Menstrual Cycle Fluctuations of Progesterone and the Effect on Sleep Regulation

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ABSTRACT

Women of reproductive age experience higher rates of sleep disturbance than their male counterparts, leading to lack of restorative sleep and increasing risk for chronic disease. The objective of this review is to overlay the menstrual cycle with sleep regulation to develop an evidence-based theoretical model that directs clinical interventions for improved sleep in affected women. Utilizing the basic mechanisms for sleep and the menstrual cycle, in addition to evidence for sleep and hormonal dysregulation, hormonal fluctuations are mapped to variations in gamma-aminobutyric acid (GABA), melatonin, and cortisol levels. Effective interventions that may be included in individualized treatment plans – varying based on the scope of practice for each practitioner – are presented, along with the impetus for future research to explore the relationship between the menstrual cycle and sleep regulation.

Keywords: Sleep; Menstrual cycle; Progesterone; Melatonin; GABA; Cortisol

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INTRODUCTION

Approximately 9–20% of adults in the US experience insomnia, making it the most prevalent sleep disorder.[1] Sleep pathology is not fully understood, and refractory insomnia may persist despite pharmacological treatments and behavioral interventions.[2] When compared to men, women have a 40% greater insomnia risk and are more likely to experience delayed sleep onset.[3]

Achieving optimal sleep extends beyond feeling energized; optimal sleep quality and quantity both prevent and manage a multitude of health conditions. Insufficient sleep interrupts physiological and neurological processes. For example, sleep impacts diverse biological functions ranging from detoxification of metabolic byproducts to immune health.[4] Sleep deficits increase the risk of developing chronic diseases such as hypertension, type 2 diabetes mellitus (T2DM), and obesity.

In addition, insufficient sleep may lead to fatigue, decreased cognitive function, and alterations in mood.[5] Total sleep deprivation, even for short periods of time, may also cause these issues.[6] These consequences may be exacerbated if women of reproductive age are also experiencing further sleep disturbances due to hormonal fluctuations. Moreover, poor sleep quality may result in decreased insulin sensitivity and the advancement of T2DM. In addition, Tasali *et al*.[7] related suboptimal glucose regulation to poor sleep quality, which is characterized by a reduction in slow-wave sleep – also referred to as deep nonrapid eye movement (NREM) sleep. Given the prevalence of T2DM and the bidirectional relationship between sleep quality and blood glucose regulation, optimizing both is critical.

While cyclical processes are part of normal physiology, sleep disturbances are associated with premenstrual symptoms,[8] and premenstrual dysphoric disorder (PMDD),[9] which is more severe. Although a paucity of research exists on the overlap of the sleep and menstrual cycles,[10] there is compelling evidence from which to depict how the quality and quantity of sleep may vary based on menstrual cycle phase.[11–13] Interestingly, nuclei such as those in the basal forebrain, hypothalamus, and locus coeruleus that regulate the sleep-wake cycle, contain receptors for estrogen and progesterone.[14] Clinicians may draw on this overlapping relationship to implement evidence-based interventions at targeted points in the menstrual cycle to reduce sleep disturbances.

BASIC MECHANISMS OF SLEEP AND SLEEP DYSREGULATION

Achieving and maintaining a state of sleep is a complex process that involves melatonin (also known as *N*-acetyl-5-methoxytryptamine),[15] gamma-aminobutyric acid (GABA), and cortisol.

MELATONIN

Regulated by the suprachiasmatic nuclei (SCN) in the hypothalamus,[16] melatonin is intricately related to sleep regulation and sleep quality.[17–20] Notably, plasma melatonin levels are highest at night.[15,16] The initial surge in melatonin corresponds to the dim-light transition into early night when light is low (i.e. <30–50 lux).[21] This nocturnal hormone is known for impacting seasonal and circadian rhythms,[22] promoting sleep onset, influencing core body temperature (CBT), and following a 24-hour light-dark cycle.[17] In particular, the enzymes involved in synthesizing melatonin are stimulated by darkness and inhibited by light.[15] Thus darkness, as is typically achieved in the normal transition from day to night, signals the pineal gland to release melatonin so as to establish an internal physiological sleep-conducive environment[16,23] (e.g. helps regulate body temperature, blood pressure,[16,25] and hormones[5]).[16,23–25] Even relatively dim light (i.e. <200 lux) is sufficient to impair melatonin production, thereby dysregulating the sleep-wake cycle.[23]

GABA

In addition to melatonin, GABA is an important central nervous system (CNS) inhibitory neurotransmitter that influences sleep and relaxation.[26] Its inhibitory properties impact areas in the

hypothalamus involved in the sleep-wake cycle,[27] and decrease activity in multiple parts of the brain. Mechanistically, GABA binds to a GABA-A receptor, which causes hyperpolarization due to the subsequent influx of chloride ions into the cell.[27] Evidence suggests that low GABA levels in the brain may be an antecedent to insomnia.[28–30] Interestingly, elevated GABA levels are found in some individuals with insomnia, which may be indicative of an adaptation to sustained periods of hyperarousal.[31]

States of CNS hyperarousal encompass a relationship between hypothalamic-pituitary-adrenal (HPA)-axis activation – resulting in increased production of corticotropin-releasing hormone and downstream cortisol secretion – and sleep disturbance such as insomnia.[28,32–34] Research indicates that evening cortisol levels positively correlate with both the number of times individuals (with and without primary insomnia) awake in the overnight period,[32,33] and severity of sleep disturbance. This is further supported by research indicating that cortisol levels measured over a 24-hour period are higher from evening to midnight in individuals with insomnia when compared to healthy controls.[32,33,35]

There are a number of causes for the low neurotransmitter and hormone levels that lead to common sleep disorders such as insomnia.[1] Dysregulated melatonin, GABA, and/or cortisol are often rooted in diet and lifestyle factors, epigenetics, and/or impaired digestion. For example, if digestion is impaired, there may be insufficient amino acids for proper neurotransmitter synthesis such as serotonin,[36,37] and thus, melatonin. The synthesis of melatonin involves the tryptophan to serotonin to melatonin conversion pathway in which *N*-acetyltransferase acetylates serotonin. Then hydroxyindole orthomethyltransferase methylates the acetylated serotonin to form melatonin.[15] Thus, micronutrient deficiencies (e.g. folate, vitamins B_6/B_{12}, choline, magnesium) needed for methylation reactions,[38] and impaired methylation (often indicated by elevated histamine or *S*-adenosyl-l-methionine [SAM]:*S*-adenosyl-l-homocysteine [SAH] ratio[39]) result in altered neurotransmitter levels (e.g. serotonin, dopamine, and norepinephrine), which lead to dysregulated sleep-wake cycles.[5,40,41]

CORTISOL

Another common cause of sleep disturbance is high cortisol. Excessively elevated cortisol impairs serotonin production,[42–44] which negatively impacts downstream melatonin production. Furthermore, this stress state is associated with magnesium and B vitamin depletions,[45] nutrients needed for methylation. Chronic stress also leads to intestinal dysbiosis. Since a healthy microbiome is needed to produce neurotransmitter precursors and GABA,[36,46] this effect further establishes the environment for sleep disturbances and HPA-axis dysregulation.

BLOOD GLUCOSE DYSREGULATION

When insomnia coincides with a high-glycemic load diet, insufficient fiber, and insufficient micronutrients such as magnesium, insulin resistance may develop.[47,48] This blood sugar dysregulation then causes nocturnal hypoglycemia. Since the brain needs glucose to survive, nocturnal hypoglycemia will trigger the release of catabolic stress hormones (e.g. cortisol, epinephrine) to increase gluconeogenesis.[45] This protective mechanism may awaken the body. Interestingly, low melatonin may also impair glucose tolerance and contribute to the development of insulin resistance.[17] Moreover, elevated cortisol levels – activated by sympathetic nervous system activity – occur in response to external factors such as chronic stress, excessive caffeine intake, inadequate intake of micronutrients important for blood sugar regulation, neutralization of oxidative stress (e.g. magnesium, B vitamins), and a dysregulated stress response. The result is disrupted neurotransmitter and HPA-axis functioning as evidenced by impaired sleep-wake cycles, situational distress, and weak coping skills. Eventually, high cortisol may promote increased intestinal permeability,[36] and impair immune functioning;[45] ultimately exacerbating dysregulated hormone and neurotransmitter levels and thus, perpetuating sleep disturbances.

In summary, sleep requires melatonin, GABA, and appropriate levels of cortisol. Their levels, timing, and interactions can be negatively impacted by numerous factors as described above. Additional influences, such as hormonal fluctuations related to the menstrual cycle, are discussed next.

THE MENSTRUAL CYCLE: AN OVERVIEW

The menstrual cycle is characterized by two phases, follicular (i.e. proliferative) and luteal (i.e. secretory) (see Figure 1 and Table 1). The menstrual cycle typically lasts for 25–30 days, with the average cycle 28 days in duration. It is defined by the span of days between the first day on which menstruation occurs and the start of the next cycle. While the luteal phase is highly constant with a 14-day duration, differences in the duration of follicular development create variability in cycle length. The follicular phase may last from 10 to 16 days and menstrual blood flow usually falls within a range of 4–6 days.[49]

Day one is marked by menstruation. Estrogen levels are low in this early follicular phase. Low estrogen stimulates the pituitary to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) to encourage the development of ovarian follicles. During this time, estrogen continues to increase, allowing a dominant follicle to develop by preventing further secretion of FSH. The dominant follicle, however, still secretes FSH. The subsequent ovulation is marked by a surge in FSH and LH. Approximately 16–32 hours following the LH surge, the egg is released. Estrogen surges when ovulation commences and then falls. Conversely, progesterone, a steroid hormone, gradually increases from the start to the end of ovulation, continuing to rise into the luteal phase.[50]

In addition to being involved in female sex characteristics and the maintenance of pregnancy,[52] progesterone influences sleep quality.[53] In healthy menstruating females, progesterone levels remain low through ovulation. Then, the corpus luteum releases progesterone to prepare the endometrium to receive an egg should fertilization occur.[54] Progesterone peaks at about day 25 of the mid-luteal phase.[49] If fertilization does not occur, the corpus luteum degrades in the process of luteolysis, stimulating a rapid decline in progesterone levels. This progesterone withdrawal stimulates menstruation, marked by the sloughing off of the functional layer of the endometrium.[54] Concomitantly, a proinflammatory response involving leukocyte recruitment, cytokines, chemokines, swelling, and matrix metalloproteinases in the area nurture the endometrium via vascular changes. In addition, repair and remodeling mechanisms (e.g. tissue repair, proliferation, and differentiation) prepare for future embryo implantation.[54–56] Fluctuations

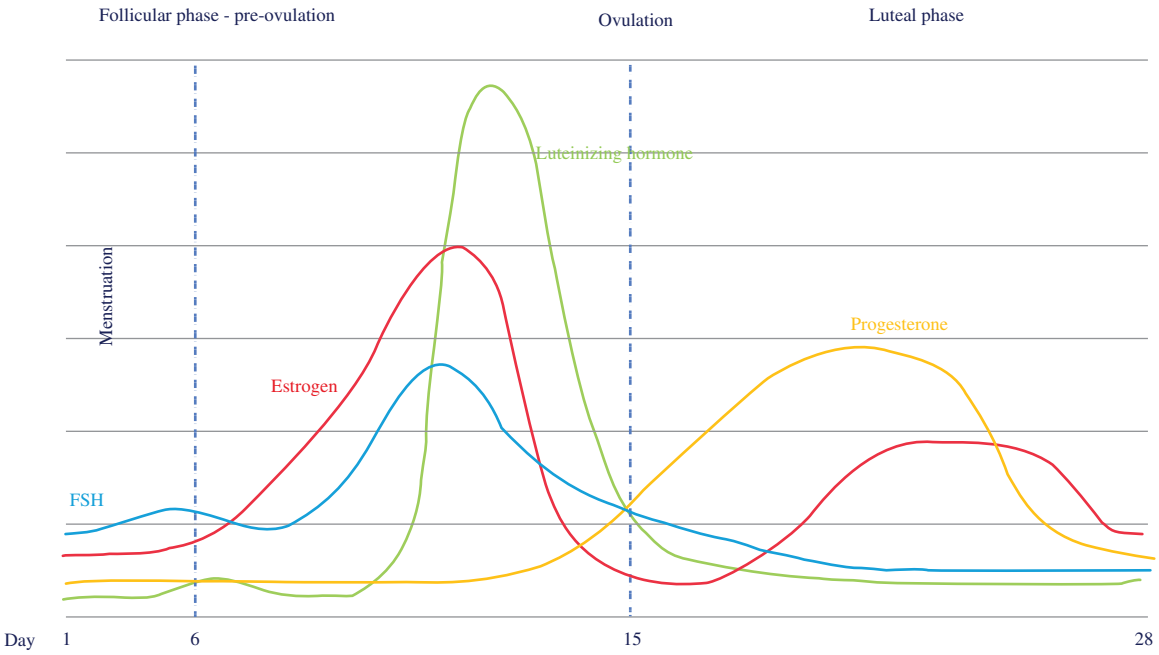

Figure 1: The menstrual cycle.
Based on Stricker *et al.*[51]

Table 1: Phases of the menstrual cycle.

Phase/event	Description	Hormonal changes (non-fertilized state)
Follicular	• Starts on first day of menstruation • Menstruation lasts between 3 and 7 days, 5 on average • Infertile during early phase • Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are produced by the pituitary gland • LH and FSH promote ovulation and stimulate the ovaries to produce estrogen and progesterone • Ends with ovulation around day 16 or 17 • This phase varies in length	FSH: starts low, ↑ ~day 3, drops slightly, peaks ~day 12, ↓ LH: ↑ sharply ~day 12, ↓ 16–32 hours before ovulation Estradiol: ↑ peaks ~day 12 & then ↓ Progesterone: starts ↑ around day 12
Ovulation	• Egg release stimulated by increases in FSH and LH • Lining of uterus continues to thicken	
Luteal	• Starts after ovulation • Lining of uterus thickens • Unless fertilization occurs, generally lasts 14 days • The ruptured follicle forms a corpus luteum, which produces progesterone • Body temperature increases slightly	FSH: low LH: low Estradiol: starts low, peaks between days 20 & 24 (lower peak than during follicular phase), ends low Progesterone: increases to a peak around day 25 and then drops

FSH, follicle stimulating hormone; LH, luteinizing hormone.

in progesterone have implications for sleep, which will be discussed later in this review.

SLEEP AND THE MENSTRUAL CYCLE

Women who are menstruating, irrespective of premenstrual symptoms, commonly report sleep difficulties spanning from the premenstrual phase of their cycle to the early phases of menses (i.e. late luteal to early follicular phases). Those with significant premenstrual syndrome (PMS), experience more intense sleep difficulties in the late-luteal phase, as well as fatigue, unsettling dreams, insufficient restorative sleep, and increased difficulty concentrating.[57] Interestingly, as women age and advance in their reproductive years, sleep efficiency progressively declines throughout the menstrual cycle; the most significant sleep difficulties occur during the premenstrual period in the last 7 days of the menstrual cycle.[58] Regardless, more robust studies investigating sleep, especially in the premenstrual period, are warranted, as preliminary evidence is based on small, poorly-designed studies.[57]

PROGESTERONE FLUCTUATIONS AND GABA

When overlaying the menstrual cycle with sleep disturbances, much disturbance activity occurs in the luteal phase when progesterone levels drop rapidly. Notably, the rate of change in progesterone levels appears to be more important than absolute hormone levels when evaluating sleep disturbance.[59] During the luteal phase, electroencephalographic (EEG) studies demonstrate sleep changes during NREMS via increased sleep spindle frequency (12–15 Hz),compared to EEG activity in the follicular phase (7–9 Hz).[14,59]

A complex network of GABAergic neurons (i.e. thalamic reticular nucleus [TRN], thalamocortical [TC], and corticothalamic) are involved in the formation of sleep spindles.[60] It is reasoned that increased sleep spindle frequency observed during the luteal phase is indicative of progesterone metabolites interacting with GABA-A membrane receptors.[61]

Experts hypothesize that sleep spindles may confer sleep protection by hindering information from reaching the cortex.[62] Moreover, increased spindle activity may support enhanced sleep quality when significant hormonal and physiological change

processes occur in the post-ovulatory phase.[59,63] Differences in sleep quality among women at different lifecycle stages, (e.g. midlife) may thus reflect increased susceptibility to menstrual cycle-associated hormonal changes and/or alterations in the ability of spindles to protect sleep based on menstrual age (e.g. within the window of menarche and the last menstrual period).[59] However, increased sleep spindle frequency may also be attributed to progesterone driving increased basal body temperature during the luteal phase.[59,64]

Researchers have found that, when compared to healthy controls, women with PMDD have decreased concentrations of plasma GABA,[65] and women with PMS have reduced sensitivity of GABA-A receptors in the brain areas responsible for saccadic eye movements.[66] These findings, at least in populations experiencing premenstrual disorders, may be associated with lower progesterone concentrations than in healthy counterparts.[63] On the other hand, even in healthy women, concentrations of GABA in the brain are lower during the luteal phase, decreasing with the progression of the menstrual cycle. Such a finding is in contrast to increased concentrations of GABA in the brain of some women experiencing premenstrual depression while in the luteal phase of their menstrual cycle. This contrast aside, progesterone and the progesterone metabolite, allopregnanolone, may act as anxiolytics[67,68] and sedatives[67] when they bind to GABA-A receptors. The clinical relevance gleaned from these findings is that GABA administered in the latter population can exacerbate premenstrual depression[69] (see Figure 2).

PROGESTERONE FLUCTUATIONS AND MELATONIN

Not surprisingly, women with PMDD exhibit changes in the amount and time at which they secrete melatonin. However, given women with PMS[70,71] and PMDD[72] respond favorably to selective serotonin reuptake inhibitors (SSRIs), this may be related to lower than normal serotonin levels. During the luteal phase, stress may have a greater impact on melatonin than during the follicular

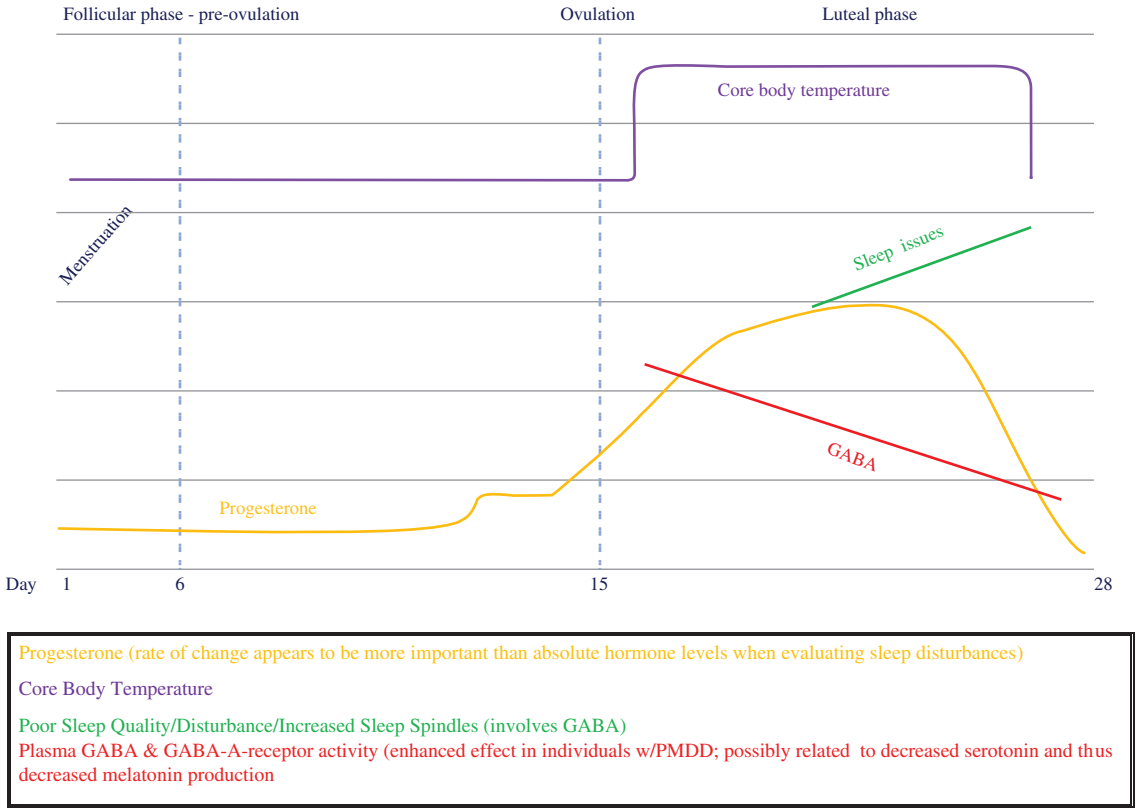

Figure 2: Mapping sleep disturbances: progesterone, melatonin, GABA, & core body temperature.

phase due to the relationship between progesterone and cortisol. Progesterone is a cortisol precursor and higher levels during the luteal phase can support greater cortisol synthesis and may result in a higher cortisol baseline.[73] In addition, more cortisol may be available because of progesterone competitively binding to corticosteroid binding globulin.[73] These mechanisms are notable because of cortisol's suppression of melatonin secretion.

MENSTRUAL CYCLE IMPACT ON OTHER SLEEP-RELATED HORMONES AND NEUROTRANSMITTERS

Progesterone fluctuations impact both GABA and melatonin. However, achieving and maintaining sleep is very complex and other neurotransmitters should be considered. Table 2 explores the impact, if any, of the menstrual cycle on sleep-related neurotransmitters.

Table 2: Influence of menstrual cycle on sleep-related neurotransmitter/hormones.

Neurotransmitter/ hormone	Function	Menstrual cycle impacts
GABA	Inhibitory neurotransmitter that promotes sleep. GABAergic neurons are involved in the formation of sleep spindles.	Decreased during late luteal phase due to increased progesterone levels. Progesterone interacts with GABA-A receptors. Women with PMS may have reduced GABA-A receptor sensitivity.
Melatonin	Regulates sleep-wake cycles.	Affected by PMDD both in timing and amount of secretion. Can also be affected by stressors (via increased cortisol) during late luteal phase. Progesterone also competitively binds to corticosteroid binding globulin, potentially increasing available cortisol and further suppressing melatonin.
Serotonin	Maintains wakefulness and muscle tone. Not active during REM. Inhibited by GABAergic neurons.	According to Wihlbäck *et al.*[74] there are phase-related differences in serotonin uptake sites and receptors. Decreased number of serotonin binding sites during progesterone's peak during the luteal phase.
Glutamate	Precursor for GABA.	Serum levels were found to be inversely correlated with progesterone and estrogen levels.[75]
Others involved in sleep process with limited or no research supporting menstrual influence		
Hypocretin (or orexin)	Stimulates release of glutamate, acts as an excitatory neurotransmitter, and is involved in regulation of sleep and arousal.	Literature search did not locate studies that investigated a direct sleep/menstrual cycle connection.
Acetylcholine	Involved in wakefulness and REM phase of sleep.	Literature search did not locate studies that investigated a direct sleep/menstrual cycle/acetylcholine connection. One small study of young women found that gonadal hormones did not appear to have an effect on plasma acetylcholine levels.[76] According to Valera *et al*.[77] progesterone "may interact with the acetylcholine binding site," but does inhibit acetylcholine competitively.
Histamine	Wakefulness results from histamine or H_1 receptor agonists while H_1 antagonists have the opposite effect.[78] Histamine-releasing neurons are not active during REM and NREM phases of sleep.[78] GABAergic neurons turn-off histaminergic activity.	Some evidence that the rate of histamine metabolism increases as estrogen levels increase;[79] however, literature search did not locate studies that investigated a sleep/menstrual cycle/histamine connection. The question of whether changes in GABA due to progesterone changes could promote changes in histamine that lead to increased wakefulness remains.
Norepinephrine	Inactive during REM sleep. Related to loss of muscle tone.	In an animal study, progesterone was found to increase levels of norepinephrine.[80]

GABA, gamma aminobutyric acid; PMDD, premenstrual dysphoric disorder; NREM, non-rapid eye movement; PMS, premenstrual syndrome; REM, rapid eye movement.

PROGESTERONE AND INCREASED WAKEFULNESS

Researchers have found that the rapid change in progesterone levels, characteristic of the follicular to the mid-luteal phase transition, corresponds to increased wakefulness following sleep onset, as well as to sleep fragmentation during the luteal phase.[81] During the luteal phase when progesterone surges, women report increased sleep disturbance.[81,82] Interestingly, this is the time when CBT rises 0.3–0.6°C in response to increased progesterone; the consequence of which is increased sleep fragmentation[81] as the normal sleep-supportive dissipation of heat from the core to the peripheral extremities is interrupted.[83] Complementing synaptic and neurohormonal signaling mechanisms, and variations in CBT and skin temperatures, hypothetically characterize another signaling pathway in the circadian-clock sleep cycle.[84]

From an evolutionary perspective, there is an advantage in relation to the normal association between elevated progesterone in the luteal phase prompting sleep disturbance. Specifically, during times of stress, whether real or perceived, circadian rhythm dysregulation ensues and HPA-axis activation decreases fertility[11,85] as metabolic resources are mobilized for survival in what is known as the "fight-or-flight" response. During this time, sympathetic nervous system dominance prevails, allowing individuals to flee from dangerous conditions that threaten homeostasis.[86] Sleep disturbance, as occurs during the luteal phase, signals to the body that conditions are unfavorable for reproduction.[11] There is a positive feedback pattern, however, in that lack of restorative sleep is also an adrenal stressor.[87]

SLEEP AND GLUCOSE METABOLISM

As detailed above, there is a relationship between sleep disturbance and impaired glucose metabolism, leading to the development of insulin resistance and T2DM.[88,89] Metabolic pathways implicated in this association include short sleep duration and circadian misalignment, which lead to increased catecholamines via sympathetic nervous system activity. Additional changes include increased cortisol in response to HPA-axis activation, increased reactive oxygen species (ROS) production due to oxidative stress, increased inflammatory cytokines, e.g. interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), in response to upregulation of proinflammatory pathways, and adipokine alterations, i.e. increased leptin, decreased adiponectin.[88] Interestingly, there is also an association between polycystic ovary syndrome (PCOS), – a condition in which hyperinsulinemia is a significant factor – and sleep disturbance.[90]

POLYCYSTIC OVARY SYNDROME AND SLEEP

The exact pathophysiology of PCOS remains elusive, but involves an interplay of genetic and lifestyle factors.[91] Alongside hirsutism, the primary characteristic of PCOS is menstrual cycle irregularity as evidenced by anovulation. Women with PCOS experience infertility, hyperandrogenism, and metabolic disorders (e.g. noninsulin dependent diabetes mellitus, insulin resistance, and glucose intolerance). It is not uncommon for women with PCOS to be obese.[91,92] Disturbed sleep is also associated with this syndrome.[93]

THE RELATIONSHIP OF PROGESTERONE, MELATONIN, GABA, AND CBT TO SLEEP DISTURBANCE: A THEORETICAL MODEL

In laying out the relationships between the menstrual cycle and sleep disturbances, it appears that there are particular times of the cycle when it would be beneficial to supplement with GABA-promoting nutrients. During the luteal phase, GABA appears to be low and CBT rises (this corresponds to a decrease in melatonin production). One may question whether increased progesterone levels override the sleep-disrupting factors, but this does not seem to be the case when considering the poor sleep/increased sleep spindles findings of de Zambotti *et al.*[59] and Shechter and Boivin.[63] Finally, the rate of change appears to be more important than absolute hormone levels when evaluating sleep

disturbance, which makes sense given the sharp changes in progesterone levels during the luteal phase (see Figure 2).

CLINICAL IMPLICATIONS

The theoretical model of sleep regulation and the menstrual cycle has meaningful implications for integrative medicine practitioners. Leveraging these implications may reduce the impact of menstrual cycle hormonal fluctuations on sleep, and with a comprehensive sleep protocol, achieve the following:

- Minimize need for pharmaceutical sleep-aids, which often have harmful side effects
- Reduce the risk of certain chronic diseases (e.g. hypertension, T2DM, and obesity)
- Improve mood, energy, and cognition

An integrative sleep protocol that factors in diet, lifestyle, sleep hygiene, medications, and – for women of reproductive age – menstrual hormones, is a critical underpinning of optimal wellness.

In addition to identifying potential sleep-disturbing side effects of both prescription and over-the-counter (OTC) drugs, it is advisable for clinicians to ask patients about their use of nonsteroidal anti-inflammatory drugs (NSAIDs; e.g. ibuprofen and naproxen), as they are often used to treat PMS/PMDD symptoms and can deplete melatonin.[94] When it is within scope of practice, clinicians may want to find alternatives to drugs that deplete melatonin, e.g. propranolol, metoprolol (Lopressor), and prednisone, in their treatment plans for individuals susceptible to, or experiencing, sleep disturbances. Addressing the root causes of sleep disruption will help reduce or eliminate the need for drugs, thereby optimizing sleep quality.

Clinicians should also educate their patients about healthy sleep hygiene, because an ongoing lack of restorative sleep chronically stresses the adrenal glands, thereby increasing inflammation[95] and compounding the impaired sleep cycle. Clinicians could advise patients to stop using electronic devices that emit blue light and impair the body's sleep

Table 3: Nutrients that may have a GABA-stimulating effect.

Supplement	Action	Note
L-Theanine	May increase GABA levels by acting as an antagonist to glutamate receptors,[111] and increasing conversion of glutamine into GABA.[102]	Use cautiously with anti-hypertensive medications and hypotensive herbs and supplements (e.g. stinging nettle, CoQ10, and L-arginine).
L-Glutamine	Supplies glutamic acid/glutamate needed for GABA production.	Use cautiously if MSG hypersensitivity exists; contraindicated with history of cancer and/or use of anti-seizure medications.
5-HTP	Serotonin enhances GABA activity and 5-HTP is an immediate precursor to serotonin (and ultimately melatonin); it freely crosses the blood-brain-barrier, unlike tryptophan, which requires a carrier (shared by other amino acids).	Do **not** take with antidepressants or other neurological drugs; consider after addressing other sleep hygiene issues; long-term use may deplete catecholamines, and it is important to include sufficient precursors for serotonin and dopamine.[112]
Vitamin B6	Co-factor for glutamate decarboxylase which synthesizes GABA from glutamate.	Consider both dietary intake and all supplements when making sure the tolerable upper limit (UL) of 100 mg/day is not exceeded.
Bifidobacterium	Produces GABA in the gut.	–
Lactobacillus	Produces GABA from glutamate.	"Lactobacillus brevis DPC6108 was the most efficient of the strains tested, converting up to 90% [corrected] of MSG to GABA."[113]

Note:
- Appropriateness of specific supplements and dosages should be assessed for each individual based on age, health condition(s), diet, medications, other supplements, etc.
- Practitioners may wish to consider the use of herbs if it is within their area of expertise and scope of practice.

5-HTP, 5-hydroxytryptophan; GABA, gamma aminobutyric acid; MSG, monosodium glutamate.

preparation signals, in the evening and at night, when melatonin production typically surges[21] or to wear amber-colored glasses starting at about 8 pm. Research demonstrates that, when used 1–3 hours before bedtime, amber-colored glasses effectively block blue light, to support the body's natural melatonin production for improved sleep quality.[96,97]

Given the relationship between progesterone and CBT, and between CBT and melatonin levels,[17] maintaining a cool sleeping environment, between 60° and 65°F (16–18°C), may also help reduce sleep disturbances.[98] Applying a cooling blanket to the back can also improve sleep quality.[99] Another method to promote sleep is to take a warm (not hot) bath or foot bath before bedtime. The rise and resulting drop in CBT reduces rapid eye movement (REM) sleep, improves sleep onset, and increases stage four and slow-wave sleep.[100,101]

For premenopausal women who are experiencing sleep difficulties, supplementing with GABA-stimulating nutrients 1 week prior to menstruation may be beneficial (see Table 3). These include L-theanine (γ-glutamylethylamide),[102,103] L-glutamine,[102] 5-hydroxytryptophan (5-HTP),[104–106] vitamin B_6 in accordance with dietary reference intakes,[107] and *Bifidobacterium*[108] and *Lactobacillus*[108–110] found in some fermented foods and probiotic supplements.

When sleep disturbance appears to be related to the menstrual cycle, an integrative approach that factors in diet, lifestyle, sleep hygiene, medications, and, – for women of reproductive age – reproductive hormones, is a critical underpinning of optimal wellness. In addition to the supplements mentioned above, Table 4 summarizes these factors that need to be addressed.

Table 4: Additional factors to support sleep throughout the menstrual cycle.

Factor	Goal	Rationale
Weight	Obtain or maintain a healthy weight.	Obesity is associated with irregular cycles, PCOS, and estrogen/progesterone imbalances.
Diet	Ensure adequate micronutrients (e.g. magnesium, vitamin B6), high fiber, and low-glycemic load.	Support production of neurotransmitters involved in sleep; support metabolism of sex hormones; avoid blood sugar spikes and dysregulation that can negatively affect sleep.
Assimilation	Optimize digestion and support gut diversity.	Support GABA-synthesizing bacteria; absorption of nutrients needed for neurotransmitter synthesis, methylation, etc.
Detoxification/ biotransformation	Reduce exposure to endocrine disruptors.	Reduce estrogen/progesterone imbalances.
Stress resilience	Decrease perceived stress and increase stress resilience.	Psychological stress impairs the function of GABA,[114] which could further exacerbate the effect of progesterone on GABA during the luteal phase; reduce cortisol level elevations that are associated with disrupted sleep; avoid depletions of magnesium and B vitamins associated with chronic stress.
Exercise	Develop a consistent exercise routine. Note: high intensity exercise in the evening may be counterproductive.	Support optimal circadian rhythms, balance sex hormone levels,[115] support blood sugar regulation, increase stress resilience, and obtain/achieve healthy weight.
Sleep hygiene: Temperature	Offset the increase in CBT associated with the luteal phase.	Sleeping in a cool room or with a cooling blanket may reduce body temperature; warm baths before bedtime and the resulting drop can simulate the natural fall in temperature associated with efficient sleep onset.
Use of electronics	Reduce exposure to blue light several hours before bedtime by avoiding use of electronic devices, utilizing blue-light limiting applications, or wearing amber-colored glasses designed to block blue light.	Blue light suppresses melatonin production, which may be negatively impacted during the latter part of the luteal phase.
Education	Improve overall sleep hygiene.	Minimize any additional sleep disruptors.

CBT, core body temperature; GABA, gamma aminobutyric acid; PCOS, polycystic ovary syndrome.

CONCLUSION

In addition to assessing diet, stress, and other lifestyle factors, it is important for practitioners to consider a woman's menstrual cycle as a possible contributor to sleep disturbances. This paper presented a theoretical model involving an overlay of progesterone, GABA, melatonin, and sleep, which suggests there are specific times during the menstrual cycle when supplementing with GABA-promoting supplements, along with foundational recommendations about sleep, may help minimize or avoid sleep disturbances in female patients who are still menstruating. Additional research investigating the theoretical model explored here is necessary to expand our understanding of the complex relationship between the menstrual cycle and sleep disturbance.

Most of the strategies outlined in this paper are good practices for sleep hygiene and overall health in general. In addition to menstrual-related sleep disturbances, these approaches may help patients as they go through the hormonal changes associated with peri- and postmenopause, and women who have PCOS. While significant drops in progesterone appear to have a greater impact on sleep than absolute progesterone levels, a discussion of direct hormone therapy is beyond the scope of this review.

COMPETING INTERESTS

The authors declare they have no competing interests.

AUTHORS' CONTRIBUTIONS

CEC and SJVL are doctoral students in Clinical Nutrition at Maryland University of Integrative Health (MUIH) in Laurel, Maryland, in addition to being on the faculty at MUIH.

CEC: apprehended the general idea and theoretical model, wrote the first drafts and preliminary outline of the review, and participated in rewriting and redrafting.

SJVL: participated in rewriting, redrafting, and data depiction.

All authors read and approved the final manuscript.

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