Influence of Sleep on Fertility in Women

Abstract: *An estimated 15.5% of women in the United States experience infertility, and a wide range of conditions, behaviors, and exposures have been linked to this reduced reproductive capacity. Sleep is a critical component to health and well-being, yet the amount of research devoted to determining the association between sleep and fertility in women is lacking. This article will discuss potential pathways by which sleep dysregulation may modulate fertility and summarize observational study data related to shift work and fertility.*

Keywords: infertility; sleep; sleep disturbance; shift work; women's health

Infertility is commonly defined as inability to achieve a successful pregnancy following 12 months of appropriately timed, unprotected intercourse. An estimated 15.5% of women in the United States experience infertility with a wide range of conditions, behaviors, and exposures attributed to this reduced reproductive capacity.¹ Sleep is a critical component to health and well-being, yet the amount of research devoted to determining the

association between sleep and fertility in women is lacking. Sleep has been shown to affect health in a number of ways including increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke.² Specific to female reproduction, disturbance in sleep has been associated with postpartum depression, menopausal transition, and premenstrual dysphoria.³

by which sleep disturbance could contribute to infertility.

Potential Mechanisms for Infertility Secondary to Sleep Disturbance

A review by Kloss et al⁴ hypothesizes at least 3 pathways by which sleep effects fertility:

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To date, the majority of research on the relationship between sleep and fertility has focused on the reproductive effects of shift work. Obstructive sleep apnea (generally through its relationship with polycystic ovary syndrome [PCOS]) and sleep continuity have also been associated with infertility, though these studies are limited. The studies evaluating shift work will be discussed along with several potential mechanisms

1. Activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is known to play a role in sleep disturbance, may interfere with reproduction.
2. Altered sleep duration and/or continuity may contribute to infertility independent of HPA activation or through potentiation of HPA axis activation.

DOI: 10.1177/1559827616641386. From the Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska. Address correspondence to Nicole D. White, PharmD, CDE, Creighton University School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, NE 68178; e-mail: nicolewhite@creighton.edu.

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3. Abnormal circadian rhythms may result in infertility.

Activation of the HPA axis is known to precipitate sleep dysregulation, but activation may also be triggered by or increased secondary to sleep dysregulation. The role of HPA activation in fertility is multifaceted. HPA activation may directly affect reproductive hormones including luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone, leading to changes in menstruation, follicle development, and infertility.⁴ HPA activation may also cause increases in melatonin levels, which have been associated with amenorrhea and altered ovulation.^{5,6} Finally, HPA activation seems to effect the unique sequence of factors that make the endometrium receptive to the embryonic implantation (uterine receptivity), thus reducing the likelihood of conception.⁷

Infertility secondary to sleep dysregulation may also occur in the absence of HPA activation through suppression or augmentation of reproductive hormones or compromised immunity. Sleep and sleep dysregulation modulate a variety of hormonal functions. It is important to note that while reproductive hormone function is altered by sleep the effect of this modulation on reproductive capacity is not well studied. Sleep, sleep disturbance, and/or sleep deprivation have been found to modulate the thyroid stimulating hormone (TSH), LH, prolactin, testosterone, estradiol, anti-Müllerian hormone (AMH), and progesterone.⁴ Increased levels of TSH, prolactin, and irregular estradiol secretion have been associated with anovulation and increased prolactin is also associated with PCOS and endometriosis. PCOS and endometriosis are both leading causes of infertility in women.⁸ Increased testosterone is also associated with PCOS. AMH has been related to diminished ovarian reserve, or a low number of eggs remaining in the ovaries, and altered levels of LH and progesterone are linked to infertility.

The third potential pathway involves circadian rhythm disturbances. At least 2

key reproductive hormones display circadian patterns under normal sleep conditions: TSH and prolactin.⁹ Two additional reproductive hormones, LH and FSH, exhibit altered secretion in women with disturbances in circadian rhythm (shift workers).¹⁰ As discussed above, alterations in these reproductive hormones have the potential to reduce fertility through various mechanisms. Melatonin, a hormone commonly related to circadian function, has also exhibited altered secretion in shift workers.¹⁰ Though not as commonly associated with fertility, altered secretion of melatonin has been shown to have both positive and negative effects related to female reproductive capacity. Additional research is needed to delineate the hormone's role in conception.

As stated previously, the aforementioned mechanisms are theoretical and most have not been studied in humans. To date, the majority of research on the relationship between sleep and fertility has focused on the reproductive effects of shift work. An overview of these studies will be discussed below.

Shift Work and Altered Fertility

While studies in humans have produced inconsistent results, several positive associations between shift work and infertility have been found including increased rates of menstrual irregularities, dysmenorrhea, and increased time to pregnancy.¹¹⁻¹³ Night work, specifically, has been hypothesized to have poorer outcomes, and 2 studies report increased time to pregnancy in women working permanent night shifts or 3 night shift rotating schedules.^{14,15}

A meta-analysis evaluating the relationship between shift work and menstrual disorders, infertility, and pregnancy loss was published in 2014.¹⁶ The analysis included observational studies of female shift workers with shift work defined as work outside of 8 AM to 6 PM. This included women working rotating, mixed, or fixed shift patterns, but not women working only

occasionally outside the 8 AM to 6 PM timeframe. Fifteen studies with more than 100 000 women were subject to analysis. There were 4 studies with more than 70 000 women included in the analysis that assessed the effects of shift work on fertility specifically. Infertility was defined as time to pregnancy exceeding 12 months across all studies.

The analysis found that compared to non-shift workers, female shift workers had increased rates of infertility (9.9% vs 11.3%, respectively; odds ratio = 1.80; 95% confidence interval = 1.01-3.20). However, when studies were adjusted (adjustments varied by study but included age, smoking status [both male and female], partner's occupation and shift work, gravidity, caffeine intake, alcohol use, coital frequency, education, body mass index, and menstrual regularity), pooled analysis was nonsignificant (adjusted odds ratio = 1.11; 95% confidence interval = 0.86-1.44).

Like any meta-analysis, this study is limited by differences in shift work exposure, with different types of shift work represented and different durations of shift work engagement. Importantly, 4 of the 5 fertility studies included only women who had conceived a pregnancy, which may underestimate effects through exclusion of sterile women. The authors of the analysis concluded that while the review provided evidence for an association between shift work and fertility, there is currently insufficient evidence to recommend restriction of shift work to women of reproductive age attempting to conceive.

Discussion and Conclusions

The relationship between sleep and fertility is complex and not well established. Complicating the issue is the question of whether sleep disturbance is a result of infertility, a cause of infertility, or whether their relationship is one of reciprocal nature.

It is clear sleep has the potential to effect the reproductive capacity of females as several theoretical pathways

have been described. However, study data to date do not consistently substantiate any of these pathways.

Additional studies with more detailed definitions of shift work (specifically, information on the amount of night-work exposure including frequency, duration, and shift schedule) are needed to further delineate the relationship between shift work and fertility. Until more consistent associations are found, it is difficult to draw conclusions from the limited available data. Despite the inconsistencies and limitation of current study data, caution and counseling for women concerned about shift work and reproductive health may be appropriate. **AJLM**

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