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Association of sleep disturbances with diminished ovarian reserve in women undergoing infertility treatment

Xue-Fen Cai[1], Bi-Ying Wang[2,3], Jian-Ming Zhao[2,3], Mei-Xin Nian[2,3], Qi-Chang Lin[2,3]✉ & Jie-Feng Huang[2,3]✉

With an aging population seeking infertility treatment, diminished ovarian reserve (DOR) is a prevalent indication for assisted reproductive technology (ART). This study aims to investigate the relationship between sleep parameters and DOR among women attending an infertility clinic. Methods We consecutively enrolled women attending an infertility clinic from July 2020 to June 2021. Participants completed the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale(ESS), and STOP-Bang Questionnaire to assess self-reported sleep quality. DOR-related indices including antral follicle count, anti-Müllerian hormone(AMH), follicle-stimulating hormone (FSH) were evaluated. A total of 979 women were enrolled, with 148 classified into the DOR group and 831 in the non-DOR group. The DOR group was notably older compared to the non-DOR group. Analysis showed that the DOR group exhibited significantly shorter sleep onset latency ($p = 0.001$) and shorter total sleep duration ($p = 0.014$) compared to the non-DOR group. Logistic regression analysis identified age, PSQI-sleep latency, and PSQI score as independent factors associated with an increased risk of DOR(all $p < 0.05$). Furthermore, stratified analysis by age group revealed that snoring and PSQI-sleep latency were particularly notable risk factors for DOR among women aged 35 years and older (OR = 2.489, $p = 0.040$; OR = 2.007, $p = 0.008$, respectively). Our study highlights that shorter sleep onset latency and shorter total sleep duration may be associated with DOR among women undergoing ART treatments. Particularly noteworthy, snoring and sleep latency were identified as additional risk factors for DOR among women aged 35 years and older.

Keywords DOR, Sleep onset latency, Sleep duration, Snoring

Abbreviations

DOR	diminished ovarian reserve
ART	assisted reproductive technology
PSQI	Pittsburgh Sleep Quality Index
ESS	Epworth Sleepiness Scale
AMH	anti-Müllerian hormone
FSH	follicle-stimulating hormone
LH	luteinizing hormone
E2	estradiol
AFC	antral follicle count
IVF	in vitro fertilization
ICSI	intracytoplasmic sperm injection
OSA	obstructive sleep apnea

[1]Center of Reproductive Medicine, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, China. [2]Department of respiratory and critical care medicine, Institute of Respiratory Disease, First Affiliated Hospital of Fujian Medical University, Fujian Medical University, Fujian Provincial Sleep-disordered Breathing Clinic Center, Fuzhou, China. [3]Department of Respiratory and Critical Care Medicine, Binhai Campus of the First Affiliated Hospital, National Regional Medical Center, Fujian Medical University, Fuzhou, People's Republic of China. ✉email: chang4e@126.com; 849387974@qq.com

BMI	body mass index
NC	neck circumference
PRL	prolactin
T	testosterone
HPG	hypothalamic-pituitary-gonadal
HPA	hypothalamic-pituitary-adrenal

Reproduction, a fundamental aspect of species evolution, has exhibited remarkable conservation across time. Over the past two decades, surveys have indicated a rising trend of infertility among younger women. Factors contributing to this phenomenon include industrialization, environmental pollution, societal pressures, and various health conditions. A pivotal marker in assessing female fertility is the ovarian reserve[1].

Clinicians employ several tests to evaluate ovarian reserve, encompassing biochemical assessments such as follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), inhibin B, and antimüllerian hormone (AMH), as well as ultrasound techniques like antral follicle count (AFC)[23]. Diminished ovarian reserve (DOR), a relatively recent appreciation within the continuum of reproductive senescence, alludes to the residual repertoire of oocytes remaining in the ovaries at a given age. According to the 2018 Society for Assisted Reproductive Technology National Summary[4], DOR was the second most common reason for assisted reproductive technology (ART) procedures, following egg/embryo banking, accounting for a third of all ART cycles that year. Clinically, DOR manifests as poor response to ovarian stimulation during in vitro fertilization (IVF) cycles, characterized by elevated basal follicle-stimulating hormone levels, diminished antimüllerian hormone levels, and/or a low antral follicle count. Women with DOR often experience lower oocyte yields and may obtain few or no viable embryos for transfer, posing significant challenges to achieving successful live births[5].

Despite extensive research, the underlying causes of DOR remain poorly understood. This complex condition is influenced by numerous factors including age, environmental exposures, the initial primordial follicular pool, diseases, medications, and other yet unidentified elements[67] [1, 6]. Notably, no studies have explored the potential relationship between sleep disorders and DOR. Hence, this study aims to investigate the impact of sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and STOP-Bang Questionnaire, on DOR. By exploring these associations, we aim to broaden our understanding of the multifaceted influences on ovarian reserve and potentially uncover new avenues for managing and preventing DOR in clinical practice.

Materials and methods

Study population

Couples seeking treatment for infertility at the Center of Reproductive Medicine, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University from July 2020 to June 2021 were included in this study. The data were gathered from male participants following their receipt of either IVF or intracytoplasmic sperm injection (ICSI) treatments at the clinic. The study's inclusion criteria specified couples scheduled for IVF or ICSI treatment. Exclusion criteria encompassed: (1) pregnancy or lactation; (2) hypothalamic-pituitary disease; (3) ovarian surgery history; (4) concurrent physical illnesses causing insomnia; (5) prior treatment for sleep disorders; (6) diagnosed inflammation of the urogenital system, epididymitis, testicular injury, incomplete orchiocatabasis, or varicocele. Written informed consent was obtained from all participants prior to enrollment in the study, and the research protocols were approved by the ethics committee of Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University.

Diagnosis and grouping

Participants were categorized into two groups based on their ovarian reserve status: DOR and non-DOR. Diagnosis of DOR required meeting at least two of the following criteria: (1) AMH < 1.2 ng/mL, (2) AFC < 7 on days 2–4 of the menstrual cycle, (3) basal serum FSH > 10 U/L[8]. Participants with normal ovarian reserve were classified into the non-DOR group. Hormone levels including FSH, LH, AMH, PRL, and E2 were assessed using the Chemiluminescence method. The study also involved calculating ovarian follicle distribution by color ultrasound.

Assessment of sleep quality

The PSQI, developed by Buysse, is a reliable tool that assesses sleep quality over the past month[9]. It comprises seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Each component is rated on a scale of 0 to 3, yielding a global score ranging from 0 to 21. A PSQI score ≥ 5 indicates poor sleep quality, with a sensitivity of 89.6% and specificity of 86.5% for identifying sleep disorders[10].

The STOP-Bang Questionnaire is employed to screen for obstructive sleep apnea (OSA)[11]. It includes two sections with eight yes/no questions: Stop Questions (snoring, daytime tiredness, observed cessation of breathing during sleep, hypertension) and Modified Stop Questions (BMI > 35 kg/m2 (or 30 kg/m2), age > 50 years, neck circumference > 40 cm, male gender). Each affirmative response scores 1 point, resulting in a total score ranging from 0 to 8, with higher scores indicating greater risk of OSA.

The ESS is an eight-item questionnaire designed to assess daytime sleepiness[12]. Respondents rate their likelihood of dozing off or falling asleep using a scale from 0 (never) to 3 (high chance), with scores ranging from 0 to 24. ESS scores effectively discriminate levels of daytime sleepiness across individuals.

Statistical analysis

The data were analyzed using IBM-SPSS version 22.0. Continuous variables were first tested for normal distribution. Normally distributed variables were expressed as mean ± standard deviation(SD), and differences between groups were compared using paired t-tests. Skewed variables were presented as median (25%, 75%) and compared using Mann-Whitney tests. Categorical variables were analyzed using Fisher's exact test. Logistic regression analysis was conducted to identify risk factors for DOR. Statistical significance was defined as $p < 0.05$.

Results

We enrolled a total of 979 women, among whom 148 were diagnosed with DOR (DOR group) with a mean age of 35.35 years, while 831 women did not have DOR (non-DOR group) with a mean age of 31.70 years ($p < 0.001$). Significant group differences were observed in Follicle count, AMH, FSH, E2, and T (all $p < 0.001$) (Table 1).

Table 2 compares sleep quality assessed by the PSQI, ESS, and STOP-Bang Questionnaire between the groups. The DOR group exhibited significantly shorter sleep onset latency (15 vs. 22 min, $p = 0.001$) and reduced total sleep duration (7.35 ± 0.93 vs. 7.57 ± 1.01 h, $p = 0.014$) compared to the non-DOR group. Regarding PSQI, both sleep onset latency and sleep time showed significant differences between the groups. However, there were no significant differences in ESS and STOP-Bang Questionnaire scores.

To further investigate the impact of sleep onset latency and total sleep duration on ovarian reserve, we categorized total sleep duration into > 8 h, 6–8 h, and ≤ 6 h, and sleep onset latency into < 30 min, 30–44 min, and ≥ 45 min. Significant differences were found in AMH, Follicle-Left, and Follicle-Right based on total sleep duration ($p = 0.007$, 0.005, 0.030, respectively), indicating higher levels in those with > 8 h of sleep compared to ≤ 6 h. Sleep onset latency also showed significant differences in AMH, Follicle-Left, and Follicle-Right ($p = 0.001$, 0.011, 0.036, respectively), with the 30–44 min group showing higher AMH levels compared to the other groups. Groups with ≥ 45 min of sleep onset latency exhibited higher Follicle counts compared to other groups(Fig. 1).

A logistic regression model identified age, PSQI-sleep latency, and PSQI as independent risk factors for DOR (adjusted odds ratios [OR] = 0.831, 1.708, 0.870, $p < 0.001$, 0.002, 0.036, respectively). Exploring subjects aged ≥ 35 years (277 subjects), snoring and PSQI-sleep latency were found to be independent risk factors for DOR (OR = 2.489, 2.007, $p = 0.040$, 0.008, respectively). Additionally, when stratified by BMI, in the BMI ≥ 25 kg/m^2 group, age was the only independent risk factor for DOR (OR = 0.822, $p < 0.001$), whereas in the BMI < 25 kg/m^2 group, both age and PSQI-sleep latency were identified as independent risk factors (OR = 0.828, 1.761, $p < 0.001$, 0.003, respectively) (Table 3).

Discussion

Our study investigated the relationship between sleep parameters and DOR among women at an infertility clinic. We found that shorter sleep onset latency and snoring were significantly associated with an increased likelihood of DOR in women aged 35 years and older. Specifically, women in this age group who experienced these sleep disturbances had approximately 2.489 and 2.007 times higher odds of developing DOR, respectively, compared to those without these issues, after adjusting for other variables. These findings suggest that sleep disruptions may contribute to ovarian dysfunction and potentially worsen DOR among our study participants.

As modern society continues to progress and pregnancy is increasingly delayed, DOR has become a significant challenge for women seeking pregnancy, as well as for future societal demographics[13]. Studies have reported varying prevalence rates of DOR among reproductive-age women, ranging from 10 to 26%, with higher incidences observed in populations undergoing ART[1415]. Women with DOR undergoing ART typically experience lower oocyte yields, reduced live birth rates, and higher rates of treatment discontinuation compared to those with normal ovarian reserve[16]. The etiology of DOR is multifaceted and includes autoimmune disorders,

	Total	DOR	non-DOR	*p* values
n	979	148	831	-
Age (years)	32.25 ± 4.47	35.35 ± 4.98	31.70 ± 4.14	< 0.001
BMI (kg/m2)	21.99 ± 3.62	31.08 ± 5.27	30.60 ± 3.00	0.541
NC	30.68 ± 3.45	22.15 ± 3.32	21.95 ± 3.67	0.122
Follicle-Left	7.00(4.00,10.00)	2.00(2.00,4.00)	7.00(5.00,10.00)	< 0.001
Follicle-Right	7.00(5.00,10.00)	3.00(2.00,4.00)	7.00(5.00,10.00)	< 0.001
AMH	3.30(1.86,5.52)	0.86(0.53,1.19)	3.78(2.48,6.09)	< 0.001
FSH	6.25(5.27,7.57)	8.33(6.51,10.75)	6.04(5.18,7.15)	< 0.001
LH	3.70(2.70,5.00)	3.50(2.50,4.80)	3.80(2.80,5.10)	0.055
FSH/LH	1.78(1.30,2.36)	2.46(1.87,3.38)	1.65(1.25,2.21)	< 0.001
PRL	13.90(9.90,20.15)	14.00(10.10,18.80)	13.90(9.90,20.30)	0.933
E2	30.00(22.00,40.00)	34.00(25.00,53.00)	30.00(22.00,39.00)	< 0.001
T	0.26(0.20,0.32)	0.23(0.18,0.27)	0.27(0.21,0.32)	< 0.001

DOR diminished ovarian reserve, BMI body mass index, NC Neck circumference, AMH anti-Müllerian hormone, FSH follicle-stimulating hormone, LH luteinizing hormone, E2 estradiol, PRL prolactin, T testosterone.

Table 1. Characteristics of DOR and non-DOR.

	Total	DOR	non-DOR	*p* values
PSQI-subjective sleep quality [b] (n,%)	0 score = 232(23.70) 1 score = 620(63.33) 2 scores = 120(6.46) 3 scores = 7(7.15)	0 score = 33(22.30) 1 score = 95(64.19) 2 scores = 17(11.49) 3 scores = 3(2.03)	0 score = 199(23.95) 1 score = 525(63.18) 2 scores = 103(12.39) 3 scores = 4(0.48)	0.217
sleep onset latency (min)	20.00(10.00,30.00)	15.00(10.00,30.00)	22.00(10.00,30.00)	0.001
PSQI-sleep latency[b] (n,%)	0 score = 269(27.48) 1 score = 464(47.40) 2 scores = 196(20.02) 3 scores = 50(5.11)	0 score = 61(41.22) 1 score = 59(39.86) 2 scores = 23(15.54) 3 scores = 5(3.38)	0 score = 208(25.03) 1 score = 405(48.74) 2 scores = 173(20.82) 3 scores = 45(5.42)	0.001
sleep duration (hr)[a]	7.53 ± 1.00	7.35 ± 0.93	7.57 ± 1.01	0.014
PSQI- sleep time[b] (n,%)	0 score = 546(55.77) 1 score = 337(34.42) 2 scores = 89(9.09) 3 scores = 7(0.72)	0 score = 75(50.68) 1 score = 48(32.43) 2 scores = 23(15.54) 3 scores = 2(1.35)	0 score = 471(56.68) 1 score = 289(34.78) 2 scores = 66(7.94) 3 scores = 5(0.60)	0.019
PSQI-habitual sleep efficiency[b] (n,%)	> 85%=751(76.71) 75-84%=172(17.57) 65-74%=33(3.37) < 65%=20(2.04)	> 85%=109(73.65) 75-84%=30(20.27) 65-74%=4(2.70) < 65%=2(1.35)	> 85%=642(77.26) 75-84%=142(17.09) 65-74%=29(3.49) < 65%=18(2.17)	0.672
PSQI-sleep disturbances[b] (n,%)	0 score = 126(12.87) 1 score = 791(80.80) 2 scores = 62(6.33) 3 scores = 0	0 score = 15(10.14) 1 score = 122(82.43) 2 scores = 11(7.43%) 3 scores = 0	0 score = 111(13.36) 1 score = 669(80.51) 2 scores = 51(6.14) 3 scores = 0	0.496
PSQI-use of sleeping medication[b] (n,%)	0 score = 972(99.28) 1 score = 5(0.51) 2 scores = 2(0.20) 3 scores = 0(0)	0 score = 148(100%) 1 score = 0(0) 2 scores = 0(0) 3 scores = 0(0)	0 score = 824(99.16) 1 score = 5(0.60) 2 scores = 2(0.24) 3 scores = 0	0.534
PSQI-daytime dysfunction[b] (n,%)	0 score = 400(40.86) 1 score = 414(42.29) 2 scores = 135(13.89) 3 scores = 30(3.06)	0 score = 62(41.89) 1 score = 60(40.54) 2 scores = 18(12.16) 3 scores = 8(5.41)	0 score = 338(40.67) 1 score = 354(42.60) 2 scores = 117(14.08) 3 scores = 22(2.65)	0.305
PSQI score[a]	4.00(3.00,6.00)	4.00(3.00,5.75)	4.00(3.00,6.00)	0.934
PSQI-sleep quality [b] (n,%)	0 score = 708(72.32) 1 score = 245(25.03) 2 scores = 24(2.45) 3 scores = 1(0.10)	0 score = 110(74.32) 1 score = 31(20.95) 2 scores = 6(4.05) 3 scores = 0(0)	0 score = 598(71.96) 1 score = 214(25.75) 2 scores = 18(2.17) 3 scores = 1(0.12)	0.352
Stop-Bang score	0.00(0.00,1.00)	0.00(0.00,1.00)	0.00(0.00,1.00)	0.999
snoring history(n,%)	74(7.59)	14(9.46)	60(7.22)	0.316
tired during the day	226(23.08)	33(22.30)	193(23.23)	0.327
hypertension history(n,%)	3(0.31)	0(0.00)	3(0.36)	0.109
ESS score	5.00(3.00,7.00)	4.00(2.25,7.00)	5.00(3.00,7.00)	0.808

DOR diminished ovarian reserve, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale. [a]Student *T* Test was used. [b]Chi-Square Test was used.

Table 2. Comparison of PSQI and stop-Bang between DOR and non-DOR.

genetic abnormalities, environmental factors, and iatrogenic causes, although many cases remain idiopathic[17]. Advanced maternal age is a well-established contributor to DOR due to diminished ovarian follicular pool and oocyte quality decline[18]. Consistent with this understanding, our study confirmed that women in the DOR group were older than those in the non-DOR group, underscoring the impact of age on ovarian reserve.

In addition to age, our findings suggest an association between sleep disturbances and DOR. Sleep disruptions, such as inadequate sleep duration and poor sleep quality, are known to disrupt the endocrine system. These disruptions can alter the secretion of reproductive hormones crucial for ovarian function and follicular development, including FSH, LH, and AMH[19]. Previous research has linked insufficient sleep (< 5–6 h) to menstrual cycle[20], sperm parameters[21], natural fertility[22], or IVF outcomes[23]. Gong et al.[24] found that poor sleep quality independently increased the risk of both of these menstrual issues. Our study adds to this body of evidence by demonstrating that the DOR group exhibited significantly shorter total sleep duration and shorter sleep onset latency. Logistic regression analysis identified PSQI-sleep latency as an independent risk factor for DOR across all subjects, particularly in those aged 35 and older. This observation suggests that rapid sleep onset, potentially indicative of underlying sleep disorders or poor sleep quality, could serve as a marker for compromised ovarian reserve. Similarly, studies have demonstrated that insufficient sleep can negatively impact natural fertility and IVF outcomes, reinforcing our findings that sleep disruptions, such as shorter total sleep duration, may contribute to ovarian dysfunction[2223].

Sleep disturbances, such as shorter sleep onset latency and snoring, disrupt both the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes, leading to hormonal imbalances and stress-related effects that can impair ovarian function[2526]. Disruptions in the HPG axis affect the secretion of key reproductive hormones like FSH, LH, and AMH, which are crucial for maintaining ovarian reserve[27]. On the other hand, rapid sleep onset may indicate dysfunction in the HPA axis, which regulates cortisol secretion[28]. Chronic stress and elevated cortisol levels have been associated with ovarian dysfunction and reduced ovarian reserve, potentially accelerating ovarian aging[2930]. Moreover, conditions like OSA exacerbate these effects

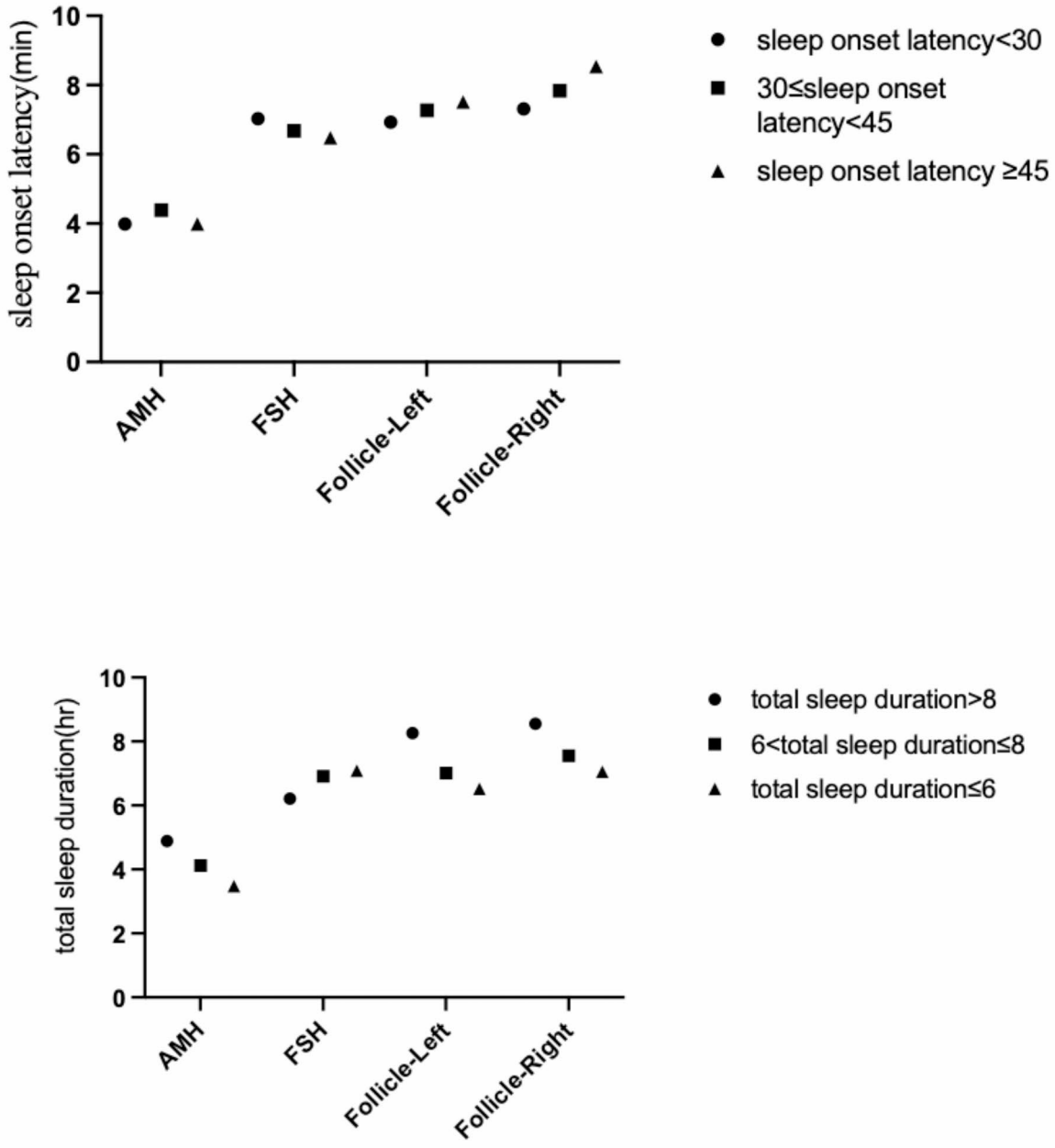

Fig. 1. illustrates AMH, FSH, Follicle-Left, and Follicle-Right levels across different sleep onset latency and duration categories.

through intermittent hypoxia, increasing oxidative stress and potentially reducing ovarian reserve[31]. Additionally, immune dysregulation resulting from sleep loss elevates pro-inflammatory cytokines, negatively affecting ovarian health and accelerating follicular depletion[32]. In summary, sleep disturbances may affect ovarian reserve through multiple interconnected pathways, including neuro-endocrine and immune dysregulation, oxidative stress, and hormonal imbalances. Further research is needed to better understand these mechanisms and their contribution to DOR.

Our study also identified snoring as a specific sleep-related factor significantly associated with DOR, especially among women aged 35 years and older. Snoring often indicates OSA, a condition characterized by

Groups	Independent variable	OR	95%CI	*p* values
	age	0.831	0.794–0.869	< 0.001
all subjects	PSQI-sleep latency	1.708	1.220–2.393	0.002
	PSQI	0.870	0.764–0.991	0.036
aged ≥ 35 years	Snoring	2.489	1.042–5.947	0.040
	PSQI-sleep latency	2.007	1.201–3.352	0.008
BMI ≥ 25 kg/m^2	age	0.822	0.738–0.915	< 0.001
BMI < 25 kg/m^2	age	0.828	0.788–0.871	< 0.001
	PSQI-sleep latency	1.761	1.212–2.559	0.003

Table 3. A logistic regression model with factors affecting DOR for all subjects and in subjects aged ≥ 35 years. DOR diminished ovarian reserve, PSQI: Pittsburgh Sleep Quality Index, BMI body mass index

repeated airway collapse during sleep, leading to oxygen desaturation and fragmented sleep patterns. OSA is known to induce oxidative stress, systemic inflammation, and endothelial dysfunction, all of which are implicated in accelerated aging processes[33]. Oxidative stress is recognized as a key mechanism in ovarian aging, and antioxidants like resveratrol have been explored as effective measures to delay oocyte aging[3435]. Studies have shown that resveratrol, an antioxidant, has also been beneficial in treating sleep apnea patients[36]. Therefore, we hypothesize that chronic intermittent hypoxia and oxidative stress associated with OSA could exacerbate ovarian aging through multiple pathways, including alterations in the secretion of hormones crucial for ovarian function and follicular development.

Our findings hold significant clinical implications for women undergoing ART treatments, especially those with DOR. Identifying sleep disturbances like shorter sleep onset latency and snoring as risk factors highlights the need to include sleep assessments in infertility evaluations. Early detection of sleep issues could offer opportunities for interventions to improve reproductive outcomes. Addressing sleep disorders through behavioral or medical therapies may help preserve ovarian function and fertility. Moreover, comprehensive care for women over 35, who are at higher risk for both sleep disturbances and DOR, should include sleep hygiene education and management. Future studies should investigate whether improving sleep quality could enhance ovarian reserve or ART success, offering new treatment possibilities for women with DOR.

Despite the insights gained, our study has several limitations. The cross-sectional design limits causal inference, and prospective longitudinal studies are warranted to establish temporal relationships between sleep patterns and DOR. Additionally, our findings are based on self-reported sleep assessments, which may be subject to recall bias and variation in reporting. Furthermore, we did not include measures of stress and anxiety, which are known to impact sleep quality and could have influenced the results. Future research could benefit from incorporating stress and anxiety scales, along with a control group without DOR but experiencing stress, to better differentiate the roles of these factors. Objective measures of sleep quality, such as actigraphy or polysomnography, should also be considered in future studies to provide more precise and detailed insights, particularly in relation to conditions like obstructive sleep apnea and its potential impact on ovarian reserve.

Conclusion

In conclusion, our study underscores the significance of sleep parameters as potential contributors to diminished ovarian reserve in women seeking infertility treatment. Addressing sleep disturbances, especially among older women, may offer a novel approach to enhancing reproductive outcomes in clinical practice. Further investigation into the mechanistic links between sleep and ovarian function is warranted to optimize fertility treatment strategies and improve overall reproductive health outcomes.

Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Q.-C.L. or J.-F.H.