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Sleep disturbances and female infertility: a systematic review

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Abstract

Background Sleep disturbances are more prevalent among women with infertility. Current research increasingly highlights the significant relationship between sleep disturbances and female infertility, suggesting that sleep may be a key factor in reproductive health. In this review, we aim to delve into the complex interplay between sleep disturbances and female infertility, as well as to assess the underlying mechanisms involved, and seek to illuminate the causes of sleep-related fertility issues. The understanding of these contents may help clinicians enhance clinical strategies for managing sleep disturbances in women facing infertility challenges and provide timely support to those seeking fertility treatments.

Methods A comprehensive literature search was conducted in the PubMed and EMBASE databases. Studies that described sleep patterns or any type of sleep disturbance, sleep breathing disorders and their associations with female infertility or female fecundity, published between January 1, 2010, and November 1, 2023, were identified and extracted. The screening, data extraction, and quality assessment processes were independently performed by paired reviewers. The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal tools for observational and cohort studies.

Results A total of 1,179 articles were initially identified from the search strategy (PubMed, $n=377$; EMBASE, $n=802$). After removing duplicates ($n=83$) and screening for eligibility ($n=75$), 19 studies were reviewed and determined to be eligible for inclusion. Infertile women generally report poorer sleep quality and exhibit more evening sleep chronotypes. Sleep disorders are significantly associated with infertility. Poor sleep quality, extreme sleep durations, and certain sleep chronotypes are associated with poorer fertility treatment outcomes, such as a reduced number of retrieved oocytes, decreased embryo quality, and lower fertilization rates. Obstructive sleep apnea (OSA) is also more prevalent in women with fertility issues, especially those with polycystic ovary syndrome (PCOS), and may negatively impact reproductive outcomes. The circadian rhythms of the *Clock gene* system, melatonin and hormone dysregulation, oxidative stress and immune response are considered to be potential mechanisms explaining how sleep disturbance impairs reproductive function, remain to be fully elucidated, and therefore, require further investigation.

Conclusions Sleep disturbances are negatively associated with female infertility and poor fertility treatment outcomes. Longitudinal studies are expected to substantiate these findings and inform more nuanced approaches to prior sleep management and lifestyle advisement for infertile women, especially those undergoing fertility treatments.

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Trial registration This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO, #CRD42024498443).

Keywords Sleep, Fertility, Sleep disturbance, Sleep breathing disorder, Female infertility, Female reproduction

Introduction

Instead of being a quality of life concern, infertility is a disease that poses a serious threat to patients' physical and social health [1]. In recent years, the female infertility rate among age-standardized populations has grown by 14.962% globally, and increased by 0.370% annually [2]. The most common risk factors for female infertility are diabetes, thyroid disease, polycystic ovary syndrome (PCOS), underweight/overweight and advanced paternal and maternal ages [3]. Lifestyle habits such as diet, smoking, drinking and sleep can also have an impact on fertility [4].

Sleep disturbance is a common public health issue that negatively affects people's physical and mental health, impairing the quality of life of patients. Sleep is involved with many physiologic systems in the human body [5], and inadequate sleep is associated with many chronic diseases and conditions, some of which may be risk factors for female infertility, such as diabetes, obesity, thyroid disease and PCOS [6–9], suggesting a potential relationship between sleep and female reproductive health. The risk of developing sleep disorders is constantly changing in each stage of a female's life cycle, from menstruation, pregnancy to menopause. These disorders uniquely affect women's emotional and physical health, hormone regulation, and even pregnancy outcomes [10–12]. Growing evidence indicates that the regulation of reproductive hormones is associated with the hypothalamic-pituitary-gonadal (HPG) axis, which follows a circadian rhythm. Sleep deprivation can disrupt this rhythmicity, leading to the dysregulation of reproductive hormones and negatively impacting fertility in women [1, 13–16].

Recent research highlights a significant relationship between sleep disturbances and female infertility, suggesting that sleep may be a key factor in reproductive health [17, 18]. Yet, the body of research exploring sleep patterns in this context remains sparse, and the association between sleep and infertility is not fully understood. As awareness of this relationship grows, more precise sleep assessments are being implemented to explore potential associations and underlying mechanisms.

In this review, we intend to: (1) explore the association between sleep disturbance, sleep patterns and female infertility, (2) evaluate the causes of and propose better management strategies for sleep disturbances in infertile women, and (3) review the potential mechanism underlying the association between sleep disorders and female infertility.

Methods

This systematic review followed the protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19], and was registered in the International Prospective Register of Systematic Reviews (PROSPERO, #CRD42024498443).

Search strategies

This review conducted a literature search utilizing the electronic databases PubMed and EMBASE from January 1, 2010 to November 1, 2023. The descriptors were included but were not limited to "sleep", "sleep disorders", "sleep dysfunction", "sleep disturbance", "fertility", "infertility", "in vitro fertilization", "fertility treatment", "sleep breathing disorder", "obstructive sleep apnea", "circadian dysrhythmia", "melatonin", "HPG axis", "HPA axis" and "oxidative stress". The overview of the search strategies and selection process is shown in Fig. 1 using the PRISMA flow diagram.

Eligibility criteria

To be included, studies had to fulfill the following criteria: (1) examined sleep, sleep disturbances or any type of sleep breathing disorders and their association with female infertility; (2) were conducted among infertile women or evaluated the fecundity among reproductive-age women; and (3) were written in English. The study exclusion criteria included: review articles, case reports, commentaries, meeting and conference abstracts, laboratory studies and animal studies.

Quality assessment

The Joanna Briggs Institute (JBI) Critical Appraisal tools for observational studies and cohort studies [20] were used to evaluate the quality of the included studies. Two authors (J.L. and Y.L.H.) independently assessed the criteria for each content, and any conflicts were resolved by discussion and agreement with another author (Y.W.). In JBI checklists, the assessor could select the answers 'Yes', 'No', 'Unclear' or 'Not applicable' for each item, and the final outcomes are synthesized in the Supplemental Tables 1 and 2.

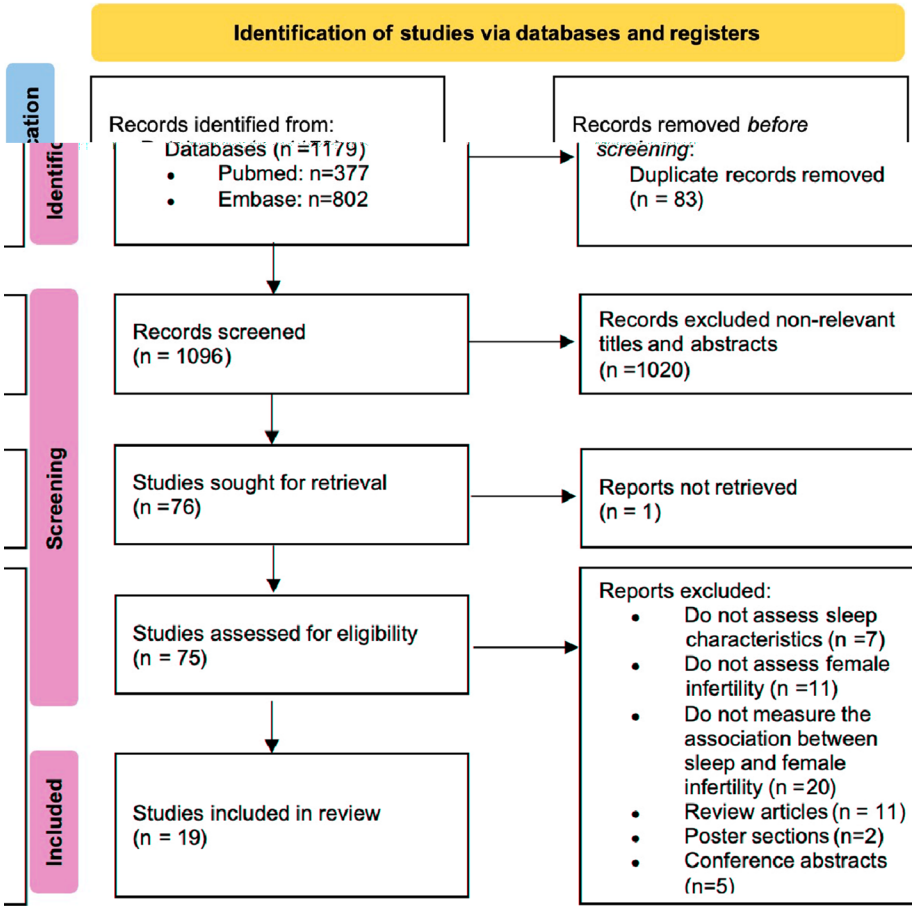

Fig. 1 PRISMA Flow diagram of search strategies and study selection for this review

Data extraction and synthesis

Two authors (J.L. and S.R.X.) independently screened the titles and abstracts of the articles based on the eligibility criteria. Full texts of the articles were evaluated and selected by a pair of independent authors (J.L. and Y.L.H.), any concerns or disagreements were resolved through discussion among the team members. Both authors (J.L. and Y.L.H.) extracted and organized the data: (1) study description (publication year, first author and country); (2) study type, population and age of the participants; (3) fertility characteristics, sleep measurements and other clinical issues; and (4) main results of the studies.

Results

A total of 1179 articles were identified from the search strategy. After screening and reevaluating 1096 titles and abstracts, 19 relevant studies focusing on the association between sleep disturbance and female infertility were ultimately extracted. The articles were synthesized and characterized into 3 groups: (1) sleep disturbance and infertility among reproductive-age females (Table 1); (2) sleep disturbance and females under fertility treatments (Table 2); and (3) obstructive sleep apnea and female infertility (Table 3).

Measurement of sleep

Insufficient sleep duration and poor sleep quality are the most intuitive manifestations of sleep dysfunction. These conditions are assessed using heterogeneous measurement tools, which we briefly outline as they pertain to the studies included in our review (Fig. 2).

For objective assessment, polysomnography (PSG), polygraphy, and actigraphy are employed [21]. PSG is considered to be the gold-standard for sleep quality and quantity measurements, offering precise and objective continuous physiological information on sleep [22]. It is routinely used to diagnose sleep-related movement disorders and breathing disorders, such as obstructive sleep apnea (OSA) and sleep apnea [21, 23], as demonstrated in two studies [24, 25]. However, due to its high cost and the inconvenience it poses,

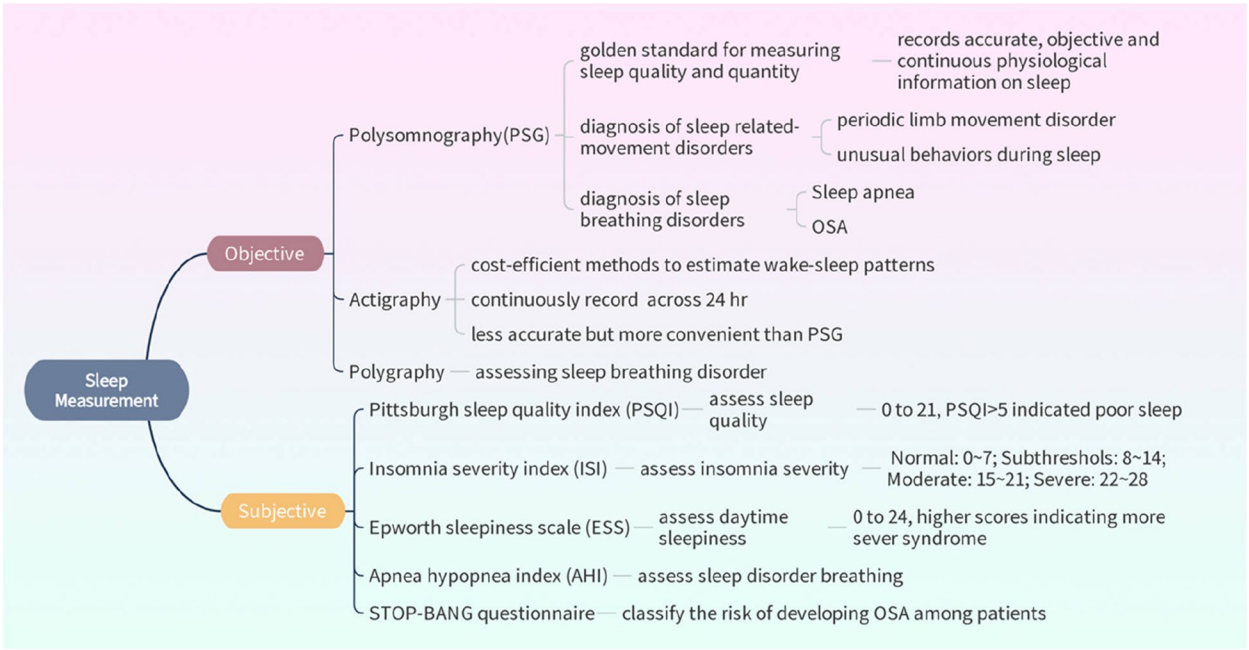

Fig. 2 Classifications of sleep measurements

the clinical use of PSG is restricted. Actigraphy, alternatively, offers a less invasive and more affordable means to analyze sleep patterns and movements over extended periods [26]. In our review, sleep was evaluated using wrist-worn actigraphy or type III portable sleep monitors in several studies [25, 27–29]. Subjective sleep assessments typically involve questionnaires and self-reported diaries. The Pittsburgh Sleep Quality Index (PSQI) is the predominant instrument for sleep quality assessment in our reviewed literature [17, 18, 29–32], with scores ranging from 0 to 21; a score above 5 suggests poor sleep quality in most of the studies. The Insomnia Severity Index (ISI) measures the insomnia symptoms and severity [33], while the Epworth Sleepiness Scale (ESS) measures symptoms of daytime sleepiness [29, 32, 34]. The Apnea Hypopnea Index (AHI) and the STOP-BANG questionnaire are utilized to assess sleep-disordered breathing and the likelihood of developing OSA, respectively [29, 32, 35].

In conjunction with sleep assessment, mental health conditions in infertile women were evaluated using the Copenhagen Multi-Centre Psychosocial Infertility scale (COMPI), Beck Depression Inventory (BDI), Perceived Stress Scale (PSS), and State-Trait Anxiety Inventory (STAI), and Depression Inventory (MDI) [17, 28, 29, 31, 36]. These instruments measure symptoms of depression, stress, and anxiety, which are hypothesized to influence sleep dysfunction.

Sleep disturbance and infertility among reproductive-age females

Epidemiologic studies of sleep disorders and female infertility are relatively rare, less is investigated regarding the association between sleep disturbance and infertility among reproductive-age females (Table 1). Correspondingly, infertile women reportedly have worse sleep quality and more evening chronotypes when compared to fertile population [30]. Women with sleep disorders were found 3.718 times more likely to develop infertility than those without sleep disorders [37]. Subsequent cross-sectional studies utilizing large datasets of reproductive-age females among the US and China currently analyzed the association between sleep duration and female infertility, offering conflicting results. A U-shaped association between female sleep duration and the probability of conception was observed in both US (National Health Interview Survey, NHIS) and China (China Health and Nutrition Survey, CHNS) populations [38], noting a critical threshold of 7 hours per day of sleep, beyond this "turning point" any deviation (longer or shorter) from 7/h day sleep was linked to an increased probability of conception. Conversely, in another study composed of females from the US (National Health and Nutrition Examination Survey, NHANES) found that sleep duration of 8.5 hours per day had the significantly lowest infertility risk, which also fit a U-shaped model. Moreover, females with healthy and regular sleep behaviors,

Table 1 Sleep disturbance and infertility among reproductive-age females

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2023	Freeman [41]	Females attempting pregnancy with history of 1–2 pregnancy loss	Prospective cohort study	$n=1220$	18–40	Time to pregnancy (TTP)	Self-reported sleep characteristics	• Sleep duration (< 6, 6-<7, 7-<8, 8-<9, ≥ 9) • Sleep midpoint (2:44, 3:36, 4:30) • Social jetlag • Shift work	n/a	n/a	Sleep duration, later sleep midpoints, social jetlag and night shift were not associated with reduced fecundability. In sensitivity analyses, sleep duration ≥ 9 hours was associated with low fecundability.
2023	Özçelik [30]	Females with infertility	Cross-sectional study	• $n=110$ infertility • $n=117$ fertility	18–40	Infertility or not	• Morningness-Eveningness Questionnaire (MEQ) • Pittsburgh Sleep Quality Index (PSQI)	• Sleep chronotype (MEQ 16–41, evening type; 42–58 intermediate type; 59–86 morning type) • Sleep quality (PSQI > 5 poor sleep quality)	n/a	n/a	Significantly worse sleep quality, and more evening chronotype were found in the patients with infertility.
2023	Zhao [40]	Females attempting pregnancy (from NHANES)	Cross-sectional study	$n=1820$ ($n=248$ infertility, $n=1572$ fertility)	20–40	Infertility or not	Sleep interview and self-report sleep duration	• Sleep disorder (question about trouble sleeping or sleep disorder) • Sleep duration (≤ 6, 7–8, > 8)	Depress	The Patient Health Questionnaire (PHQ-9)	The risk of infertility was 2.14-fold higher in individuals with sleep disorders than in those without.
2022	Liang [39]	Females attempting pregnancy (from NHANES)	Cross-sectional study	$n=2175$ ($n=212$ infertility, $n=1963$ fertility)	18–44	Self-reported infertility	Self-reported sleep characteristics	• Sleep duration • Sleep behavior (bedtime, waketime)	n/a	n/a	Sleep-wake behavior was significantly associated with infertility and participants with early-bed/early-rise behavior had the lowest risk.

Table 1 (continued)

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2020	Shi [38]	Females and males in reproductive-age (from NHIS, CHNS)	Cross-sectional study	• $n = 9137$ females from NHIS • $n = 2687$ females and male mates from CHNS	• Mean 34 (range 27–41) from NHIS • Mean 38 (range 32–42) from CHNS	Self-reported pregnancy status	Sleep questionnaire	Sleep duration • NHIS (≤ 5, 6, 7, 8, ≥ 9) • CHNS (≤ 6, 7, 8, 9, ≥ 10)	n/a	n/a	A U-shaped association between female sleep duration and conception probability was observed, 7 h/day was associated with a lower probability of conception when compared to either longer or shorter sleep duration times in both NHIS and CHNS populations.
2019	Willis [36]	Females attempting pregnancy (from PRESTO)	Prospective cohort study	$n = 6,873$	21–45	Time to pregnancy (TTP)	Sleep questionnaire	• Sleep duration (< 6, 6, 7, 8, ≥ 9) • Sleep quality (MDI, have you had trouble sleeping at night?) • Shift work	Depress, stress and anxiety	• Perceived stress scale (PSS-10), • Major Depression Inventory (MDI)	Trouble sleeping at night and shorter sleep duration were associated with modestly reduced fecundability, the results were slightly stronger among women with higher depressive symptoms and perceived stress levels. Little association was seen between shift work and fecundability.

Table 1 (continued)

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2018	Wang [37]	Females with infertility (from NHIRD)	Retrospective cohort study	*n* = 16,718 NASD, *n* = 33,436 control	35.45 ± 6.62 (NASD), 35.26 ± 6.60 (control)	ICD-9-CM diagnosed infertility	ICD-9-CM diagnosed non-apnea sleep disorder	n/a	n/a	n/a	NASD patients had a 3.718-fold risk of female infertility compared with the control cohort and the younger age group patients were more likely to become infertile which may be due to high level of stress.

CHNS China Health and Nutrition Survey, *NHANES* National Health and Nutrition Examination Survey, *NHIRD* National Health Insurance Research Database, *NHIS* National Health Interview Survey, *PRESTO* Pregnancy Study Online, *ICD-9-CM* International Classification of Diseases, Ninth Revision, Clinical Modification

such as early-bed time or early-rise time, were relatively least likely to develop infertility relatively [39]. After adjusting for sleep duration, sleep disorders were also found to be significantly associated with female infertility in the NHANES dataset [40].

Another web-based cohort preconception study among 6,873 females in North America prospectively estimated the time to pregnancy (TTP) and sleep patterns, revealing that disturbed sleep and shorter sleep duration (< 6 hours per day) were related to modestly reduced fecundability. A U-shaped association was also observed in this study when stratifying sleep quality, females with longer sleep durations (≥ 9 hours per day) experiencing reduced fecundability, whereas no association was seen between shift work and fecundability [36]. A recent similar prospective cohort study indicated that for women with history of pregnancy loss, sleep duration ≥ 9 hours (relative to 7 to < 8 h/day) was associated with longer TTP in certain subgroups, while sleep duration, sleep chronotype and shift work were not associated with fecundability or live birth among the full cohort [41].

Sleep disturbance and females under fertility treatment

Sleep disturbances are prevalent among females receiving fertility therapy, as evidenced by poor sleep quality (PSQI > 5) in 24.1%–57% of infertile patients and sleep duration less than 7 hours during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in 42%–69% of patients [17, 29, 31, 42]. Sleep disorders not only degrade the quality of life for infertile patients, but also may be associated with poor reproductive treatment outcomes. These findings are concisely captured in Table 2.

Emerging evidence suggests that sleep quality is a modifiable risk factor that may negatively influence fertility treatment outcomes. Poor subjective sleep quality has been inversely associated with embryo quality and the number of retrieved oocytes [17, 18]. Later, in a larger sample size of 1276 females receiving IVF/ICSI [18], Yao QY et al. reported that the number of mature oocytes and good-quality embryos decreased in patients who had difficulty falling asleep more than 3 times a week, compared to women without such problems. Additionally, women with poor sleep quality (PSQI > 5) reported reduced fertilization rate [17, 18, 43] and Liu Z et al. reported that poor sleep quality (PSQI > 5) was significantly associated with lower clinical pregnancy and live birth rates in a cohort study of 3,183 infertile women undergoing their first IVF-ET cycle [44].

Associations between sleep duration and fertility treatment outcomes have also been examined, with limited and contradictory studies. Yao QY et al. reported that women with shorter sleep durations (< 7 h) exhibited a decreases in the number of retrieved and mature oocytes when compared with those who slept 7–8 h a night [18], but this conclusion was contradicted by Li QL et al [17]. Goldstein CA reported a positive trend, with an increase of 1.5 oocytes for every additional hour of sleep, although the correlation did not reach statistical significance [29]. Other research revealed no differences in fertilization rates or the number of retrieved oocytes across various sleep durations [45]. Notably, extreme sleep durations appear to be detrimental; one study demonstrated that shorter sleep duration (< 7 h), later bedtime and sleep midpoint significantly decreased the likelihood of completing IVF cycles [28]. A study of 656 women undergoing IVF treatment suggested that 7–8 hours of sleep is optimal, with pregnancy rates decreasing for both shorter (4-6h) and longer (9-11h) sleep durations [45]. A similar conclusion was drawn by Yao QY et al. [18], investigators observed that women with considerably longer sleep durations (9-10h) were less likely to become pregnant, particularly among women under the age of 30. Sleep duration was found to have no significant association with any clinical pregnancy or live birth [17, 44].

Research examining the relationship between sleep chronotype and IVF/ET outcomes is sparse, and the definitions of sleep chronotypes are also inconsistent between these studies resulting in misclassification and conflicting conclusions. One study indicated that women with a morningness chronotype (sleep midpoint earlier than 2:30 AM) estimated by the Munich ChronoType Questionnaire [46] experienced lower clinical pregnancy and live birth rates and a higher miscarriage rate [44]. Another study observed a U-shaped association between mid-sleep time (MST) and fertilization rate, that MST earlier than 2:21 a.m. or later than 3:00 a.m. was inversely associated with the fertilization rate [18], and the MST was divided into three categories based on tertiles (i.e. earlier than 2:21 a.m., 2:21 a.m. to < 3:00 a.m. and later than 3:00 a.m.).

Variability in sleep duration categorization, sleep chronotype definitions, assessment timelines (before ovulation induction vs. on the day of oocyte retrieval), and study population characteristics may contribute to these inconsistent findings.

Obstructive sleep apnea and female infertility

Sleep breathing disorders such as OSA are more prevalent in women with fertility problems (Table 3). Prior research has primarily concentrated on the association between OSA and PCOS. According to Eisenberg et al. [34], OSA is approximately 4 times more common among reproductive-age women with PCOS. Furthermore, a comprehensive 14-year retrospective cohort study revealed that infertile women had a significantly

Table 2 Sleep disturbance and females under fertility treatment

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2023	Li [17]	Females receiving IVF/ICSI	Prospective cohort study	$n = 1002$	32.66 ± 5.06	• Oocytes retrieved • Oocyte retrieval rate • Number of mature oocytes, high-quality embryos • Fertilization rate • Clinical pregnancy.	Pittsburgh Sleep Quality Index (PSQI)	• Sleep quality (PSQI > 5 poor sleep quality) • Sleep duration (< 7, 7-<8, 8-<9, 9-<10, ≥ 10) • Sleep disturbances	Mental stress	• Beck Depression Inventory-Short Form (BDI-13) • Zung's self-rating anxiety scale (SAS) •Perceived Stress Scale (PSS)	24.1% of participants reported poor sleep quality. Women with depression, anxiety, and perceived stress were associated with poor sleep. Poor subjective sleep quality, sleep disturbances, and poor sleep efficiency, decreased the quantity and quality of oocytes retrieved, fertilization rates, and clinical pregnancy rates.
2023	Liu [44]	Females receiving IVF	Prospective cohort study	$n = 3183$	31.07 ± 4.19	• Clinical pregnancy • Live birth • Preterm birth • Pregnancy miscarriage	• Pittsburgh Sleep Quality Index (PSQI) • Munich ChronoType Questionnaire	• Sleep duration (< 7, 7–8, 8–9, 9–10, > 10)、 • Sleep quality (PSQI > 5 poor sleep quality) • Sleep chronotype (sleep midpoint, < 2:30 morning type, > 3:30 evening type, 2:30 – 3:30 intermediate type)	n/a	n/a	Women reporting good sleep quality showed higher clinical pregnancy and live birth rates. Women with the morningness chronotype had the lowest rates of clinical pregnancy and live birth and had the highest rate of miscarriage. Sleep duration was found to have no significant association with any outcomes.

Table 2 (continued)

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2022	Yao [18]	Females receiving IVF/ICSI	Prospective cohort study	$n = 1276$	30.9 ± 4.8	• Number of retrieved oocytes, mature oocytes, 2PN, good quality embryos • Maturation rate, fertilization rate • Implantation • Clinical pregnancy	Pittsburgh Sleep Quality Index (PSQI)	• Sleep duration (< 7, 7–8, 8–9, 9–10, > 10) • Mid-sleep time (< 2:21, 2:21-<3:00, ≥ 3:00) • Subjective sleep quality • Sleep disturbance • Shift work	n/a	n/a	Short and disturbed sleep were associated with decreased oocyte quantity and quality, and that a long sleep duration was associated with reduced chance of pregnancy, especially among women younger than 30 years old.
2022	Philipsen [31]	Females and partners receiving IVF/ICSI	A part of a randomized controlled trial	• $n = 163$ female • $n = 132$ partners	• 32 ± 4.5 (female) • 34 ± 6 (partner)	Clinical pregnancy rate	Pittsburgh Sleep Quality Index (PSQI)	• Sleep quality (PSQI > 5 poor sleep quality) • Sleep duration	Psychological distress	• Beck Depression Inventory (BDI) • Copenhagen Multi-Centre Psychosocial Infertility scale (COMPI) • State-Trait Anxiety Inventory (STAI)	91% of participants have poor sleep quality, which is associated with depression and anxiety. Women with good sleep quality have higher clinical pregnancy rates, but the differences did not reach statistical significance.
2021	Stocker [32]	Females with RIF or RM	Prospective cohort study	• $n = 21$ RIF • $n = 33$ RM • $n = 34$ control	Mean 35 (range 20–48)	With RIF, RM or not	• Pittsburgh Sleep Quality Index (PSQI) • Epworth Sleepiness Scale (ESS) • Wrist-worn actigraphy (Actiwatch)	• Sleep quality (PSQI > 5 poor sleep quality) • Daytime sleepiness (ESS) • Sleep-wake patterns (Actiwatch)	n/a	n/a	Women with recurrent miscarriage slept less than the comparison women but more than women with recurrent implantation failure, quality of their objective sleep, and quantity of their subjective sleep, were not significantly different.

Table 2 (continued)

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2021	Pimolsri [28]	Females receiving IVF	Prospective cohort study	$n = 48$	Mean 33 (range 25–42)	IVF cycle completion status	Wrist-worn actigraphy (Actiwatch2)	• Total sleep time • Sleep onset latency • Sleep efficiency • Sleep midpoint	Mental health	Concerns of women undergoing Assisted Reproductive Technology (CART)	Shorter sleep duration (< 7 h) and later sleep midpoints or later bedtimes increase the odds of uncompleted cycles prior to embryo transfer.
2017	Goldst [29]	Females receiving IVF	Prospective cohort study	$n = 22$	Mean 32.5 (range 26–42)	• Number of oocytes retrieved • Level of AMH, day 3 FSH	λ• Pittsburgh Sleep Quality Index (PSQI) • Epworth sleepiness scale (ESS), Insomnia Severity Index (ISI) • STOP questionnaire λ• wrist-worn actigraphy (Actiwatch2)	• Sleep quality (PSQI > 5 poor sleep quality) • Insomnia (ISI, < 8 no, 8–14 subthreshold, 15–21 moderate severity, 22–28 severe) • Sleepiness (ESS > 10, excessive daytime sleepiness) • Obstructive sleep apnea (STOP) • Objective sleep-wake cycles (Actiwatch2)	Stress and anxiety	• Perceived Stress Scale (PSS) • The Concerns of Women Undergoing Assisted Reproductive Technologies (CART)	Although not reaching statistical significance, there was the trend for a linear association between sleep duration and oocytes retrieved with the number of oocytes retrieved increasing by 1.5 on average for every one-hour increase in total sleep time.

ART assisted reproductive technology, *ICSI* Intracytoplasmic sperm injection, *IVF* in vitro fertilization, *NASD* Non-apnea sleep disorder, *RIF* recurrent implantation failure, *RM* recurrent miscarriage

Table 3 Association between obstructive sleep apnea and female infertility

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2023	Zhang [49]	Females with PCOS	Prospective cohort study	$n = 156$	Unknown	• Level of AMH, LH • Number of retrieved oocytes, high-quality, and available embryos • Biochemical and clinical pregnancy rates	Unknown	OSA	n/a	n/a	OSA was found in 37.2% of the PCOS patients, with longer infertility duration and lower levels of AMH and LH than non-OSA patients. OSA patients required significantly higher doses of gonadotropin and had fewer retrieved oocytes, high-quality, available embryos and lower biochemical and clinical pregnancy rates.
2023	Ibrahim [50]	Females with infertility	Cross-sectional study	$n = 258$	Unknown	• Infertility or not • Time to pregnancy • Miscarriage • Irregular menstruation • PCOS	• Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) • STOP Questionnaire (STOP) • Berlin Questionnaire	OSA	n/a	n/a	6% infertile women was found with OSA. OSA diagnosis was associated with miscarriage, but no association was found between OSA and infertility outcomes (PCOS, time to pregnancy, irregular menstruation).
2022	Yang [27]	Females with PCOS	Cross-sectional study	$n = 328$	19–39	Sex hormones' assessment	Type III portable sleep monitor, apnea hypopnea index (AHI)	OSA	n/a	n/a	Among infertile patients with PCOS of childbearing age, 40% were found with mild OSA and 5% with severe OSA. OSA in patients with PCOS was associated with multiple alterations in indexes of reproductive endocrine and metabolic disorders.

Table 3 (continued)

Year	Authors	Study object	Study type	Study population	Age (Mean ± SD)	Fertility characteristics	Sleep measurements	Sleep characteristics	Other clinical features	Other evaluations	Results
2021	Eisenberg [34]	Females with PCOS and UI	Prospective cohort study	• *n* = 739 PCOS • *n* = 864 UI	• 28.9 ± 4.2(PCOS) • 32.2 ± 4.3 (UI)	• Sex hormones' assessment • Conception and live birth	• Sleep Habits Questionnaire • Epworth sleepiness scale (ESS)	• OSA • Sleep duration (< 6)	n/a	n/a	Infertile women with PCOS more commonly report sleep disturbances than those with UI. The presence of clinical symptoms of OSA or short sleep duration does not affect fertility treatment response.
2021	Lim [25]	Females with infertility	Retrospective cohort study	• *n* = 2400 infertility • *n* = 4800 control	32.19 ± 6.20	With Infertility or not	Polysomnography	OSA	n/a	n/a	Infertile women were more likely to have OSA, and women with OSA had 2.101- times the risk of female infertility compared to women without OSA.

PCOS Polycystic Ovary Syndrome, *UI* unexplained infertility, *OSA* Obstructive Sleep

elevated likelihood of being diagnosed with OSA, while females with OSA were more likely to have a diagnosis of PCOS, diminished ovarian reserve and infertility than females without such issues [25, 47].

Moreover, OSA potentially increases the risk of glycolipid metabolic abnormalities and exacerbates insulin resistance in patients with PCOS. Previous studies have indicated a probable association between the heightened incidence of OSA in PCOS patients and factors such as obesity, increased waist circumference, and hyperandrogenemia [27, 48]. According to Yang et al., elevated BMI was found to significantly increase the occurrence and severity of OSA in patients with PCOS, but after correlation for BMI, the probability of sleep disordered breathing in patients with PCOS was still found to be significantly higher than those in a general control group [27].

Additionally, OSA was found to be related to various abnormalities in reproductive endocrine metabolism and had adverse effects on fertility treatment, while controlling for BMI. The severity of sleep apnea or sleep hypopnea and the consequent hypoxia were proportionally related to lower levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [24], potentially exacerbating hormone dysregulation and menstrual irregularities in PCOS patients. Anti-Müllerian hormone (AMH) levels were also found to be significantly reduced in PCOS patients with OSA [27, 49]. A negative correlation exists between sleep disordered breathing and IVF cycle outcomes; for instance, PCOS patients with OSA need significantly higher gonadotropin doses and had lower peak estradiol levels, as well as fewer retrieved oocytes, high-quality and available embryos during ovarian stimulation [49]. Sleep disordered breathing could also lead to poorer clinical outcomes for women undergoing IVF [49]. However, the presence of OSA clinical symptoms may not correlate with live birth rates [34].

Discussion

In general, the associations between sleep, sleep disturbances and female infertility are reviewed and summarized in Fig. 3. Among females of reproductive-age, the association between sleep duration and female infertility appears to be non-linear, fitting a U-shaped pattern, and it might be expected that excessive sleep duration would be associated with reduced fecundability and a higher risk of infertility. However, it is essential to consider that most of the studies were cross-sectional or observational, and the reverse causation is difficult to define since infertility itself may also disrupt female sleep patterns. Studies regarding sleep and IVF/ICSI outcomes have focused mainly on the fertility treatment characteristics, such as the number of oocytes retrieved, good quality embryos and the fertility rates, and have yielded various and conflicting results. Sleep breathing disorders were found to be prevalent among infertile patients with PCOS, dysregulating sex hormone levels, and were negatively associated with fertility, clinical pregnancy and live birth rate.

Sleep parameters were mainly measured using variable questionnaires, which may introduce potential recall bias. The methods used to evaluate sleep parameters were highly heterogeneous, and the definitions and classifications of sleep disturbance, sleep quality, sleep chronotype and sleep duration vary across studies, making it difficult to compare the results. While actigraphy and polysomnography offer more accurate assessments, their higher costs may limit their application in extensive epidemiological studies. In addition, sleep breathing disorders were defined by sleep questionnaires in most studies rather than PSG examination, which may underestimate the patient's condition and severity and underpower the perception of sleep breathing problems and their impact on female infertility. Furthermore, the criteria for defining infertility differ among studies, utilizing TTP, self-reported infertility, pregnancy status and fertility treatment outcomes to assess natural fecundability and female infertility. The sample size, study type, duration of sleep measures and self-reported infertility also varies across studies, and it is unable to assess whether sleep patterns changed over time. These biases may lead to some underestimation of the association between sleep disturbance and female infertility.

Although many factors were considered and adjusted for, such as age, race, BMI, other covariates, such as anxiety or depression disorders, frequency of sexual intercourse, and sleep patterns of their male partners, were poorly considered in most studies.

Causes and management of sleep disturbance in infertile females

Depression, stress and anxiety

Studies highlight that sleep disturbances in infertile women often correlate with mental health issues. For instance, Huang et al. [42] reported that 42.9% of women undergoing IVF treatment suffer from anxiety, while 30% suffer from depression. Additionally, Lin et al. [51] observed that sleep disturbance significantly contributed to psychological distress during IVF processes. Fear of fertility treatment, cultural pressures and the stress of fertility outcomes may exacerbate these issues [52]. Interventions like mindfulness, led by psychological counselors, have shown promise in alleviating depressive symptoms and improving sleep quality, although it did not significantly affect anxiety levels or improve pregnancy outcomes [53].

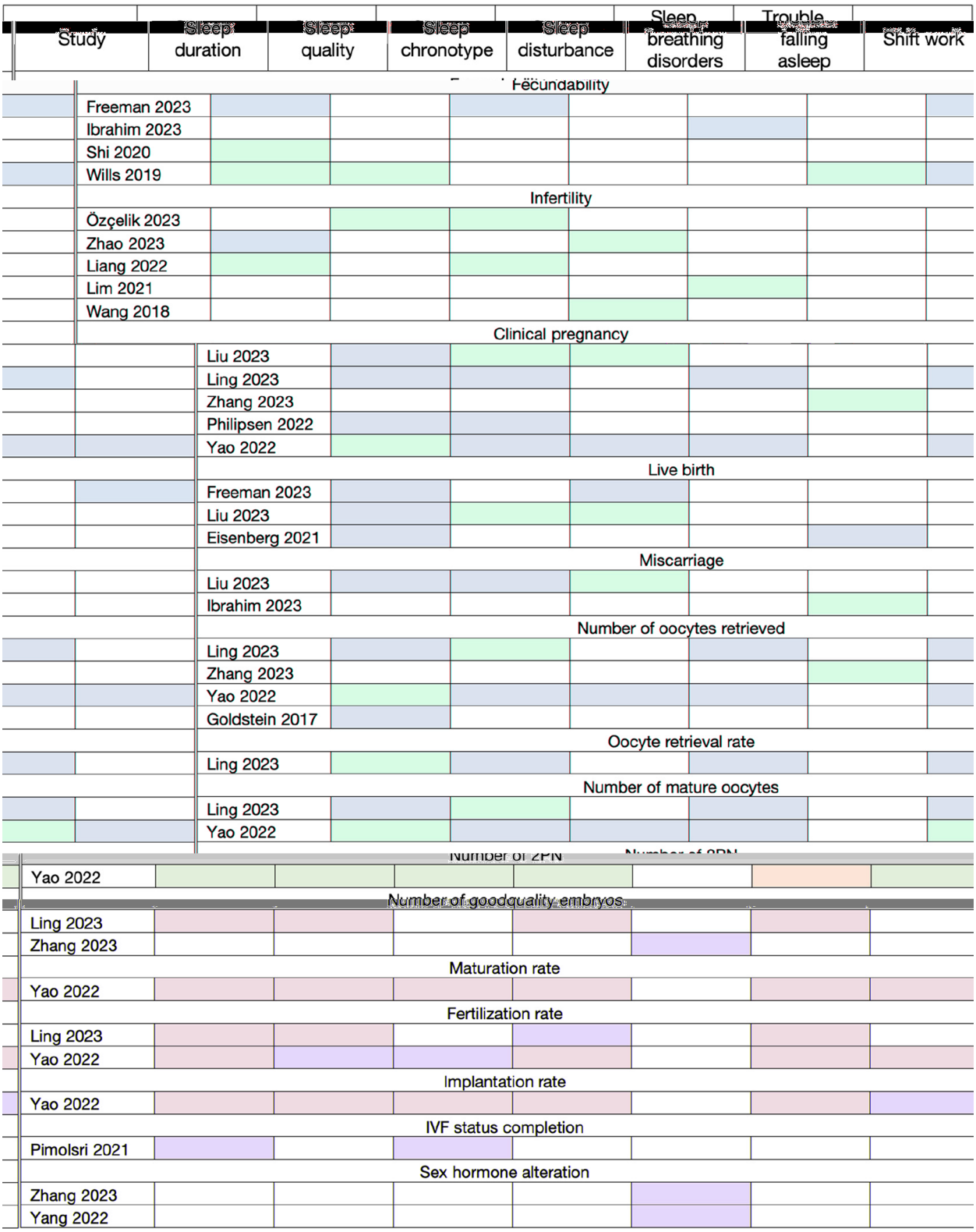

Fig. 3 Association between sleep disturbance and female reproduction. Studies were classified according to fertility aspect (i.e. fecundability, infertility, clinical pregnancy, live birth, and fertility treatment characteristics) and to sleep disturbance (i.e. sleep duration, sleep quality and sleep chronotype). The orange boxes indicate a significant association between sleep disturbances and fertility, while the green boxes indicate no association detected

Obesity, OSA, PCOS

Obesity and OSA are both recognized as risk factors for PCOS. A study revealed that while a significant portion of untreated PCOS patients reported sleep-breathing disorders, obesity appeared to be a crucial factor for developing sleep disorder breathing in patients with PCOS [48]. Obesity may lead to fat accumulation in the parapharyngeal space, abdomen, and chest wall. This accumulation may disrupt neural compensation mechanisms and alter the respiratory control system, leading to the development of OSA [27]. Hyperandrogenemia is also a notable feature in patients with PCOS. It is hypothesized that hyperandrogenemia could contribute to the development of OSA by promoting the accumulation of soft tissue in the pharynx and disrupting the ventilation control mechanism. These changes can compromise pharyngeal patency and cause it to collapse during sleep [27, 54].

PCOS was also found to be associated with increased daytime sleepiness, short sleep duration (< 6h), insomnia, habitual snoring, and sleep-disordered breathing [34, 55], suggesting a potential relationship between obesity, OSA, and PCOS, which may lead to sleep dysfunction. Despite the notable prevalence of sleep breathing disorders among patients with infertility problems [27, 56], there is scant research on the relationship between the two, and sleep breathing disorders are often underdiagnosed. The evidence suggests a considerable deficiency in screening for OSA among reproductive health specialists caring for PCOS patients, even at academic centers [57]. It is suggested that screening for OSA should be considered as routine assessments for patients with PCOS, especially infertile patients seeking assisted reproductive therapy [27]. Weight management and therapies such as Continuous Positive Airway Pressure (CPAP) are recommended for improving sleep quality and reducing associated reproductive and cardiovascular risks in PCOS patients with OSA [58].

Fertility treatment itself

Fertility treatment can induce feelings of depression, stress, anxiety, hopelessness and guilt due to the process of infertility diagnosis, as well as the financial and emotional burden of social and healthcare costs, impacting sleep quality of the infertile women [59–61]. Among females undergoing fertility treatments, the hormone changes coupled with physical discomfort, such as tiredness, dizziness, nausea, vomiting and breast tightness, can deteriorate their sleep quality as treatment progresses. [29, 51, 62, 63].

Potential mechanisms underlying the association between sleep disturbance and female infertility

In this review, we briefly summarize 3 potential mechanisms that may explain how sleep disturbance negatively affects female fertility (Fig. 4).

Circadian dysrhythmia

Physiological and behavioral processes in the human body are regulated by the suprachiasmatic nuclei (SCN), and the autonomous fluctuation in metabolism, serum hormone levels, gene expression and activity patterns, with an approximately 24-hour period are described as the term "circadian rhythm" [64]. In mammals, the body circadian rhythm is regulated by the clock system genes, which can control behavior, feeding, and reproduction through neurotransmitters and hormones [65]. Increasing evidence have suggested that the circadian clock genes are also expressed in the pituitary, ovary, uterus and oviduct tissues, which may in some way regulate and coordinate the timing of reproductive events [66]. The molecular clock in gonadotrophs might regulate rhythms of cell proliferation, secretory responses to gonadotropins, and gonadotropin gene expression. Clock genes exhibit rhythmic expression in the ovary, influenced by gonadotropins. These rhythms may regulate follicular growth, differentiation, and ovulation. Circadian clocks in the uterus and oviduct contribute to implantation, embryo development, and parturition [66]. While animal studies provide insight into circadian function in reproduction, the connection to human infertility remains under-researched [67].

Clock systems

Molecular basis of circadian regulation

The rhythmic feedback loop of transcription and translation constitutes the circadian clock system and the main transcriptional activators are Brain and Muscle ARNT-like 1(BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK) coded by *BMAL1* clock genes that activate the transcription of target genes such as *PER1, CRY1, CRY2*, and *RORA et al.* [68, 69]. The BMAL1 and CLOCK proteins form the heterodimers that control their own expression through a delicate balance of activation and suppression processes [64, 70, 71].

Clock Genes and Reproduction

Clock gene functions extend to ovarian tissues, influencing the cyclical production of reproductive hormones and reflecting the bidirectional interaction between circadian regulation and fertility, mediated by the hypothalamic-pituitary-gonadal (HPG) axis [64, 70, 72].

Regular functions generated by clock genes were found to oscillate in the ovarian tissues, especially within

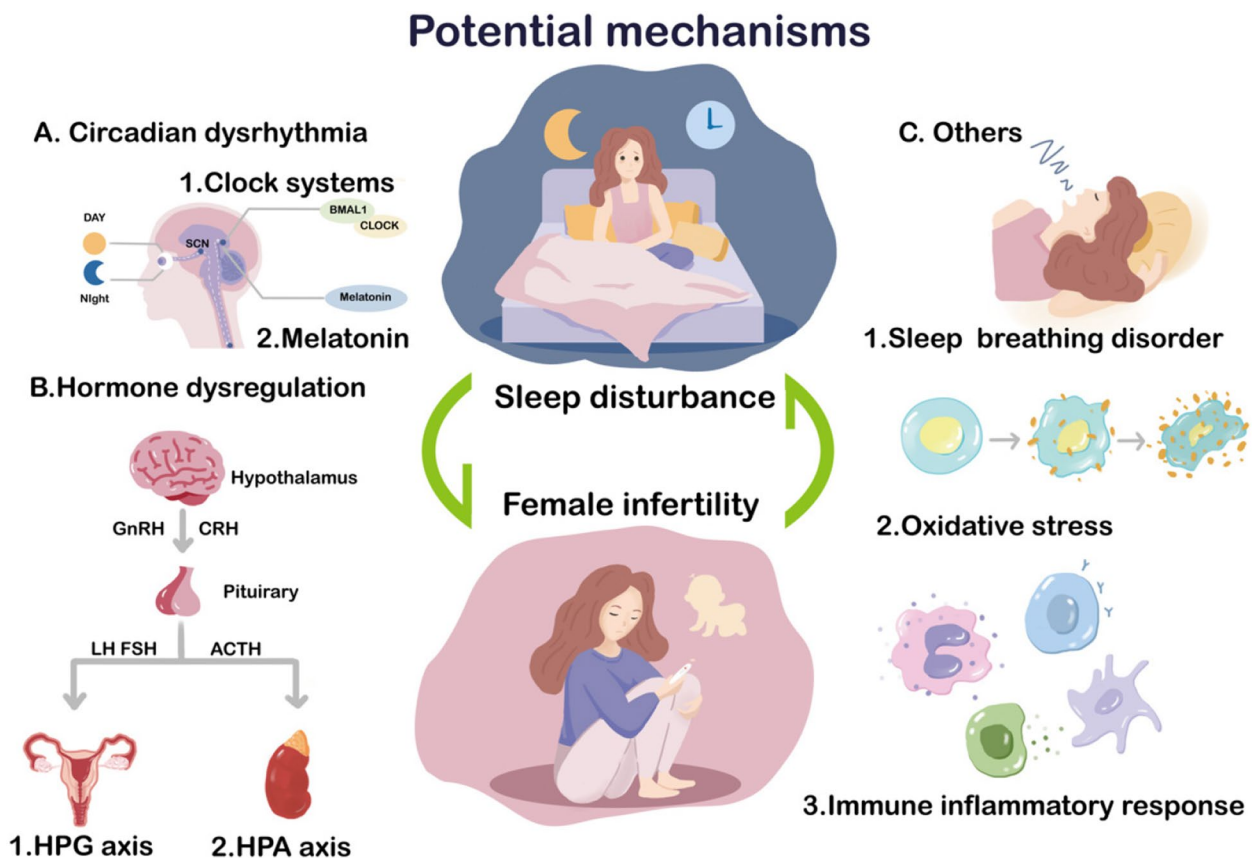

Fig. 4 Potential mechanisms of the association between sleep disturbance and female infertility

the granulosa cells, theca cells, and oocytes [73, 74]. The regulation of *CLOCK* gene expression may generate a circadian rhythm at the E2 level and may also play an essential role in sustaining androgen homeostasis [13, 75, 76], and the loss-of-function mutations in Per1/Per2 lead to premature ovarian insufficiency, indicating a relationship between circadian rhythm and ovary preservation [70]. Studies in *BMAL1*-KO mice showed decreased progesterone and prostaglandin E2 (PGE2) levels, no LH or FSH surges, impaired fertility and unsuccessful implantation [77]. Ovulatory dysfunction and decreased fertility were found in *Clock* and *Bmal1* deficient mice [78], while higher rates of pregnancy failure or lower numbers of litters were observed in *Per* and *Cry* mutated female mice and *Nr1d1-KO* mice [76, 79, 80]. Variations in the regulation of *CLOCK* genes are linked to human reproductive outcomes, with evidence suggesting that a higher pregnancy rate or lower miscarriage rate were found to be linked to variants of *BMAL1* [81]. *BMAL1* expression was also found to be downregulated in recurrent miscarriage patients [82].

Circadian medicine is a disease-treatment strategy based on the body's natural circadian cycles [70], which is possible to reduce the fertility impairment caused by PCOS. Light therapy was seen to relieve anxiety in premenstrual dysphoric disorder patients [83], similarly, light modulation could also reset circadian rhythm which is a potential treatment strategy for PCOS. In animal models of rats, researchers found that circadian molecule drugs were able to promote the activity of transcription factors such as CRY and therefore reduced PCOS-induced damage to ovarian tissue, reproductive disturbances and insulin resistance [70].

Melatonin

Melatonin is secreted only at night by the pineal gland, regulating biological rhythms through its receptors located in the SCN, which are altered through the light-dark cycles [84, 85]. Its circadian secretion is crucial for maintaining the body's rhythmic stability [86], with disruptions potentially affecting female fertility as well as oocyte maturation, embryo development and fertilization [13].

Peripheral reproductive cells, including granulosa cells and oocytes, also produce melatonin [87]. Higher concentrations of melatonin were detected in human ovarian

follicles compared to peripheral blood serum, exhibiting a 24-hour rhythm that increases as the follicle enlarges and ovulation approaches [88]. Melatonin was discovered as an efficient endogenous radical scavenger that has potent antioxidant capabilities to neutralize free radicals such as reactive oxygen species (ROS) in granulosa cells and oocytes [84, 89, 90].

In vitro, melatonin promoted oocyte maturation. However, the mechanism of this process is not fully understood, and its effect may also relate to various factors [91]. According to Zhang Z et al. melatonin may be utilized for the cryopreservation of human oocytes as a cryoprotectant additive by reducing oxidative stress and maintaining the permeability of the oolemma [92].

Several studies observed that melatonin therapy can improve the outcomes of fertility treatments. The initial clinical trial was conducted by Tamura H et al. [93]. Infertile patients with poor oocyte quality were given supplemental melatonin tablets (3 mg/day) for one month, and the fertility rate and pregnancy rate of the melatonin subject were greatly increased than those of the control group. Similar conclusions [94, 95] were drawn in other studies showing that the melatonin therapy may lower oxidative stress in oocytes by increasing the melatonin concentration in the follicular fluid and therefore increasing the number of mature oocytes [96] and high-quality embryos [84, 97], suggesting its utility in fertility treatments.

In females with PCOS, the level of melatonin in follicular fluid was significantly lower than that in healthy women. Thus, the increased oxidative stress and follicular damage depicted in PCOS conditions led to follicular atresia [98, 99]. Melatonin supplementation was also shown to improve the oocyte and embryo quality by altering the ovarian microenvironment to reduce insulin resistance in a randomized double-blind trial of PCOS patients using melatonin and inositol combination [100].

In addition to its reproductive benefits, melatonin is a pharmacological treatment for insomnia, improving sleep quality and latency [101–103], further supporting its potential in managing sleep-related fertility issues. However, the complex interplay between melatonin levels, sleep disturbances, and infertility necessitates further research.

Hormone dysregulation

HPG axis

Reproductive hormone regulation associated with the hypothalamic-pituitary-gonadal (HPG) axis, adheres to a circadian rhythm. Disruptions in SCN rhythmicity may lead to the dysregulation of reproductive hormones, thereby impacting fertility [13–15]. Studies have correlated long sleep durations with higher FSH [104], and identified that both poor sleep quality and sleep variability can lead to increased E2 levels [14, 16]. Fluctuations in other reproductive hormones, such as AMH, prolactin (PRL), thyroid stimulating hormone (TSH), testosterone and progesterone, have also been observed in relation to varied sleep patterns [1].

HPA axis

Activation of the hypothalamic-pituitary-adrenal (HPA) axis due to sleep disturbances can adversely affect fertility. The HPA axis activation may affect reproductive hormone regulation, normal follicular development, fecundity and menstruation among women [1, 105]. Constant stress stimulation increases activation of the HPA axis and therefore generates a higher level of glucocorticoids, which may cause sleep disturbances [106], and negatively affect the fertilization capacity of oocytes [107]. Exposure to acute or chronic stress may impair the reproductive function [108], and studies have found that increased stress impairs uterine receptivity [109], possibly leading to reduced fertility. Stress induced HPA activation may suppress HPG function, interfere with gonadotropin secretion and indirectly suppress hypothalamic GnRH levels [106, 107]. Moreover, chronic insomnia was found to increase ACTH and cortisol levels, indicating a bidirectional relationship between sleep disturbances and HPA activation [110].

Metabolic disorders and sleep breathing disorders

Sleep-disordered breathing is prevalent among women with PCOS, and is associated with metabolic disorders and multiple reproductive endocrine alterations. Insulin resistance and hyperandrogenemia are defining features of PCOS. Hyperandrogenism and insulin resistance increase the chance of patients with PCOS to developing sleep breathing disorders, and then sleep breathing disorders in turn exacerbate the metabolic and biochemical abnormalities, resulting in a vicious cycle [54]. Studies have shown that independent of obesity, fasting plasma glucose, and fasting insulin levels were significantly higher in patients with PCOS and comorbid OSA than in those without OSA [27], suggesting a strong relationship between OSA and increased risk of insulin resistance. Sleep fragmentation caused by OSA and its subsequent effects on sympathetic nervous system activity, increased cortisol secretion, and elevated levels of free fatty acids, which potentially contribute to the insulin resistance and impaired glucose metabolism [111]. Insulin resistance can also increase the production of androgens by the ovaries [112]. A high level of androgen inhibits FSH induction of LH receptors on granulosa cells and interferes with the maturation of dominant follicles, leading to impaired fertility.

Oxidative stress

In reproductive systems, oxidative stress has the potential to damage the oocyte quality [84], impair the oocyte proteome, and disrupt critical processes such as meiosis, fertilization and embryonic development [113]. The level of ROS is crucial for the follicle development and survival, and increased ROS levels were found to be associated with granular cell death [114].

Studies have shown that ROS levels and their by-products present circadian rhythms in blood and tissues in vivo, which are disrupted in the presence of circadian clock mutations, leading to increased oxidative damage [115, 116]. Moreover, oscillations in oxidative stress are found to be directly related to the daily rhythm of antioxidant enzyme expression and activity levels [115, 117]. While sleep has been proposed to promote anti-oxidative mechanisms and remove accumulated free radicals [118], insufficient sleep was found to promote oxidative stress [119]. Other studies have indicated that short-term sleep deprivation enhances antioxidant responses, but long-term sleep deprivation decreases antioxidant responses, inducing chronic oxidative stress [120]. Intermittent hypoxia caused by OSA may also lead to tissue hypoxia and oxidative stress [121], which may lead to oocytes damage, embryo fragmentation and other developmental abnormalities, potentially increasing the risk of miscarriage in infertile women with OSA [50].

Immune inflammatory response

The inflammatory cytokines in follicular fluid may impair ovarian function, and negatively impact the meiotic and cytoplasmic maturation of the oocyte, leading to reduced oocyte quality, embryo loss and reduced pregnancy rates [122]. Reproductive disorders such as endometriosis, adenomyosis, PCOS, and uterine fibroids are also associated with inflammatory pathways, leading to an increased risk of infertility, miscarriage and impaired pregnancy success [123]. In some patients with sleep disorders, an abnormal cytokine profile was detected, showing elevated levels of high-sensitivity C-reactive protein (H-CRP), interleukin (IL)−1, IL-6, IL-8 and tumor necrosis factor (TNF)-α [69], and acute sleep loss or short sleep duration were found to activate inflammatory signaling pathways [124]. H-CRP was found to be significantly higher in PCOS patients with OSA [27]. Studies have also identified higher levels of IL-6 and TNF-α in infertile patients compared to those fertile controls [125, 126], suggesting a link between the immune inflammatory response and fertility challenges.

Conclusion

This review uncovered the potential association between sleep disturbances and female infertility. Various aspects of disturbed sleep, including excessive sleep duration, poor sleep quality, late bedtimes, insomnia, and sleep-disordered breathing, may negatively impact reproductive health in women of reproductive age, potentially affecting the outcomes of fertility treatments. The mechanisms connecting sleep disturbances with female infertility are complex and not yet fully evidenced. The circadian rhythms of *Clock* gene systems, melatonin and hormone dysregulation, oxidative stress and immune responses are considered to be potential mechanisms explaining how sleep disturbance impairs reproductive function. With ongoing research efforts to unravel these mechanisms, there is hope for mitigating infertility's disease burden, at least partially, through improved sleep health. Clinicians are advised to prioritize the management of sleep disorders in childbearing-aged women as a potential intervention strategy. Continued research is essential to deepen our understanding of how sleep patterns and disturbances intersect with female reproductive health from different perspectives or from a more in-depth mechanism.

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions
J.L and Y.W. preformed the study conception and design, J.L wrote the main manuscript text and prepared Figs. 1, 2 and 3, J.L, Y.L.H. and S.R.X conducted the process of literature search, quality assessment, data extraction and prepared Tables 1, 2 and 3 and supplementary table 1-2. Y.W. edited and revised the manuscript. All the authors read and approved the final version of the manuscript.

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Data availability
The data are extracted and synthesized based on the stated methods, and all the data are contained within the paper and the additional file.

Declarations

Ethics approval and consent to participate
Ethics approval was not required for this review.

Consent for publication
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Competing interests
The authors declare no competing interests.

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