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Obstructive Sleep Apnea Is Associated With Late-Onset Preeclampsia in Overweight Pregnant Women in Korea

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is closely related to maternal obesity in pregnant women, and the association increases with later pregnancy. Obesity and OSA are risk factors of pregnancy-related complications, including gestational hypertension, gestational diabetes mellitus (GDM), and fetal morbidities. We aimed to determine the prevalence of OSA and to assess the impact of OSA on pregnancy-related disorders in overweight pregnant women.
Methods: Eligible participants who were overweight [body mass index (BMI) ≥ 23 kg/m^2] in gestational age 30 weeks or more, assessed OSA using a portable polysomnography at home. Clinical data were collected from pregnant women and their babies.
Results: The average age of 51 participants was 34.5 years (27–44 years). The number of primipara was 25 (49%) and that of multipara was 26 (51%). Eight cases of GDM (15.7%) and five cases of preeclampsia (9.8%) were reported, and six patients (11.8%) experienced preterm delivery. In results of polysomnography, 14 patients (27.5%) were diagnosed as OSA. Apnea-hypopnea index moderately correlated with BMI (r = 0.515, P < 0.001). The BMI (P < 0.005) and preeclampsia rate (P < 0.017) were higher in the OSA group compared to the control group. Odds ratios (ORs) adjusting age, BMI, parity, and abortion history were calculated. The presence of OSA increased OR of preeclampsia (OR, 13.1; 95% confidence interval, 1.1–171.3). The majority of preeclampsia patients (4/5, 80%) underwent preterm delivery.
Conclusion: OSA is an important risk factor for preeclampsia, resulting in preterm delivery. For overweight pregnant women, an OSA evaluation should be mandatory.

Keywords: Obstructive Sleep Apnea; Polysomnography; Pregnancy; Overweight; Preeclampsia

INTRODUCTION

Obstructive sleep apnea (OSA) can cause adverse pregnancy-related outcomes and has been confirmed by several nationwide data studies.[1,2] OSA is associated with hypertensive disorders in pregnancy, gestational diabetes mellitus (GDM), preterm delivery, cesarean

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Ryu G, Oh SY, Kim HY. Data curation: Choi SJ, Hong SD, Oh SY, Kim HY. Formal analysis: Ryu G, Kim YM, Lee KE. Funding acquisition: Kim HY. Methodology: Jung YG, Oh SY, Kim HY. Visualization: Ryu G. Writing - original draft: Ryu G, Oh SY. Writing - review & editing: Kim YM, Choi SJ, Hong SD, Oh SY, Kim HY.

delivery, and small for gestational age neonates during pregnancy.[3] Notably, many studies have been conducted on the relationship between OSA and gestational hypertensive disorders, including preeclampsia.[4] The possible pathophysiologic mechanism of OSA on preeclampsia is that intermittent hypoxia induces endothelial dysfunction and vasoconstriction.[5] This mechanism was verified using a hypoxia-induced preeclampsia mouse model in which a hypoxic environment increased blood pressure and proteinuria.[6]

Obesity is one of the significant risk factors for pregnancy-related adverse outcomes.[7] Also, obesity and hypertension are associated with OSA in the general population.[8,9] Previous studies demonstrated that maternal obesity is strongly related to OSA during pregnancy, particularly in the third trimester.[10] However, another study demonstrated that there was no significant difference in the respiratory disturbance index between normotensive and hypertensive pregnant women with similar body mass index (BMI).[11] A BMI-matched study with pregnant and non-pregnant women also showed that OSA prevalence was not different between the two groups, and the suspected reason for this was most participants were not obese.[12] Collectively, it remains still controversial whether OSA affect the development or aggravation of hypertensive disorders in pregnancy, including preeclampsia.

However, OSA is still lacking in diagnosis and understanding in pregnant women. Previously reported prevalence of OSA in pregnant women varies according to race, body weight, and timing of the polysomnography (PSG) test. Few studies have been conducted on the association of OSA and pregnancy-related outcomes in Asians, particularly in Korea.[13,14] Although obesity in women of childbearing age has been increasing, Koreans still have lower BMI values compared to Western pregnant women.[15,16] For this reason, we assumed that the prevalence of OSA and that of obesity would be relatively low in general pregnant women and planned to evaluate OSA in overweight pregnant women during the third trimester. Weight gain during the third trimester exaggerated compared to that in the first and second trimesters, and OSA might worsen as the gestational weeks progress.[7] Many studies have evaluated the association between OSA and hypertensive disorders in pregnancy, whereas the causality or chronology has not been elucidated. Usually, early-onset preeclampsia, with onset before 34 weeks, has a higher risk of fetal growth restriction, cardiovascular disease, and other maternal morbidities compared to late-onset preeclampsia.[17,18] OSA is aggravated during the late phase of pregnancy due to weight gain, which may cause or worsen late-onset preeclampsia, but no previous study evaluates this relationship.

This prospective cohort study aimed to evaluate the prevalence of OSA in pregnant women who were overweight in the third trimester and to elucidate the effects of OSA on pregnancy-related complications, especially late-onset preeclampsia. We also compared the concentration of serum biomarkers related to preeclampsia and those of OSA between pregnant women with and without OSA. Some part of this study was previously published as an abstract.[19]

METHODS

Study Subjects

This prospective cohort study was conducted in a tertiary referral hospital from June 2017 to December 2018. Pregnant women were enrolled who met the following criteria: 1) older than 19 years, 2) gestation over 30 weeks; 3) overweight (BMI ≥ 23 kg/m^2 according to the Asia-Pacific regional guidelines of the WHO guidelines)[15]; and 4) singleton pregnancy.

Polysomnography

Testing for OSA was performed in all participants using at-home portable PSG with WatchPAT (Itamar Medical, Caesarea, Israel). Test results were assessed by an otolaryngologist within two weeks of study enrollment. Apnea-hypopnea index (AHI), respiratory disturbance index, and oxygen saturation were reviewed as previously reported.[20] OSA was defined as AHI ≥ 5 and normal control was defined as AHI < 5.

Clinical parameters

We prospectively collected data from pregnant women, including age, body weight, height, BMI, parity, history of spontaneous abortion, mode of delivery, and gestational complications (GDM, preeclampsia, or preterm delivery). Preeclampsia was diagnosed when a pregnant woman developed a blood pressure > 140/90 mmHg and proteinuria > 300 mg in a 24-hour urine collection after 20 weeks' gestation.[21] The Berlin questionnaire was administered at study enrollment and consists of three categories related to risk of sleep apnea. Scoring can be classified into high risk or low risk groups according to the patient's symptoms. Clinical information about the infants was collected, such as body weight at birth, Apgar scores at one and five minutes, and perinatal complications.

Blood test

The patient's whole blood was collected at the time of enrollment. Blood samples were centrifuged, and separated serum were stored at −80°C until analysis of enzyme-linked immunosorbent assay (ELISA). We measured serum markers related to preeclampsia,[22] such as serum soluble fms-like tyrosine kinase-1 (sFlt-1; MBS262972-96T, MyBiosource, San Diego, CA, USA), endoglin (DNDG00, R&D Systems, Minneapolis, MN, USA), and placental growth factor (PlGF; LS-F1231, LSBio, Seattle, WA, USA). Biomarkers of OSA were evaluated, including interleukin (IL)-6 (D6050, R&D Systems), myeloid-related protein (MRP)8/14 (439707, Biolegend, San Diego, CA, USA), and tumor necrosis factor (TNF)-α (DTA00D, R&D Systems).[23]

Statistical analysis

Data were presented as median with interquartile range. Continuous variables were analyzed using the Mann-Whitney test and categorical variables were tested by Fisher's exact test, respectively. Logistic regression models were used for calculating odds ratio (ORs) and 95% confidence intervals (CIs) to determine the association between OSA and pregnancy-related complications. Models were adjusted for BMI, maternal age, parity, and history of spontaneous abortion. Stata software v16.0 (StataCorp LP, College Station, TX, USA) was used.

Ethics statement

The Institutional Review Board of Samsung Medical Center approved this study (No. 2017-05-005) and informed consent was obtained from all patients.

RESULTS

Of a total of 137 pregnant women were screened, 51 (37.2%) were enrolled in the study and completed a PSG, while 80 women (58.4%) refused to participate in the study and six (4.4%) were dropped from the study due to various reasons. The mean age of participants was 34.5 years (27–44 years), and the mean gestational age was 32/6 weeks (range of 30/1–37/2 weeks). Of these, the number of primipara was 25 (49%) and that of multipara was 26 (51%). Eight patients were diagnosed as having GDM (15.7%), five had preeclampsia (9.8%), and six

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experienced preterm delivery (11.8%). Five patients were diagnosed with preeclampsia after study enrollment. Among them, three patients already had pregnancy-induced hypertension. Two patients had previously been diagnosed with hypertension before pregnancy, one of whom developed preeclampsia. Two patients had overt diabetes before pregnancy, and diabetes persisted during pregnancy. After PSG, 14 of the pregnant women (27.5%) were diagnosed OSA. The demographics between pregnant women with (OSA group) and without OSA (control group) are presented in **Table 1**. The BMI was higher in the OSA group before pregnancy (P = 0.005) and at enrollment (P = 0.013) compared to the control group. Preeclampsia was more frequently observed in the OSA group compared to the control group (P = 0.017).

Fourteen women with OSA were categorized according to severity of AHI, which were comprised of 12 cases of mild (5 ≤ AHI < 15), one of moderate (15 ≤ AHI < 30), and another of severe OSA (AHI ≥ 30) (**Fig. 1A**). In all subjects, AHI was well correlated with BMI at enrollment (r = 0.515, P < 0.001, **Fig. 1B**), whereas the correlation between AHI and age was not significant (r = 0.177, P = 0.215, **Fig. 1C**). Sleep parameters, including respiratory disturbance index, mean oxygen saturation (SpO2), and SpO2 nadir, were significantly different between the OSA and control groups (**Table 2**). Using the Berlin questionnaire for evaluating high risk of OSA, nine pregnant women (17.6%) were at high risk, and six of them were diagnosed with OSA by portable PSG. The remaining eight OSA patients at low risk according to the Berlin questionnaire had no subjective symptoms such as snoring, witnessed apnea, or fatigue.

Additionally, we analyzed serum markers related to preeclampsia and OSA (**Fig. 2A and B**). The serum sFlt-1/PlGF ratio, the clinically used serological marker for predicting preeclampsia,[22] was significantly elevated in the OSA group compared to the control group (12.0 ± 8.7 vs. 5.3 ± 6.5, P < 0.008). The ratio of sFlt-1/PlGF was higher in the four patients

Table 1. Comparison of demographic characteristics between pregnant women with obstructive sleep apnea and controls

Variables	OSA (n = 14)	No OSA (n = 37)	*P* value
Age, yr	35.5 (34–38)	34 (32–36)	0.131
Gestational age, enrollment, wk	32/4 (31/5–34/3)	32/6 (31/3–34)	0.958
BMI, pre-pregnancy, kg/m^2	26.05 (24.8–28.69)	22.75 (21.8–24.1)	0.005*
BMI, at enrollment, kg/m^2	30.4 (27.6–32.5)	27.8 (26.16–29.3)	0.013*
Weight gain during pregnancy, kg	9.7 (9.3–12)	11.2 (7.7–14.8)	0.259
Obesity, pre-pregnancy	12 (85.7)	16 (43.2)	0.010*
Hypertension, pre-pregnancy	2 (14.3)	0	0.071
Diabetes, pre-pregnancy	1 (7.1)	1 (2.7)	0.478
Primipara	8 (57.1)	17 (46.0)	0.475
Spontaneous abortion	3 (21.4)	3 (8.1)	0.188
Preeclampsia	4 (28.6)	1 (2.7)	0.017*
GDM	4 (28.6)	4 (10.8)	0.192
Caesarean section	10 (71.4)	17 (46.0)	0.127
Preterm delivery	3 (21.4)	3 (8.1)	0.327
Gestational age, delivery, wk	38/5 (37/2–39/5)	39/1 (38/2–39/6)	0.336
Infant weight, kg	3.18 (2.85–33.4)	3.37 (3.0–3.7)	0.095
SGA	1 (7.1)	2 (5.4)	1.000
LGA	4 (28.6)	9 (24.3)	0.734
Apgar score, 1 min	9 (9–9)	9 (9–9)	0.170
Apgar score, 5 min	10 (9–10)	10 (9–10)	0.343

Values are presented as number (%) or median (interquartile range).
BMI = body mass index, GDM = gestational diabetes mellitus, SGA = small for gestational age, LGA = large for gestational age.
*Statistical significance at P < 0.05.

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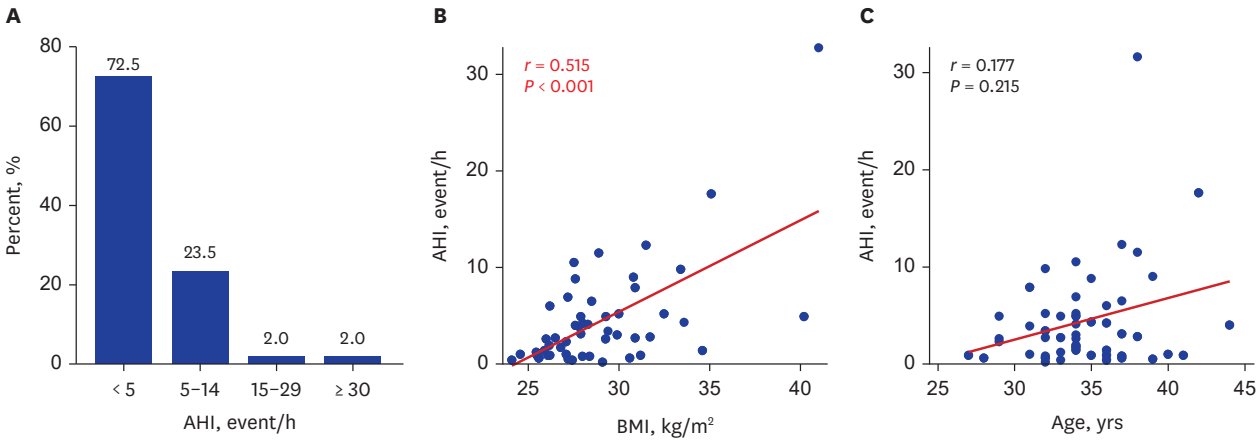

Fig. 1. OSA evaluated by portable polysomnography in pregnant women. (**A**) The percentage of OSA patients according to AHI. (**B**) Correlation analysis between AHI and BMI at enrollment. (**C**) Correlation analysis between AHI and age at enrollment.
AHI = apnea-hypopnea index, BMI = body mass index, OSA = obstructive sleep apnea.

Table 2. Polysomnographic sleep characteristics and Berlin questionnaire results between pregnant women with obstructive sleep apnea and controls

Variables	OSA (n = 14)	No OSA (n = 37)	*P* value
Total sleep time, min	350 (321–399)	383 (308–417)	0.479
AHI (event/hr)	8.9 (6.5–11.5)	1.7 (0.9–3.1)	< 0.001*
RDI (event/hr)	12.3 (9.8–13.6)	6 (3.8–8.1)	< 0.001*
Mean SpO2, %	95 (95–96)	96 (95–96)	0.010*
SpO2 nadir, %	89.5 (88–92)	92 (91–94)	0.001*
Snoring	10 (71.4)	20 (54.1)	0.346
Witnessed apnea	2 (14.3)	0	0.071
Berlin questionnaire high risk	6 (42.9)	3 (8.1)	0.008*

Values are presented as number (%) or median (interquartile range).
OSA = obstructive sleep apnea, AHI = apnea-hypopnea index, RDI = respiratory disturbance index.
*Statistical significance at $P < 0.05$.

with preeclampsia than in those without preeclampsia (16.8 ± 10.8 vs. 5.7 ± 5.8, $P < 0.019$). Other proinflammatory markers, such as IL-6, MRP8/14, and TNF-α, were not different between the two groups (**Fig. 2B**).

Pregnant women with OSA had increased risk of preeclampsia, and the unadjusted OR was 14.4 (95% CI, 1.4–143.7). The OR remained high (OR, 11.1; 95% CI, 1.1–116.4) after adjusting for pre-pregnancy BMI (**Table 3**). We calculated adjusted ORs with adjustment for pre-pregnancy BMI, age, parity, and abortion history. OSA was strongly related to increased OR of preeclampsia (OR, 13.1; 95% CI, 1.1–168.0).

Table 3. Odds ratios and 95% confidence intervals for the association between obstructive sleep apnea and pregnancy-related outcomes

Outcomes	Unadjusted	Adjustment for pre-pregnancy BMI	Additional adjustment*
Preeclampsia	14.4 (1.4–143.7)	11.1 (1.1–116.4)	13.1 (1.1–171.3)
GDM	3.3 (0.7–15.6)	1.8 (0.2–14.1)	4.2 (0.1–15.2)
Preterm delivery	3.1 (0.5–17.6)	2.7 (0.4–16.4)	2.8 (0.3–26.1)

Values are presented as median (interquartile range).
BMI = body mass index, GDM = gestational diabetes mellitus.
*Adjustment for pre-pregnancy BMI, pre-pregnancy hypertension, pre-pregnancy diabetes, age, parity, and spontaneous abortion history.

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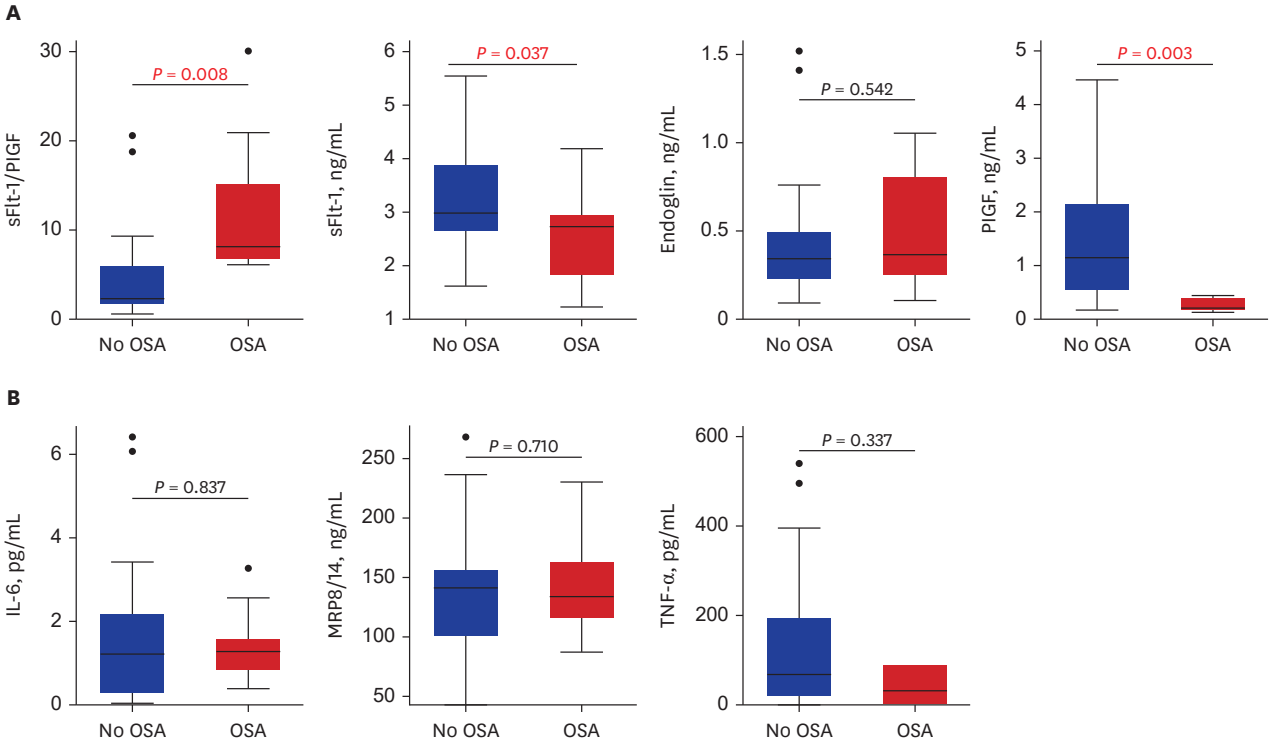

Fig. 2. Comparison of serum markers between OSA patients and controls. (**A**) Preeclampsia-related markers; sFlt-1/PlGF ratio, sFlt-1, Endoglin, and PlGF. (**B**) Proinflammatory markers for OSA; IL-6, MRP8/14, and TNF-α.
sFlt-1= soluble fms-like tyrosine kinase-1, PlGF = placental growth factor, OSA = obstructive sleep apnea, IL = interleukin, MRP = myeloid-related protein, TNF = tumor necrosis factor.

All preeclampsia patients underwent cesarean section, four patients experienced preterm delivery, three had comorbid GDM, and four were diagnosed with OSA. OSA was prevalent in patients with pregnancy-related adverse outcomes, such as preeclampsia, GDM, preterm delivery, and small for gestational age neonates (**Fig. 3**) Taken together, these findings

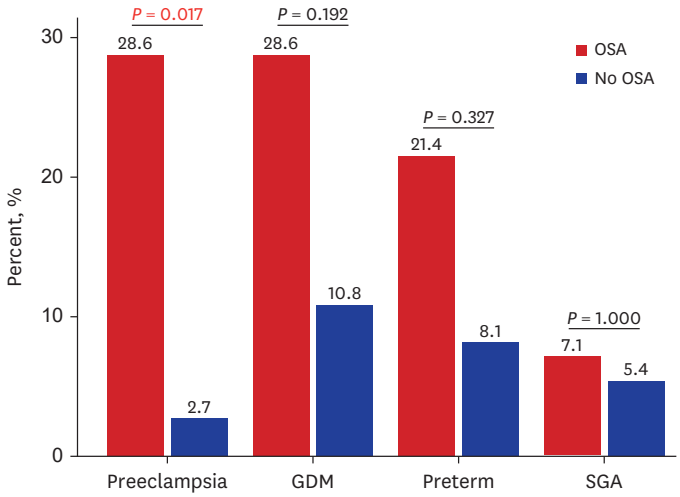

Fig. 3. The prevalence of pregnancy-related complications between OSA patients and controls.
OSA = obstructive sleep apnea, GDM = gestational diabetes mellitus, SGA = small for gestational age.

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indicate that OSA is associated with pregnancy-related complications, and that such complications affect one other.

DISCUSSION

This is the first study to diagnose OSA in pregnant women using portable PSG in Korea. We found that the prevalence of OSA was 27.5% in overweight (BMI ≥ 23) pregnant women over 30 weeks of gestational age. Between pregnant women with and without OSA, BMI was higher and comorbid preeclampsia was prevalent in the OSA group. When adjustment was made for pre-pregnancy BMI, age, parity, and abortion history, OSA was related to increasing risk of preeclampsia. According to previous studies, OSA increased the odds of preeclampsia (OR, 2.5; 95% CI, 2.2–2.9), as shown in a nationwide database in the USA,[2] and maternal sleep-disordered breathing was associated with gestational hypertension or preeclampsia (pooled adjusted OR, 2.34; 95% CI, 1.60–3.09) in a systematic review.[24] In a study conducted with the International Classification of Diseases (ICD)-9 code in Taiwan, the same Asian country, the odds ratio of OSA for preeclampsia was 1.6.[25] The possible reason for the difference from our study (OR, 13.1) is that the PSG was performed at a different time. The previous study defined OSA patients with two or more OSA diagnosis after PSG within one year prior to index delivery. However, since this study was conducted with women over 30 weeks pregnant, factors that may affect the occurrence of OSA, such as weight gain during pregnancy, may have been reflected.

Pamidi et al.[10] reported that pregnant women diagnosed with OSA had increased risk of small for gestational age neonates. Contrarily, an Australian population-based study found that OSA was associated with large for gestational age infants (OR, 1.27; 95% CI, 1.04–1.55).[26] The relationship between OSA and GDM in pregnant women has varied in several studies.[1,24,26,27] In the present study, other pregnancy-associated disorders were also related to OSA but did not reach statistical significance. A recent long-term cohort study with nulliparous found that OSA (AHI ≥ 5) during pregnancy was associated with an increased risk of hypertension at 2–7 years after delivery.[28] Taken together, OSA in pregnancy is strongly related with adverse outcomes for both mother and fetus in the short and long term.

We performed portable PSG to evaluate OSA in pregnant women. The criterion standard for diagnosing OSA is level 1 attended PSG,[29] whereas it is very difficult for pregnant women in the third trimester to be tested with full PSG in a sleep laboratory. Some of the previous studies used at-home portable PSG for convenience of the subjects who are pregnant.[10,30] Portable PSG based on peripheral arterial tonometry was validated, and respiratory indexes of portable PSG were well correlated with those of level 1 PSG.[20,31] PSG is reimbursed by the National Health Insurance for the general population,[32] but there are no standard for the PSG test in pregnant women.

We additionally evaluated the risk of OSA using the Berlin questionnaire. In this study cohort, 6 out of 14 OSA patients (42.9%) were identified as high-risk in the Berlin questionnaire, and most of the confirmed OSA cases were mild (12/14, 85.7%). The sensitivity of Berlin questionnaire was reported to be 61.3% in Korean population, and this questionnaire is useful for screening for moderate to severe OSA.[33] An accuracy of subjective symptom screening for sleep disordered breathing through administration of a questionnaire has been debated, especially in patients with asymptomatic or mild OSA. Objective measurement

of OSA using PSG was strongly associated with small for gestational age infants, while subjective symptoms evaluated by a sleep questionnaire were not related to the outcome.[10] Even in asymptomatic or mild OSA patients, there was increased risk of worse pregnancy-related outcomes. Therefore, objective PSG testing is required for pregnant women who are overweight or at high risk of hypertensive disorders in pregnancy.

Considering that the association between obesity and preeclampsia is stronger in late-onset preeclampsia.[10] We enrolled our study population after 30 weeks gestational and who had regular visits until delivery. Therefore, some cases with early-onset preeclampsia or severe hypertension requiring hospitalization were not included. There is little information on the relationship between the causes and effects of OSA and preeclampsia, but it is well known that OSA causes hypertension in the general population.[8,34] Serum analysis revealed that the sFlt-1/PlGF ratio was higher in OSA patients compared to pregnant women without OSA. In OSA patients without preeclampsia, the mean level of sFlt-1/PlGF was elevated over the normal controls. This finding suggests that OSA-induced intermittent hypoxia might play a part in the pathogenesis of preeclampsia. The sFlt-1/PlGF ratio was determined by a laboratory-based ELISA in this study.[22] This value may differ from the electrochemiluminescence immunoassay, which is measured with automated device used in clinical practice.[35]

The present study has some limitations. First, more than half of the pregnant women asked to participate declined because they were reluctant to join clinical studies, being subject to a selection bias in which pregnant women with more severe sleep apnea are selected. Due to the relatively small number of sample size, no significant results were drawn for other pregnancy-associated outcomes, and any subgroup analyses were possible including pre-pregnancy obesity, hypertension, diabetes, or other metabolic diseases. Second, we prescribed a portable PSG instead of an attended level 1 PSG, limiting comprehensive information regarding whole sleep quality. Lastly, there were a few patients with hypertension or diabetes before pregnancy, but the numbers were too small to evaluate the actual impact.

However, to our knowledge, it has never been investigated in Korean pregnant women. The novelty of the present study is that we performed a comprehensive survey of PSG and questionnaires in this prospective cohort. We also checked the levels of serum markers related to preeclampsia including sFlt-1, PlGF, and endoglin and biomarkers of OSA (IL-6, MRP8/14, and TNF-α) according to the presence or absence of OSA. High BMIs were associated with OSA in the third trimester of pregnancy. We confirmed that OSA was a significant and independent risk factor for preeclampsia and was associated with preterm delivery. Collectively, our data suggest that OSA work-up is considered as mandatory for pregnant women who are overweight or have hypertensive disorder of pregnancy. These results also imply that management of OSA in pregnant women may prevent late-onset preeclampsia. Further mechanistic studies about the relationship between OSA and preeclampsia are warranted.

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