOP-BANG questionnaire has eight questions. Participants in this study automatically scored 0 for age (above 50) and male gender. For each positive answer a patient scored one mark. The following questions were asked:

The STOP-BANG questionnaire utilises BMI as one of its scoring points. To simplify the BMI in pregnancy, Cooley *et al.* used the MUAC as a surrogate. A correlation between BMI and MUAC was clearly demonstrated. The BMI can easily be calculated by a simple equation where BMI = MUAC +/– 2 cm. In this study we substituted BMI with MUAC.[12] By doing so we modified the STOP-BANG questionnaire. Mid-upper arm circumference was measured and if 33 cm or more a positive mark was scored. The right upper arm was measured at the midpoint between the tip of the acromion and the tip of the olecranon. Neck circumference greater than 40 cm also scored one mark. Measurement was made around the neck in a horizontal plane at the level of the most prominent portion of the thyroid cartilage.

Pre-eclampsia was diagnosed as new-onset hypertension after 20 weeks gestation with proteinuria or end organ damage. Hypertension was classified as SBP > 140 mmHg or DBP > 90 mmHg and proteinuria > 1+protein on urine dipsticks or 0.3 g/24 h. End organ damage is classified as platelet count < 100 000ug/l or doubling of serum creatinine or elevated transaminase.

The primary aim of the study was to determine the proportion of females at Kalafong's obstetric unit who are at risk of OSA. A secondary aim was to relate OSA to pre-eclampsia.

Statistical analysis

A sample size of 196 participants was calculated to be sufficient to estimate the proportion of patients at risk for OSA during pregnancy (primary aim) with an accuracy of 5%, assuming an anticipated proportion of OSA of about 15% and a CI of 95%.

The primary outcome of the study was to determine the proportion of patients with OSA based on the STOP-BANG score. The STOP-BANG score, however, does not make a definitive diagnosis of OSA and only indicates the risk as low, moderate and high for OSA. The proportion of patients in each of these risk categories was calculated with related 95% confidence intervals.

A chi-square test for trend was done to relate the risk categories of OSA to the presence of pre-eclampsia.

Additional analysis included a logistic regression modelling where relevant potential risk factors and confounders were entered to adjust for potential confounding with the STOP-BANG as dependent variable. This was also repeated with pre-eclampsia as dependent variable and the STOP-BANG as independent variable with other risk factors and confounders.

Modified STOP-BANG questionnaire

1. Do you snore?
2. Do you feel tired to such an extent that you fall asleep during a conversation or in circumstances endangering yourself or others?
3. Has anyone observed you choking or gasping while sleeping?
4. Do you have hypertension – new onset or prior?
5. MUAC ≥ 33 cm
6. Neck circumference > 40 cm

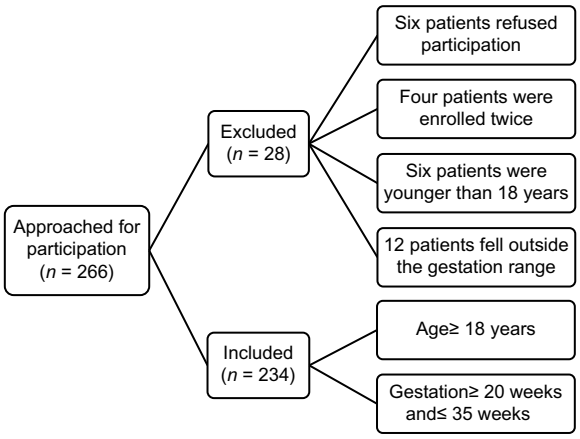

Figure 1: Patient flow.

Table 1: Patient characteristics and demographics

Variable	*n* = 234
Age (mean, standard deviation)	30 (25–36)
Race: African	216 (92.3%)
Other	18 (7.7%)
Parity, median (range)	1 (0–7)
Gravida median (range)	3 (0–9)
Gestational age (median, IQR)	28.5 (24–32)
HIV status positive	45 (19.2%)
Comorbid medical conditions	
Hypertension pre-conception	17 (7.2%)
Asthma	11 (4.7%)
Diabetes	10 (4.3%)
Renal disease	6 (2.6%)
Cardiac disease	2 (0.8%)
Epilepsy	1 (0.4%)
Comorbid conditions and complications associated with pregnancy	
Fibroid uterus	1 (0.4%)
HELLP syndrome	1 (0.4%)
Intrauterine growth restriction	1 (0.4%)
Previous pre-eclampsia	1 (0.4%)
Placenta previa	2 (0.9%)
Preterm labour	3 (1.3%)
Premature rupture of membranes	2 (0.8%)
Pyelonephritis	1 (0.4%)
Twin pregnancy	2 (0.8%)

The performance and accuracy of STOP-BANG as diagnostic indicator of pre-eclampsia was done with ROC statistics without adjusting for confounders.

Results

Pregnant patients were consecutively recruited from the Antenatal Clinic and ward at Kalafong hospital. A number of patients were excluded after being approached for inclusion based on the exclusion criteria for the study (Figure 1). A total of 234 participants were interviewed and measured.

Of the pregnant women enrolled only 18 (7.7%) were not African. The majority of participants 97 (41.1%) were para 1 and 54 (23.1%) para 2. A large proportion of the patients 63 (26%) had had a previous spontaneous abortion or termination of pregnancy. Among the participants 45 (19.2%) were HIV positive although 15 patients did not know their HIV status.

Of the 234 patients included in the study 47 (20.1%) had a premorbid medical condition of which hypertension 17 (7.2%) was the most prevalent. Fourteen (5.98%) of the patients enrolled had a condition that complicated pregnancy or delivery (Table 1).

Table 2 indicates the proportion of pregnant patients with different scores on the STOP-BANG questionnaire. This means that 188 patients (80.3%, CI 74.62–85.2%) were at low risk (score 0 to 2), 36 patients (15.4%, CI 11.01–20.65%) were at moderate risk (score 3 to 4) and 10 (3%, CI 6.47–14.58%) were at high risk (score 5 to 8) for obstructive sleep apnoea.

If hypertension due to pre-eclampsia is also included in the scoring of the STOP-BANG score: 6 (3.2%) patients had pre-

Table 2: STOP-BANG criteria and proportions of patients with each criterion

Criterion	*n* (%) fulfilling the criterion	Mean (SD)
Do you snore loudly?	89 (38%)	
Do you often feel tired, fatigued, or sleepy during daytime?	39(16.7%)	
Has anyone observed you stop breathing while sleeping?	26 (11.1%)	
Do you have or are you treated for hypertension (including pre-eclampsia)	46 (19.7%)	
Mid-upper arm circumference ≥ 33 cm (replacement for BMI in pregnancy)	97 (41.5%)	32 (4.7)
Neck circumference > 40 cm	13 (5.6%)	35.7 (2.88)

*Gender was excluded due to the population of the study.

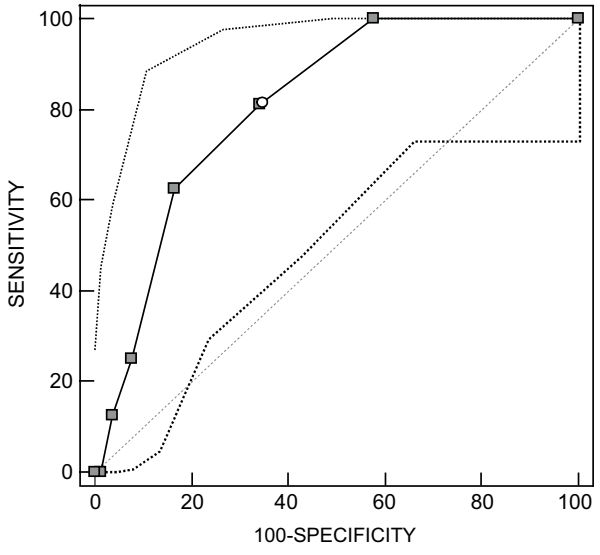

Figure 2: ROC curve for STOP-BANG diagnosing pre-eclampsia.

Table 3: Accuracy of STOP-BANG scores for different cut-off values

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	95% CI	−LR	95% CI
One or more	100.00	79.4–100.0	42.20	35.6–49.1	1.73	1.5–1.9	0.00	
Two or more	**81.25**	**54.4–96.0**	**64.68**	**57.9–71.0**	**2.30**	**1.7–3.1**	**0.29**	**0.1–0.8**
Three or more	62.50	35.4–84.8	82.11	76.4–87.0	3.49	2.2–5.6	0.46	0.2–0.9
Four or more	31.25	11.0–58.7	90.83	86.2–94.3	3.41	1.5–7.9	0.76	0.5–1.1
5 or more	12.50	1.6–38.3	95.87	92.3–98.1	3.03	0.7–12.9	0.91	0.8–1.1
Six	0.00	0.0–20.6	98.62	96.0–99.7	0.00		1.01	1.0–1.0

eclampsia in the low-risk category, 8 (22.2%) patients had pre-eclampsia in the intermediate risk category and 2 (20%) had pre-eclampsia in the high-risk category (chi-square for trend $p < 0.001$).

Of the 234 patients included in the study 16 (6.8%) had pre-eclampsia. A ROC curve analysis was done which indicated that a cut-off of 2 STOP-BANG criteria has the best trade-off between sensitivity (81.25%, CI 54.4–96.0) and specificity (64.68%, CI 57.9–7.0) for diagnosing pre-eclampsia during pregnancy (AUC 0.805, CI: 0.748 to 0.853) (Figure 2). The accuracy of the STOP-BANG score in diagnosing pre-eclampsia at different cut-off values is displayed in Table 3. However, a score of 3 or more is required to be categorised into a high-risk group, which is clinically relevant. A cut-off of 3 or more had a sensitivity of 62.5% and a specificity of 82.11% for diagnosing OSA.

A STOP-BANG score of 3 or more had an OR of 8.4 (CI 2.88–24.6) for pre-eclampsia and a relative risk ratio was calculated to be 6.8 (CI 2.24–22.8). The questionnaire showed a high negative predictive value of 96.8% if a score of 3 or more was achieved.

Multiple logistic regression was done to evaluate factors that may increase or reduce the Odds ratio of the STOP-BANG score to predict pre-eclampsia (hypertension only included pre-conception hypertension). The following independent variables were investigated in a univariate analysis: gestation age (p = 0.787), gravidity (p = 0.303), patient age (p = 0.02), race (p = 0.416), current smoking (p = 0.502), and HIV positivity (p = 0.635). Of these only age was significant ($p < 0.2$) in a univariate analysis to be included in a multivariate model. In the multivariate model age was not significant and did not change the performance with only the STOP-BANG score of ≥ 2 (OR 4.55, CI 1.525–13.6, p = 0.007).

Discussion

The main results showed that 80.3% of pregnant females had a low risk for OSA, 15.4% had an intermediate risk and 3% had a high risk for OSA. If a score of 3 or more was scored the individual had an 8.4 higher odds of having pre-eclampsia as well and a relative risk for pre-eclampsia 6.8 times higher than if she had no OSA. This corresponds to other studies, which showed a 6.1 higher odds of having pre-eclampsia with a positive score on the STOP-BANG.[14] The high negative predictive value of 96.8% of the STOP-BANG score means that patients scoring < 3 can be considered to be at low risk for OSA and do not have to undergo any further formal sleep studies.

OSA in pregnancy in the USA has a prevalence of 11–20%; this corresponds to our at-risk group of 18.4%.[15] The highest prevalence of OSA in the US group was in obese patients.[15] In our study group 41.5% of participants scored positive due to their high BMI. The median patient age in this study was 28 weeks; thus results in a term population may look different. The incidence of pre-eclampsia has increased by one-third in the last decade.[16] This could correspond to the increase in obesity, which is an independent risk factor for OSA and pre-eclampsia.[15,17] The median BMI for a pregnant South African female is 32, which places her in the obese group and increases her risk for OSA. The prevalence of pre-eclampsia in this sample was 6.8%.

Because hypertension is part of the STOP-BANG criteria and is a major finding in pre-eclampsia, if patients without pre-pregnancy hypertension are considered as hypertensive on the STOP-BANG score it may lead to incorporation bias, which may lead to over-diagnosis of OSA. This may be one of the limitations of using the STOP-BANG score during pregnancy.

Chung *et al.*[18] showed how specific combinations of components of the STOP-BANG improved the specificity of the questionnaire. Patients with a STOP score of ≥ 2, male gender and a BMI greater than 35 kg/m^2 were more predictive of OSA than age greater or equal to 50 and neck circumference > 40 cm.[18] Another combination that was looked at was a STOP-BANG score > 2 combined with serum bicarbonate of at least 28 mmol/l, which indicated a higher risk of moderate to severe OSA.[8,18] BMI greater than 35 kg/m^2, falling asleep while talking to someone and a history of hypertension are found to be significant independent predictors of OSA. Combining the above components to devise a screening tool specific for the pregnant population to diagnose OSA needs further investigation. Two risk factors for pre-eclampsia (chronic hypertension and increased BMI) are two questions on the STOP-BANG questionnaire, and may influence the prediction of pre-eclampsia.

In the pregnant population we propose a score that looks at the following components: snoring, tiredness, witnessed obstruction, hypertension, BMI > 35 kg/m^2 or a MUAC > 33 cm and bicarbonate > 28 mmol/l. These values need to be validated against formal sleep studies in the pregnant population. In the majority of public patients in South Africa an overnight polysomnogram is practically impossible to perform due to limited resources and patient willingness. The clinician should be alerted to the high possibility of OSA and its complications with a positive score on the above components. Patients with OSA are more sensitive to the sedative effects of central acting agents, e.g. opioids and benzodiazepines, which increases the risk of postoperative upper airway obstruction.[19] Opioids induce or worsen obstructive breathing in all patients.[20] Non-sedating pharmacology and regional techniques should be implemented as far as possible.[20] Whitehead *et al.*[21] reported a case where early pre-eclampsia associated with severe sleep-disordered breathing was treated with CPAP. The clinical and biochemical markers of pre-eclampsia improved and the pregnancy could continue for an extra 30 days.

Conclusion

In the local South African setting a convenience cohort found 18.4% of pregnant females (median gestation of 28 weeks) to be at risk of suffering from OSA as assessed by a modified STOP-BANG questionnaire. Our reported incidences correspond to international studies. The previously reported association between OSA and pre-eclampsia was confirmed in our study. Future studies need to focus on early treatment of OSA when associated with pre-eclampsia, so that the clinical and biochemical picture of pre-eclampsia may be potentially reversed and the intra-uterine gestation prolonged.

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