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Screening of Obstructive Sleep Apnea during Pregnancy: Differences in Predictive Values of Questionnaires across Trimesters

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Study Objectives: Evaluation of Berlin and Stop-Bang questionnaires in detecting obstructive sleep apnea (OSA) across trimesters of pregnancy.

Methods: Pregnant women from a high-risk pregnancy clinic were recruited to complete sleep evaluations including Berlin and Stop-Bang questionnaires. Overnight testing with Watch-PAT200 for diagnosis of OSA (cutoff point of apnea-hypopnea index ≥ 5 events/h) was performed.

Results: Seventy-two singleton pregnant women participated in the study. Enrollment consisted of 23, 24, and 25 women during first, second, and third trimesters, respectively. Of 72 pregnancies, 23 patients (31.9%) had OSA. Prevalence of OSA classified by trimesters from first to third was 30.4%, 33.33%, and 32.0%, respectively. Overall predictive values of Berlin and Stop-Bang questionnaires were fair (ROC area under curve, AUC 0.72 for Berlin, p = 0.003; 0.75 for Stop-Bang, p = 0.001). When categorized according to trimesters, predictive values substantially improved in second (AUC: 0.84 for Berlin; 0.78 for Stop-Bang) and third trimesters (AUC: 0.81 for Berlin; 0.75 for Stop-Bang), whereas performances of both questionnaires during first trimester were poorer (AUC: 0.49 for Berlin; 0.71 for Stop-Bang). Multivariate analyses show that pre-pregnancy body mass index (BMI) in first trimester, snore often in second trimester, and weight gain and pregnancy BMI in third trimester were significantly associated with OSA.

Conclusions: In high-risk pregnancy, Berlin and Stop-Bang questionnaires were of limited usefulness in the first trimester. However their predictive values are acceptable as pregnancy progresses, particularly in second trimester. OSA in pregnancy seems to be a dynamic process with different predictors association during each trimester.

Keywords: obstructive sleep apnea, pregnancy, screening questionnaire, Berlin questionnaire, Stop-Bang questionnaire

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Sleep disordered breathing (SDB) occurring during pregnancy is associated with adverse maternal and fetal outcomes as shown by several studies. These complications include preeclampsia, gestational diabetes, preterm birth, low Apgar score, and fetal growth retardation with small-for-age infants at delivery.[1–7]

The prevalence of SDB in pregnancy remain uncertain, mainly due to different evaluation methods in various research studies, lack of objective testing for definitive diagnosis in studies using only questionnaire screening, and small group sample size.[6–12] However, the prevalence of snoring increased during pregnancy as found by Loube et al.[3] In the United States, 14% of healthy pregnancy are reported to be associated with snoring.[10] The prevalence of snoring in Thai pregnant women was 35.29%.[12] The increased reports of snoring should suggest presence of SDB during pregnancy.

Physiological and hormonal changes during pregnancy alter sleep architecture and predispose to development and worsening of OSA.[9,13] A recent large study in the US demonstrated that OSA in pregnant women is associated with increased in-hospital mortality, pulmonary embolism, and cardiomyopathy.[14] Thus screening strategy to identify pregnant women at risk of developing or exacerbating of OSA should be studied for validity and feasibility. Early treatment of OSA in pregnant

BRIEF SUMMARY

Current Knowledge/Study Rationale: During pregnancy physiological changes occur continuously until delivery. Prevalence of sleep disordered breathing increased from first trimester to third trimester. Symptoms of sleep disordered breathing changes as pregnancy progressed. Therefore, performances of OSA screening questionnaires might be different in each trimester.

Study Impact: Our study suggests that screening questionnaires in high-risk pregnancy, particularly the Berlin questionnaire, are poorly predictive of OSA during the first trimester. The most appropriate time to use Berlin and Stop-Bang questionnaires is during the second and third trimesters. Significant predictors varied according to each trimester. Serial monitoring and screening for OSA throughout the course of pregnancy may be needed.

women should be implemented given the potential benefit on pregnancy outcome.[15,16]

At present, there is no specific guideline for screening of OSA in pregnant women. The Berlin and Stop-Bang questionnaires were developed to indicate high probability of OSA in non-pregnant population.[17–20] In non-pregnant populations, the Berlin questionnaire has good sensitivity (range 68% to 86%), with a variable specificity range from 46% to 95% for OSA screening.[17,19] The results of a recent study using the Berlin questionnaire during pregnancy show limited results,[21] but pregnant women were not classified according to gestational age.

During pregnancy there are hormonal, physical, and physiological changes that occur continuously until delivery. Pregnancy is arbitrarily divided into 3 periods, or trimesters, each lasting 12–14 weeks. This subdivision is useful in describing fetal development and maternal physiological changes.[22]

In this study we evaluate the efficacy of the Berlin and Stop-Bang questionnaires in screening for OSA in high risk pregnancy compared to results obtained with Watch-PAT device used to objectively diagnose OSA. The validation of the usefulness of the questionnaires was performed for each trimester due to the dynamic changes of pregnancy and OSA with time.

METHODS

Subjects

In this prospective observational study, women with singleton pregnancies were recruited from high risk antenatal clinic at Ramathibodi hospital, Mahidol University from July 2011 through December 2013. High risk pregnancies were those with chronic hypertension, preeclampsia, gestational diabetes, pre-pregnancy obesity (Asian cutoff point at body mass index (BMI) $\geq$ 27.5 kg/m^2),[23–25] or history of previous pregnancy complication. Women were eligible if they were $\geq$ 18 years old. The exclusion criteria were severe medical conditions such as immunocompromised host, active pulmonary tuberculosis, chronic structural pulmonary disease, pulmonary hypertension, and hyperthyroidism. This study was approved by the ethics committee of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. All subjects signed informed consent form in order to participate in the study.

All subjects attended their routine antenatal visits and received regular standard care according to the obstetrician's clinical decision. Demographic data including body weight, BMI, neck circumference, blood pressure, and fasting blood glucose were collected. Screening evaluations for OSA included Thai versions of Berlin questionnaire, Stop-Bang questionnaire, and Epworth Sleepiness Scales (ESS). Validations of Thai version of Berlin questionnaire and ESS have been published and have demonstrated good reliability.[26,27]

Overnight home-based, wrist-worn portable monitoring with Watch-PAT 200 device (Itamar, Cesarea, Israel) was then scheduled within a week of recruitment, and data retrieval occurred on following day.[28–30]

The Berlin questionnaire consists of 3 categories designed to elicit information regarding snoring (category 1), daytime somnolence (category 2), and presence of obesity and/or hypertension (category 3). OSA is considered if significant symptoms exist in 2 of 3 categories. The Stop-Bang questionnaire shows a high probability of OSA if the score is $\geq$ 3.[17–19]

The Watch-PAT 200 (Itamar, Cesarea, Israel)[29,30] is an unattended portable monitoring for diagnosis of OSA, which has been validated in pregnancy and shown good reliability.[30] It is an overnight simple wrist-worn, home-based device, approved for ambulatory diagnosis of SDB using peripheral arterial tonometry (PAT), finger plethysmography, and standard pulse oximetry probe. The Watch-PAT 200 records the PAT signal, heart rate, oxyhemoglobin saturation (SpO_2), and actigraphy. Respiratory events are identified by the digital vasoconstriction mediated by α-adrenergic receptors that are exquisitely sensitive to surges in sympathetic activity. Vasoconstriction results in attenuated PAT signal along with SpO_2 and heart rate to estimate the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI). Watch-PAT was scored automatically by the manufacturer's proprietary software. OSA was diagnosed if AHI was $\geq$ 5 events/h.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Categorical data are shown as percentage. Numerical data are shown as mean and standard deviation (SD) if they demonstrated normal distribution; otherwise median and interquartile range (IQR) are shown for non-normally distributed data. Comparison of demographic data was analyzed with χ^2 test for categorical data, and independent *t*-test and nonparametric Mann-Whitney test for numerical data. Validity of questionnaires to detect OSA was assessed using the area under the curve (AUC) derived from the receiver operating characteristics (ROC) compared to diagnosis of OSA from Watch-PAT 200 with cutoff point of AHI $\geq$ 5 events/h. Univariate and multivariate logistic analyses were performed to identify associated predictors of OSA in relation with each trimester of pregnancy. A p value < 0.05 was considered as statistically significant.

RESULTS

Seventy-two pregnant women attending the high-risk antenatal clinic participated in this study. Twenty-three pregnant women were enrolled during the first trimester visit, while 24 and 25 women were recruited during the second and third trimesters, respectively. Overall the prevalence of OSA in high-risk pregnancy from this study was 31.9% (23 of 72 women). The mean age of the pregnant women group was 33.1 ± 5.2 years with a mean gestational age (GA) of 22.8 ± 9.2 weeks. Fifty-one percent of pregnant women were nulliparous, and 47% were considered as obese prior to pregnancy based on their pre-pregnancy BMI. Hypertension was found in 13 women (18.1%), with chronic hypertension in 2 subjects, and preeclampsia in 11 subjects. Gestational diabetes was present in 35 women (48.6%) women.

Pregnant women in the OSA group were more obese prior to pregnancy and their BMI during pregnancy were also significantly higher than the non-OSA group. Hypertensive disorders and gestational diabetes were more prevalent among OSA subjects. Demographic data are shown in **Table 1**.

Table 1—Demographic data of pregnant women recruited in the study.

Mean ± SD	Total (n = 72)	OSA (n = 23)	Non-OSA (n = 49)	p value
Age, years	33.1 ± 5.2	34.8 ± 5.1	32.7 ± 5.0	0.16
Gestational age, weeks	22.8 ± 9.2	22.6 ± 10.2	20.1 ± 9.5	0.54
Pre-pregnancy weight, kg	62.6 ± 18.3	76.0 ± 22.1	56.4 ± 12.0	< 0.001
Pre-pregnancy BMI, kg/m^2	24.2 ± 5.3	30.3 ± 8.5	22.8 ± 4.6	< 0.001
Obesity (pre-pregnancy BMI ≥ 27.5 kg/m^2), n (%)	34 (47.2%)	20 (87.0%)	14 (28.6%)	< 0.001
Weight during pregnancy, kg	68.0 ± 17.2	81.9 ± 19.0	61.5 ± 11.8	< 0.001
BMI during pregnancy, kg/m^2	26.9 ± 5.3	32.6 ± 7.1	25.1 ± 4.8	< 0.001
Weight gain during pregnancy, median (IQR)	5.0 (7.1)	5.3 (6.4)	4.6 (4.2)	1.0
Neck circumference (cm)	33.6 ± 2.9	35.7 ± 3.5	32.9 ± 2.5	0.002
ESS, median (IQR)	9.0 (6.0)	9.0 (5.0)	9.0 (6.5)	0.94
ESS ≥ 10, n (%)	29 (40%)	9 (39.1%)	20 (40.4%)	0.9
FBS, mg/dL	94.9 ± 26.8	122.4 ± 67.8	92.9 ± 22.9	0.03
Systolic blood pressure, mm Hg	119.7 ± 12.3	121.4 ± 13.3	117.6 ± 12.3	0.29
Diastolic blood pressure, mm Hg	76.4 ± 8.7	77.3 ± 10.0	75.2 ± 8.1	0.23
AHI, events/h, median (IQR)	2.4 (8.0)	11.7 (10.8)	0.6 (2.3)	
RDI, events/h, median (IQR)	6.9 (9.8)	18.9 (9.4)	4.9 (3.1)	
ODI, events/h, median (IQR)	0.8 (3.4)	5.3 (2.8)	0.2 (0.6)	
Hypertension, n (%)	13 (18.1%)	8 (34.5%)	5 (10.2%)	0.01
Diabetes, n (%)	35 (48.6%)	17 (73.9%)	18 (36.7%)	0.003

Data are shown as mean ± standard deviation (SD) in case of normal distribution and median and interquartile range (IQR) for the non-normal distribution data.

Since there is no stratification of BMI during pregnancy, obesity is defined based on the pre-pregnancy BMI as recommended by the Institute of Medicine.[24,25] In this study, the cutoff point of pre-pregnancy BMI ≥ 27.5 kg/m^2 rather than 30 kg/m^2 was selected for calculation when considering questionnaire responses.[23] The Berlin questionnaire was positive in 26.4% of the total pregnant women group, with higher positive rates in the OSA group than the non-OSA group (56.5% versus 12.2%, p < 0.001). Throughout all trimesters, the sensitivity and specificity of the Berlin questionnaire were 56.5% and 87.8%, respectively. The positive predictive value (PPV) was 68.4%, whereas the negative predictive value (NPV) was 81.1% with AUC of 0.72, p = 0.003, 95% confidence intervals (CI) 0.59–0.86.

Across all trimesters, the Stop-Bang questionnaire was positive in 19 (26.4%) pregnant women. Rates of positive Stop-Bang questionnaire were higher in the OSA group than the non-OSA group (60.9% versus 10.2%, p < 0.001). The sensitivity and specificity for the Stop-Bang questionnaire during pregnancy were 60.9% and 89.9%, with a PPV of 73.3, a NPV of 89.8%, and an AUC of 0.75, p = 0.001, 95% CI 0.62–0.89.

With the pre-pregnancy obesity stratification of BMI ≥ 27.5 kg/m^2, the positive identification obtained with the Berlin and Stop-Bang questionnaires (AUC 0.72 for Berlin; AUC 0.75 for Stop-Bang) were better than when using a BMI ≥ 30 kg/m^2 (AUC 0.71 for Berlin; AUC 0.71 for Stop-Bang).

Trimester 1 (1–12 weeks)

Twenty-three pregnant women were enrolled during their first trimester with a mean gestational age 10.3 ± 1.6 weeks and mean age 33.5 ± 6.0 years. Obstructive sleep apnea was diagnosed in 7 (30.4%) of them. Compared to the non-OSA groups, those with OSA had higher AHI (median [IQR] 7.6 [10.0] versus 0.3 [1.3] events/h], RDI (median [IQR] 16.6 [7.7] versus 5.5 [5.2] events/h), and oxygen desaturation index (ODI; median [IQR] 4.2 [3.2] versus 0.15 [0.6] events/h). Pregnant women with OSA had higher BMI both during pregnancy (28.7 ± 4.1 versus 24.1 ± 6.6 kg/m^2, p = 0.008) and prior to pregnancy (27.9 ± 4.7 versus 21.7 ± 3.6, p = 0.005). But there was no difference in maternal age (36.2 ± 4.6 versus 31.9 ± 6.5 years, p = 0.3), gestational age (10.6 ± 1.3 versus 10.1 ± 1.8 weeks, p = 0.2), fasting plasma glucose (93.2 ± 7.7 versus 92.1 ± 16.0 mg/dL, p = 0.5), and systolic (120.4 ± 8.1 versus 119.4 ± 21.3 mm Hg, p = 0.2), and diastolic blood pressure (76.2 ± 4.1 versus 77.5 ± 10.3 mm Hg, p = 0.5).

The ability of the Berlin questionnaire to recognize OSA during the 1st trimester was poor. The results obtained with the Berlin and Stop-Bang questionnaires are shown in **Table 2**.

The symptoms, components of both the Berlin and Stop-Bang questionnaires, were clinically assessed in our group and results are shown in **Tables 3** and **4**. There was no significant difference in terms of symptoms of OSA such as snoring, daytime sleepiness, witnessed apnea, tiredness, and hypertension between the OSA and non-OSA groups during first trimester. The Epworth Sleepiness Scale (ESS) was similar between groups (median [IQR] 9.0 [4.8] versus 9.0 [3.3], p = 0.9).

Trimester 2 (13–27 weeks)

Twenty-four pregnant women in their second trimester (GA 20.3 ± 4.4 weeks) participated in the study. Their mean age was 32.8 ± 5.2 years. Eight of 24 pregnant women (33.3%) had OSA. Compared to their non-OSA counterparts, the pregnant women with OSA had higher AHI (median [IQR] 16.6 [8.7] versus 0.75 [2.5] events/h), RDI (median [IQR] 19.1 [8.6] versus 5.0 [2.0]) and ODI (median [IQR] 8.8 [6.6] versus 0.2 [0.7]

Table 2—Result of sensitivity, specificity, positive and negative predictive values of Berlin and Stop-Bang questionnaires for OSA diagnosis, classified according to trimesters.

Berlin Questionnaire	**First Trimester**	**Second Trimester**	**Third Trimester**
Sensitivity (%)	28.6	75.0	62.5
Specificity (%)	68.8	93.8	100.0
PPV (%)	28.6	85.7	100.0
NPV (%)	68.8	88.2	85.0
AUC	0.49	0.84	0.81
p value (95% CI)	0.92 (0.23–0.75)	0.007 (0.67–1.00)	0.013 (0.56–1.00)
Stop-Bang Questionnaire	**First Trimester**	**Second Trimester**	**Third Trimester**
Sensitivity (%)	57.1	62.5	62.5
Specificity (%)	87.5	93.8	88.2
PPV (%)	66.7	83.3	71.4
NPV (%)	82.7	83.3	83.3
AUC	0.71	0.78	0.75
p value (95% CI)	0.23 (0.47–0.92)	0.03 (0.56–1.00)	0.04 (0.53–0.97)

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC area under curve.

Table 3—Result of Berlin questionnaire and its components comparisons between OSA and non-OSA pregnant women.

	First Trimester (n = 23)			**Second Trimester (n = 24)**			**Third Trimester (n = 25)**		
Berlin Questionnaire	**OSA (n = 7)**	**Non-OSA (n = 16)**	**p value**	**OSA (n = 8)**	**Non-OSA (n = 16)**	**p value**	**OSA (n = 8)**	**Non-OSA (n = 17)**	**p value**
Positive questionnaires	28.6%	31.3%	0.89	62.5%	6.3%	0.003*	62.5%	5.9%	0.002*
Snore ever	83.3%	50.0%	0.20	87.5%	43.8%	0.04*	87.5%	41.2%	0.03*
Snore loudly	16.7%	0.0%	0.23	12.5%	0.0%	0.15	37.5%	0.0%	0.007*
Snore often	28.6%	25.0%	0.87	87.5%	6.3%	< 0.001*	62.5%	23.5%	0.058
Snoring bothers others	16.7%	0.0%	0.23	62.5%	12.5%	0.01*	66.7%	18.2%	0.046
Witnessed apnea	0.0%	0.0%	1.00	12.5%	0.0%	0.15	12.5%	0.0%	0.14
Feel tired after sleep	28.6%	18.8%	0.60	37.5%	25.0%	0.53	50.0%	23.5%	0.19
Fell tired while awake	28.6%	25.0%	0.86	62.5%	25.0%	0.07	50.0%	17.6%	0.09
Ever nod off while driving	42.9%	12.5%	0.10	62.5%	6.3%	0.003*	25.0%	17.6%	0.67
Hypertension	28.5%	12.5%	0.35	50%	6.3%	0.013*	25.0%	11.8%	0.40

* Statistically significant with $p < 0.05$.

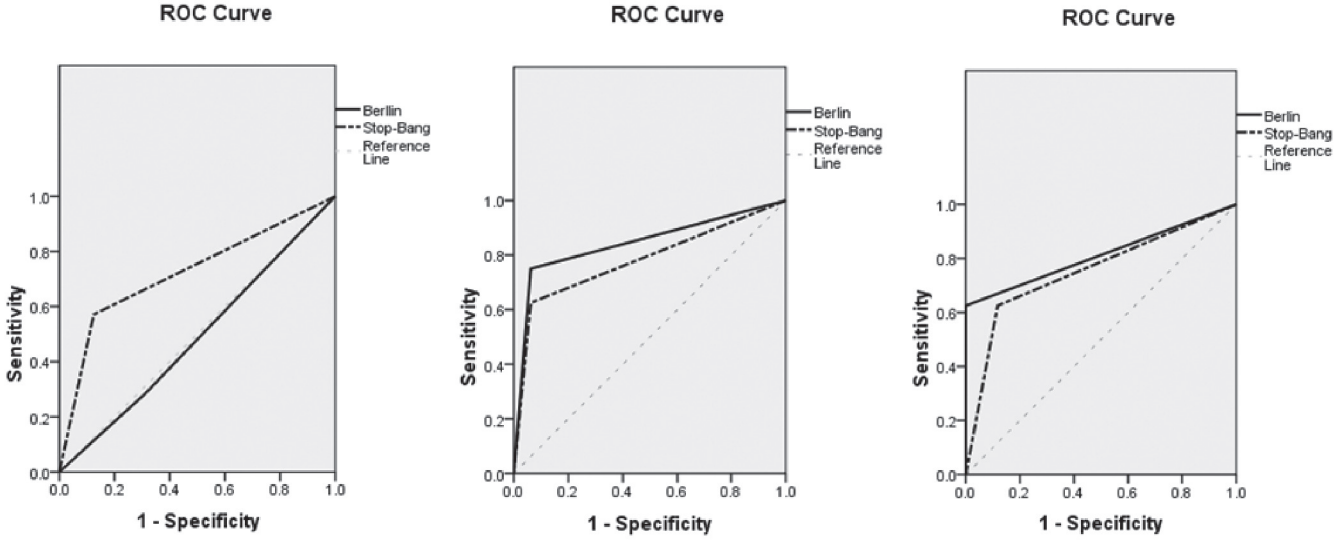
Table 4—Result of Stop-Bang questionnaire and its components comparisons between OSA and non-OSA pregnant women.

	First Trimester (n = 23)			**Second Trimester (n = 24)**			**Third Trimester (n = 25)**		
Stop-Bang Questionnaire	**OSA (n = 7)**	**Non-OSA (n = 16)**	**p value**	**OSA (n = 8)**	**Non-OSA (n = 16)**	**p value**	**OSA (n = 8)**	**Non-OSA (n = 17)**	**p value**
Positive questionnaires	57.1%	12.5%	0.03*	50.0%	6.3%	0.01*	62.5 %	11.8%	0.008*
Snore loudly	71.4%	31.3%	0.07	25.0%	18.8%	0.004*	87.5%	29.4%	0.007*
Feel tired, fatigue/sleepy during daytime	85.7%	68.8%	0.39	25.0%	18.8%	0.72	75.0%	88.2%	0.40
Hypertension	33.3%	25.0%	0.73	50.0%	6.3%	0.01*	37.5%	11.8%	0.13
Witnessed apnea	0.0%	6.3%	0.50	25.0%	0.0%	0.04*	12.5%	0.0%	0.14
Neck circumference ≥ 16 inches	14.3%	0.0%	0.10	25.0%	0.0%	0.04*	12.5%	0.0%	0.14

* Statistically significant with $p < 0.05$.

events/h), respectively. There was no significant difference in regards to maternal age (34.3 ± 5.2 versus 32.1 ± 5.2 years, p = 0.9), gestational age (21.7 ± 4.3 versus19.4 ± 4.4 weeks, p = 0.2), systolic (125.6 ± 17.9 versus 116.6 ± 6.1 mm Hg, p = 0.2) and diastolic (77.6 ± 12.2 versus 74.3 ± 6.2 mm Hg, p = 0.5) blood pressure, and fasting plasma glucose (87.7 ± 15.2 versus 97.6 ± 35.2 mg/dL, p = 0.5). The pregnant women with OSA had higher BMI prior to pregnancy (29.5 ± 6.8 versus 23.0 ± 5.5 kg/m^2, p = 0.007) and during pregnancy (BMI, 31.4 ± 5.4 versus 24.9 ± 5.5 kg/m^2, p = 0.006), and their neck circumference during pregnancy was significantly larger (36.1 ± 4.0 versus 32.4 ± 2.3 cm, p = 0.009). However, the weight gain during

Figure 1—Sensitivity and specificity of Berlin and Stop-Bang questionnaires to detect OSA (cutoff point of AHI ≥ 5 events/h) during pregnancy classified according to trimesters.



pregnancy was similar (median [IQR]) 3.5 [7.8] versus 3.9 [4.6] kg, p = 0.6). The ESS was similar in the OSA and non-OSA groups (median [IQR] 8.0 [7.5] versus 9.5 [9.3], p = 0.9).

During the second trimester, the power of both questionnaires to recognize OSA improved compared to the first trimester. The most substantial improvement occurred with the Berlin questionnaire as shown in **Table 2**. Analyses of its components showed that the snoring scores particularly "snore ever," "snore often," "snoring bothers others" were present more frequently in women with OSA. Positive response to "ever nod off while driving" was significantly higher in the OSA group, despite similar reports of "tiredness after sleep" and "tiredness while awake" in both groups (see **Table 3**).

Analysis of the responses to the Stop-Bang questionnaire revealed that pregnant women with OSA had significant higher reports of "snore loudly," hypertension, "witnessed apnea," and neck circumference larger than 16 inches as shown in **Table 4**.

Trimester 3 (28–40 weeks)

The pregnant women enrolled during the third trimester (GA 32.2 ± 3.1 weeks) had a mean age of 33.2 ± 5.0 years. OSA was present in 8 (32%) of them. Compared to the non-OSA group, the pregnant women had higher AHI (median [IQR] 10.4 [17.7] versus 0.4 [2.7] events/h), RDI (median [IQR] 16.6 [17.2] versus 3.4 [4.0]), and ODI (median [IQR] 4.4 [13.5] versus 0.2 [1.2]); they had higher BMI during pregnancy (30.7 ± 2.4 versus 26.3 ± 3.9 kg/m^2, p = 0.003) and prior to pregnancy (28.4 ± 8.4 versus 22.9 ± 4.5 kg/m^2, p = 0.04). Weight gain during pregnancy was significantly higher in the OSA group (13.3 ± 3.5 versus 8.4 ± 3.5 kg, p = 0.03). There was no difference in age (33.4 ± 6.8 versus 33.1 ± 4.3, p = 0.9) and gestational age (33.7 ± 3.1 versus 31.5 ± 3.0, p = 0.09) between groups, and the ESS was similar in the 2 groups (median [IQR] 8.0 [6.3] versus 10.0 [7.0], p = 0.4].

The predictive values of the Berlin and Stop-Bang questionnaires discerning OSA during pregnancy in the third trimester were acceptable (see **Table 2**). Clinical evaluation of the symptoms part of the Berlin questionnaire indicated higher reports to "snore ever," "snore loudly," and "snoring bothers others" as shown in **Table 3**. Similar results were obtained when looking at the responses from the Stop-Bang questionnaire, with higher reports of "snore loudly" in pregnant women with OSA as shown in **Table 4**.

Table 5—Univariate analysis for factors associated with OSA classified according to trimesters.

	Odds Ratio	p value	95% CI
Trimester 1			
BMI pre-pregnancy	1.4	0.04	1.01–2.0
Trimester 2			
Snore often	10.5	0.002	5.7–19.3
Snoring bothers others	11.7	0.02	1.48–19.1
Ever nod off while driving	25.0	0.01	2.1–29.8
Snore loudly	21.0	0.01	1.9–27.2
Pre-pregnancy snoring	30.3	0.006	2.6–4.8
Obesity (pre-pregnancy BMI ≥ 27.5 kg/m^2)	13.3	0.01	1.7–34.9
Pre-pregnancy BMI	1.2	0.03	1.02–1.4
BMI during pregnancy	1.2	0.03	1.02–1.4
Neck circumference	1.6	0.04	1.02–2.4
Hypertension	15.0	0.03	1.3–17.4
Trimester 3			
Snore loudly	16.8	0.02	1.6–17.5
BMI during pregnancy	1.43	0.02	1.04–2.0
Weight change	1.35	0.04	1.01–1.8

Factors Associated with OSA

A univariate analysis identifying the factors associated with OSA at each trimester was performed (see **Table 5**). Multivariate logistic regression analyses were further performed looking at each trimester. The significant predictors of OSA varied according to gestational age. In the first trimester, pre-pregnancy

BMI (odds ratio 1.4, 95% CI 1.01–2.0, p = 0.04) was the only significant predictor. In the 2nd trimester, only "snore often" remained significant after adjusting for other factors (odds ratio 10.5, 95% CI 5.7–19.33, p = 0.002). In the 3rd trimester, the significant predictors were weight gain (odds ratio 1.6, 95% CI 1.02–2.5, p = 0.04) and BMI during pregnancy (odds ratio 1.47, 95% CI 1.03–2.10, p = 0.049).

DISCUSSION

This prospective observational study evaluated two screening questionnaires for OSA in high-risk pregnancy. The Berlin and Stop-Bang questionnaires performed differently at each trimester of pregnancy, as shown in **Figure 1**. Both questionnaires had limited predictive values in screening OSA in high-risk pregnancy during the first trimester of pregnancy; the best results were noted during the second trimester.

Despite poorer performance than the Stop-Bang questionnaire during the first trimester, the Berlin questionnaire showed better predictive values during the second and third trimesters of pregnancy.

In the third trimester, the Berlin questionnaire had also decent screening results recognizing OSA (AUC0.81) with a high specificity (100%) but a more limited sensitivity of 62.5%, with a PPV of 100% and a NPV of 85%. The results from the Stop-Bang questionnaire were comparable with an AUC of 0.78. The two questionnaires may be useful as screening tool for OSA in pregnancy during the second and third trimesters.

Previous studies of the value of the two OSA screening questionnaires in pregnancy had shown unimpressive results. Similar to our finding, unreliable performance from the Berlin questionnaire was reported in a study by Facco et al., when the questionnaire was tested in early pregnancy (GA 6–20 weeks).[21] As in our study, with usage of the WatchPAT100, a low sensitivity of 39%, low specificity of 48%, and AUC 0.54 (95% CI-0.67, p = 0.6) were reported.

In our investigation the typical symptoms of OSA—snoring, tiredness, daytime sleepiness, and witnessed apnea—could not discriminate women with OSA during early pregnancy between those with and without risk of abnormal pregnancy. Only the pre-pregnancy BMI was strongly associated with OSA during this first trimester. This may be explained by the under-recognition of OSA in women as previously reported by our group, as the hallmark symptoms of OSA (snoring and witnessed apnea) were often absent in the premenopausal women.[31] The most frequent complaints were related to daytime symptoms more particularly excessive daytime sleepiness, fatigue, and non-refreshing sleep, and these daytime symptoms may be overlapping with the symptoms of pregnancy. Sleepiness is prevalent in pregnancy (37.5% at 6 to 7 weeks of gestation), which is attributable to the somnogenic effect of progesterone and fragmented sleep.[32,33] From our study, screening for OSA in first trimester should be done in pregnant women who were obese prior to pregnancy regardless of classic OSA symptoms.

During the second trimester the symptom of snoring is more prominent in pregnant women with OSA, particularly those with the "snore often" symptom; and weight gain during pregnancy and BMI during pregnancy were significant predictors of OSA during the third trimester. New onset OSA and snoring have been reported to develop as pregnancy progresses.[7] Therefore, monitoring excessive weight gain during pregnancy is crucial.

Our findings are supported by several prior studies showing increases in prevalence of snoring in pregnant women as pregnancy progresses.[3,9,34] Worsening symptoms associated with SDB in pregnancy had been reported: sleep-disordered-breathing (SDB) symptoms and ESS increase significantly from the first trimester to the month of delivery.[35] Such increase was detected by 28–29 weeks of gestation compared to the first trimester.

A recent longitudinal study also showed that prevalence of OSA increased from 10.5% in first trimester to 26.7% in the third trimester.[36] Therefore, the serial monitoring and screening for OSA during each trimester of pregnancy may be important.

Olivarez et al. looked at the response to the Berlin questionnaire in the third trimester of pregnancy compared to polysomnography and reported a poor sensitivity and specificity of 35% and 63.8%, respectively[37]; the authors explained their limited results by usage of BMI in the algorithm as categorical variable, despite the suggestion from the data of more linear relationship between BMI and OSA.

Antony also showed that the Berlin questionnaire and ESS were poorly predictive of OSA in pregnancy, but the study was performed with usage of a non-validated type 3 recorder.[38] Kho et al., using Berlin questionnaire and BMI $\geq$ 30 kg/m^2 cutoff point stratification in the third trimester of pregnancy showed no correlation between positive questionnaire and preeclampsia and small for gestational age.[11] In our study, all subjects were Thai nationals, and we used the cutoff point at pre-pregnancy BMI $\geq$ 27.5kg/m^2, and we had better findings. Differences in selection of population, ethnicity, BMI cutoff point for questionnaires, and methods of gold standard tests may explain the different results in finding with usage of the two OSA screening questionnaires studied. Results including ours may have to be limited to the ethnic group investigated. Despite the limitation of validity of the two OSA screening questionnaires during pregnancy, positive screen on questionnaires showed association with pregnancy complications.[8] A cross-sectional study by Goldfarb showed association between pregnant women who had positive screening on the Stop-Bang and pre-eclampsia (odd ratio, OR 6.1)[39]; and a large prospective study of 1,509 gravidae showed that subjects with positive Berlin questionnaire showed a positive association with hypertensive disorders (adjusted relative risk 1.9).[40]

Our study had some limitations. First, our study population was high-risk pregnant women, who may not be representative of all other groups of pregnant women. But given limitations in health resources in clinical practice and a high prevalence of SDB in high-risk pregnant women as in our study, these women would be the first priority in screening for OSA. Second, we did not study the same pregnant women longitudinally throughout pregnancy; this might have demonstrated better results in terms of changes overtime.

CONCLUSION

The Berlin and Stop-Bang questionnaires have different predictive values depending of the trimester of pregnancy

when it is administered. Their predictive values are acceptable as pregnancy progresses particularly in the second trimester. Gestational age should be considered when using OSA screening questionnaires in pregnancy.

Current screening questionnaires for OSA were originally developed for non-pregnant population that use only single point of testing. Whereas in pregnancy, there are continuous changes of physiology of pregnancy itself and of OSA, therefore serial monitoring and screening for OSA during each trimester may be needed.

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