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Human fertility and sleep disturbances: A narrative review

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ABSTRACT

Introduction: Many factors may be hidden behind the global fertility decline observed in Western countries. Alongside the progressively increased age of infertile couples, environmental and behavioural factors, including non-optimal lifestyle habits, should be considered. Among these, sleep disorders have been suggested to be linked to human fertility.
Methods: This is a narrative review, describing first sleep physiology, its disturbances, and the tools able to quantify sleep dysfunction. Then, we consider all available studies aimed at investigating the connection between sleep disorders and human fertility, providing a comprehensive view on this topic.
Results: Forty-two studies investigating the relationship between sleep habits and human reproduction were included. All the published evidence was grouped according to the aspect of human fertility considered, i.e. i) female reproductive functions, ii) male reproductive functions, iii) natural conception and iv) assisted reproduction. For each of the sub-groups considered, the connection between sleep dysregulation and human fertility was classified according to specific sleep characteristics, such as sleep duration, quality, and habits. In addition, possible physio-pathological mechanisms proposed to support the link between sleep and fertility were summarized.
Conclusion: This review summarizes the most relevant findings about the intricate and still largely unknown network of molecular pathways involved in the regulation of circadian homeostasis, to which sleep contributes, essential for reproductive physiology. Thus, many mechanisms seem correlate sleep disorders to reproductive health, such as adrenal activation, circadian dysregulation, and genetic influences. This review highlights the need to properly designed trials on the topic.

1. Introduction

The last “Aging report” of the European Commission warned about a projected decline of the total population in EU over the long term of about 5% between 2019 (447 million) and 2070 (424 million) [1]. Many scientific attempts have been made to explain the reason for this progressive fecundity decline. First, an increase in the age at which couples begin to seek a pregnancy is advocated when the fertility potential of the couple is reduced, leading to the expected ‘time-dependent’ fertility reduction. The negative role of the female age on pregnancy chances is largely demonstrated, while the increasing male age related detrimental effects on couple fertility are just suggested. Second, a progressive claimed in male infertility incidence increase is detected. A progressive decline in sperm quantity and quality was described in last decades [2,3]. The remarkable changes in semen quality could be explained by environmental and behavioural factors, although a clear cause-effect is still lacking. In this setting, the detrimental role of environmental pollution on spermatogenesis has been advocated [4–6], together with sub-optimal lifestyle conditions, such as obesity [7,8], smoking habit [9–11] alcohol consumption [12,13], and thermodysregulation links to cell phone use [14,15]. In this scenario, sleep habits and their dysregulation should be considered among lifestyle components potentially affecting fertility. Sleep disorders are associated with many health problems like depression, hypertension, glucose deregulation, cardiovascular disease, and anxiety disorders both in men and in women. In women, sleep disturbances are found in postpartum depression, pregnancy, menopausal transition and premenstrual dysphoria [16]. However, the

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evaluation of sleep in connection with reproduction is little investigated and was recently reviewed [17,18].

The main purpose of this review is to elucidate the link between sleep and human fertility. We evaluated the role of sleep dysregulation, as a novel and innovative parameter to consider in the context of couple infertility management.

2. Sleep physiology

Sleep is a common physiological status, occurring from *Drosophila melanogaster* to humans and characterized by species-specific peculiarities [19]. In mammals, while wakefulness is the time to energy gathering and expenditure, maximizing reproductive output, sleep is mandatory to optimize energy allocation, replenishing deficits accumulated in the waking state, and preparing the next wakefulness bout [19]. Moreover, sleep is fundamental to maintain cellular homeostasis, anabolism, proper immune function, and normal neural plasticity [20,21].

Different sleep patterns are described and several stages could be recognized. Non-rapid eye movement (NREM) phases are common to all animal sleep paths and are characterized by a cortical electroencephalography (EEG) deceleration which results in a state of generalized immobility, regular breathing and stable heart rate [21], reducing metabolic heat production [22,23]. On the other hand, rapid eye movement (REM) sleep shows a cortical EEG activation, associated with a generalized skeletal muscle atony with intermittent muscle twitches of the distal extremities, penile or clitoral erections, and increased respiratory and heart rate variability [21].

In humans, seven-eight hours of daily sleep are essential to maintain and restore metabolic body homeostasis [24]. Children and adolescents sleep more than adults, and young adults sleep more than older ones. In general, normal sleep consists of four to six EEG-defined cycles, preceded by four progressively deeper and quieter sleep stages graded 1 to 4 on the basis of increasingly slow EEG patterns [25]. REM sleep occurs cyclically throughout the night at intervals of approximately 90 min [25,26]. Strong circadian pacemakers control the succession of NREM and REM stages and the sleep patterns are different in humans, considering age, gender and exogenous sleep-influencing factors. Thus, the underlying sleep-wake cycle regulating mechanisms should be evaluated when sleep should be considered in relation to physiological/pathological states.

The physiological sleep-wake cycle is under the control of several circadian regulators modulated at hypothalamic level [27]. Incoming light is the primary factor synchronizing the circadian rhythm, transduced by retinal ganglion cells in stimuli to the midbrain periaqueductal grey area [28]. Serotoninergic stimuli regulate the circadian timing, which is generated in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus through a series of interlocked positive and negative transcription/translation feedback loops [29]. The main actors of the transcriptional circuit of clock genes are *BMAL1*, coding the Brain and Muscle ARNT-like 1 (BMAL1) protein, and coding Circadian Locomotor Output Cycles Kaput (CLOCK) [29] (Fig. 1). These proteins regulate the transcription of target genes, such as *PER1* gene, coding the period circadian protein homolog 1 protein (PER1), *CRY1* and *CRY2,* coding cryptochromes CRY1 and CRY2, *RORA* and *RORB*, coding RAR-related orphan receptors α and β (RORα and RORβ), *NR1D1*, coding REV-ERBα, and other clock-controlled genes [30] (Fig. 1). The PER-CRY heterodimer is activated by phosphorylation mediated by Casein Kinase 1 (CK1) and move into the cell nucleus, repressing BMAL1/CLOCK functions [31,32] (Fig. 1). ROR and REV-ERB participate to the network, competing for binding ROR-binding elements (RORE), providing positive (ROR) and negative (REV-ERB) regulation of *BMAL1* and *CLOCK* transcription [32] (Fig. 1). These molecular mechanisms are fundamental to translate the hypothalamic signals into circadian rhythms regulating the sleep-wake cycle.

3. Sleep dysregulation

Sleep disturbances could be not unified in a single category. They are characterized by disorders either in sleep amount and/or quality, or in sleep behaviours. Insomnia, the best-known example of sleep disturbance, is characterized by a reduction in both quantity (hours) and quality of sleep [33]. Insomnia is related to noticeable reduction in quality of life, together with mental and organic sicknesses [33], related to psychologic difficulties [34,35] and increased cardio-metabolic morbidity and mortality [36–40]. While sleep deprivation results harmful to health, also excessive daytime sleepiness could be detrimental, as observed in case of sleep apnoea, narcolepsy, and idiopathic hypersomnia [26]. Among them, sleep apnoea represents the most frequent sleep dysfunction, occurring predominantly in middle-aged men and postmenopausal women, in association with obesity and cardiovascular complications [41]. On the contrary, narcolepsy and idiopathic hypersomnia are chronic brain disorders with an onset at a younger age [41]. These examples describe well how the sleep duration alteration, both in defect and in excess, could negatively affect human homeostasis.

3.1. How to measure sleep dysregulation

Sleep disorders are currently heterogeneously evaluated, using both quantitative and qualitative tools. These instruments evaluate different sleep-related characteristics, which could be grossly referred to the sleep duration (quantity), sleep quality and dysfunctional sleep habits.

Self-filled questionnaires are widely used to gather information in the assessment of sleep quality and quantity, daytime sleepiness, and circadian rhythm disturbances [18,42]. In particular, they investigate different sleep features, such as time of awakening, number of night-time awakenings and sleep-induced drugs' intake [43], and sleep quality through depth of sleep and difficult awakening [43]. The number of questionnaires potentially available is enormous and is progressively increasing, either validated or constructed by clinicians themselves and structured on specific cohort's characteristics, depending on the sub-field of sleep disturbances wanted to be explored. Among the wide range of questionnaires, sleep diary represents the first, simplest example of sleep dysfunction register. This instrument is useful, cost-effective, and practical, providing daily subjective information of some sleep parameters [44–46]. However, it should be considered only an adjunctive instrument when repeated measurements are indicated and a broader assessment of sleep is needed. The Insomnia Severity Index (ISI), measuring patient's perception of insomnia [45,47], the Pittsburgh Sleep Quality Index (PSQI), assessing sleep quality and disturbances over a one-month interval [48], and the Epworth Sleepiness Scale (ESS), measuring the excessive daytime sleepiness [49], are three examples of self-reported questionnaires validated in large surveys. However, they could be influenced by many biases, and they do not provide direct information about the sleep structure [50].

The gold-standard tool to evaluate and measure sleep quality and quantity is the polysomnography (PSG) [51]. PSG provides accurate, objective, qualitative and quantitative information on the physiological indices of sleep quality [42,52] continuously collecting multiple physiologic signals occurring in many different organ systems in relation to sleep stages [52]. Despite PSG advantages, this exam remains difficult and expensive to carry out only in a

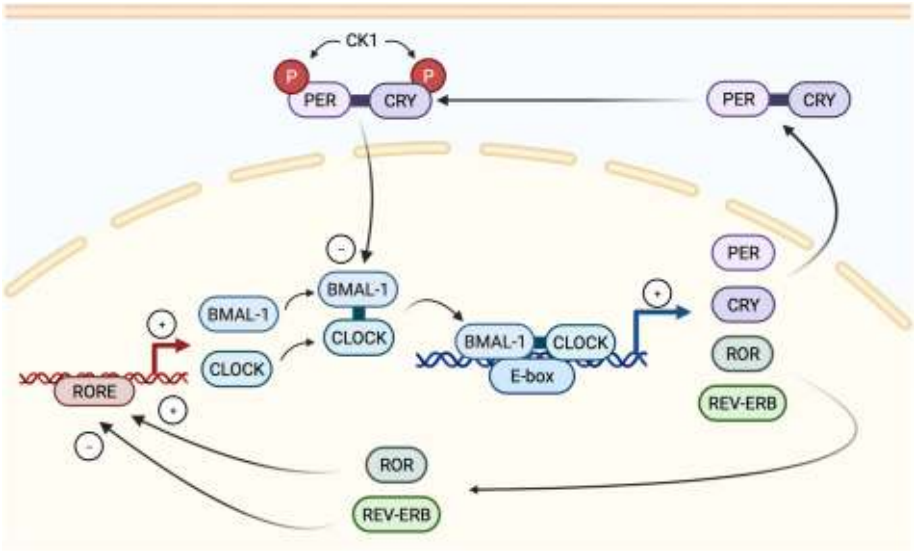

Fig. 1. A schematic representation of the main circadian interlocking loops at the cellular level. [BMAL-1 = Brain and Muscle ARNT-like 1; CLOCK = Circadian Locomotor Output Cycles Kaput; CK1 = Casein Kinase 1; CRY = cryptochrome; PER = period; ROR = retinoid acid-related orphan receptor; RORE = ROR-binding elements].

hospital setting, under the supervision of expert physicians [42,51]. Thus, PSG is not currently recommended for screening or diagnosis of insomnia in clinical practice [43,53,54]. Actigraphy is another quantitative tool able to objectively assess sleep time parameters and the motor activity during sleep [18]. Actigraphy's advantages over PSG are the possibility to record continuously for 24-h a day for days, weeks or even longer [55,56] and the home-assessing performance with minimal disturbance [57]. However, actigraphy lacks precision since body movements could influence the registration, limiting its application for the routine diagnosis, assessment, or management of sleep disorders in clinical practice [57].

3.2. Clinical classification of sleep dysregulation

Sleep dysregulations could be classified according to different sleep variables. Referring to the sleep duration, adult population could be distinguished in average sleepers (7.5 h/night), long sleepers (9–10 h/night) and short sleepers (<6 h/night) [18].

Considering sleep habits, sleep dysregulations could be further classified in individual different chronotypes considering sleep-wake cycles. This subdivision considers information about when the patient typically goes to bed and when he/she wakes up. These chronotypes are so-called 'morning', 'evening' or 'intermediate' sleepers, considering information about the time of day when they are most mentally active [18]. Intuitively, morning types go to bed and wake up early, preferring to conduct activities in the morning, while evening types go to bed and wake up late being more active in the evening. On the contrary, the intermediate type could not be classified in the previous categories [18].

Considering sleep quality, in most clinical studies, its assessment is obtained by questionnaires, as described in the previous section. Thus, a standardized clinical classification of sleep quality alterations is not possible, ranging from dichotomous evaluation (i.e. good quality/poor quality) to the possible presence of sleep disturbances (for example difficulty falling asleep, number of nocturnal awakenings, early awakening), to a continuous evaluation depending on the score obtained through the specific questionnaire applied.

Another clinical classification considering sleep disorders is the so-called 'circadian desynchrony', which occurs when sleep/wake schedules are discordant with the individual inner biological clock [58]. This condition is a 'side effect' of shift work but could also possibly be due to the excessive use of the mobile phone which could affect physiological sleep/wake patterns independently from work activities [59]. The presence of circadian desynchrony was linked to an increased risk for metabolic and cardiovascular comorbidities [60–62] and also identified as a probable risk factor for cancer onset [63].

4. Pathophysiologic mechanisms underlying the relationship between sleep dysregulation and infertility

Despite the relationship between sleep and human fertility remains far to be elucidated, some possible mechanisms connecting sleep disturbances and reproductive health could be advocated. The principal mechanisms suggested are summarized in Fig. 2.

4.1. Circadian dysrhythmia - the alteration in melatonin secretion

The bidirectional connection between circadian rhythms and reproductive functions is largely described in the literature and it is finely regulated by a sort of 'circular feedback'. Sexual hormones, such as androgens, estrogens and progesterone, may act at the core of the circadian homeostasis [64], while exogenous disturbances of circadian timekeeping are demonstrated to modulate reproductive hormones levels [64]. The main circadian clock physiologically dialogues with the pineal gland through melatonin rhythmic secretion, needed to maintain circadian rhythms [65] and their phenotypical manifestations, such as chronotypes. When melatonin rhythmicity is disrupted, this neural connection fails and the circadian homeostasis collapses [66]. The first hypothesis explaining a possible melatonin involvement in reproductive physiology derived from the observation of impaired pubertal development in case of pineal gland tumours [67]. Further researches highlighted the melatonin capability to regulate circadian clock genes expression in several reproductive tissues [68]. More recently, the melatonin involvement in the whole human reproduction physiology has been suggested, highlighting its antioxidant and hormone regulatory properties [69–71].

In female mice, melatonin secretion inhibition affects negatively

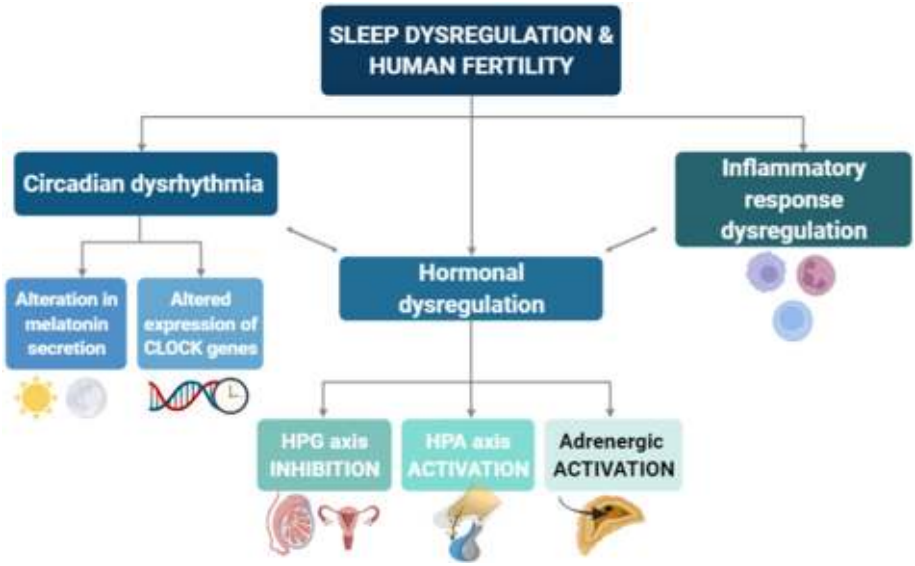

Fig. 2. The main physio-pathological mechanisms advocated to explain the network connecting sleep dysregulation and reproductive health. [HPA = hypothalamic-pituitary-adrenal; HPG = hypothalamic-pituitary-gonadal].

the pituitary-gonadal axis, increases visceral obesity and chronic inflammation, leading to a PCOS-like phenotype [72]. Moreover, through the increased production of the antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase [73], the melatonin scavenger activity allows to improve oocyte quality and to support the follicular phase in female mice [74]. This evidence is also supported by the detection of higher levels of melatonin in the pre-ovulatory follicular fluid than in the serum, likely required to inhibit follicular *atresia* [75]. Increased amount of melatonin in follicular fluid was also connected to better ART outcomes [76]. In addition, both *in vitro* and *in vivo* studies suggested a pivotal role of melatonin in blastocyst activation and embryo development, preventing implantation failure [77–79]. Given these results, several randomized clinical trials were designed to investigate the effect of melatonin supplementation in ART protocols. A very recent meta-analysis was conducted on this topic, documenting an increased retrieval of mature oocytes in the melatonin-treated group, although no differences in clinical pregnancy rate was found [80]. While the melatonin defect seems to have a clear detrimental role in female reproduction, the effect of its excess is not clear. There is only limited evidence that an excess of melatonin could induce amenorrhea and hypogonadism in women [81–83].

In men, a connection between melatonin and testicular function has been proposed. Melatonin acts as a local modulator of the endocrine activity in both Leydig and Sertoli cells, regulating their proliferation, energy metabolism and steroidogenesis [84]. Moreover, melatonin seems to exert antioxidant and anti-inflammatory effects also in testicular tissues [85], together with the capability to modulate the gonadotropin-releasing hormone (GnRH) secretion [86]. Alongside the antioxidant enzymatic activity [73], recent studies highlighted melatonin-mediated, anti-apoptotic properties, together with a reduction in sperm DNA fragmentation and in lipid peroxidation [87]. Few attempts to connect melatonin levels, plasmatic or seminal, to semen parameters have been performed, highlighting a positive correlation with sperm motility [88]. Comprehensively, reduced plasmatic and seminal melatonin concentrations were linked to impaired semen quality, while physiological hormone levels were found in normozoospermic men [88]. However, to date, no clinical trials were conducted to investigate the possible beneficial effect of melatonin supplementation on human semen quality, although studies in rodents and humans supported a hypothetical beneficial effect [87,89–92].

In summary, circadian dysrhythmia due to sleep dysregulations could lead to a melatonin secretion pattern alteration that, in turn, could negatively affect both the male and female reproductive health. However, no studies evaluated the association between alterations of the melatonin secretion pattern in sleep disorders and human reproduction.

4.2. Circadian dysrhythmia - the altered expression of CLOCK genes

The link between fertility and chronotypes may have a genetic basis. Alongside the central control of circadian activity, peripheral clockwork mechanisms have been identified in most body tissues [93]. Circadian rhythmicity of gene expression was demonstrated at both the central and peripheral level, with a certain degree of functional autonomy [94], and finely regulated by *CLOCK* and *BMAL1* gene expression [95]. In reproductive tissues, the expression of circadian genes was demonstrated in salpinges, uterus, testis and in the embryo [96–99], suggesting that these molecules may be involved in the regulation of mammalian reproduction. As reported above, the connection between reproductive hormones and clock genes is bidirectional. Therefore, it is not surprising that reproductive functions, including ovarian cyclicity and steroidogenesis, luteinizing hormone (LH) fluctuations and spermatogenesis are influenced by the expression of clock genes [100–103]. On the other hand, it is well known that hormones involved in reproduction, such as follicle-stimulating hormone (FSH), LH, estrogens, androgens and glucocorticoids have circadian rhythmicity, essential for their biological functions [95]. The lack of hormone secretion rhythmicity leads to hypogonadism in both the sexes, although the molecular mechanism is not completely understood [104,105]. Information about the complex network linking clock genes and reproduction derived from murine knockout models. *Clock*-knockout (KO) mice exhibited a reduced fertility with higher rate of pregnancy failure in females and a lower rate of fertilization in males [94,106,107]. *Bmal1* KO was associated with irregular ovarian cycles and increased implantation failure for defective progesterone production [108,109], while male mice were sterile with low

testosterone levels due to impairment of Leydig cells compartment [110,111]. Moreover, *Per1* and *Per2* loss-of-function mutations lead to premature ovarian insufficiency, suggestive of a link between circadian rhythm and depletion of ovarian reserve [112]. Couples of *Nr1d1* KO mice, lacking Rev-Erbα protein, showed a reduction of average number of pups per mating, as well as lower number of litters per mating period, compared to wild type [113]. In fact, Nr1d1 is involved in the modulation of autophagic mechanisms at the basis of the atretic processes [114], suggesting that granulosa cell metabolism is strictly connected with clock molecules. Taken together, data from mice indicate that circadian regulators play a relevant role in modulating the reproductive functions. In humans, the picture is less clear since most available studies focused on *BMAL1* and *CLOCK* polymorphisms, showing inconclusive results on seminal parameters and on pregnancy outcomes [115–117]. However, decreased expression levels of *BMAL1*, *CLOCK*, *CRY1*, *PER1*, and *PER2* clock genes were found in infertile men with asthenozoospermia [118], strengthening the concept that proper functioning of circadian regulators is required for human reproduction. The negative impact of circadian dysregulation on male reproductive parameters may be due to the indirect effect of sleep deprivation on vascular endothelial functions [119], as a parameter strictly connected with male reproductive issues [120]. Moreover, expression levels of some of these genes are regulated by sex steroids, even in the female [121], thus, it is not surprising that they may be involved in the pathogenesis of ovarian dysfunctions, such as PCOS. In pregnancy, progesterone has a regulatory effect of BMAL1 functions, which is involved in trophoblast migration and invasion [122], and is dysregulated in cases of recurrent miscarriage, due to a possible implication of this gene in decidualization [123].

These data clearly suggest that circadian dysrhythmia due to the sleep dysregulation-derived impairment of the circadian melatonin-clock genes system could negatively impact reproductive outcomes However, whether and to what extent this dysregulation, estimated to affect approximately 60% of the general population [58], could contribute to the globally observed fertility decline remains to be clarified.

4.3. The hormonal dysregulation

Sleep phases present endocrine properties, considering their capability to modulate hormone secretion. In particular, SWS influences growth hormone (GH) and cortisol secretion, with expected repercussions on metabolism and inflammatory status [124]. A subclinical hormonal dysregulation could be hypothesized in short sleepers, resulting from sleep deprivation. An indirect detrimental effect of short sleep on fertility could derive from sexual dysfunction [125] and reduced sexual activity [126] observed in these subjects. Short sleep could be a manifestation of chronic comorbidities which could impact the fertility status *per se*, such as obesity, diabetes, cardiovascular diseases, and depression [124,127,128]. Thus, sleep deprivation could negatively impact fertility i) in a direct manner, modulating reproductive hormones secretion, ii) in a behavioural way, influencing sexual functions and habits, and iii) indirectly, representing a spectrum of underlying pathological conditions themselves impacting fertility.

Sleep dysregulation could be identified as a source of stress for body homeostasis, with potential negative impact on reproductive functions, although the inner link remains unclear. While it is well known that couple infertility causes stress, the opposite is not clearly demonstrated, leaving the question unanswered [129]. The absence of a univocal and quantifiable method to measure stress attenuates the reliability of the results of every experimental clinical setting, since we are able to measure only stress-derived surrogates [130]. In this complex scenario, it is well known that increased stress could act at the central level on the paraventricular nucleus, which is a crossroad for several downstream pathways. First, a central block of the hypothalamic-pituitary-gonadal axis due to the loss of GnRH pulsatility has been proposed, as clinically observed in case of hypothalamic amenorrhea [131]. Moreover, the autonomic system recruitment mediates noradrenergic and adrenergic pathways, inducing metabolic and cardiovascular responses [132]. Since catecholamine receptors are expressed in the reproductive tract, a possible sympathetic-induced impairment of reproductive functions after an acute or chronic stress exposure could be hypothesized [129]. In this context, the hypothalamic-pituitary-adrenal (HPA) axis remains the main endocrine effector of stress response, exploiting its action through glucocorticoids secretion by adrenal glands [133]. Glucocorticoids, endogenously produced and/or exogenously administered, are demonstrated to interfere with the reproductive system both at the central and at the peripheral level. HPA hormones interfere with gonadotropins' secretion acting on the pituitary gland and indirectly inhibiting hypothalamic GnRH pulsatility [134]. Glucocorticoids exhibit a detrimental activity directly on the gonads, affecting both steroidogenesis and gametogenesis [135], as demonstrated in animal models exposed to glucocorticoid excess [136–138]. The impairment of gonadal physiological functions seems, at least in part, due to steroid-induced arrhythmic expression of clock genes within the gonads [139], contributing to the complex scenario composed of hormones and circadian rhythmicity.

In humans, the cortisol/cortisone ratio, linked to the ovarian 11β-hydroxysteroid dehydrogenase activity, seemed associated with pregnancy rate after *in vitro* fertilization (IVF) [129]. In men, a limited number of trials investigated the impact of steroid treatments, showing contradictory results [140,141], despite clear *in vitro* and *in vivo* demonstrations of glucocorticoid capability to influence testicular homeostasis [142]. In summary, sleep dysregulation could represent an example of a stressor that, mainly through the HPA axis recruitment, could impair fertility in both sexes.

4.4. The inflammation response dysregulation

Another possible mechanism connecting sleep and fertility concerns stimulation of inflammatory response. In some sleep disorders abnormal cytokine profiles are detected, showing increased levels of high-sensitivity C-reactive protein, tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 [143,144]. Similar patterns of inflammatory markers were observed in case of sleep loss and poor sleep quality [145–148]. On the other hand, higher levels of IL-6 and TNF-α were detected in infertile patients compared to fertile controls [149–151]. Involvement of the immune system has been associated with recurrent miscarriage, preeclampsia and pre-term birth [152] suggesting the potential association between inflammation and infertility. However, a clear cause-effect relationship between sleep dysregulation and human reproduction through altered cytokines secretion, albeit plausible, remains speculative.

5. Association between sleep dysregulation and human reproduction

Several studies investigated the connection between sleep habits and human reproduction. However, since sleep dysregulation is a heterogeneous condition, it is difficult to reach clear conclusions. Trying to simplify this complex picture, we decided to classify published data according to the aspect of human fertility considered, i.e. i) female reproductive functions, ii) male reproductive functions, iii) natural conception and iv) assisted

reproduction (Table 1 and Fig. 3). Within each of these items, the relationship between sleep dysregulation and human fertility was evaluated considering sleep characteristics, i.e. duration, quality and habits.

5.1. Sleep dysregulation and female reproduction

The association between sleep and the female reproductive sphere appears evident, especially considering the known impact on reproductive hormones [153]. Not surprisingly, specific physiological periods of life characterized by peculiar hormonal secretions (i.e. pregnancy, lactation and menopause) or pathological conditions (i.e. polycystic ovary syndrome - PCOS), are often associated with sleep disturbances [127,154]. However, also the opposite association is demonstrated and female sleep disorders are known to lead to menstrual abnormalities [155].

The knowledge about the connection between sleep and female reproduction is limited since most studies are focused on ovarian function measured through the regularity of ovarian cycles. Reports on the correlation between sleep duration and female reproduction are contradictory. While four studies did not highlight a relationship between ovarian cycle irregularities and sleep debt [33,156–158], an increased incidence of menstrual cyclicity disorders was reported in case of sleep duration below 5 h in two studies [61,159].

Some evidence indicates a direct correlation between sleep quality and high incidence of ovarian cycle irregularities [33,61,160]. Recently, sleep quality reduction is suggested as a risk factor for reduced ovarian reserve measured by antral follicular count in women aged 31–36 years [161].

Considering biological sleep chronotypes, no relation with ovarian function emerged [156,158,162], except for one study in which a longer menstrual cycle duration was reported in evening chronotype women [163]. More robust data are available regarding shift work, which resulted associated with menstrual disruption [156,164–167]. The largest study including more than 71000 nurses reported a higher incidence of irregular cycles and impaired cycle length (<21 days and >40 days) in case of rotating shift work that lasted over 20 months [165]. Published data on shift work were also meta-analysed confirming that any kind of shift work was associated to a higher risk of ovarian cycle length impairment, despite the relevant heterogeneity existing between studies [168]. Comprehensively, a very recent meta-analysis was conducted including four studies investigating sleep disturbance and ovarian function [61,158,165,166], highlighting an increased risk of menstrual cycle irregularities [169].

All these data confirm the potential influence of sleep disorders on female reproduction. However, these studies remain still inconclusive since ovarian cycles are evaluated only by questionnaires (Fig. 3) and the evaluation of the ovarian cycle implies only a partial view of female fertility.

5.2. Sleep dysregulation and male reproduction

The association between sleep and male fertility *status* is mainly based on semen analysis, providing inconclusive results. Several studies reported worst semen parameters in long and/or short sleepers [170–175], while two studies detected no differences [176,177]. Interestingly, two studies enrolling healthy men highlighted an inverse U-shaped association between sleep duration and sperm count and between sleep disorders and sperm count and morphology [178,179].

Similar, discordant results were obtained considering sleep quality. Three studies comparing 970 and 382 infertile men and one recruiting 842 healthy men reported a negative association between sleep quality reduction and either sperm concentration or motility [173,180,181]. On the contrary, three studies did not detect any association between sleep quality alteration and semen parameters [171,177,178].

Considering chronotypes, only two studies were available, highlighting the evening type as the carrier of the worst seminal profile [171,175]. Finally, several studies evaluated the impact of shift work on male fertility, reporting either no association [182–185], or a higher rate of oligozoospermia in the shift work group compared to non-shift workers [170,186]. Only in one study, sperm DNA fragmentation was considered as an end-point [187,188], resulting higher, thus indicative of an impaired semen quality [189], in case of irregular sleep habits [174]. A meta-analysis of five studies [178–182] reported sleep dysregulation associated with lower sperm number (mean difference −32.17; 95%CI, −53.52 to −10.82), lower sperm concentration (mean difference −8.09; 95%CI −12.26 to −3.92), and lower sperm morphology (mean difference −0.84; 95%CI −1.24 to −0.43) [169]. In a very recent study, Wang et al. elaborated a sleep model combining sleep duration, sleep midpoint, social jetlag and chronotype for 667 healthy young men. An elegant statistical approach allowed to emphasize that early chronotype men are more frequently short or long sleepers, while late chronotype subjects tend to present social jetlag, correlating with impaired sperm count. This innovative approach suggested that sperm number could be influenced by different sleep behaviours, that could act synergistically [161].

In conclusion, unlike the female counterpart, the male fertility status was evaluated with a more objective marker of fertility, i.e. semen analysis, although it is well known that semen parameters do not exactly match with male fertility [190]. Despite these data, the influence of sleep dysregulation on male fertility, however, is far to be elucidated.

5.3. Sleep dysregulation and natural conception

A limited number of studies are available concerning the interaction between natural fertility and sleep dysregulation. The largest cohort study on this topic enrolling 6873 women with desire for conception failed to detect an association between fecundability and sleep duration, sleep quality and shift work [191]. Similar results about shift work were obtained in an American cohort of 1739 nurses [192] and in a Thai study enrolling 907 pregnant couples [184]. Interestingly, in another study, a connection between shift work and subfecundity was detected only in women but not in men [185]. On the contrary, in a Chinese cohort of 3907 women, a longer time to pregnancy was found in case of fixed evening and night workers compared to day workers, but not in case of shift work [193]. In a Finnish study involving 2672 women, the intermediate chronotype resulted with a higher risk for infertility (OR 1.62, 95%CI 1.09–2.40) [163]. Finally, two studies enrolling 1176 and 255 men, respectively, highlighted an association between short sleep and lower fecundability (OR 0.62, 95%CI 0.45–0.87) [194] and shift work as a risk factor for infertility (OR 3.60, 95%CI 1.12–11.57) [195]. Considering these data, it is not possible to conclude in favour or against a causal role of sleep dysregulation and reduction of natural fecundability. This could be due, at least in part, to the limited number of studies available and the high heterogeneity among clinical settings considered.

5.4. Sleep dysregulation and assisted reproduction

A low number of studies considered the role of sleep disorders in the assisted reproduction setting. While the impact of assisted reproductive technology (ART) paths on female sleep habits has been described so far, less is known about the role of sleep

Table 1
Characteristics of published studies investigating the relationships between sleep and human reproduction.

Year	Authors	Gender	Patients' characteristics	Number (n)	Age (mean ± SD) (years)	Sleep parameters - methods	Fertility parameters
2021	He H. et al.	Females	Healthy	2260	Mean 21 (range 17–30)	Sleep duration and quality - questionnaire	Menstrual cycle pattern
2021	Stocker LJ et al.	Females	Couple infertility	44 cases vs 34 controls	Mean 35 (range 20–48)	Sleep quality, chronotype - Wrist-worn actigraphy and questionnaire	IVF outcomes
2021	Pimolsri C et al.	Females	Couple infertility	48	Mean 33 (range 25–42)	Sleep duration and quality - Wrist-worn actigraphy	IVF outcomes
2020	Michels KA et al.	Females	Healthy	259	24 [20–35] median IQR	Sleep duration, quality, chronotype, shift work - questionnaire	Sex hormones' assessment
2020	Xing X et al.	Females	Healthy	1006	21.7 ± 2.8	Sleep duration and quality - questionnaire	Menstrual cycle pattern
2020	Demirkol MK et al.	Males	Couple infertility	220	31.9 ± 5.0	Shift work - questionnaire	Semen parameters
2020	Hvidt JEM et al.	Males	Couple infertility	104	34.0 ± 5.5	Sleep duration, quality, chronotype - questionnaire	Semen parameters
2020	Green A et al.	Males	Healthy	116	35.2 ± 7.2	Sleep duration, quality, chronotype - questionnaire	Semen parameters
2020	Du C-Q et al.	Males	Couple infertility	970	31.8 ± 6.0	Sleep quality - questionnaire	Semen parameters and sex hormones' assessment
2020	Chen HG et al.	Males	Healthy	842	28.0 ± 5.3	Sleep duration and quality - questionnaire	Semen parameters
2020	Liu K et al.	Males	Healthy	1346	34 [29–37] median IQR	Sleep duration and quality - questionnaire	Semen parameters and sex hormones' assessment
2019	Komada Y et al.	Females	Healthy	150	18.8 ± 0.7	Sleep quality, chronotype - questionnaire	Menstrual cycle pattern
2019	Kang W et al.	Females	Healthy shift-workers	238	24.5 ± 1.3	Sleep quality - questionnaire	Menstrual cycle pattern
2019	Pokhrel G et al.	Males	Underwent routine semen analysis	1101	Not available	Sleep duration - questionnaire	Semen parameters
2019	Willis SK et al.	Females	Healthy	6873	Mean 29.9	Sleep duration, quality, shift work - questionnaire	Time to pregnancy
2018	Kim T et al.	Females	Healthy	4445	33.6 ± 0.3	Sleep duration - questionnaire	Menstrual cycle pattern
2018	Shi X et al.	Males	Healthy	328	38.2 ± 5.6	Sleep duration, quality, shift work - questionnaire	Semen parameters and sperm DFI
2018	Wise LA et al.	Both	Healthy	1176 couples	Median F 29.5, M > 21	Sleep duration, shift work - questionnaire	Time to pregnancy
2018	Lyttle BMW et al.[a]	Females	Couple infertility referring to IVF	50	Not available	Sleep quality - questionnaire	IVF outcomes
2017	Nam GE et al.	Females	Healthy	801	15.4 ± 0.2	Sleep duration - questionnaire	Menstrual cycle pattern
2017	Liu MM et al.	Males	Healthy	981	Range 18-50	Sleep duration, chronotype - questionnaire	Semen parameters and antisperm antibody detection
2017	Viganò P et al.	Males	Couple infertility	382	39.0 [37.0–42.0] median IQR	Sleep duration and quality - questionnaire	Semen parameters
2017	Llaneza P et al.[a]	Females	Couple infertility referring to IVF	200	24–41	Sleep duration, quality - questionnaire	IVF outcomes
2017	Minguez-Alarcòn L et al.	Females	Couple infertility	473	35.0 [32.0–38.0] median IQR	Shift work - questionnaire	IVF outcomes
2017	Goldstein CA et al.	Females	Couple infertility referring to IVF	22	32.5 [26–42] median range	Sleep duration and quality - Wrist-worn actigraphy and questionnaire	IVF outcomes
2016	Wang Y et al.	Females	Healthy shift-workers	473	28.7 ± 5.2	Shift work - questionnaire	Menstrual cycle pattern
2016	Chen Q et al.	Males	Healthy	796	20 ± 0.5	Sleep duration and quality - questionnaire	Semen parameters and sex hormones' assessment
2015	Lawson CC et al.	Females	Healthy shift-workers	6309	35.2 ± 6.1	Shift work - questionnaire	Menstrual cycle pattern
2015	Eisenberg ML et al.	Males	Healthy	456	31.9 ± 4.9	Shift work - questionnaire	Semen parameters
2015	Gaskins AJ et al.	Females	Healthy shift-workers	1739	Median 33	Shift work - questionnaire	Time to pregnancy
2013	Jensen et al.	Males	Healthy	953	>18	Sleep duration and quality - questionnaire	Semen parameters and sex hormones' assessment
2013	Toffol E et al.	Females	Healthy	2672	51.9 ± 13.7	Chronotype - questionnaire	Menstrual cycle pattern and time to pregnancy
2013	Park I et al.[a]	Females	Couple infertility	656	Not available	Sleep duration - questionnaire	IVF outcomes
2012	Wan GH et al.	Females	Healthy shift-workers	151	Median 27.7	Shift work - questionnaire	Menstrual cycle pattern
2012	Wogatzky J et al.	Males	Couple infertility	1683	40.4 ± 5.9	Sleep duration and quality - questionnaire	Semen parameters
2011	Lawson CC et al.	Females	Healthy shift-workers	71077	37.8 ± 4.3	Shift work - questionnaire	Menstrual cycle pattern
2010	El-Helaly M et al.	Males	Couple infertility	255	30.1 ± 6.2	Shift work - questionnaire	Semen parameters
2009	Negriff S et al.	Females	Healthy	210	15.7 ± 1.7	Chronotype - questionnaire	Menstrual cycle pattern
2005	Gracia CR et al.	Males	Couple infertility vs proven fertile men	650 cases vs	34.3 ± 0.4 vs 33.5 ± 0.5	Shift work - questionnaire	Semen parameters
2003	Zhu JL et al.	Females	Proven fertility	21438	Not available	Shift work - questionnaire	Time to pregnancy
1998	Tuntiseranee P et al.	Females	Proven fertility	1496	Not available	Shift work - questionnaire	Time to pregnancy
1996	Bisanti L et al.	Females	Healthy	6630	Not available	Shift work - questionnaire	Time to pregnancy
1996	Bisanti L et al.	Females	Proven fertility	4035	Not available	Shift work - questionnaire	Time to pregnancy

DFI = DNA fragmentation index; F = females; IQR = interquartile range; IVF = *in vitro* fertilization; M = males; SD = standard deviation.
[a] Only study's abstract available.

Fig. 3. Studies investigating the connection between sleep and human reproduction. Available studies were classified according to the fertility aspect (i.e. female fertility, male fertility, natural fertility, medically assisted reproduction) and to the sleep characteristic (i.e. duration, quality, chronotype and circadian dysregulation) considered. Green boxes indicate the detection of a significant association between sleep characteristics and fertility. Orange boxes showed studies without a significant association detected. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

dysregulation on ART success. Most studies are mainly descriptive, underlining various degrees of sleep disturbances reported in small cohorts of ART women in the absence of control groups [196]. Five studies described the possible sleep influence on assisted reproduction outcomes, showing inconclusive results. One study did not report associations between sleep dysregulation and retrieved/cryopreserved oocytes and embryos [197]. On the contrary, a negative correlation between sleep disorders and retrieved oocytes number was highlighted in a cohort of 200 ART women [198], in a cohort of 22 ART women [199], and in a cohort of 462 ART women in case of nocturnal shift work [200]. Moreover, the largest retrospective study on this topic involving 656 IVF women detected a higher pregnancy rate in average sleepers compared to long sleepers ($p = 0.045$) and a trend to statistical significance in comparison to short sleepers ($p = 0.090$) [201]. A recent small, controlled study highlighted a significantly reduced sleep duration in women with recurrent implantation failure compared to control group ($p = 0.030$) [202]. Shorter sleep duration and later sleep timing seemed to increase the odds of ART cycles interrupted prior to embryo transfer, resulting possibly associated with poor ovarian response or inadequate embryo development [203]. A similar approach was performed by other authors, seeking for a seasonal difference in ART success, although with inconclusive results [204–208]. Although sleep disturbance could be influenced by seasons, the real sleep pattern was not evaluated in these studies.

The influence of sleep dysregulation on ART outcome was

suggested. However, it should be noted that in these studies the sleep dysregulation was mainly evaluated only in the female partner of the couple. It is well known that the psychological distress due to ART could reduce the chance of the assisted reproduction success itself [209]. Many trials tried to consider the strength of this correlation. Probably, the evaluation of the sleep habits of both partners should be included in this context and future studies should consider this behavioural aspect in the baseline couple characteristics.

6. Conclusions

In conclusion, several physio-pathological mechanisms have been advocated trying to explain the connection between sleep and human fertility. However, it would be simplistic to consider them separately, since a complex network of interconnected molecular pathways acts synergically to obtain a fine regulation of circadian homeostasis, essential for reproductive physiology.

Although we can assume that sleep disruptions represent a potential damaging factor for human health, including reproductive health, no clear evidence is available on the clinical effect of sleep dysregulation so far. Starting from these considerations, future studies should be designed on this specific topic, aimed to unravel the complex interconnection between sleep and fertility. To this purpose, future studies should use the most validated tool to properly evaluate sleep disturbances, in order to obtain reliable results. This approach could also allow to evaluate the impact of the effectiveness of infertility treatments according to sleep disturbances.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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