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Obstructive sleep apnea increases risk of female infertility: A 14-year nationwide population-based study

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Abstract

Objectives

To determine the risk of having OSA in a cohort of female subjects who are infertile and the odds of being infertile in women with OSA.

Patients and methods

A nationwide, case-control study of female patients 20 years or older diagnosed with female infertility living in Taiwan, from January 1, 2000, through December 31, 2013 (N = 4,078). We identified women who were infertile and created a 2:1 matched control group with women who were not infertile. We used multivariable logistic regression analysis to further estimate the effects of OSA on female infertility.

Results

In this 14- year retrospective study, we included 4,078 patients having an initial diagnosis of female infertility. Of those women with infertility, 1.38% had a history of OSA compared with 0.63% of fertile controls (p = 0.002). The mean ages in the study groups were 32.19 ± 6.20 years, whereas the mean ages in the control groups were 32.24 ± 6.37years. Women with OSA had 2.101- times the risk of female infertility compared to women without OSA (p<0.001).

Protection Act in Taiwan, personal data cannot be obtained publicly. Interested researchers can sent a formal proposal to the NHIRD (https://dep.mohw.gov.tw/dos/cp-5119-59201-113.html).

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Abbreviations: ACOG, American College of Obstetricians and Gynecologists; COPD, Chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NASD, Non-apnea sleep disorders; NHIRD, National Health Insurance Research Database; OSA, Obstructive sleep apnea; PCOS, Polycystic ovary syndrome.

Conclusion

Our study showed that OSA is more commonly seen in infertile women and increases the odds that a woman will be infertile. More studies need to be done on the whether or not diagnosing and treating OSA can decrease the rate of infertility.

Introduction

Obstructive sleep apnea (OSA) is a widely prevalent but often underdiagnosed respiratory disorder characterized by recurrent upper airway obstruction during sleeping. Approximately 5% of the general population experiences OSA; among those aged 30–60 years, the prevalence is 9% in women and 24% in men [1, 2]. The risk of OSA is higher with a family history of OSA, obesity, hypertension, menopause, cigarette smoking, and alcohol consumption [3]. OSA results in sleep fragmentation and repetitive hypoxemia and is associated with various comorbidities, including hypertension, diabetes mellitus, ischemic heart disease, and obesity [4, 5].

According to the American College of Obstetricians and Gynecologists (ACOG), the definition of infertility is the failure to conceive after 1 year or more of regular unprotected sexual intercourse [6]. The prevalence of infertility has increased since 1990; in 2010, approximately 48.5 million individuals worldwide suffered from infertility [7]. Moreover, according to the data published by Taiwan's Ministry of the Interior, the fertility rates of women within childbearing age decreased from 1.680 births per woman in 2000 to 1.080 births per woman in 2018, with the mean age of the women at their first birth increasing from 22.88 years to 30.90 years during that period. Female infertility can result from various conditions, including endometriosis, pelvic adhesion, polycystic ovary syndrome, tubal blockage, hyperprolactinemia, and congenital or acquired uterine or ovarian abnormalities [8].

Infertility can be associated with multiple factors, such as inflammation, obesity, intermittent hypoxia and sympathetic activation [9, 10]. In our previous study, we have found an increased risk of infertility in female patients with non-apnea sleep disorder [11]. However, little is known about whether OSA is associated with a risk of female infertility.

The aim of the present study was to investigate whether women with OSA had an increased risk of subsequent female infertility. Accordingly, we used Taiwan's National Health Insurance Research Database (NHIRD) for conducting the largest retrospective study to date discussing the association of female infertility with OSA.

Materials and methods

Data source

Taiwan launched its National Health Insurance program in 1995. This program covers approximately 99% of the 23.74 million individuals in Taiwan, and 97% of clinics are covered by the system [12]. Taiwan's health care system is insurance-based, and is characterized by its good accessibility, high efficiency, comprehensive population coverage (99% of the 23.74 million residents in Taiwan), relatively low costs and short waiting times [13]. The NHIRD contains health registration records for most of the general population in Taiwan, including details of outpatient, inpatient, and emergency department visits, with diagnoses coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9). The high accuracy and validity of diagnoses in the NHIRD have been demonstrated in previous studies, confirming that the NHIRD offers representative data for medical and health-related research [14–16]. A subset of approximately 1 million patient records from the NHIRD was randomly chosen for inclusion in the Longitudinal Health Insurance Database as

an aid to research projects. The privacy of all individuals registered in the program is ensured via the encryption and conversion of the identification numbers of all records.

The protocol for this study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB No. 1-106-05-169).

Study population

From the outpatient and inpatient data of 989,753 individuals for the period 2000 to 2013 in Taiwan's Longitudinal Health Insurance Database, we identified female patients aged 20–45 years who were diagnosed with infertility. We excluded women who received radiation therapy, chemotherapy, and genital organ surgery (Fig 1). Patients who met the criteria were assigned to the study group. We used two-fold propensity score matching to create a control group by matching each case group member with two other women from the database according to age (by 5-year span) and index date, applying the same exclusion criteria [17, 18]. We compared differences between both groups for the prior exposure of OSA. Both groups were followed until the end of 2013. Our study was conducted by extracting the ICD-9 codes from the NHIRD. The diagnosis of OSA is made by polysomnography and the diagnosis of female infertility is confirmed by the obstetrician and gynecologists. We listed several covariates in our study, including season (Spring, Summer, Autumn, Winter), urbanization level of residence and level of care (medical center, regional, and local hospital). Moreover, common

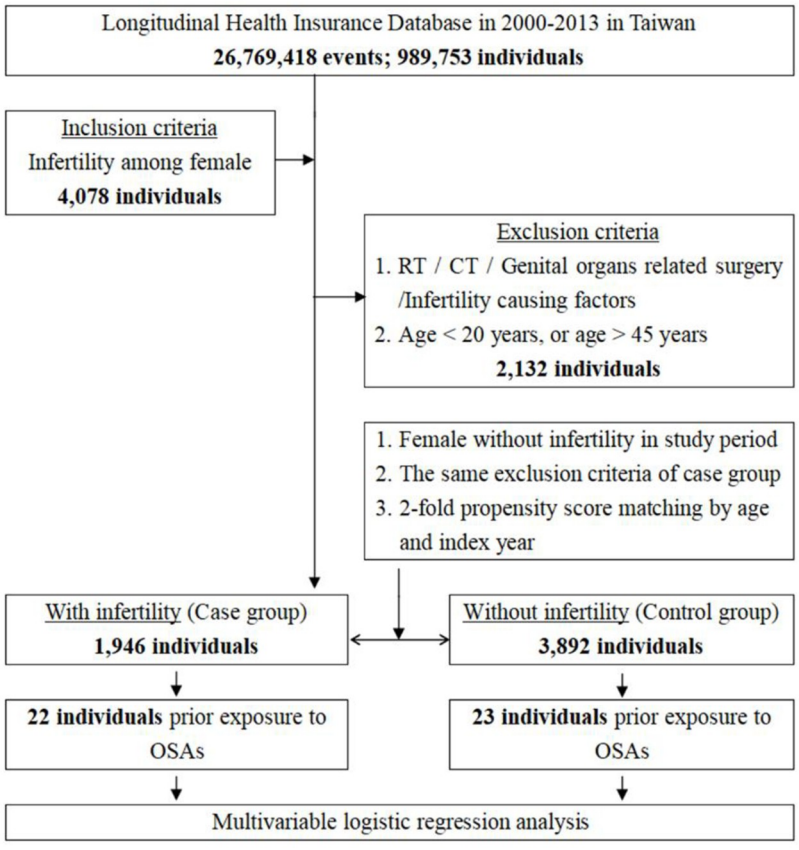

Fig 1. The flowchart of study design (nested case-control study) from National Health Insurance Research Database in Taiwan.

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comorbidities as well as endocrine and gynecological diseases, such as obesity, Cushing's syndrome, thyroid disease, PCOS, and endometriosis, were used in the analysis to evaluate the cause of infertility and their effects on OSA.

Statistical analysis

We compared the study and control groups with regard to characteristics and common comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, and COPD, by using chi-squared tests. The mean ages of the two groups were compared using Student's t-test. The odds ratio (OR) for factors potentially associated with female infertility were evaluated using multivariable logistic regression with and without stratification. The variables that adjusted in the odds ratio were the variables that listed in the table. Correlation analysis was used to study the strength of a relationship between age groups and the variables listed in S2 Table. All comparisons were two-tailed, and p-values <0.05 were considered statistically significant. The statistical analyses were performed using IBM SPSS v 22.0 software.

Results

We identified 4,078 female patients in the database who had been diagnosed with infertility by the end of the study. After applying the exclusion criteria, 2,400 patients were included and assigned as the study group in the analysis. The control group comprised 4,800 matched women without infertility. The mean ages in the study groups were 32.19 ± 6.20 years, whereas the mean ages in the control groups were 32.24 ± 6.37 years. Table 1 summarizes the characteristics of the study and the control groups. There were significantly more patients who had been diagnosed with OSA in the study group than in the control group (1.38% vs. 0.63%; p = .002). In addition, we have found that 33 patients in the study group and 30 patients in the reference group, who have had prior exposure to OSA. Women aged 26–30 years and 31–35 years were more than other aged groups in our study population (28.0% and 32.29% respectively).

Multivariable logistic regression analysis was used in this retrospective study. We listed factors for female infertility in Table 2. There were no significant differences in the risk of female infertility between patients with and without gynecological disorders, endocrine disorders, or concomitant comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, COPD, chronic kidney disease, coronary heart disease, stroke, obesity, anxiety, and depression (Table 2). The increased likelihood of subjects with OSA to be infertile was also showed in Table 2 (adjusted odds ratio, 2.101; $p<0.001$). ICD-9-CM and correlation analysis were listed in S1 and S2 Tables, respectively.

Discussion

Our study is the largest retrospective study to date demonstrating the association of female infertility with OSA. In this nationwide, population-based, case-control study of over 14 years, we have found that infertile women have an odds ratio of 2.1 of having OSA compared with women who were fertile but also infertile women were more likely to have OSA. This article is the second study in which our group has shown that women with sleep disorders could link to female infertility. In our previous article, we have found that women with non-apnea sleep disorder had a 3.718-fold risk of female infertility compared with the control cohort [11].

OSA is defined as presence of sleep disordered breathing, excessive daytime sleepiness, and a high apnea–hypopnea index [1, 2, 19]. Changes in the frequency of apneas, hypopneas, and respiratory-effort-related arousal cause increases in sympathetic tone, circadian disruption, systemic inflammation, and intermittent and chronic hypoxia. These factors may gradually

Table 1. Characteristics of study.

Infertility	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Total	7,200		2,400	33.33	4,800	66.67	
OSAs							0.002
Without	7,137	99.13	2,367	98.63	4,770	99.38	
With	63	0.88	33	1.38	30	0.63	
Age (years)	32.22 ± 6.31		32.19 ± 6.20		32.24 ± 6.37		0.751
Age group (yrs)							0.999
20–25	972	13.50	324	13.50	648	13.50	
26–30	2,016	28.00	672	28.00	1,344	28.00	
31–35	2,325	32.29	775	32.29	1,550	32.29	
36–40	1,386	19.25	462	19.25	924	19.25	
41–45	501	6.96	167	6.96	334	6.96	
Insured premium (NT$)							0.952
<18,000	6,787	94.26	2,265	94.38	4,522	94.21	
18,000–34,999	272	3.78	88	3.67	184	3.83	
≧35,000	141	1.96	47	1.96	94	1.96	
HTN							<0.001
Without	6,751	93.76	2,204	91.83	4,547	94.73	
With	449	6.24	196	8.17	253	5.27	
DM							0.163
Without	6,850	95.14	2,271	94.63	4,579	95.40	
With	350	4.86	129	5.38	221	4.60	
Hyperlipidemia							<0.001
Without	7,081	98.35	2,324	96.83	4,757	99.10	
With	119	1.65	76	3.17	43	0.90	
COPD							0.003
Without	7,075	98.26	2,342	97.58	4,733	98.60	
With	125	1.74	58	2.42	67	1.40	
CKD							0.116
Without	6,993	97.13	2,342	97.58	4,651	96.90	
With	207	2.88	58	2.42	149	3.10	
IHD							<0.001
Without	7,085	98.40	2,334	97.25	4,751	98.98	
With	115	1.60	66	2.75	49	1.02	
CHD							0.018
Without	7,142	99.19	2,372	98.83	4,770	99.38	
With	58	0.81	28	1.17	30	0.63	
Stroke							0.001
Without	7,119	98.88	2,358	98.25	4,761	99.19	
With	81	1.13	42	1.75	39	0.81	
Cancer							0.208
Without	6,989	97.07	2,321	96.71	4,668	97.25	
With	211	2.93	79	3.29	132	2.75	
Obesity							0.001
Without	7,154	99.36	2,374	98.92	4,780	99.58	
With	46	0.64	26	1.08	20	0.42	
Hyperestrogenism							-

(*Continued*)

Table 1. (Continued)

Infertility	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Without	7,200	100.00	2,400	100.00	4,800	100.00	
With	0	0.00	0	0.00	0	0.00	
Polycystic ovaries							0.479
Without	7,199	99.99	2,400	100.00	4,799	99.98	
With	1	0.01	0	0.00	1	0.02	
Irregular menstrual cycle							<0.001
Without	7,191	99.88	2,391	99.63	4,800	100.00	
With	9	0.13	9	0.38	0	0.00	
Endometriosis							-
Without	7,200	100.00	2,400	100.00	4,800	100.00	
With	0	0.00	0	0.00	0	0.00	
Uterine leiomyoma							-
Without	7,200	100.00	2,400	100.00	4,800	100.00	
With	0	0.00	0	0.00	0	0.00	
Cushing's syndrome							-
Without	7,200	100.00	2,400	100.00	4,800	100.00	
With	0	0.00	0	0.00	0	0.00	
Thyrotoxicosis with or without goiter							0.139
Without	7,149	99.29	2,378	99.08	4,771	99.40	
With	51	0.71	22	0.92	29	0.60	
Acquired hypothyroidism							0.056
Without	7,175	99.65	2,387	99.46	4,788	99.75	
With	25	0.35	13	0.54	12	0.25	
Anxiety							<0.001
Without	6,920	96.11	2,216	92.33	4,704	98.00	
With	280	3.89	184	7.67	96	2.00	
Depression							<0.001
Without	6,974	96.86	2,262	94.25	4,712	98.17	
With	226	3.14	138	5.75	88	1.83	
Tobacco use disorder							0.011
Without	7,162	99.47	2,380	99.17	4,782	99.63	
With	38	0.53	20	0.83	18	0.38	
Alcoholism							0.019
Without	7,011	97.38	2,322	96.75	4,689	97.69	
With	189	2.63	78	3.25	111	2.31	
Season							0.720
Spring (Mar-May)	2,004	27.83	672	28.00	1,332	27.75	
Summer (Jun-Aug)	1,892	26.28	644	26.83	1,248	26.00	
Autumn (Sep-Nov)	1,581	21.96	528	22.00	1,053	21.94	
Winter (Dec-Feb)	1,723	23.93	556	23.17	1,167	24.31	
Location							<0.001
Northern Taiwan	3,160	43.89	1,125	46.88	2,035	42.40	
Middle Taiwan	1,920	26.67	568	23.67	1,352	28.17	
Southern Taiwan	1,528	21.22	533	22.21	995	20.73	
Eastern Taiwan	411	5.71	109	4.54	302	6.29	
Outlets islands	181	2.51	65	2.71	116	2.42	

(*Continued*)

Table 1. (Continued)

Infertility	Total		With		Without		*P*
Variables	**n**	**%**	**n**	**%**	**n**	**%**	
Urbanization level							<0.001
1 (The highest)	3,068	42.61	1,086	45.25	1,982	41.29	
2	2,541	35.29	863	35.96	1,678	34.96	
3	622	8.64	197	8.21	425	8.85	
4 (The lowest)	969	13.46	254	10.58	715	14.90	
Level of care							<0.001
Hospital center	2,433	33.79	1,077	44.88	1,356	28.25	
Regional hospital	2,170	30.14	621	25.88	1,549	32.27	
Local hospital	2,597	36.07	702	29.25	1,895	39.48	

P: Chi-square / Fisher exact test on category variables and t-test on continue variables

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increase oxidative stress, leading to infertility [20]. Lifestyle factors such as obesity and reproductive pathological and physiological factors such as PCOS, endometriosis, and pregnancy can result in the generation of reactive oxygen species by suppressing the production of NO, promoting the production of endothelium-derived vasoconstrictors, and increasing hemoglobin-mediated inactivation [21, 22]. Therefore, excessive oxidative stress can result in poor oocyte quality, abnormal fertilization, the impairment of blastocyst or embryo development and growth, and increased embryo fragmentation, leading to apoptosis and ultimately leading to failed implantation [23]. It has also been reported that an imbalance of pro-inflammatory cytokines, anti-inflammatory cytokines, chemokines, growth factors, and anti-apoptotic proteins were associated with infertility and unsuccessful in vivo fertilization [24–26].

Patients with OSA are at risk of metabolic disorders, including an irregular menstrual cycle and obesity [27]. The menstrual cycle is modulated by the hypothalamus–pituitary–gonadal axis. The hypothalamus releases gonadotropin-releasing hormone, the pituitary gland produces follicle-stimulating hormone and luteinizing hormone, and the ovary produces estrogen and testosterone. Kloss et al. hypothesized that sleep disorders may activate the hypothalamus–pituitary–gonadal axis and alter sex hormones in the follicular, ovulation, luteal, and menstruation phases, ultimately resulting in infertility [28]. In addition, the interruption of breathing during sleep as a result of OSA can cause circadian dysrhythmia due to the increased levels of melatonin and cortisol [29]. The increase of cortisol levels can downregulate the hypothalamic-pituitary-adrenal axis and inhibit GnRH at the pituitary level, which may alter sex hormone profiles and thus lead to infertility [30].

Scientists have demonstrated the prevalence of OSA in women is lower than in men [2]. There is also likely underdiagnosis of OSA in women due to atypical symptoms such as depression, headache, anxiety and insomnia are more frequent presented in women [31]. In addition, women with OSA have been shown to have greater hypoxic chemosensitivity than those without OSA [32]. In contrast, no central compensatory respiratory drive adaptation has been observed in obese men with or without OSA [32]. The sex hormones progesterone and estrogen have been reported to increase ventilatory control and hypercapnic and hypoxia chemosensitivity [33, 34]. In addition, sex hormone also participated in the distribution of adipose tissue and muscle function in upper respiratory tract [35]. Scientist have demonstrated that high progesterone level in pregnancy status had the protective role in developing OSA, even in obese pregnant women [36, 37]. Greater activity of dilator muscle in upper respiratory tract was also seen in progesterone-dominant luteal phase [38]. However, these effects decreased

Table 2. Factors of infertility by using multivariable conditional logistic regression.

Variables	Crude OR	95% CI	95% CI	*P*	Adjusted OR	95% CI	95% CI	*P*
OSAs	**Reference**				**Reference**			
	1.900	1.056	3.417	0.001	2.101	1.118	3.950	<0.001
Age group								
20–25	1.000	0.818	1.193	0.999	0.947	0.772	1.160	0.753
26–30	1.000	0.821	1.188	0.999	0.852	0.697	1.040	0.179
31–35	1.000	0.804	1.213	0.999	0.781	0.626	0.989	0.050
36–40	1.000	0.739	1.320	0.999	0.783	0.572	1.071	0.165
41–45	Reference				Reference			
Insured premium								
<18,000	Reference				Reference			
18,000–34,999	0.858	0.544	1.352	0.536	1.047	0.640	1.712	0.759
≧35,000	0.861	0.459	1.618	0.663	0.782	0.396	1.543	0.511
HTN	Reference				Reference			
	1.860	0.537	2.379	0.532	1.745	0.450	2.264	0.315
DM	Reference				Reference			
	1.932	0.593	2.465	0.761	1.874	0.534	2.460	0.668
Hyperlipidemia	Reference				Reference			
	1.988	0.478	3.041	0.987	2.030	0.466	3.319	0.850
COPD	Reference				Reference			
	1.598	0.328	2.091	0.101	1.593	0.320	2.133	0.139
CKD	Reference				Reference			
	1.282	0.035	3.292	0.238	1.193	0.024	2.743	0.151
IHD	Reference				Reference			
	1.517	0.257	2.041	0.069	1.393	1.184	1.826	0.017
CHD	Reference				Reference			
	1.538	0.150	2.931	0.347	1.397	0.107	2.558	0.201
Stroke	Reference				Reference			
	1.564	0.117	3.717	0.479	1.449	0.087	3.442	0.371
Cancer	Reference				Reference			
	1.231	1.120	1.447	<0.001	1.125	1.058	1.256	<0.001
Obesity	Reference				Reference			
	1.705	0.253	2.959	0.511	1.744	0.258	3.206	0.627
Hyperestrogenism	Reference				Reference			
	-	-	-	-	-	-	-	-
Polycystic ovaries	Reference				Reference			
	-	-	-	-	-	-	-	-
Irregular menstrual cycle	Reference				Reference			
	-	-	-	-	-	-	-	-
Endometriosis	Reference				Reference			
	-	-	-	-	-	-	-	-
Uterine leiomyoma	Reference				Reference			
	-	-	-	-	-	-	-	-
Cushing's syndrome	Reference				Reference			
	-	-	-	-	-	-	-	-
Thyrotoxicosis with or without goiter	Reference				Reference			
	2.414	0.727	3.749	0.286	1.877	0.437	2.796	0.778

(*Continued*)

Table 2. (Continued)

Variables	Crude OR	95% CI	95% CI	*P*	Adjusted OR	95% CI	95% CI	*P*
OSAs	**Reference**				**Reference**			
Acquired hypothyroidism	Reference				Reference			
	2.098	0.367	4.280	0.840	1.917	0.281	4.061	0.914
Anxiety	Reference				Reference			
	1.759	0.270	3.132	0.610	1.879	0.272	3.904	0.859
Depression	Reference				Reference			
	1.600	0.257	2.400	0.246	1.644	0.253	2.689	0.404
Tobacco use disorder	Reference				Reference			
	1.852	0.896	2.571	0.184	1.829	0.885	2.540	0.182
Alcoholism	Reference				Reference			
	1.532	0.722	2.386	0.223	1.513	0.714	2.357	0.220
Season								
Spring	Reference				Reference			
Summer	1.018	0.875	1.186	0.684	0.980	0.831	1.154	0.937
Autumn	0.960	0.824	1.118	0.702	0.938	0.796	1.105	0.622
Winter	0.871	0.746	1.017	0.110	0.823	0.696	0.972	0.044
Location								
Northern Taiwan	Reference				**Had multicollinearity with urbanization level**			
Middle Taiwan	0.794	0.696	0.906	0.001	**Had multicollinearity with urbanization level**			
Southern Taiwan	0.865	0.751	0.996	0.045	**Had multicollinearity with urbanization level**			
Eastern Taiwan	0.871	0.659	1.153	0.377	**Had multicollinearity with urbanization level**			
Outlets islands	0.899	0.419	1.929	0.799	**Had multicollinearity with urbanization level**			
Urbanization level								
1 (The highest)	3.459	2.808	4.262	<0.001	1.639	1.304	2.060	<0.001
2	2.003	1.624	2.469	<0.001	1.182	0.947	1.475	0.087
3	0.900	0.665	1.218	0.539	0.907	0.667	1.235	0.629
4 (The lowest)	Reference				Reference			
Level of care								
Hospital center	6.324	5.418	7.381	<0.001	5.734	4.841	6.791	<0.001
Regional hospital	2.272	1.939	2.662	<0.001	2.322	1.974	2.730	<0.001
Local hospital	Reference				Reference			

OR = odds ratio, CI = confidence interval, Adjusted OR: Adjusted variables listed in the table

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with age because of the higher incidence rate of OSA and the greater severity of OSA in postmenopausal women than in premenopausal women [33, 39]. It has been reported that estradiol withdrawal was associated with a predisposition to OSA in peri- and postmenopausal women with depression [40]. As a result, sex hormones may influence the severity of OSA, especially in younger women who desired to get pregnant [41].

This study had some limitations. First, although the diagnosis of OSA is made by polysomnography, we could not obtain the severity of OSA due to the de-identification in the database. Therefore, studies regarding the severity of OSA and subsequent female infertility are warranted. Second, although the study draws subjects from a large database, however, the number of infertility and OSA was only 33 and the number of OSA with no infertility in the control group was only 30 subjects. Third, the absence of women with endometriosis and PCOS in the infertile cohort potentially limits the applicability in populations where these disorders are

more common. Despite the listed limitations, our study provided a large group of patients and its longitudinal effects of over 14 years.

Conclusion

In conclusion, this study showed that OSA is more commonly seen in infertile women and increases the odds that a woman will be infertile. Therefore, infertile women should be screened for signs and symptoms of OSA, which may help to increase female fertility rate.

Supporting information

S1 Table. Abbreviation and ICD-9-CM.
(DOCX)

S2 Table. Correlation between variables listed in the table and age group.
(DOCX)

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