

OBSTETRICS

Obstructive sleep apnea and the risk of adverse pregnancy outcomes

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OBJECTIVE: We examined the risk of adverse pregnancy outcomes, including low birthweight (LBW), preterm birth, small for gestational age (SGA), cesarean section (CS), low Apgar score (at 5 minutes after delivery), and preeclampsia in pregnant women with and without obstructive sleep apnea (OSA).

STUDY DESIGN: Our subjects included 791 women with OSA and 3955 randomly selected women without OSA. We performed conditional logistic regression analyses to examine the risks of adverse pregnancy outcomes between women with and without OSA.

RESULTS: Compared with women without OSA, adjusted odds ratios for LBW, preterm birth, SGA infants, CS, and preeclampsia in women

with OSA were 1.76 (95% confidence interval [CI], 1.28–2.40), 2.31 (95% CI, 1.77–3.01), 1.34 (95% CI, 1.09–1.66), 1.74 (95% CI, 1.48–2.04), and 1.60 (95% CI, 2.16–11.26), respectively.

CONCLUSION: Pregnant women with OSA are at increased risk for having LBW, preterm, and SGA infants, CS, and preeclampsia, compared with pregnant women without OSA.

Key words: cesarean section, obstructive sleep apnea, pregnancy outcome

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Obstructive sleep apnea (OSA), a common sleep-related breathing disorder, is characterized by recurrent collapse or blockage of the pharynx during sleep that causes intermittent cessation of airflow and a hallmark snoring-gasping pattern.¹⁻³ The prevalence of OSA among women ranges from 0.3% to 5%.⁴⁻⁸ A study by Loube et al,⁹ based on

self-reports, found that frequent snoring is reported more often in pregnant women than in nonpregnant women. However, the incidence of OSA in pregnant women is unknown.

Patients with OSA commonly had decreased quality of life. In particular, OSA affects sleep quality and duration of sleep in pregnant women.^{10,11} Pregnancy causes anatomic, physiologic, and endocrinologic changes, including narrowing of the upper respiratory tract, which may increase the risk for OSA or worsen preexisting sleep apneas.^{12,13} Studies have associated OSA in pregnant women with low birthweight (LBW),^{14,15} preterm birth,¹⁶ small for gestational age (SGA),^{9,17} cesarean section (CS),³ lower Apgar scores at birth,^{14,18} and preeclampsia.^{7,12}

On the other hand, an empirical study by Loube et al⁹ reported no association between mothers with frequent snoring and LBW infants (mean birthweights were 3534 ± 474 g and 3450 ± 652 g for women with and without OSA, respectively). Furthermore, previous studies on OSA and pregnancy outcomes were limited to case reports^{7,8,17} and selective data or small sample sizes^{9,15}; furthermore, all the studies reported on sub-

jects from Western countries. Therefore, whether there was an association between OSA and adverse pregnancy outcomes remains unanswered.

Using 2 large-scale, nationwide, population-based datasets, this study aimed to examine the risk of adverse pregnancy outcomes, including LBW, preterm birth, SGA, CS, lower Apgar score (at 5 minutes after delivery), and preeclampsia/eclampsia, between pregnant women with and without OSA in Taiwan. The large dataset available from Taiwan presents an exceptional opportunity to examine this issue among Asian women.

MATERIALS AND METHODS

Database

We linked 2 nationwide, population-based datasets and used the resulting compilation for our analyses. In March 1995, Taiwan initiated its National Health Insurance (NHI) program to finance health care for all its citizens. Taiwan's NHI has a unique combination of characteristics: universal coverage, a single-payer payment system with the government as the sole insurer, unrestricted access to any medical institution of the patient's choice, and a wide variety of providers including primary care physicians.

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The Taiwan National Health Insurance Research Dataset (NHIRD) is derived from the NHI program and includes all the original claims data as well as registry files of contracted medical facilities, board-certified specialists, other medical service providers, and prescriptions covered by the program for the 25.68 million enrollees in Taiwan (the coverage rate was greater than 98.5% in 2007). Therefore, the NHIRD includes comprehensive information on the medical utilization of virtually all the pregnant women in Taiwan and thus offers an excellent opportunity to examine the relationship between OSA and pregnancy outcomes.

The national birth certificate registry is maintained and publicly released by the Taiwanese Ministry of the Interior. According to law, all births in Taiwan must be registered within 10 days following the birth. This dataset contains both infants' and parents' demographic, reproductive, and socioeconomic characteristics and infants' birth characteristics, including birthweight, gestational age, birth order, and sex. A previous study has verified the completeness and showed high levels of validity in Taiwan's birth registry.¹⁹

These 2 nationwide, population-based datasets were linked with assistance from the Bureau of Health Promotion, Department of Health, Taiwan. Because the NHIRD consists of deidentified secondary data released to the public for research purposes, this study was granted approval via summary review by the institutional review board.

Study sample

This cross-sectional design includes a study group and a comparison group. To form the study group, we first identified 218,776 women in Taiwan who had live singleton births between Jan. 1, 2005, and Dec. 31, 2005. If the selected women had more than 1 singleton birth during the study period, we included only the first in the study sample and designated it an index delivery. Of the 218,776 women, 791 had been diagnosed with OSA (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 780.51, 780.53,

780.57, or 327.23) after receiving polysomnograms during ambulatory care visits within 1 year prior to their index deliveries.

When a physician suspects that a patient has OSA, the physician may give the patient a tentative diagnosis of OSA during their first visit to perform the related clinical or laboratory tests to confirm the OSA diagnosis and avoid any possible fines for performing unnecessary or inappropriate procedures. Therefore, we selected only women who had been given at least 2 consensus OSA diagnoses after undergoing polysomnographic studies to increase coding reliability and validity from this administrative database.

To form the comparison group, we randomly extracted 3955 women (5 women for every woman with OSA) matched with the study group in terms of age group (<20, 20-24, 25-29, 30-34, and ≥ 35 years) using the SAS surveyselect procedure (SAS System for Windows, version 8.2; SAS Institute Inc, Cary, NC). We also assured that selected women in the comparison group had never received a diagnosis of OSA since the initiation of the NHI program in 1995.

Variables of interest

The independent variable for this study was whether each woman was diagnosed with OSA within 1 year prior to her index delivery. The outcome variables selected for this study were all dichotomous. They included LBW (<2500 g); preterm gestation (<37 completed weeks of gestation); SGA babies (SGA has been defined as a birthweight of less than the 10th percentile for gestational age by Lubchenco et al¹⁹ and Battaglia and Lubchenco²⁰ in the 1960s); Apgar score at 5 minutes less than 7; CS; preeclampsia (eclampsia); gestational diabetes; and gestational hypertension.

We also adjusted for several maternal characteristics (highest educational level, marital status, geographic region, coronary heart disease [ICD-9-CM codes 410-414 or 429.2], anemia [ICD-9-CM codes 280-285], hyperlipidemia [ICD-9-CM codes 272 and 272.0-272.9], and obesity [ICD-9-CM codes 278,

278.0, 278.00, and 278.01]); infant sex and parity; and father's age in the regression modeling to assess the independent effect of OSA on the specified pregnancy outcomes.

Statistical analysis

We performed all analyses in this study using the SAS package (SAS Institute). Pearson χ^2 tests were used to compare differences between women with and without OSA in terms of the characteristics of mother, infant, and father identified in the above-mentioned text. We also used conditional logistic regression analyses that were conditioned on maternal age to examine the risk of adverse pregnancy outcomes between women with and without OSA. A 2-sided $P < .05$ was considered statistically significant for this study.

RESULTS

The mean age of the 4746 sampled women was 30.3 ± 4.4 years (SD; range, 14-45 years). The mean birthweight for women with OSA and women without OSA were 3063 ± 584 g (SD; range, 361-4650 g) and 3147 ± 418 g (SD; range, 1426-4760 g), respectively. Moreover, the mean gestational age for women with OSA and women without OSA were 38 ± 2.28 weeks (SD; range, 24-41 weeks) and 38 ± 1.45 weeks (SD; range, 29-43 weeks), respectively.

Table 1 reports the distribution of characteristics of mothers, infants, and fathers across the study and comparison groups. After matching for maternal age, we found no significant differences between women with and without OSA in infant sex ($P = .216$), maternal education level ($P = .156$), anemia ($P = .989$), and hyperlipidemia ($P = .998$). However, there were significant differences in infant parity ($P < .001$), maternal marital status ($P < .001$), coronary heart disease ($P < .001$), obesity ($P < .001$), geographic region ($P < .001$), and paternal age ($P = .003$) between women with and without OSA.

Table 2 presents the prevalence of LBW, preterm birth, SGA infants, and CS by group. Women with OSA had higher prevalences of LBW infants (8.6% vs 4.2%, $P < .001$), preterm birth (12.1%

vs 5.4%, $P < .001$), SGA infants (18.3% vs 13.5%, $P < .001$), CS (50.4% vs 37.3%, $P < .001$), Apgar score at 5 minutes less than 7 (1.3% vs 0.1%, $P < .001$), preeclampsia (1.4% vs 0.5%, $P = .002$), and gestational hypertension (6.7% vs 2.2%, $P < .001$) than women without OSA.

Conditional logistic regression analyses (conditioned on maternal age group) revealed that the odds ratios (ORs) for LBW, preterm birth, SGA infants, CS, Apgar score at 5 minutes less than 7, preeclampsia, gestational diabetes, and gestational hypertension in women with OSA were 2.16 (95% confidence interval [CI], 1.61–2.90), 2.40 (95% CI, 1.86–3.10), 1.44 (95% CI, 1.17–1.76), 1.73 (95% CI, 1.48–2.02), 10.11 (95% CI, 3.45–29.67), 3.08 (95% CI, 1.45–6.55), 1.45 (95% CI, 0.99–2.11), and 3.32 (95% CI, 2.32–4.74), respectively, compared with women without OSA (Table 2).

Table 2 also presents the adjusted ORs of adverse pregnancy outcome by group after adjusting for maternal highest educational level, marital status, geographic region, gestational diabetes, gestational hypertension, coronary heart disease, anemia, hyperlipidemia, obesity, infant sex and parity, and paternal age. As compared with women without OSA, the adjusted ORs in women with OSA for LBW, preterm birth, SGA infants, CS, and preeclampsia were 1.76 (95% CI, 1.28–2.40), 2.31 (95% CI, 1.77–3.01), 1.34 (95% CI, 1.09–1.66), 1.74 (95% CI, 1.48–2.04), and 1.60 (95% CI, 2.16–11.26), respectively.

Furthermore, we found that mothers with OSA were 1.63 and 3.18 times more likely than unaffected mothers to have gestational hypertension and gestational diabetes, respectively, after adjusting for other confounders. The adjusted ORs for lower Apgar score at 5 minutes was not presented because of the small number of cases in which Apgar score at 5 minutes was less than 7.

COMMENT

After adjusting for mother and infant characteristics, we found that mothers with OSA were 1.76, 2.31, 1.34, 1.74,

TABLE 1

Sociodemographic characteristics of pregnant women with and without obstructive sleep apnea in Taiwan, 2005 (n = 4746)

Variable	Women with obstructive sleep apnea (n = 791)		Women in the comparison group (n = 3955)		P value
	n	%	n	%	
Infant characteristics					
Sex					.216
Male	415	52.5	2170	54.9	
Female	376	47.5	1785	45.1	
Parity					< .001
1	364	46.0	1885	47.7	
2	274	34.6	1575	39.8	
≥3	153	19.3	495	12.5	
Maternal characteristics					
Age, y					1.000
<20	5	0.6	25	0.6	
20–24	68	8.6	340	8.6	
25–29	263	33.3	1315	33.3	
30–34	329	41.6	1645	41.6	
>34	126	15.9	630	15.9	
Marital status					< .001
Married	680	86.0	3690	93.3	
Education level					.156
Junior high school or lower	84	10.6	325	8.2	
Senior high school	516	65.2	2670	67.5	
College or above	191	24.2	960	24.3	
Anemia	60	7.3	290	7.3	.989
Coronary heart disease	20	2.5	20	0.5	< .001
Hyperlipidemia	19	2.4	95	2.4	.998
Obesity	17	2.1	60	1.5	< .001
Geographic region					< .001
North	511	64.6	2190	55.4	
Center	190	24.0	965	24.4	
South	80	10.1	695	17.6	
East	10	1.3	105	2.7	
Paternal age, y					.003
<30	291	36.8	1330	33.6	
30–34	251	31.7	1510	38.2	
>34	249	31.5	1115	28.2	

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TABLE 2
Distribution and ORs of pregnancy outcomes across study and control groups, 2005 (n = 4746)

Variable	Women with obstructive sleep apnea (n = 791)		Women in the comparison group (n = 3955)		P value
	n	%	n	%	
LBW	68	8.6	165	4.2	< .001
OR (95% CI) ^a	2.16 (1.61–2.90) ^b		1.00		
Adjusted OR (95% CI) ^c	1.76 (1.28–2.40) ^d		1.00		
Preterm birth	96	12.1	215	5.4	< .001
OR (95% CI) ^a	2.40 (1.86–3.10) ^b		1.00		
Adjusted OR (95% CI) ^c	2.31 (1.77–3.01) ^d		1.00		
SGA	145	18.3	535	13.5	< .001
OR (95% CI) ^a	1.44 (1.17–1.76) ^b		1.00		
Adjusted OR (95% CI) ^c	1.34 (1.09–1.66) ^e		1.00		
CS	399	50.4	1475	37.3	< .001
OR (95% CI) ^a	1.73 (1.48–2.02) ^b		1.00		
Adjusted OR (95% CI) ^c	1.74 (1.48–2.04) ^d		1.00		
Low Apgar score at 5 min	10	1.3	5	0.1	< .001
OR (95% CI) ^a	10.11 (3.45–29.67) ^d		1.00		
Adjusted OR (95% CI) ^c	—		1.00		
Preeclampsia/eclampsia	11	1.4	18	0.5	.002
OR (95% CI) ^a	3.08 (1.45–6.55) ^e		1.00		
Adjusted OR (95% CI) ^c	1.60 (2.16–11.26) ^d		1.00		
Gestational diabetes	37	4.7	130	3.3	.053
OR (95% CI) ^a	1.45 (0.99–2.11)		1.00		
Adjusted OR (95% CI) ^f	1.63 (1.07–2.48) ^b		1.00		
Gestational hypertension	53	6.7	85	2.2	< .001
OR (95% CI) ^a	3.32 (2.33–4.74) ^d		1.00		
Adjusted OR (95% CI) ^g	3.18 (2.14–4.73) ^d		1.00		

CI, confidence interval; CS, cesarean section; LBW, low birthweight; OR, odds ratio; SGA, small size for gestational age.

^a Calculated by conditional logistic regression (conditioned on maternal age group); ^b $P < .05$; ^c Adjustments made for mother's education, marital status, gestational diabetes, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity; ^d $P < .001$; ^e $P < .01$; ^f Adjustments made for mother's education, marital status, gestational hypertension, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity; ^g Adjustments made for mother's education, marital status, gestational diabetes, anemia, coronary heart disease, hyperlipidemia, obesity, geographic region, paternal age, infant's sex, and parity.

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1.60, 1.63, and 3.18 times more likely than unaffected mothers to have LBW, preterm, SGA babies, CS, preeclampsia, gestational diabetes, and gestational hypertension, respectively.

Our findings parallel the conclusions of many prior studies.^{3,7,9,12,14–17} For example, Sahin et al¹⁵ reported that fetuses of women with OSA had lower mean birthweights than those of women without OSA in Turkey. Kapsimalis and Kryger¹⁶ found that of 9 pregnant women with OSA in the United States, 3 had pre-

term deliveries and 6 had preeclampsia. Another study by Louis et al³ also found that women with OSA were more likely to have preterm births than obese controls and normal-weight controls (30% vs 10% and 12%, respectively; $P < .01$).

A survey study by Loube et al⁹ showed that SGA occurred in 7.1% of mothers with frequent snoring, compared with 2.6% of mothers without frequent snoring. In a case report, Sagheer et al⁷ described a 26 year old pregnant woman with OSA, who delivered a healthy baby

but experienced preeclampsia and other medical problems during the pregnancy. Another case report by Roush and Bell¹⁷ described a 25 year old woman with OSA who was treated for preeclampsia and delivered an SGA infant.

In addition, prior studies have reported that pregnant women with OSA delivered babies with Apgar scores at birth lower than the comparison group.^{9,14,21} We did not calculate the adjusted ORs for this outcome because only 10 of the 791 women with OSA in our sample had Apgar score at 5 minutes of less than 7. However, consistent with prior observations, we found that the crude OR of low Apgar score at 5 minutes for infants of women with OSA was 10.11 times higher than for infants of women without OSA.

The mechanisms underlying the relationship between OSA and adverse pregnancy outcomes remain obscure. It has been suggested that the frequency and intensity of OSA-associated apnea and hypopnea may be low enough to spare mothers of adverse effects yet still be harmful to their more oxygen-sensitive fetuses.^{7,12}

One study by Kambam et al²² reported that greater resistance to airflow had a significantly greater impact on the overall oxygen homeostasis in pregnant women than in nonpregnant women. Another study by Loube et al⁹ also found that the consequences of increased upper airway resistance during pregnant women's sleep might negatively affect their infants. Further studies are still needed to characterize the contributions of biochemical, metabolic, and immune changes arising from OSA to pregnancy outcome.

Our large datasets, examined for integrity and validity as described in previous text, provided sufficient statistical power to detect differences and minimized probabilities for selection and nonresponse biases. Furthermore, more than 98% of Taiwanese inhabitants are of Han Chinese ethnicity. Although this limits generalizability to other ethnic groups, its homogeneity in this respect also reduces the probability of ethnic/genetic confounding effects.

Despite the strengths of our study, the findings should be interpreted in the context of some limitations. First, previ-

ous studies have suggested that obesity may be a major risk factor for the development of OSA.^{23,24} However, although we have taken obesity into consideration in the regression model, our datasets did not contain data on body mass index. This may have compromised our findings.

Second, the NHIRD lacks information on the severity of OSA, such as apnea-hypopnea index (AHI) scores or respiratory disturbance index scores. Therefore, we could not test for relationships between severity of OSA and adverse pregnancy outcomes.

Third, because the NHI database included only patients who sought treatment, it is possible that some women might have been suffering from OSA but were not diagnosed on account of seeking care. Furthermore, because these women could have been selected and recruited in the comparison cohort, our findings might be biased toward the null. Although the NHI in Taiwan did not establish criteria for the diagnosis of OSA, to the best of our knowledge, most of the sleep centers in Taiwan follow the guidelines and criteria established by the American Academy of Sleep Medicine (defined as an AHI >5 in symptomatic case or AHI >15).²⁵ Nevertheless, the variability of AHI across different nights of the same patient, the variability of the instruments and protocols across different sleep laboratories, and the variability of polysomnographic scorings across different raters and centers are still present despite conducting a large population-based study.²⁶ Therefore, these factors may bias our conclusions.

Fourth, the status and compliance of continuous positive airway pressure (CPAP) treatment for OSA patients during pregnancy cannot be determined from our database. Therefore, although having been suggested by some case reports, whether CPAP treatment minimizes adverse outcomes during pregnancy still needs to be elucidated by further studies.²⁷

Our study shows that there was a relationship between OSA and an increased risk of having LBW, preterm, and SGA infants and for experiencing CS and pre-eclampsia. To effectively promote ma-

ternal and infant health in Taiwan, policymakers cannot rely solely on the current practice of offering 10 free prenatal care visits to medical institutions contracted under the NHI program. Health authorities should promote screening to recognize OSA in pregnant women and provide such women with heightened levels of health care.

CPAP, a treatment for upper airway narrowing during sleep, appears to represent a safe treatment with minimal adverse effects. Moreover, we expect that increased monitoring of mothers with OSA in gestation would decrease the risk of adverse pregnancy outcomes. ■

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