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Mini-Review

Sleep Disturbances Across a Woman's Lifespan: What Is the Role of Reproductive Hormones?

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Abstract

Fluctuations of reproductive hormones are associated with various forms of sleep disturbances and specific sleep disorders, such as insomnia or sleep-disordered breathing, across different stages of reproductive aging. During the menstrual cycle, sleep is particularly disrupted during the late luteal phase, as demonstrated by both objective and subjective measurements of sleep. Progesterone and its metabolites generally have sleep-promoting effects. A steep decline in progesterone, for example, during the late luteal phase, is associated with sleep disruption. Endogenous estrogen shows no clear correlation with sleep alterations in relation to the menstrual cycle. During pregnancy, sleep disruption is not associated with changes in estrogen or progesterone but rather with changing physiological factors, such as nocturnal micturition, gastroesophageal reflux, or musculoskeletal discomfort, all substantial factors that most likely mask any effect of hormones. Both endogenous and exogenous estrogen, as well as progesterone, are positively associated with sleep during the menopausal transition. A marked improvement of sleep disturbances is observed with perimenopausal hormone therapy. As this effect is not seen in younger women receiving contraceptive therapy, other causes of sleep disturbances, such as aging and related changes in metabolism of stress hormones, secondary effects of vasomotor symptoms, or depression, must be considered. Gonadotropins are less associated with sleep disturbances than ovarian hormones, except for during the menopausal transition where follicle-stimulating hormone is related to sleep disruption. Further, hyperandrogenism, as seen in women with polycystic ovary syndrome, is associated with sleep disturbances and specific sleep disorders, for example, obstructive sleep apnea.

Key Words: sleep, reproductive hormones, menstrual cycle, pregnancy, menopause

Abbreviations: EEG, electroencephalography; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; POI, premature ovarian insufficiency; REM, rapid eye movement; RLS, restless legs syndrome; TST, total sleep time.

Sleep disturbances are reported by nearly one-third of the general population across all age groups and further increase with advancing age, affecting nearly 50% of individuals older than 65 years [1]. Important quality-of-life domains, such as physical functioning or emotional well-being, are significantly affected in patients experiencing chronic sleep disturbances [2]. While the involvement of reproductive hormones in various medical conditions, such as metabolic disorders, cardiovascular disease, and bone health is well documented, their role in sleep disturbances is less clear.

There are multiple causes of sleep disturbances in women and the pathophysiology is currently poorly understood. As women are more affected by sleep disturbances than men [3] and sleep disturbances are highly prevalent during times of hormonal changes, such as pregnancy or menopausal transition, the type, level, and changes in reproductive hormones are likely to contribute to these sleep complaints. Various clinical aspects, such as physical discomfort in pregnant women, interferences caused by the infant's sleeping rhythm in the postnatal phase, or vasomotor symptoms in perimenopausal women, are also likely to be significant contributors to sleep disturbances. A review of the relationship between female reproductive hormones and sleep disturbances is very timely since sleep disturbances constitute a growing challenge in patient care and it is critical to understand the potential contributions from the hormone environment. New wearable electronics allow for a more representative measurement of sleep in the home environment so that more and more women present with self-diagnosed sleep disorders. Also, hormone therapies, such as oral contraceptives or menopausal hormone therapies, are among the most frequently used medications worldwide. Providing background knowledge about the causal links between hormonal changes and sleep disturbances is therefore highly clinically relevant and may help in choosing appropriate treatment.

Background

Stages of Reproductive Aging

Hormone levels vary across the different stages of reproductive aging (Fig. 1), which may be divided by applying the STRAW criteria. The STRAW criteria divide the adult female life into 3 broad phases: reproductive, menopausal transition, and postmenopause [4]. These 3 phases are further subdivided into 7 stages. These life phases represent a good model to evaluate hormonal influences on sleep. The follicular phase

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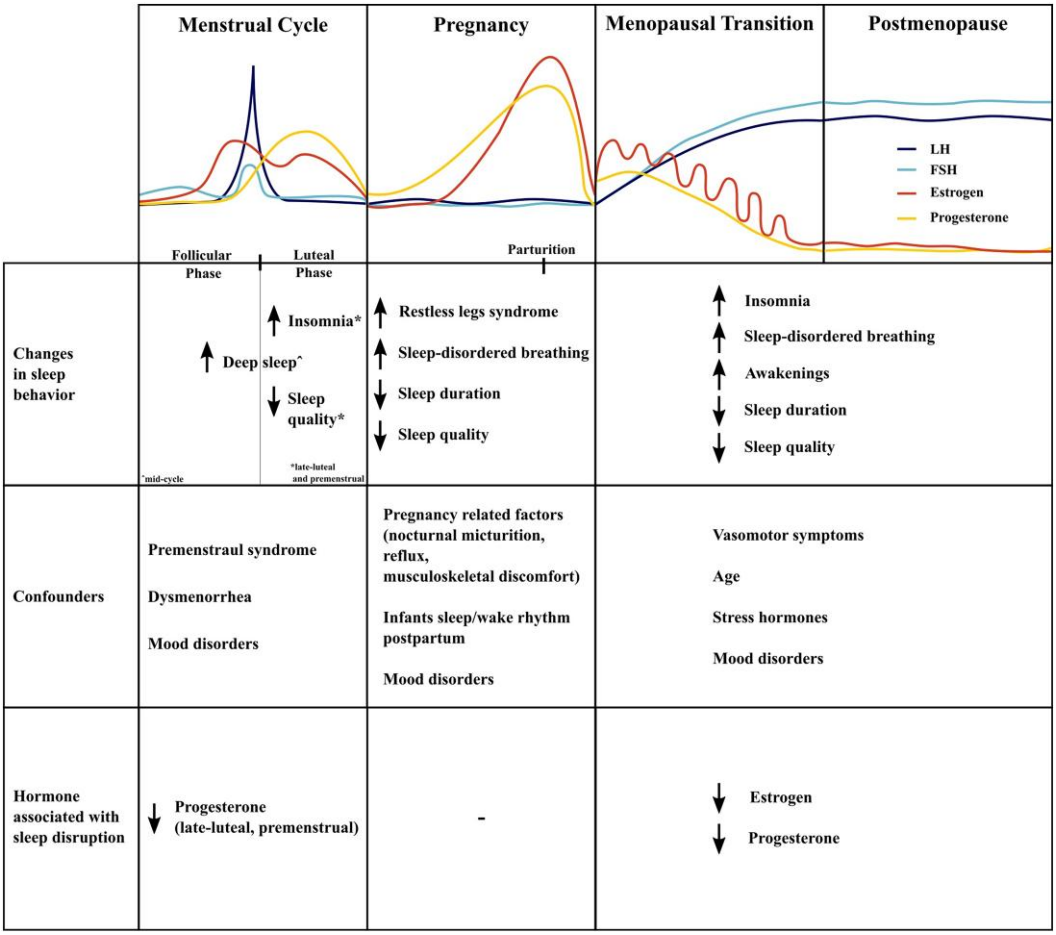

Figure 1. Hormone levels and sleep across stages of reproductive aging.

of the menstrual cycle is predominantly controlled by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which are pulsatively released by the pituitary under regulation of the hypothalamus [5]. Both hormones control the maturation of ovarian follicles and FSH particularly induces estrogen production. With the growth of the ovarian follicle carrying the oocyte during the follicular phase, estrogen, which is generated though aromatization of androgens in the granulosa cells of these follicles, increases [6]. An estradiol level above 200 pg/mL for more than 50 hours induces the LH surge via a positive feedback mechanism, which results in ovulation [7]. Ovulation marks the end of the follicular phase and is followed by the luteal phase. The luteal phase of the menstrual cycle is characterized by rising levels of progesterone, produced in the now transformed granulosa cells of the postovulatory follicular wall forming the corpus luteum. Progesterone declines when the corpus luteum reaches the end of its natural life span in absence of a pregnancy and degenerates before the onset of menses. Additionally, part of the granulosa cells continues to aromatize androgens after ovulation which induces a second but smaller rise in estrogen during the luteal phase. Under physiologic circumstances, the menstrual cycle repeats until a woman becomes pregnant or reaches menopause.

During pregnancy, there is a massive increase in estrogen levels until the second trimester and progesterone levels until the third trimester to about 7000 and 300 ng/mL, respectively [8], which decline abruptly after parturition [9]. In early pregnancy, up until about 8 to 10 weeks of gestation, estrogen metabolites and progesterone are produced by the corpus luteum [10]. Afterwards, the placental syncytiotrophoblast becomes a major source of progesterone und estrogen production [11]. During pregnancy, FSH and LH are at very low levels of <1 mIU/mL [12]. Prolactin levels increase throughout pregnancy until they reach about 300 ng/mL at term [8]. However, lactation only begins after delivery as the lactogenic activity of prolactin is suppressed by high levels of circulating estrogen and progesterone during pregnancy. The postpartum decline of estrogen and progesterone disinhibits the action of prolactin, thereby, resulting in lactation [13].

As women age and ovarian reserves diminish, the pattern of reproductive hormones first becomes acyclic and ultimately ovarian hormones return to very low levels as there is no longer follicular growth [14]. In the case of estrogen, this decline may be erratic and irregular, thereby causing a variety of climacteric symptoms [15]. Due to a negative feedback mechanism, FSH and LH increase as the ovarian hormones estrogen and progesterone decline [14]. There is a relative increase in androgens due to the decline of ovarian hormones and the increase of sex hormone-binding globulin (SHBG) [16]. In addition to reproductive hormones, stress hormones may play a dominant role in later reproductive stages as stress hormones increase with age [17] and also affect sleep [18].

Brief Overview of Sleep Physiology

Sleep is broadly defined as 2 states, rapid eye movement (REM) sleep and non-REM sleep, which is further divided into different stages (N1, N2, and N3 [N3 is also known as *slow wave sleep*]) [19, 20]. The depth of sleep progressively increases from N1 through to N3. N1 is characterized by a low-voltage, mixed-frequency electroencephalography (EEG) and is considered a transitional stage of sleep, comprising 2% to 5% of total sleep time (TST) in adults [21]. N2 sleep is characterized by the presence of sleep spindles (burst of 9-16 Hz waves, ≥ 0.5 seconds) and K-complexes (consisting of a positive-negative-positive waveform ≥0.5 seconds) on the EEG and comprises 45% to 55% of TST. N3 sleep is characterized by the presence of high amplitude, low frequency delta waves, comprising 13% to 23% of TST in adults [21]. Finally, REM sleep constitutes 20% to 25% of TST and is defined by the presence of muscle atonia in electromyography, episodic bursts of rapid eye movements, and low amplitude, mixed-frequency EEG. Non-REM and REM sleep alternate cyclically (every 90-120 minutes) across the night, with REM sleep proportions progressively increasing across the night. REM sleep facilitates learning and memory and is important for the development of the central nervous system [22, 23]. Lack of REM sleep may result in enhanced emotional reactivity [24], adverse health effects, and higher mortality [25].

Common Specific Sleep Disorders

The International Classification of Sleep disorders (ICSD-3) divides sleep disorders into 7 major categories: "Insomnia," "Sleep-related breathing disorders," "Sleep-related movement disorders," "Central disorders of hypersomnolence," "Circadian rhythm sleep-wake disorders," "Parasomnias," and "Other sleep disorders" [26]. Each of these are categorized into subsections with individual disorders. The following gives a brief overview of the most common relevant sleep disorders that we will investigate with regard to their potential association with female reproductive hormones. We chose the following sleep disorders due to their high prevalence.

Insomnia

Insomnia is the most common sleep disorder [27]. A meta-analysis of insomnia prevalence in the general population across different continents revealed a pooled overall prevalence of 22% and that women were 1.5 times more likely to have insomnia compared to men [28]. Besides female sex, other risk factors such as advanced age, depressive symptoms, and high stress levels have been identified [27]. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, insomnia is classified as a dissatisfaction with sleep quantity or quality associated with one or more of the following: the difficulty of initiating sleep, the difficulty of maintaining sleep, and morning awakening with inability to return to sleep [29].

Sleep-related breathing disorders

Sleep-disordered breathing occurs in 24% of young-middle aged men and 9% of women, with a male-to-female ratio estimated between 3:1 to 5:1 in the general population [30]. It is characterized by abnormal breathing during sleep. There are different types of sleep apnea, specifically, obstructive sleep apnea (OSA) or central sleep apnea. Although men are generally more affected by sleep apnea than women [31], the prevalence in women increases as they reach menopause [32]. Sleep-disordered breathing occurs in 70% of older men and 56% of older women [30]. Additionally, pregnancy is a risk factor for sleep apnea [33]. Besides other known risk factors, such as obesity, this suggests a hormonal component in the pathophysiology of this sleep disorder.

Sleep-related movement disorders

Restless legs syndrome (RLS) is classified as a sleep-wake disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [29]. It is characterized by a continuous urge to move the legs which is most severe at night [34]. Compared with men, the prevalence in women is twice as high (9% vs 5%) [35]. Further, there is a significant increase in prevalence of RLS in pregnant women, particularly during the last trimester [36]. Periodic limb movement disorder (PLMD) is another sleep-related movement disorder where patients involuntarily move their limbs during sleep. It often occurs together with RLS [37]. Periodic limb movements are common in the elderly [38], especially females [39], but also in pregnant women [40].

Methods

The search strategy included keywords related to (i) "reproductive hormones" such as estrogen, progesterone, and their respective metabolites, FSH, LH, prolactin, and androgens (ii) any form of "sleep disturbances" both objectively and subjectively measured and specific sleep disorders such as insomnia, sleep-related breathing disorders, or sleep-related movement disorders and (iii) keywords related to "reproductive aging" such as menstrual cycle, pregnancy, postpartum, and menopause. Studies investigating the association between female reproductive hormones and general sleep disturbances or common specific sleep disorders were included. We focused on human studies. Study groups included women of reproductive age who either had a regular menstrual cycle, were taking contraceptives, or were pregnant, as well as peri- and postmenopausal women. We also considered studies which included women with known endocrine pathologies, for example polycystic ovary syndrome (PCOS) or premature ovarian insufficiency (POI). We considered studies where hormone levels were either measured directly in serum, urine, or saliva, where assumptions were made based on phase of menstrual cycle, or where hormone therapy was given. While searching for studies regarding the relationship between progesterone and sleep, we also included studies discussing the luteal phase effect on sleep. In cases where no direct hormone measurements were taken, we assumed that progesterone levels were highest during the mid-luteal phase and declined in the late luteal phase. Specific terminology regarding sleep physiology is explained in Table 1. The *Study Quality Assessment Tools* of the National Institutes of Health (NIH) were used to rate the quality of studies [47].

Results

Menstrual Cycle

In premenopausal women, sleep is influenced by the menstrual cycle [48]. The follicular phase and early luteal phase are marked by a longer duration of deep sleep compared with the time around menstruation [49]. Women reported sleeping

Table 1. Specific terminology regarding sleep physiology

Slow wave sleep	Another term for stage 3 (N3) of non-REM sleep, also referred to as deep sleep [41]
REM latency	Time between onset of sleep to the first REM stage, changes in REM latency are considered biological markers for a number of sleep-related disorders [42]
Rapid eye movement densities	Frequency of rapid eye movements, can be used as a measure of sleep need, decreases with reduction of sleep duration [43]
Sleep efficiency	Ratio of total sleep time to time spent in bed [44]
Arousals	Central nervous system activation associated with increased sympathetic tone, characterized by an abrupt EEG frequency, which may include alpha and/or theta waves and/or delta waves and/or frequencies greater than 16 Hz lasting at least 3 s [45]
Sleep spindles	Contribute to memory consolidation and neuronal plasticity [46]

better in their follicular and ovulatory phases compared with their premenstrual phase [50], although individual differences are reported [51].The luteal phase is characterized by less REM sleep and a higher spindle frequency [52]. Insomnia and poor sleep quality worsen in the late luteal and premenstrual phase [53]. An overview of studies examining the relationship between reproductive hormones and sleep in premenopausal women is shown in Table 2.

Estrogen

No clear association could be demonstrated between estrogen and sleep in cycling women. While studies described a positive association between estrogen and sleep efficiency in premenopausal women [74] and an inverse relationship between estradiol and number of arousals during sleep [75], other studies found higher levels of estrogen to be associated with decreased REM sleep and increased wakefulness after sleep onset [56, 71]. Further, retrieved studies were unable to detect any relation between estrogen or estrone and general sleep, wake after sleep onset and wake-index in premenopausal women [69-73].

Progesterone

Women demonstrate more slow wave sleep during the luteal phase [63] which supports a sleep-promoting effect of progesterone. One study detected a direct correlation between progesterone and deep sleep [56] and in another study, the anovulatory group with low levels of progesterone experienced significantly more wake time during the night compared to an ovulatory group [62]. Objective measurements indicated that women experience poor sleep during the late luteal phase [44]; specifically, they reported more wakefulness after sleep onset and brief arousals in the late luteal phase [63, 71]. A sleep-promoting effect of progesterone is also supported by subjective data, as women reported decreased quality of sleep during their late luteal [44] and premenstrual phase [50, 66], when progesterone levels are declining. However, patterns of sleep disturbance may show individual differences and vary across the menstrual cycle, with some women showing no change, others showing more sleep disturbances around ovulation, and others showing sleep disturbances in the premenstrual phase [51]. REM sleep was affected by progesterone during the luteal phase. Studies discovered a shorter REM latency and an increase of the amount of REM sleep with the luteal rise of progesterone [57, 59]. Additionally, a high sleep spindle frequency during the luteal phase is described [58]. Sleep spindles are uniquely altered by menstrual phase, hypothesized to reflect the actions of progesterone metabolites on $GABA_A$ receptors in these networks [61].

Gonadotropins

Although no specific measurements related to the menstrual cycle have been published, several studies have addressed the association between gonadotropins and sleep. Polysomnographic measures indicated no association between FSH and sleep efficiency or any other sleep parameter in cycling women [56, 72]. Although FSH seemed significantly associated with early morning sleep alterations, the association no longer remained significant after statistical adjustment [60]. Few other studies discovered that objective wakefulness measured by polysomnography was associated with high FSH levels [75] and FSH levels were positively related to trouble sleeping in premenopausal women [67]. Further, FSH levels are positively correlated with partial upper airway obstruction [55]. Another study reported a significant association between FSH levels and sleep duration [65]. The authors discovered that FSH levels were 20% higher in women sleeping more than 8 hours compared with women sleeping less than 8 hours. LH pulses occurred in association with awakenings [68]. Additionally, LH levels correlated with light sleep [56]. One study found no association between LH and sleep [65] while another study found a significant correlation between sleep efficiency and LH [72].

Hormonal contraception

Objective measurements revealed that women taking hormonal contraceptives had fewer arousals [70]. Furthermore, they had a higher sleep efficiency and a lower apnea-hypopnea index [72]. In subjective reports, women taking oral contraceptives had a longer sleep duration [54]. One study discovered that women taking monophasic combined oral contraceptives had less deep sleep, but subjective sleep quality did not differ from the ratings of naturally cycling women [64]. The effect on REM latency is inconclusive, as one study found a longer REM latency in women taking hormonal contraceptives [70] and another study reported a short REM latency in these women [57]. Other studies reported more sleep disturbances or fatigue [63] and increased excessive daytime sleepiness [76] by women using hormonal contraceptives. Women with progestin-only therapies presented shorter sleep duration compared to combined therapy [76]. Another study found that women taking monophasic combined oral contraceptives had more stage 2 sleep and less deep sleep [63].

Pregnancy

Pregnancy and postpartum are both associated with more frequent sleep disruption [77]. Physiological adaptations to pregnancy cause nocturnal micturition, as early as the first trimester, and gastroesophageal reflux which may disrupt sleep [78]. Sleep quality worsens and sleep duration is shortened as pregnancy progresses [78]. Sleep disruptions during pregnancy mainly include awakenings and wakefulness

Table 2. Overview of included studies examining the relationship between sleep and reproductive hormones in premenopausal women

Author	Year	Type of study	Sample size (n)	Method of sleep disorder assessment	Method of hormone measurement	Duration of data acquisition	Multiple measurements	Overall rating[a]
Hoffmann et al [44]	1978	Cross-sectional	15	Polysomnography, questionnaires	Blood	1 menstrual cycle	Yes	Fair
Hicks and Cavanaugh [54]	1982	Cross-sectional	49	Sleep logs, questionnaires	—	2 complete menstrual cycles	No	Poor
Stahl et al [55]	1985	Cross-sectional	11	Polysomnography	Blood	1 menstrual cycle	Yes	Fair
Parry et al [56]	1989	Case-control	16	Sleep EEG, daily sleep logs	Blood	1 menstrual cycle	Yes	Fair
Lee et al [57]	1990	Cross-sectional	17	Polysomnography, diary	Saliva	1 menstrual cycle	Yes	Fair
Ishizuka et al [58]	1994	Cross-sectional	5	Polysomnography	Blood	1 menstrual cycle	Yes	Fair
Armitage and Yonkers [59]	1994	Case study	1	Polysomnography, sleep diary	Blood	1 menstrual cycle	Yes	Fair
Huerta et al [60]	1995	Cross-sectional	151	Questionnaires	Blood	Not stated	Yes	Fair
Driver et al [61]	1996	Cross-sectional	9	Polysomnography, questionnaires	Blood, urine	32-36 days	Yes	Good
Lee et al [62]	2000	Cohort	8	Polysomnography	Blood	2 consecutive nights	Yes	Good
Baker et al [63]	2001	Cross-sectional	19	Polysomnography, questionnaires	Blood	6-month period	Yes	Fair
Baker et al [64]	2001	Cross-sectional	16	Polysomnography, questionnaires	Blood	3-month period	Yes	Fair
Touzet et al [65]	2002	Cross-sectional	106	Questionnaires	Urine	1-4 consecutive menstrual cycles	Yes	Fair
Baker and Driver [66]	2004	Cross-sectional	26	Questionnaires, sleep-diaries	Urine	1 month	No	Fair
Kravitz et al [67]	2005	Cross-sectional	630	Questionnaire	Urine	1 menstrual cycle	Yes	Fair
Hall et al [68]	2005	Cross-sectional	11	Polysomnography	Blood	40 hours protocol	Yes	Fair
D'Ambrosio et al [69]	2005	Pre-Post	12	Polysomnography	Blood	5 weeks	No	Fair
Hachul et al [70]	2010	Cross-sectional	931	Polysomnography, questionnaire	—	Not stated	No	Fair
Baker et al [71]	2012	Cross-sectional	36	Polysomnography, questionnaires	Blood, urine	1 menstrual cycle	Yes	Fair
Hachul et al [72]	2013	Cross-sectional	297	Polysomnography, questionnaires	Blood	6-month period	No	Fair
Sharkey et al [73]	2014	Cross-sectional	27	Polysomnography	Blood, urine	1 menstrual cycle	Yes	Fair
Li et al [74]	2015	Cross-sectional	19	Actigraphy, self-report	Urine	42 days	Yes	Fair
De Zambotti et al [75]	2015	Cross-sectional	44	Polysomnography, questionnaire	Blood	1 month	No	Fair
Bezerra et al [76]	2020	Cross-sectional	1286	Questionnaires	—	6-month period	No	Fair

[a]as rated by the NIH Quality Assessment Tools.

during the night [36]. Musculoskeletal discomfort due to the growing uterus increases in the second and third trimester causing sleep problems [78]. Further, pregnancy is a risk factor for sleep-disordered breathing and restless legs syndrome [33]. Postpartum is a time when women experience increased difficulties with sleeping, which may on the one hand be related to the important hormonal changes following delivery and on the other hand to the specific characteristics of the neonatal period, like sleeping rhythms of newborns and the necessity to feed the child at night [36]. An overview of studies examining the relationship between reproductive hormones and sleep in pregnant and postpartum women is presented in Table 3.

Estrogen

Altogether, only few studies investigated the role of estrogen in sleep disturbances during pregnancy. One cohort study discovered that longer sleep duration was inversely correlated with estradiol [81], implying a negative effect of estrogen on sleep in pregnant women. Another study demonstrated that pregnant women with restless legs syndrome (RLS) had higher levels of estrogen than pregnant women without RLS, suggesting that estrogens play a pathophysiological role in triggering RLS symptoms during pregnancy [80]. However, there are opposite results [82]. None of these studies has included physical changes related to pregnancy in their analysis.

The only available study investigating postpartum women revealed no association between estradiol levels and postpartum insomnia [84]. Unfortunately, there are no data controlling for the effect of the babies sleeping rhythm postpartum, especially when breastfeeding.

Progesterone

Pregnant women with OSA had lower levels of progesterone compared to pregnant women without OSA, suggesting that progesterone may play a protective role against OSA [85]. While progesterone itself was not associated with worse sleep quality, low serum concentrations of its metabolite allopregnanolone showed a trend to predict worse subjective sleep quality in pregnant women [83]. No association between progesterone and RLS was found during pregnancy [80]. The dramatic decrease in progesterone from the third trimester to postpartum was unrelated to changes in REM sleep parameters [62]. In a randomized clinical trial, pregnant women with previous preterm birth received either vaginal or intramuscular progesterone, but neither vaginal nor intramuscular progesterone improved sleep disturbances [86].

Gonadotropins

Data regarding FSH levels and sleep during pregnancy is limited, as studies in pregnant women focus on estrogen and progesterone. The only available study pertaining to FSH as well as LH and sleep in a group of pregnant women found that there was not an association between periodic limb movements during sleep with either FSH levels or with LH levels [80].

Prolactin

Prolactin has a positive effect on sleep, as lactation was associated with increased deep sleep [79]. Further, prolactin was positively correlated with high sleep efficiency [44]. In a group

Table 3. Overview of included studies examining the relationship between sleep and reproductive hormones in pregnant and postpartum women

Author	Year	Type of study	Sample size (n)	Method of sleep disorder assessment	Method of hormone measurement	Duration of data acquisition	Multiple measurements	Overall rating[a]
Blyton et al [79]	2002	Case-control	31	Polysomnography, questionnaires	—	Not stated	No	Good
Dzaja et al [80]	2009	Case-control	19	Polysomnography, questionnaires	Blood	36 weeks of gestation until 12 weeks postpartum	Yes	Fair
Wada et al [81]	2012	Cohort	236	Questionnaires	Blood	18 months	Yes	Fair
Hübner et al [82]	2013	Case-control	109	Wrist actigraphy, questionnaires	Blood	Course of pregnancy and 8 weeks postpartum	Yes	Fair
Crowley et al [83]	2016	Cross-sectional	14	Actigraphy, questionnaire	Blood	2 weeks	No	Fair
Drozdowicz-Jastrzębska et al [84]	2017	Cross-sectional	84	Questionnaire	Blood	24-48 hours after labor	No	Fair
Lee et al [85]	2017	Case-control	91	Retrospective review of polysomnography for cases, questionnaires for controls	Blood	2 years	Yes	Fair
Hantoushzadeh et al [86]	2019	Randomized parallel group	100	Questionnaire	—	14 months	Yes	Good

[a]as rated by the NIH Quality Assessment Tools.

of postmenopausal women, prolactin levels were positively associated with increased sleep duration [87].

Endocrine Pathologies

Reproductive endocrine pathologies such as PCOS or POI are also associated with sleep disturbances [88, 89]. PCOS is a reproductive endocrine pathology often accompanied by excess production of androgens. These androgens can also be converted into additional estrogen via the aromatase enzyme. An excessive as well as an insufficient amount of testosterone affects sleep quality [90]. In a group of premenopausal women, a shorter sleep duration was associated with higher testosterone levels [91]. PCOS is a known risk factor for sleep apnea [92]. Even though PCOS is also associated with obesity, overweight women with PCOS have more sleep-disordered breathing than weight-matched women without PCOS [93]. As testosterone also contributes to sleep-disordered breathing [94], the excess in testosterone is one explanation for increased sleep-disordered breathing in women with PCOS. POI is the premature cessation of ovarian function in women younger than 40 years [95]. In these women, the hormone profile is analogous to postmenopausal women. Women with POI have poor sleep quality and more insomnia despite the use of hormone therapy [89].

Menopausal Transition

The prevalence of sleeping difficulties during the menopausal transition is higher compared with premenopausal women [96-100]. Known causes are the occurrence of vasomotor symptoms and an increase in mood disorders [36]. Aging, which disrupts the normal circadian rhythm, is another cause for sleep fragmentation [78]. Additionally, the risk of sleep-disordered breathing is increased after menopause [96]. Table 4 provides an overview of studies examining the relationship between reproductive hormones and sleep in peri- and postmenopausal women.

Estrogen

Polysomnographic measurements demonstrated a positive relationship between estrogen and sleep, specifically low estradiol was associated with lower sleep efficiency [125], sleep-disordered breathing [115], and a high frequency of movement arousals [107]. Subjective sleep measures from questionnaires demonstrating a positive association between estrogen and sleep found significantly lower levels of estradiol in women with insomnia [103]. In addition, decreasing estradiol levels were associated with poor sleep and trouble falling and staying asleep [112, 128]. A higher estrogen level was significantly associated with decreased awakening during the night as well as early morning awakenings [121, 132]. Two studies discovered that rather the fluctuations and degree of change in estrogen than the absolute level was associated with sleeping problems [120, 126] but in summary, the results clearly demonstrate a positive effect of estrogen on sleep in perimenopausal women.

Progesterone

During the menopausal transition, declining or low progesterone levels, resulting from the failure of a growing follicle to reach sufficient maturation for ovulation, are associated with sleep disturbances. Cycling late-reproductive-age women (aged 48-59) had lower sleep efficiency and shorter sleep time during the final 7 days of the menstrual cycle compared with the third week of the menstrual cycle [133]. In women approaching menopause, increased arousals during the luteal phase were demonstrated by more wake after sleep onset [134]. In addition, more rapid eye movement densities were displayed during the luteal phase [44]. Furthermore, low levels of progesterone were associated with sleep-disordered breathing [115]. In subjective questionnaires, lower concentrations of progesterone were associated with increased frequency of sleep disturbances and insomnia [139]. Likewise, allopregnanolone levels were negatively correlated with shallow sleep and sleep disturbances [136].

Gonadotropins

Plasma levels of FSH were significantly higher in peri- and postmenopausal women with insomnia compared to those without insomnia [103]. FSH was related to prolonged stage 2 sleep latency and prolonged slow wave sleep latency [108]. High FSH values were negatively related to sleep efficiency and associated with greater wake after sleep onset and higher apnea-hypopnea index [129]. Further, there was a negative correlation between FSH and deep sleep after menopause [44]. Increasing FSH levels were associated with more trouble falling asleep [140] as well as staying asleep, that is, awakening [132]. Likewise, subjective sleep quality was worse with high levels of FSH [129, 130]. In perimenopausal and postmenopausal women, LH was not associated with sleep disturbances [67, 112]. There was a difference in correlation between gonadotropins and poor sleep depending on reproductive age [44]. The authors discovered that in premenopause, LH and stage 3 sleep were positively correlated and after menopause, LH and number of stage shifts, number of awakenings, percentages of stages 1 and 2 and REM latency were positively correlated. Frequent stage shifts result in complaints of nonrestorative sleep [42]. This negative effect after menopause was also observed in another cross-sectional study in which higher LH levels were associated with lower sleep efficiency and higher numbers of awakenings [125].

Hormonal treatment during the menopausal transition

A recent systematic review [141] demonstrated that estrogen-only therapy, progesterone-only therapy, combined hormone therapy, selective estrogen receptor modulators, and selective tissue estrogenic activity regulators were all effective in alleviating sleep complaints. Oral estrogen-only therapy reduced insomnia and improved subjective sleep disturbances [101-135]. Likewise, this positive effect was observed with a transdermal application of estrogen [105, 110]. In one study, the effect of a sequential transdermal application was greater than with oral administration [111]. Intranasal estradiol was also effective in reducing sleep problems [123]. The combination of estrogens and progestins was similarly successful in improving sleep disturbances [113-137]. While most studies reported an amelioration, few studies reported a complete disappearance of sleep disturbances [102, 104]. Oral estrogen with micronized progesterone was more successful in improving sleep disturbances than oral estrogen combined with medroxyprogesterone [113, 122]. Progesterone-only treatment likewise improved sleep; both oral application [131, 142] and intranasal application [143] were successful. Hormone therapy users had less sleep-

Table 4. Overview of included studies examining the relationship between sleep and reproductive hormones in peri- and postmenopausal women

Author	Year	Type of study	Sample size (n)	Method of sleep disorder assessment	Method of hormone measurement	Duration of data acquisition	Multiple measurements	Overall rating[a]
Thomson and Oswald [101]	1977	Controlled trial	34	Electrophysiological recording	—	14 weeks	Yes	Fair
Furuhjelm and Carlström [102]	1977	Pre-Post	209	Self-report	Blood	3.5 years	Yes	Poor
Hagen et al [103]	1982	Cross-sectional	313	Questionnaires	Blood	Not stated	No	Fair
Shargil [104]	1985	Controlled trial	100	Questionnaires	—	3 years	Yes	Fair
Erkkola et al [105]	1991	Pre-Post	249	Interviews	—	6 months	Yes	Fair
Yang et al [106]	1995	Pre-Post	20	Questionnaires	—	3 months	No	Fair
Polo-Kantola et al [107]	1999	Cross-sectional	63	Polysomnography, self-report	Blood	4 months	Yes	Good
Polo-Kantola et al [108]	1999	Randomized controlled	66	Polysomnography, self-report	Blood	7 months	Yes	Fair
Strickler et al [109]	2000	Randomized controlled	398	Questionnaires	Blood	12 months	Yes	Good
Antonijevic et al [110]	2000	Pre-Post	11	Polysomnography, questionnaire	—	Not stated	No	Fair
Li et al [111]	2000	Cross-sectional	693	Questionnaires, interviews	—	3 years	No	Good
Hollander et al [112]	2001	Cohort	436	Questionnaire	Blood	2 years	Yes	Good
Montplaisir et al [113]	2001	Randomized parallel group	21	Polysomnography, questionnaires	—	6 months	Yes	Good
Barnabei et al [114]	2002	Randomized controlled	2763	Questionnaires	—	4 years	Yes	Good
Netzer et al [115]	2003	Cross-sectional	53	Polysomnography	Blood	Not stated	No	Fair
Shahar et al [116]	2003	Cross-sectional	2852	Polysomnography, questionnaires	—	51 months	No	Fair
Young et al [117]	2003	Cohort	589	Polysomnography, questionnaire	—	8 years	Yes	Good
Polo-Kantola et al [118]	2003	Randomized controlled	62	Polysomnography, static-charge-sensitive bed	Blood	7 months	Yes	Fair
Manber et al [119]	2003	Within subject	6	Polysomnography, sleep diary	Blood	40 days	No	Good
Freeman et al [120]	2004	Cohort	436	Interviews, questionnaires	Blood	5 years	Yes	Good
Ford et al [121]	2005	Cohort	660	Interviews, questionnaires	Blood	10 years	Yes	Good
Gambacciani et al [122]	2005	Randomized controlled	60	Questionnaires	—	12 weeks	Yes	Fair
Nielsen et al [123]	2006	Randomized controlled	335	Questionnaires	Blood	2 years	Yes	Fair
Rowley et al [124]	2006	Pre-Post	35	Polysomnography	Blood	30 days	No	Fair
Murphy and Campell [125]	2007	Cross-sectional	10	Polysomnography, self-report	Blood	2 weeks and 3 nights	Yes	Fair
Dennerstein et al [126]	2007	Cohort	204	Interviews, questionnaires	Blood	13 years	Yes	Good

(*continued*)

Table 4. Continued

Author	Year	Type of study	Sample size (n)	Method of sleep disorder assessment	Method of hormone measurement	Duration of data acquisition	Multiple measurements	Overall rating[a]
Carranza-Lira et al [127]	2007	Pre-Post	14	Questionnaires	—	3 months	No	Fair
Kravitz et al [128]	2008	Cohort	3045	Self-report	Blood	7 years	Yes	Good
Sowers et al [129]	2008	Cross-sectional	365	Polysomnography, questionnaire	Blood	35 days	Yes	Good
Pien et al [130]	2008	Cohort	436	Questionnaires	Blood	8 years	Yes	Good
Schüssler et al [131]	2008	Randomized cross-over	10	Polysomnography, questionnaire	—	2x 21 days	No	Good
Woods and Mitchell [132]	2010	Cohort	286	Self-report diary	Urine	17 years	Yes	Good
Zheng et al [133]	2015	Cross-sectional	163	Wrist actigraphy, diaries	—	35 days	No	Fair
Baker et al [134]	2015	Case-control	72	Polysomnography, diary	Blood	2 weeks	No	Fair
Santoro et al [135]	2016	Randomized controlled	727	Self-report	Blood	2 years	Yes	Fair
Slopien et al [136]	2018	Cross-sectional	140	Questionnaires	Blood	Not stated	No	Fair
Cintron et al [137]	2018	Randomized controlled	727	Questionnaire	—	2 years	Yes	Good
Geiger et al [138]	2019	Placebo-controlled	172	Questionnaires, self-report	—	12 months	Yes	Fair
Hatcher et al [139]	2020	Cohort	762	Questionnaire	Blood	1 year	Yes	Good
Luo et al [140]	2020	Cohort	458	Questionnaires	Blood	Recruited in 2005, follow-up ongoing in 2020	Yes	Good

[a]as rated by the NIH Quality Assessment Tools.

disordered breathing [116, 117] when compared to non-users. Estrogens and progestins positively influenced the apnea threshold and controlled breathing [124]. Estrogen replacement therapy decreased the occurrence and frequency of sleep apnea [118, 119] and progesterone treatment decreased breathing irregularities and arousals from sleep [72].

Discussion

Studies describing a positive relationship between endogenous estrogen and sleep are mostly limited to perimenopausal women. Likewise, the positive effect of hormone therapy on sleep during the menopausal transition is not seen in younger women taking oral contraceptive therapy. It is possible that giving hormones, that is, oral contraceptives, to young women who do not have sleep disturbances means that there is no room for improvement from the hormones. Whereas giving hormones to perimenopausal women, where the prevalence of sleep disturbances is much higher, results in an effect as there is room for improvement in this group of women. Perimenopausal estrogen therapy alleviates symptoms of insomnia by directly targeting the estrogen deficiency associated with sleep disturbances as well as other causes of sleep disturbances, such as vasomotor symptoms [141]. In younger cycling women the data were inconclusive, and in pregnant women other mechanical and physiological factors such as nocturnal micturition or gastroesophageal reflux appear to be more responsible for sleep disruption during pregnancy [78] than the absolute change in hormone level. The discrepancy in associations between reproductive hormones and sleep depending on stage of reproductive aging will on the one hand have to be attributed to different intensities and rhythms of changes in hormone levels and on the other hand to the presence of confounders such as physical changes related to pregnancy, effects of the babies' sleeping and eating rhythms in the neonatal period, age-related changes in stress hormones as well as symptoms of the perimenopausal transition such as vasomotor symptoms. Although an effect of reproductive hormones on sleep independent of vasomotor symptoms has been established [138], the presence of these confounders could explain why the association between reproductive hormones and sleep is stronger during later stages of life.

Results concerning the associations between endogenous progesterone and sleep demonstrated that progesterone was mostly positively associated with sleep in both younger and older women, indicating a sleep-promoting effect. This was also confirmed by the fact that women slept worse during their late luteal phases when progesterone levels were declining. One explanation might be that progesterone has hypnotic anesthetic properties and induces changes in sleep comparable to those of agonistic $GABA_A$ receptor modulators [144]. Furthermore, progesterone was protective of sleep-disordered breathing in young cycling as well as pregnant and perimenopausal women. Progesterone stimulates respiration through a steroid receptor–mediated mechanism in the central nervous system [145] and may have a direct effect on upper airway dilator muscle activity [146] which could account for its positive effect on sleep-disordered breathing.

Sleeping problems were highly associated with the rate of change in estradiol [126], indicating that the dynamics of changing hormone levels seem more important than absolute levels. This is also supported by the fact that sleep is especially impaired during the late luteal phase, a phase of rapidly declining hormone levels. A more rapid rate of FSH change was associated with poor subjective sleep quality [129], and women with bilateral oophorectomy, who experience a very sudden change in hormone level, experience more severe symptoms [147], indicating that rapidly changing hormones are responsible for the occurrence of distressing sleep symptoms.

Gonadotropins have less effect on sleep disturbances than ovarian hormones. There was no correlation between FSH levels and sleep parameters in most studies. However, it should be noted that studies with large sample sizes found an association between rising FSH levels and sleep disturbances in women around the menopausal transition [128-130]. Like the relationship between endogenous estrogen and sleep, the association between FSH and sleep disturbances seems to predominantly play a role in mid-life women around the time of menopause and not in younger cycling women. An important consideration is whether the findings concerning FSH and sleep represent an independent effect of FSH or if high FSH levels merely represent a lack of estradiol. As FSH rises when estrogen is low, one would expect opposite associations in absence of individual relationships. However, studies examining both FSH and estradiol did not simply find opposite associations between the 2 hormones and sleep, but an individual association between FSH and sleep measures was described without a co-occurring association between estrogen and sleep measures [65, 67, 75, 129], thereby indicating that FSH findings are not merely a consequence of estradiol's effect. No available literature on possible pathophysiologic mechanisms was found, but one consideration is a reflection of an overall interaction between the reproductive system and sleep system and not necessarily that FSH is the driver of sleep disturbance. The studies pertaining to LH and sleep disturbances mostly found no association between the two, neither in young cycling women nor in women past menopause.

Limitations

Available studies are currently very inhomogeneous regarding not only the timing and technique used to measure hormone levels but also with regard to the type of sleeping disorders and the definition of parameters used to evaluate each disorder. Due to different measurements of sleep, objective (eg, polysomnography) vs subjective (eg, questionnaires), it is difficult to find consistencies since the results do not necessarily align. Studies conducted with polysomnography often have low sample sizes and a low sampling frequency across the menstrual cycle, meaning that there are quite a few spurious findings in the literature that need to be replicated. Therefore, comparison of data and the development of final conclusions are hampered, and future studies should ideally base on predefined core outcome measures as well as measurement techniques.

Conclusion

Female reproductive hormones are implicated in women's sleep disturbances across different stages of reproductive aging. Most importantly, progesterone has a sleep-promoting effect. If there are no contraindications for hormone therapy and the benefits outweigh the risks, sleep disturbances during

the menopausal transition can successfully be treated with estrogen and progesterone therapy. In younger women, sleep is affected by the phase of menstrual cycle. However, the associations between reproductive hormones and sleep disturbances in cycling women are less clear than in perimenopausal women; therefore, other forms of treatment are warranted.

Disclosures

The authors declare no conflict of interest related to the current work.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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