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RUNNING TITLE

Sleep and fertility

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CAPSULE

Although results are heterogeneous and scarce, published studies suggest an association between short sleep duration or shift work with menstrual cycle irregularities, low sperm parameters and reduced fecundability.

ABSTRACT

Objective: To evaluate the association of sleep parameters on female and male reproductive functions.

Design: Systematic review.

Setting: Not applicable.

Patient(s): Both female and male individuals, either healthy or infertile.

Intervention(s): Relevant articles were identified according to the PRISMA recommendations in the PubMed and EMBASE databases from January 1, 2000 to June 8, 2020.

Main Outcome Measure(s): The association between sleep and ovary function, spermatic function, natural fertility and *in vitro* fertilization (IVF) outcomes was assessed.

Results: A total of 33 studies that looked at the association between sleep and either ovary function (n = 10), spermatic function (n = 12), natural fertility (n = 5), or IVF outcomes (n = 6) were included. Overall, female and male fertility, as well as IVF outcomes may be affected by short sleep duration, evening chronotype, or shift/night work schedules. However, the results were hardly comparable due to the heterogeneous study methodologies used.

Conclusion: Sleep may be an original and innovative parameter to consider in the reproduction field. Further investigation is needed to elucidate how sleep and fertility are interrelated and how sleep might constitute a useful modifiable target in infertility management.

KEY WORDS

Sleep; ovarian function; sperm parameters; fertility; chronotype

INTRODUCTION

A significant increase in the prevalence of infertility has been observed over the past several decades and has been paralleled with the increasing prevalence of non-optimal lifestyle components such as obesity (1,2) and tobacco (3) or alcohol consumption. Since such environmental and lifestyle factors are modifiable, they represent paths for improvement in infertility management. Further, beyond the widely studied unhealthy lifestyle parameters associated with infertility, sleep may also constitute a novel and innovative parameter to consider in this context.

Sleep is organized in four to six cycles, each lasting 90 to 100 minutes and consisting of several stages: light slow-wave sleep, deep slow-wave sleep, and Rapid-Eye-Movement sleep. A majority of adults sleep an average of 7.5 hours per night, with some needing nine to 10 hours of sleep, known as "long" sleepers, and others termed "short" sleepers requiring less than six hours. Sleep is controlled by homeostatic regulation, which corresponds to the propensity to fall asleep, and by circadian regulation, which is under the control of the central clock located in the suprachiasmatic nuclei. Melatonin is the main hormone regulating these chronobiological rhythms.

Individual differences in sleep-wake cycles lead to the onset of distinct behavioral phenotypes known as chronotypes. Individuals can be classified either as a i) « morning » type (these individuals go to bed and get up early and prefer to be physically and mentally active in the morning); ii) « evening » type (these individuals go to bed and wake up late, tend to sleep for longer periods of time during weekends, and favor conducting activities in the evenings); iii) « intermediate » type (individuals who are neither « morning » nor « evening » types). The reference test for assessing sleep is polysomnography, which combines electroencephalography, electrooculography and electromyography, alongside recordings of heart rate, breathing rate and leg movements. In practice, performing this in-hospital assessment is rarely feasible, thus self-assessment questionnaires are more often used to evaluate total sleep duration, sleep quality, daytime sleepiness, and circadian rhythm disturbances. Finally, more recently, actigraphy systems that employ a piezoelectric sensor to detect motion-related accelerations have been developed that allow the objective determination of sleep time parameters such as start, end and duration of sleep, in addition to the evaluation of the motor activity during sleep.

One-third of our lives is dedicated to sleep and it appears that a good quality of sleep is essential for health and well-being. Nevertheless, 30% of the adult population complains about the nature of their sleep, including 10% with chronic insomnia (4). There is mounting evidence regarding the link between sleep disorders and an increased risk of mental or metabolic disorders, such as depression, diabetes and/or obesity (5,6). Environmental and lifestyle factors are also closely correlated with sleep and to the sleep-wake cycle, especially because of societal and work-related trends (e.g., late-night electronic device use, shift work, noise) (7).

The circadian timekeeping and reproductive systems seem to be closely intertwined with one another. Estrogens, progesterone, and androgens are circadian-regulated and travel into the suprachiasmatic nucleus, the master circadian clock, so that circadian rhythm disturbances (e.g., shift work) can affect the levels of reproductive hormones (8). Certain periods of life, such as pregnancy and lactation, perimenopause and menopause are particularly prone to occurrence of sleep disorders, including obstructive sleep apnea, insomnia, and excessive daytime sleepiness, due to hormonal fluctuations (9). In women, the circadian modulation of sleep also depends upon the menstrual cycle phase (10). Reproductive hormone levels have been correlated with sleep duration or quality in both men and women (11,12), albeit with some differences attributed to gender (5,13). Although associations between sleep and the hormonal status of men and women have been described (11,14), little is known to date regarding the impact of sleep on male and female reproductive functions. The objective of this study was therefore to conduct a systematic review of the literature to assess the impact of sleep, sleep parameters (i.e., duration and quality), sleep disorders, and chronotype on reproductive functions and fertility in both women and men.

METHODS

Literature search strategy

A literature search was conducted with the use of the PubMed and EMBASE electronic databases focusing on identifying articles published in English or French between January 1, 2000 and June 8, 2020. The following key words were used: "sleep” OR “sleep wake disorders” OR “sleep disturbance” OR “sleep disorders” OR “chronobiology disorders” OR “biological clocks” OR “chronobiology” in combination with “fertility” OR “infertility” OR “time to pregnancy” OR “ovulation” OR “menstrual cycle” OR “ovarian reserve” OR “anti-Müllerian hormone” OR “follicle stimulating hormone” OR “endometrium” OR “antral follicle count” OR “semen” OR “sperm” OR “testosterone” OR “assisted reproductive techniques” OR “in vitro fertilization” OR “oocyte” OR “spermatozoa” OR “embryo” OR “blastocyst” OR “pregnancy rate” OR “live birth rate”. The systematic review was performed in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (15). Considering that this study was a systematic review, an Institutional Review Board was not required.

Study selection and data extraction

After eliminating duplicates, two independent reviewer groups (GC/DL and IB/NS) independently performed a screening from the title +/- the abstract of all articles to exclude irrelevant citations. Any disagreement or uncertainty was resolved by the involvement of a third reviewer (CD). Full texts of potentially relevant articles were retrieved and assessed for inclusion by two reviewers (GC and IB), and data were extracted from the included articles using a data-extraction form developed for the present review.

The following studies were included: those dealing with the impact of sleep on natural fertility or the outcomes of assisted reproductive techniques, those evaluating the prevalence of sleep disorders or sleep disturbances in infertile populations, those assessing the relationship between sleep characteristics and fertility and those examining the impact of night or shift work on fertility. Meanwhile, we excluded review articles, studies involving animal models and studies reporting on associations between hormonal levels and circadian rhythm or sleep disorders.

Data synthesis

The following elements were extracted to characterize the included studies: authors, publication year, country, study design, studied population and sample size, control group, sleep evaluation methods, and major results.

RESULTS

Study selection

Our search strategy identified a total of 1,276 articles, including duplicates and articles that had no relevance to the primary research questions. After a review of 1,205 titles and abstracts, we retained 84 full-text articles for eligibility. Among them, 33 articles were finally included in the systematic review (Figure 1).

The final study group for assessment consisted of cross-sectional, retrospective, and prospective observational studies published between 2000 and 2020, in a variety of different countries including Austria, China, Denmark, Israel, Italy, Finland, South Korea, Spain, Taiwan and the United States.

Association between sleep and ovarian function

Ten studies (six cross-sectional studies, one case-control study and three prospective cohort studies) evaluating the association between sleep and ovarian function were selected (Table 1) (16–25).

One single study concluded that self-reported poor sleep quality was an independent risk factor for premature ovarian failure (22), but this result was not confirmed by any other research team.

Five studies assessed the impact of sleep quality and/or sleep duration on menstrual cycle regularity and/or menstrual cycle disorders. Although no association was found between shorter sleep duration and menstrual problems or regularity (17,19,25), an increased risk of menstrual cycle irregularities was observed If the mean sleep duration was less than five hours as compared with when it was more than eight hours among both 801 female adolescents (20) and 4,445 women (17), respectively. Poor sleep quality was also associated with an increased incidence of menstrual cycle problems, such as longer menstrual flow length or premenstrual syndrome, in 1,006 female university students (25), whereas insomnia was associated with a two-fold increase in the incidence of menstrual cycle irregularity in a population of 287 nurses (16). Meanwhile, no association between chronotype and menstrual cycle regularity or the risk of sporadic anovulation was found in another two studies (21,25).

Four studies evaluated the impact of shift work on ovarian function. Except for one study that did not show any relationship in 259 healthy and regularly menstruating women (19), the remaining investigations revealed the existence of a deleterious effect of rotating shift work on the menstrual cycles (18,23,24). In particular, in a large study involving 71,077 nurses, women who experienced more than 20 months of rotating shift work were more likely to have irregular menstrual cycles (adjusted risk ratio 1.23, 95% confidence interval 1.14-1.33), and abnormally short or long cycle durations (< 21 days or > 40 days; adjusted risk ration 1.27 and 1.49, respectively) (18).

Association between sleep and sperm parameters

Twelve eligible studies evaluating the association between sleep and sperm parameters were identified (Table 1) (26–37).

A study of 953 young Danish men concluded that there was an inverse U-shaped association between sleep quality as assessed by the four-item Karolinska sleep questionnaire (KSQ (38)) and sperm concentration, total sperm count, and normal sperm morphology (32). Sperm parameters were significantly lower among both men with lower and higher KSQ sleep scores, as compared with the reference group. In three other studies carried out involving infertile men (28,36) or healthy sperm donor candidates (26), an association was found between sleep quality as evaluated by the Pittsburgh Sleep Quality Index (PSQI (39)) or a self-reported questionnaire and sperm concentration and/or motility. In 796 Chinese students (27), the authors found a significant inverse U-shaped association between sleep duration and sperm counts; specifically 7.0-7.5 hours of sleep/day was associated with the highest sperm counts, whereas shorter and longer sleep durations correlated with decrease in such. Further, these authors did not observe any association between sleep quality and sperm parameters after adjustment on sleep duration (27). An association between short sleep duration and altered sperm parameters has also been observed in other studies performed on infertile (31) or healthy (26,30,35) men. The influence of sleep duration and bedtime on male fertility was examined in a group of randomized 981 healthy men (33). Short sleepers (< 6.0 hours) were compared to average (7.0–8.0 hours) and long (> 9 hours) sleepers. Chronotypes were roughly estimated according to bedtime (8–10 PM, after 10 PM, and after midnight). The authors' conclusions were consistent with those of previous studies, revealing significantly lower sperm counts, survival and motility in short sleepers when compared to other groups. Worse parameters were recorded for short sleepers with late bedtimes as compared with individuals who went to bed before 10 PM. Late bedtimes were also associated with reduced semen quality in a recent study of 104 infertile men (odds ratio 3.97, 95% confidence interval 1.2-13.5) (31).

Conversely, no significant association was noted between self-reported sleep duration or and semen parameters in two studies (34,37). Elsewhere, no influence of night or shift work on sperm parameters was reported in a single study of 456 men from couples planning a pregnancy (29).

Association between sleep and natural fertility

Five studies evaluating the effect of sleep on natural fertility were included (Table 2) (40–44).

In 6,873 female partners of couples attempting to become pregnant for less than six months, no significant association was reported between fecundability and sleep duration during the previous month (including for < 6, 6, 7, and ≥ 9 hours of sleep/day), trouble sleeping at night, or night and/or shift work (42). On the contrary, in a study evaluating 39,913 pregnant women, the time to conceive was significantly longer among those who worked in fixed evening or night shifts than those working only day shifts (44). However, the time to pregnancy did not significantly differ between day and shift workers without or with night work (44). Finally, the odds of it being difficult to conceive were higher among "intermediate" than "morning" chronotypes in a population-based survey of 2,672 Finish women (41).

In 1,176 male partners of couples attempting to become pregnant for less than six months, a significant relationship was found between infertility and sleeping less than six hours/day when compared with eight hours/day (43). These results were not significantly explained by night or shift work. In a case-control study, a significant association between shift work in men and infertility was also reported (40), but the studied groups were significantly different in terms of body mass index and tobacco consumption, limiting the interpretability of the results.

Association between sleep and IVF results

Six articles evaluating the association between sleep and IVF were selected (Table 2) (45–50). These studies focused on women receiving ovarian stimulation for IVF purposes in an infertility context or, in one study, for fertility preservation (48).

A high prevalence of impaired sleep quality among women before and during IVF treatments was apparent, using the Pittsburgh Sleep quality index (PSQI) (45,46). A small pilot study assessed the variations in sleep quantity and quality by different methods (e.g., actigraphy, sleep journal, questionnaires) during the IVF treatments of 22 women. Sleep quality was lower throughout the pre-transfer period and was improved after embryo transfer, although only actigraphic total sleep time and subjective sleepiness significantly changed throughout the IVF cycle (45). Baseline total sleep time, alongside with anti-Mullerian hormone and day 3 follicle-stimulating hormone, explained 40% of the variance in the number of oocytes retrieved (45).

Four studies evaluated the association between sleep disorders and IVF outcomes, offering conflicting results. Lyttle et al. did not find any correlation between sleep disturbance during controlled ovarian stimulation and the number of cryopreserved oocytes or embryos in a population of 32 women with cancer undergoing fertility preservation and 50 infertile patients undergoing IVF (48). However, they did report the existence of impaired sleep quality at the time of oocyte retrieval in the IVF group when compared with in the fertility preservation group. Evening, night, or rotating shift work was also found to be associated with poor oocyte retrieval outcomes in a population of 462 women undergoing IVF (49). Aside from the previously mentioned published papers, two poster contributions were also found to exist on this subject, one of which reported a significant association between sleep disorders and poor ovarian response or a low number of retrieved oocytes in a series of 200 women undergoing IVF (47). Finally, a study of 656 women undergoing IVF did not find any correlation between sleep duration and either the number of oocytes retrieved or the fertilization rates (50). However, the authors did observe a significantly higher pregnancy rate in the medium-sleeper group (7-8 hours) than in the long-sleeper group (9-11 hours), alongside a trend toward a higher pregnancy rates in the medium-sleeper group than in the short-sleeper group (4-6 hours).

DISCUSSION

In this systematic literature review, we aimed to report and discuss the association between sleep and reproductive functions in both men and women. We considered ovarian function, sperm parameters, natural fertility, and IVF outcomes. Although the impact of sleep on fertility seems to be quite poorly documented at this time, some published studies suggest there is an association between short sleep duration, chronotype or irregular/night shift work and reproductive parameters.

First, we found that short sleep (< 5-6 hours) might interfere with the menstrual cycle (17,20), sperm parameters (26,27,30,31,33,35), natural fertility (43), or IVF outcomes (45). One crucial role of sleep, especially slow-wave sleep, is its hormonal function, with both the secretion of growth hormone and cortisol, which drastically influence metabolism and inflammation, occurring during this stage (5,51). The secretion of reproductive hormones, in both women and men also seems to be narrowly linked to sleep duration (11). We could hypothesize that hormonal secretion in short sleepers might become chronically subclinically disturbed, as a result of sleep debt. Furthermore, short sleep could impair fertility from a behavioral point of view, as it has been linked to sexual dysfunction (52) and lower odds of partnered sexual activity in a large study (53). Short sleep is also significantly associated with chronic conditions and diseases, such as obesity, type 2 diabetes, cardiovascular diseases, and depression, which might by themselves influence fertility (5,6,54).

Fertility was also found to be associated with the biological clock chronotype. Indeed, a decreased sperm count and motility in the “evening” type (31,33) and more reproductive troubles in the “intermediate” than in the “morning” type (41) were reported. Chronotype is closely related to melatonin. Mainly produced by the pineal gland in response to darkness, this serotonin-derived hormone regulates the sleep-wake cycle and circadian rhythms. It could also play a key role in the mechanisms involved between sleep and fertility. It has been shown that melatonin is also produced by granulosa cells and oocytes. Further, melatonin's role in capturing free radicals makes it a powerful protector of oocytes against oxidative stress (55) and its use as a treatment for premature ovarian failure has even been proposed (56). Melatonin is also thought to have a role in testicular function through its action on the secretion of GnRH (14) and a recent study suggests direct antioxidant and antiinflammatory roles of melatonin at the testicular level (57). Some associations between plasma or seminal melatonin levels and sperm parameters have also been described, particularly with regard to sperm motility (58). Some interventional studies have been performed to evaluate the possible benefit of melatonin supplementation before IVF, albeit with no formal conclusion (59), suggesting the need for further investigation. Moreover, the association between chronotype and fertility could also rely on genetic regulation of the central biological clock. Indeed, studies carried out on murine knock out models for the CLOCK gene (60) have reported that circadian rhythm disorders could have an impact on fertility, independently of the hypothalamic-pituitary axis.

Finally, our review confirms the association between irregular and night work schedules and some degree of fertility dysfunction, encompassing irregular menstrual cycles (18,23,24), a longer time to pregnancy (42), and male infertility (40). In this review, only one cohort study evaluating the association between night and shift work and semen parameters was included and it did not find any significant association (29), in contrast with a very recently published article (61) that could not be included in the review because of its publication date being beyond the end date of our systematic review. In this cross-sectional study analyzing the association between work-related circadian desynchrony and semen parameters in 1,346 Chinese men, sperm count was significantly lower in rotating shift workers than those who were not shift workers (61). Moreover, the authors showed that each hour of desynchrony resulted in a 5.9% lower total sperm count but contented that this negative impact may be reversible following attenuation of the desynchrony (61). The impact of irregular and night work schedules on fertility might have a in relationship with the reduced amount of sleep often associated with such schedules, as those participating in this kind of work arrangement experienced on average one hour less of sleep as compared with day workers (51). We also point out that irregular and night work schedules are significantly associated with chronic metabolic and cardiovascular diseases that could be deleterious to fertility (51). Moreover, irregular and night work schedules can disturb the circadian modulation of gonadotropic hormones, resulting in fertility impairment (62). At last, from a behavioral point of view, irregular and night work schedules do not facilitate optimal interpersonal and sexual relationship in couples (Figure 2).

Our systematic review presents some limitations that should be noted. First, few relevant studies are currently available in the literature, with relatively small sample sizes in most of those published to date. Also, the methods used to evaluate sleep parameters were very heterogeneous, making it difficult to compare results between studies. We mainly found that self-reported questionnaires, inducing subjective evaluations, and sometimes limited to one or two questions, were adopted. Only one study was conducted using actigraphy (45). Finally, no publication proposed a sleep study carried out in a specialized sleep center, or using ambulatory polysomnography, probably due to the complexity of the implementation of this approach. Ideally, complementary studies should be proposed that include larger study populations and using more homogeneous and rigorous methods for sleep assessment. Regarding shift work, none of the studies accurately measured the frequency of night work or shift duration, or provided details of the work cycles of the participants. Finally, while the majority of the published studies made adjustments according to main confounding factors, such as age or body mass index, other covariates, such as depression or anxiety disorders, were poorly considered. Indeed, sleep is totally intertwined with the quality of life and mental health. Although the impact of stress on couples' fertility has not been fully investigated, some authors have suggested a negative impact of stress on sperm parameters (63), an increased time to pregnancy (64), or an accelerated degree of ovarian reserve exhaustion (65). Moreover, stress has been correlated with sleep disorders and is more frequent in infertile couples than in fertile couples. Consequently, it would be interesting to include these confounders in future research focusing on the impact of sleep on couples' fertility. Sleep-improvement efforts could also be fully integrated into a global and personalized pre-conception care plan for infertile couples (66), which might include screening for short sleep duration or sleep disturbances, providing sleep hygiene advice, and even carrying out sleep improvement actions including light exposure for example (67).

CONCLUSIONS

Sleep could represent an original and innovative parameter to consider in the reproduction field. Although an effect of short sleep duration, chronotype, and irregular/night work schedules on various reproductive outcomes was suggested following this review, no strong conclusion can be drawn due to the heterogeneous and scarce results of the included studies. Further large-scale investigation needs to elucidate how sleep and fertility are interrelated and how sleep could represent a useful modifiable target in infertility management.

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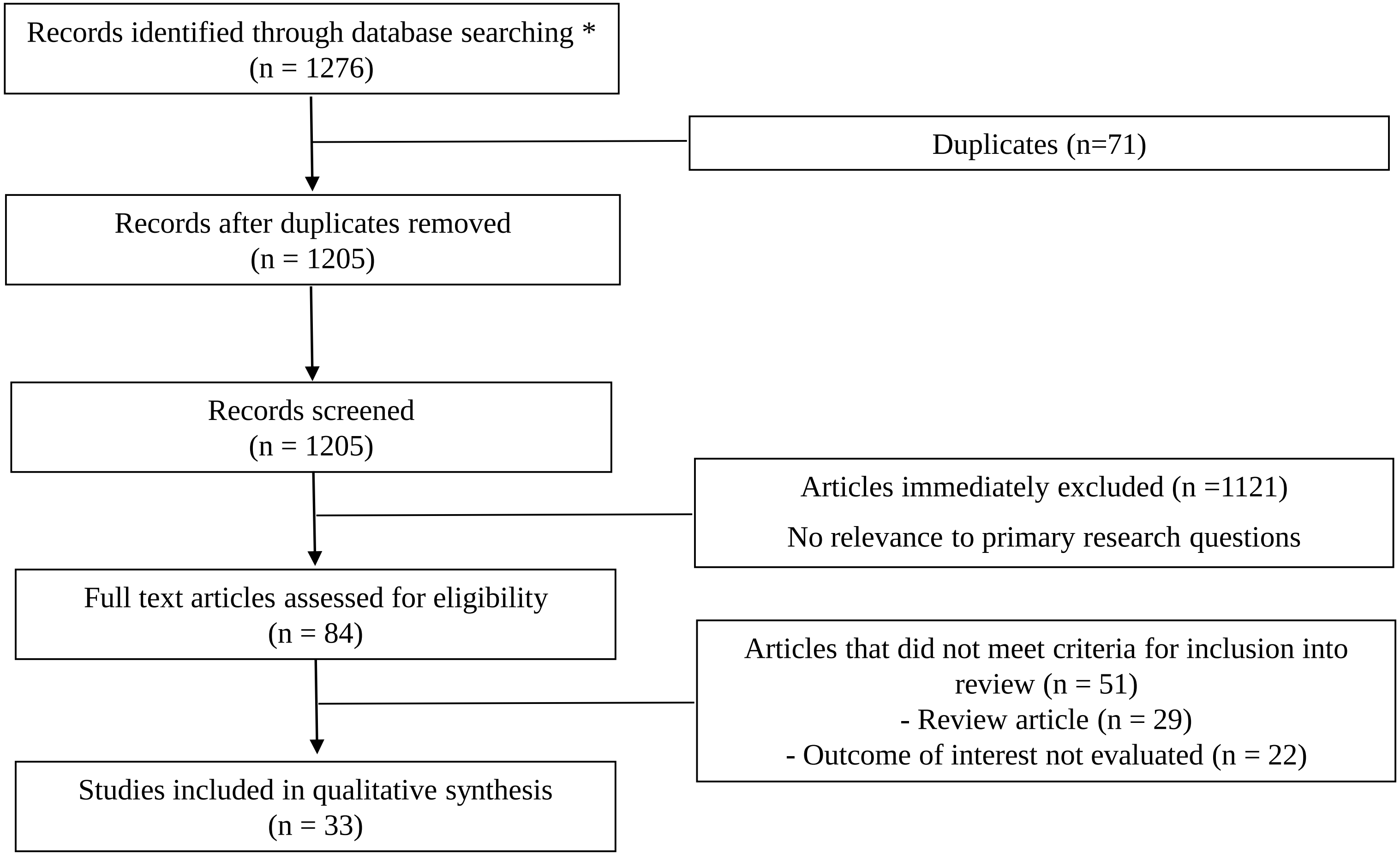
FIGURE LEGENDS

Figure 1: Flow chart of study selection for systematic review and meta-analysis.

Figure 2: Association between sleep and fertility, an overview.

INWS Irregular/night work schedules



* Pubmed, EMBASE and Cochrane Library January 1, 2000 to June 8, 2020

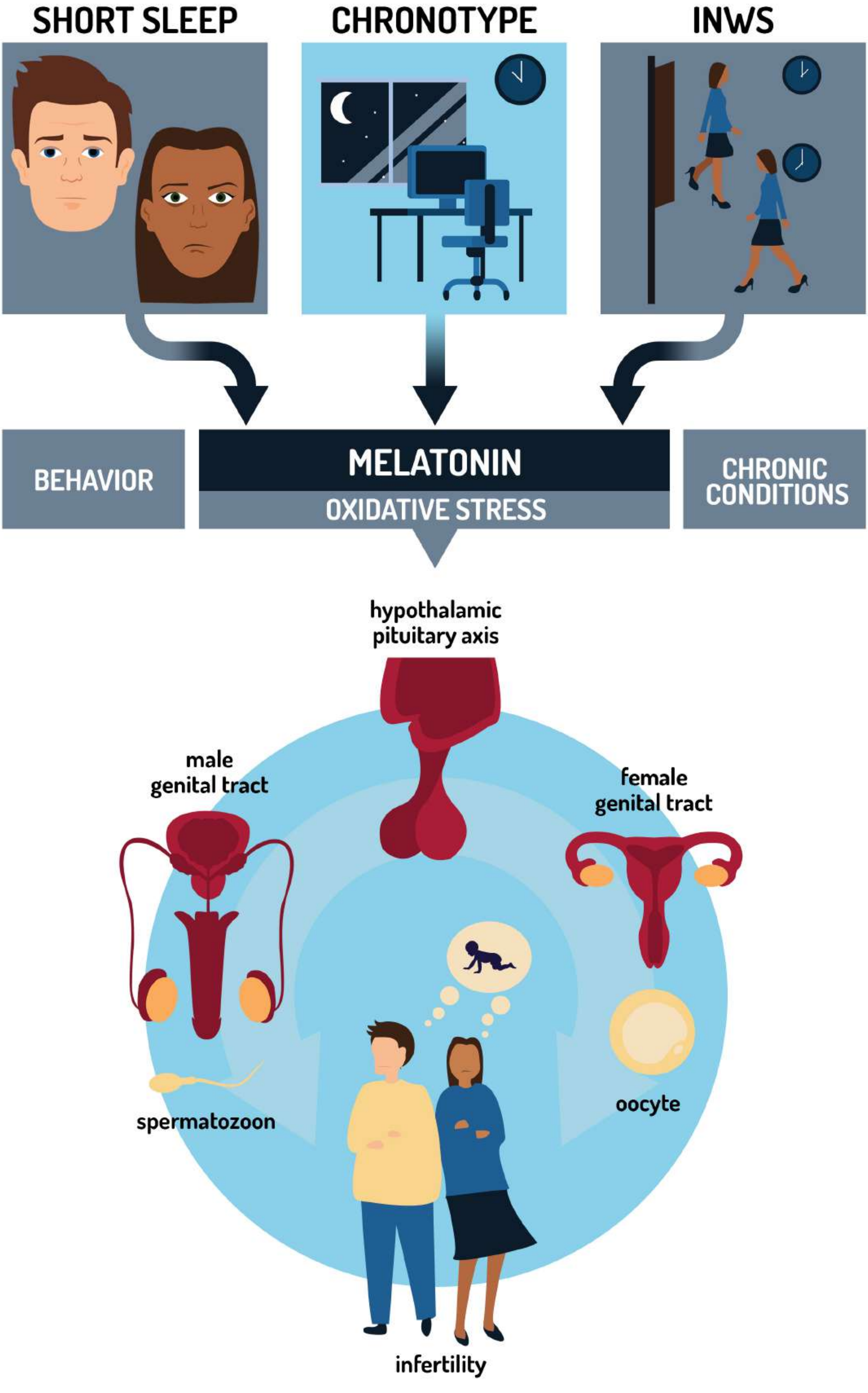

SHORT SLEEP
CHRONOTYPE
INWS
BEHAVIOR
MELATONIN
OXIDATIVE STRESS
CHRONIC CONDITIONS
hypothalamic pituitary axis
male genital tract
female genital tract
spermatozoon
oocyte
infertility

Table 1: **Characteristics of studies included in the systematic review about the association between sleep and ovarian function or sperm parameters.**

Author, year	Country	Study type	Studied population	Control group	Sleep evaluation	Results
Sleep and ovarian function						
Xing et al, 2020	China	Cross-sectional study	n = 1006 female university students	No	Pittsburg Sleep Quality Index (PSQI) Insomnia Severity Index (ISI) Self-reported total sleep time	Increased incidence of menstrual cycle problems (longer menstrual flow length, period pain, premenstrual syndrome) in both women with poor sleep quality or insomnia symptoms Increased incidence of menstrual cycle irregularities in women presenting insomnia (OR 1.36, 95% CI 1.02–1.80) ; heavy menstrual blood volume associated with poor sleep quality (OR = 1.75, 95% CI 1.12–2.72) Short sleep duration (≤ 6 h) associated with premenstrual syndrome, earlier menarche, and history of gynecological disease
Michels et al, 2020	USA	Prospective cohort study	n = 259 healthy, regularly menstruating women aged 18-44 years	No	Daily sleep journal Chronotype score	No association between mean total sleep time, night/shift work status or chronotype and risk of sporadic anovulation
Kang et al, 2019	South Korea	Prospective cohort study	n = 287 nurses	No	Insomnia Severity Index (ISI)	Increased incidence of menstrual cycle irregularities in women presenting insomnia (OR 2.05, 95% CI 1.12–3.77)
Kim et al, 2018	South Korea	Cross-sectional study	n = 558 women from Korea National Health and Nutrition Examination Survey (KNHANES) cohort with	n = 3887 women from KNHANES cohort with regular menstrual cycles	Questionnaire (self-reported total sleep time)	No significant association between mean total sleep time and menstrual cycles regularity. Short sleep time (≤ 5 h), but not long sleep time (≥ 9 h) was associated with the odds of severe menstrual cycle irregularity (OR 2.67, 95% CI 1.35-5.27), compared to those who reported sleeping for 6–8 h a day

			irregular menstrual cycles			
Nam et al. 2017	South Korea	Cross-sectional study	n = 801 female adolescents from Korea National Health and Nutrition Examination Survey (KNHANES)		Questionnaire (self-reported total sleep time)	Inverse association between sleep duration and menstrual cycle irregularity: mean sleep duration was shorter in subjects with menstrual cycle irregularities (6.6 $\pm$ 0.2) when compared to subjects with regular menstrual cycles (7.1 $\pm$ 0.1, p=0.003); increased incidence of menstrual cycle irregularities if sleep duration <5h when compared to >8h / day (OR 2.36, IC95% 1.02-5.47); prevalence of menstrual cycle irregularity tended to decrease as sleep duration increased (p for trend = 0.004).
Wang et al. 2016	China	Cross-sectional study	n = 139 nurses with regular working	n = 334 nurses with shift work	Questionnaire (shift work schedules and self-reported total sleep time)	Higher proportion of menstrual cycle irregularities in the shift work group compared with the day workers (32.2% vs 18.3%). Shorter cycle length when night work > 7 times/month
		Case-control study	n = 45 nurses presenting variations of cycle length after starting shift work	n = 67 nurses without variations of cycle length after starting shift work n = 30 nurses with no shift work		Cycle length variation of 4.115 $\pm$ 2.084 days after starting shift work in the case group, with no recovery of the original cycle length after 2 years of follow-up
Li et al, 2015	Taiwan	Case-control study	n = 168 women with POF	n = 42 women with no POF	Questionnaire (poor vs good sleep quality)	Poor quality of sleep as an independent risk factor for POF (OR=3.72, 95% CI 1.17-11.81)
Wan et al, 2012	Taiwan	Cross-sectional study	n = 151 nurses with regular monophasic (n = 83), regular biphasic (n = 30) or Irregular (n = 38) cycles	No	Daily sleep journal (14 weeks) N = 72 day shift only N = 29 evening / night sleep only N = 50 rotating shift	Rotating shift work significantly associated with irregular menstrual cycles (p = 0.048) Mean self-reported sleep duration did not differ between the 3 ovarian cycle pattern groups (p = 0.41)

Lawson et al. 2011	USA	Cross-sectional study (Nurses' Health Study II)	n = 71,077 nurses aged 28-45 years	No	Questionnaire	Women with > 20 months of rotating shift work were more likely to have irregular cycles (> 7 days variability; adjusted RR 1.23,CI 1.14-1.33); cycle length <21 days (1.27, 0.99-1.62) or > 40 days (1.49, 1.19-1.8])
Negriff et al. 2009	USA	Prospective cohort study	n = 210 adolescent girls aged 15.69±±1.74 years	No	Morningness/Eveningness scale	No association between chronotype and menstrual cycle regularity
Sleep and sperm parameters						
Hvidt et al. 2020	Denmark	Ancillary study from a randomized controlled trial	n = 104 infertile men	No	Pittsburgh Sleep Quality Index (PSQI) Self-reported total sleep time Self-reported bedtime	No association between sleep quality and semen quality (self-reported) Lower semen quality in short (7.0–7.49 h) and very short (< 7.0 h) sleepers (p = 0.03 and p=0.01) Association between late bedtime and reduced semen quality (OR 3.97, IC95% 1.2-13.5, p = 0.03)
Du et al. 2020	China	Cross-sectional study	n = 970 infertile men	No	Pittsburgh Sleep Quality Index (PSQI)	Negative association between sleep quality and sperm concentration, motility and morphology (p<0.001)
Green et al. 2020	Israel	Cross-sectional study	n = 116 healthy men	No	Pittsburgh Sleep Quality Index (PSQI) Questionnaire (self-reported total sleep time)	Positive association between sleep duration and sperm motility Negative association between subjective sleepiness and sperm motility
Chen et al. 2020	China	Cross-sectional study	n = 842 healthy men candidates for being sperm donor	No	Pittsburgh Sleep Quality Index (PSQI)	Association between short (<6h) or long (>9h) sleep duration and reduced sperm motility Association between poor sleep quality and reduced sperm count and motility
Pokhrel et al. 2019	China	Cross-sectional study	n = 1101 young healthy men	No	Questionnaire (self-reported total sleep time)	No association between sleep duration and sperm parameters

Shi et al. 2018	China	Cross-sectional study	n = 328 healthy men	No	Questionnaire (self-reported total sleep time)	Decreased sperm concentration if sleep < 4.7h/day Higher sperm DNA fragmentation index associated with irregular sleeping habits ($p = 0.008$)
Vigano et al. 2017	Italy	Cross-sectional study	n = 382 infertile men	No	Self-report questionnaire	Negative association between sleep quality (difficulty in initiating sleep or lying awake most of the night) and sperm parameters (sperm concentration or motility, respectively)
Liu et al. 2017	China	Randomized interventional study	n = 981 healthy men	No	Imposed bed times (8–10 PM, after 10 PM, and after midnight) and 3 groups of sleep duration (<6.0 h (short), 7.0–8.0 h (average), >9.0 h (long))	Lower total sperm count and motility in short sleepers ($p < 0.05$) Association between late bedtime and low total sperm count ($p < 0.05$) No significant differences in sperm morphology
Chen et al, 2016	China	Prospective cohort study (MAle Reproductive Health in Chongqing college Students (MARHCS))	n = 796 male students	No	Modified Munich Chronotype Questionnaire (MCTQ)	Inverse U-shaped association between sleep duration and semen volume and total sperm count ($p = 0.002$ and 0.014, respectively)
					Pittsburgh Sleep Quality Index (PSQI)	No significant association between sleep quality and semen parameters after adjustment on sleep duration
Eisenberg et al, 2015	USA	Prospective cohort study (Longitudinal Investigation of Fertility and the Environmen	n = 456 men during pre-conception period	No	Interview	No significant association between night or shift work and semen parameters

		t (LIFE))				
Jensen et al, 2013	Denmark	Cross-sectional study	n = 953 healthy men	No	Karolinska Sleep Questionnaire (modified 4-item version)	Inverse U-shaped association between sleep disorders and sperm concentration and morphology ($p = 0.03$ and $p < 0.01$, respectively)
Wogatzky et al, 2012	Austria	Cross-sectional study	n= 1683 men from infertile couples	No	Questionnaire (self-reported sleep duration and regularity of sleep/wake cycle)	No significant association between sleep and semen parameters

POF: premature ovarian failure

<u>Table 2:</u> Characteristics of studies included in the systematic review about the association between sleep and natural fertility or IVF outcomes.

Author, year	Country	Study type	Studied population	Control group	Sleep evaluation	Results
Sleep and natural fertility						
Willis et al, 2019	USA	Prospective cohort study (Pregnancy Online Study PRESTO)	n = 6,873 women from couples attempting pregnancy ≤ 6 months	No	Questionnaire (self-reported sleep duration)	No significant association between sleep duration and fecundability
					Night or shift work	No significant association between work schedules and fecundability
					Major Depression Inventory ("having trouble sleeping at night")	No significant association between sleep problems and fecundability
Wise et al, 2018	USA	Prospective cohort study (Pregnancy Online Study PRESTO)	n = 1,176 men from couples attempting pregnancy < 6 months	No	Questionnaire (self-reported sleep duration)	Sleep duration <6h associated with significantly lower fecundability than sleep duration 8h (FR 0.62, 95% CI 0.45–0.87), non-explained by working nights or rotating shifts, or history of infertility
Toffol et al, 2013	Finland	Cross-sectional study (National FINRISK Survey)	n = 2672 women	No	Horne-Östbergs Morningness-Eveningness Questionnaire (MEQ) 139 (5.6%) evening, 1217 (48.7%) intermediate, and 1145 (45.8%) morning chronotypes	Association between intermediate chronotype and significantly higher risk of infertility than morning chronotype (OR 1.62, 95% CI 1.09- 2.40; p<0.05)
El-Helaly et al, 2010	Egypt	Case-control study	n = 255 men from infertile couples	n = 267 husbands from pregnant couples	Questionnaire (occupational exposures)	Shift work as a risk factor of infertility (OR 3.60, 95% CI 1.12–11.57)
Zhu et al, 2003	Denmark	Prospective cohort study	n = 39,913 pregnant women	No	n = 493 evening workers n = 177 night workers n = 1,572 day workers n = 1,665 shift workers	Longer TTP in fixed evening workers (OR 0.80, 95% CI 0.70-0.92) and fixed night workers (0.80, 95% CI 0.63-1.00)) *vs.* day workers

						No TTP difference between day and shift workers without or with night work (OR 0.99, 95% CI 0.91-1.07) and 1.05, 95% CI 0.97-1.14), respectively
IVF outcomes						
Huang et al., 2019	Taiwan	Cross-sectional study	n = 97 women during IVF	No	Pittsburgh Sleep Quality Index (PSQI)	Frequency of poor sleep quality (PSQI total scores> 5: 43.3% of the studied population
Lyttle et al, 2018	USA	Prospective cohort study	n = 50 IVF women n = 32 FP women	No	Medical Outcomes Study Sleep Scale (MOS-SS)	No significant association between sleep disorders and number of retrieved oocytes, cryopreserved oocytes or embryos Sleep disturbance significantly increased in infertile patients but not in FP patients
Goldstein et al, 2017	USA	Prospective cohort study	n = 22 women during IVF	No	Actigraphy and sleep journal	Reduced TST of 0.3h and 0.5h during controlled ovarian stimulation and after oocyte retrieval, respectively, when compared to sleep duration after embryo transfer
					Pittsburgh Sleep Quality Index (PSQI)	Frequency of poor sleep quality: 57% baseline, 43% during ovarian stimulation, 29% after embryo transfer
					Insomnia Severity Index (ISI)	Frequency of clinical significant insomnia: 4.8% baseline, 4.8% during ovarian stimulation, 14.3% after embryo transfer
					Epworth Sleepiness Scale (ESS)	Frequency of ESS >10: 24% baseline, 33% during ovarian stimulation, 36% after embryo transfer
Llaneza et al, 2017	Spain	Cross sectional study (abstract form)	n =200 women during IVF	No	Jenkins Sleep Scale Cohen Stress Scale	Negative correlation between sleep disorders and number of retrieved oocytes (p = 0.013) Association between sleep disorders and poor ovarian response (p = 0.048)

Mínguez-Alarcón et al, 2017	USA	Prospective cohort study (Environment and Reproductive Health Study)	n = 462 women during IVF	No	n = 426 day work n = 36 evening/night/rotating shift work	Lower numbers of retrieved and mature oocytes in women with evening/night/rotating shift work vs. women with day work (p<0.001)
Park et al, 2013	South Korea	Retrospective study (abstract form)	n = 656 women during IVF	No	Sleep duration (unclear metrics used to quantify sleep duration, estimated before starting IVF) n = 120 (4-6 hours) n = 445 (7-8 hours) n = 91 (9-11 hours)	Similar number of retrieved oocytes and fertilization rates Higher pregnancy rates in mid-sleepers *vs.* long-sleepers [52.6%(234/445) vs. 42.9%(39/91), p=0.045].

IVF: in vitro fertilization
TTP: time to pregnancy
TST: Total Sleep Time
FP: fertility preservation patients undergoing controlled ovarian stimulation