



THEORETICAL REVIEW

Sleep, sleep disturbance, and fertility in women



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SUMMARY

Sleep and sleep disturbances are increasingly recognized as determinants of women's health and well-being, particularly in the context of the menstrual cycle, pregnancy, and menopause. At present, however, little is known about whether fertility is affected by sleep quantity and quality. That is, to what degree, and by what mechanisms, do sleep and/or its disturbances affect fertility? The purpose of this review is to synthesize what is known about sleep disturbances in relation to reproductive capacity. A model is provided, whereby stress, sleep dysregulation, and circadian misalignment are delineated for their potential relevance to infertility. Ultimately, if it is the case that sleep disturbance is associated with infertility, new avenues for clinical intervention may be possible.

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Introduction

The relationship between sleep and fertility is largely unknown. This paucity of research is surprising, given that sleep is such a critical component to one's physical and emotional health and well-being. Among both women and men, it is well established that sleep disorders, particularly insomnia, contribute to, or are associated with, myriad health conditions, including cardiovascular disease, hypertension, glucose dysregulation, depression, and anxiety disorders. Specific to women, sleep disturbances coincide with premenstrual dysphoria, pregnancy, postpartum depression, and the menopausal transition [1]. While there appears to be a relationship between sleep disturbance and reproductive health, little is known about which form of sleep disturbance is related to reproductive capacity and which specific aspects of reproductive capacity are particularly affected. With respect to sleep disturbance, the relevant domains could include sleep fragmentation, sleep continuity disturbance, short or long sleep duration, circadian dysrhythmia, and/or hypoxia. With respect to reproductive capacity, the relevant domains could include problems with fertility,

conception, implantation, gestation, delivery, and/or neonatal health. Finally, it is possible that the relationship between these domains is reciprocal in nature, such that sleep disturbances and their associated sequelae may not only ensue from, but also interfere with, reproductive processes.

To date, the majority of evidence for the association between sleep disturbance and diminished reproductive capacity has been within the area of shift work [2–6]. In general, adverse reproductive health outcomes were observed (e.g., menstrual irregularities, dysmenorrhea, increased time to, and reduced rates for, conception, increased miscarriages, lower birth weights) and were taken to implicate the negative effects of circadian misalignment, and/or the sleep disturbance that coincides with shift work. There is a more limited literature with respect to sleep disordered breathing and infertility. Polycystic ovary syndrome (PCOS) is known to reduce reproductive potential and is believed to be one of the most common causes of female infertility. Two key studies demonstrate the association between sleep disordered breathing and PCOS. One seminal study showed that premenopausal women with PCOS were 30 times more likely to suffer from sleep disordered breathing (SDB) than controls [7]. Another key study similarly showed obstructive sleep apnea (OSA) was prevalent in 44% of obese women with PCOS, compared to 6% of age- and weight-matched reproductively normal women [8]. OSA is believed to contribute

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Abbreviations

ACTH	adrenocorticotrophic hormone
AMH	anti-Mullerian hormone
BMI	body mass index
CPAP	continuous positive airway pressure
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
FHA	functional hypothalamic amenorrhea
FSH	follicle-stimulating Hormone
GCS	glucocorticoids
GnRH	gonadotropin-releasing hormone
HDA	(I think you are referring to HPA)
HPA	hypothalamic-pituitary-adrenal

HPG	hypothalamic-pituitary-gonadal
IL	interleukin
IVF	in vitro fertilization
LH	luteinizing hormone
OSA	obstructive sleep apnea
PCOS	polycystic ovarian syndrome
PLMS	periodic limb movements
PRL	prolactin
RLS	restless legs syndrome
SDB	sleep disordered breathing
T4	thyroxine
TSH	thyroid stimulating hormone
TNF	tumor necrosis factor
WASO	wake after sleep onset

to the metabolic abnormalities (insulin resistance and decreased glucose tolerance) in women with PCOS [9]. Therefore, it is possible that OSA contributes to one form of female factor infertility. Finally, with respect to sleep continuity disturbance, only two studies have evaluated the direct association between sleep continuity disturbance and infertility. First, Pal et al. found that sleep disturbance, assessed using the single item query “do you experience disturbed sleep?”, occurred in 34% of infertile women [10]. In addition, women with diminished ovarian reserve were found to be 30 times more likely to have disturbed sleep, while controlling for race, body mass index (BMI), and vasomotor symptoms. Second, Lin and colleagues [11] found that greater than 35% of women receiving intrauterine insemination reported disturbances in their sleep. While these studies are among the first to examine sleep disturbance in relation to successful pregnancy outcomes and in populations of infertile women, sleep disturbance was assessed globally (i.e., is phrased in such a way to be all-inclusive and non-specific with respect to individual sleep disorders). Further, the direction of the findings suggests that the observed sleep disturbance is a consequence of infertility. The purpose of the present paper is to examine the reciprocal proposition, that sleep disturbance may adversely affect fertility.

In order to lay the foundation for the possibility that sleep disturbance contributes to infertility, several domains of information are provided. First, the prevalence and significance of infertility are highlighted. Second, three proposed pathways by which sleep disturbance could contribute to infertility are presented. Theoretical and empirical support for each is reviewed. Third, clinical relevance and implications, not only for extending sleep medicine practices to this population, but also for addressing infertility from a behavioral sleep medicine perspective, are discussed.

Infertility*Definition and prevalence*

Infertility is defined as “the failure to achieve a successful pregnancy after 12 mo or more of appropriate, timed unprotected intercourse or therapeutic donor insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 mo for women over age 35 y” [12]. An estimated 72.4 million women worldwide currently encounter infertility, with approximately 6.1 million having difficulty becoming pregnant or carrying a pregnancy to term in the United States [12–14]. Among a sample of 7643 females, infertility rates in the US approximated 15.5% (95% CI 8.6%–27.5%) for all women and 24.3% (95% CI 12.4%–43.5%) for nulliparous women [15].

Consequences

The American Society for Reproductive Medicine considers infertility a disease, rather than a mere quality of life issue. In addition, a recent US Supreme Court opinion expressed that conditions interfering with reproduction should be considered a *disability* as defined under the Americans with Disabilities Act since reproduction is a major life activity, which when disturbed, can be severely debilitating [16]. As such, infertility, in and of itself, presents a profound challenge to one's emotional and social well-being [16]. For example, anticipatory anxiety of “failed” attempts, repeated disappointments, uncomfortable physical procedures, relationship constraints, and unfulfilled life values can produce high levels of psychosocial distress. It is not surprising that this level of psychological distress constitutes risk for psychiatric disorders. Anxiety is among the most common form of psychological distress followed by depression, with the prevalence of anxiety and depression exceeding that of their fertile counterparts [16]. The fact that anxiety and depression are associated with disorders of initiating and maintaining sleep make it even more likely that sleep disturbance will occur in this context. Taken together, insomnia should be highly prevalent in this population; yet to date, there is a paucity of research on the prevalence of insomnia among women with infertility, let alone whether or not there is a reciprocal relationship between sleep disturbance and infertility.

Causes of infertility

Infertility may be attributed to, or a consequence of, organic (e.g., anovulation, tubal obstruction), iatrogenic (e.g., adverse effects of chemotherapy or radiation), and/or lifestyle (e.g., weight, nutrition, and substance use) factors (see Fig. 1). As discussed above, the psychological stress involved with infertility can also be extensive, leading one to further question whether stress/distress itself contributes to infertility [16,17]. While it is certainly the case that stress produces sleep continuity disturbance, normal sleep and sleep disturbances have yet to be investigated for their capacity to impede and/or facilitate reproductive function.

How might sleep affect fertility?

Provided here is both a) a synthesis of literature that relates sleep and/or sleep disturbance to reproductive indices and b) a framework encompassing the pathways by which sleep disturbance can interfere with fertility (see Fig. 2). There are at least three possible pathways by which sleep disturbance may be related to

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