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# Research progress and future directions in circadian rhythms for uterine-related diseases (Review)

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**Abstract.** Circadian rhythms are ~24 h endogenous rhythms driven by both central and peripheral clocks, with their core mechanism being a transcription-translation feedback loop mediated by master clock genes. The present review outlines the organizational features and regulatory mechanisms of uterine circadian rhythms: Clock genes in the endometrium exhibit phasic rhythmic changes, which are lost after decidualization; rhythmic expression of clock genes in the myometrium influences uterine contractions and regulates the timing of labor. Estrogen and progesterone can modulate core clock genes and affect the decidualization process. As a key output hormone of the central clock, melatonin also modulates the uterine environment and influences delivery timing. Circadian rhythm disruption is associated with the development of diseases such as endometriosis, endometrial cancer and menstrual disorders. Finally, limitations of current research and future directions are discussed to inform rhythm assessment and intervention strategies.

## Contents

## 1. Introduction

Circadian rhythms refer to the periodic changes in physiological, behavioral and metabolic activities that organisms develop to adapt to the 24 h light-dark cycle of the Earth (1). As a key regulatory mechanism in maintaining homeostasis, circadian rhythms coordinate physiological indicators such as heart rate, body temperature and blood pressure, while organizing behavioral rhythms including sleep-wake cycles, feeding-fasting patterns and activity-rest cycles (2). These rhythms are jointly regulated by the central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks widely distributed throughout nearly all organs and tissues, including the liver, heart, lungs, kidneys,

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*Abbreviations:* SCN, suprachiasmatic nucleus; CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle ARNT-like 1; PER, period; CRY, cryptochrome; TTFLs, transcription-translation feedback loops; AVP, arginine vasopressin; VIP, vasoactive intestinal peptide; CCK, cholecystokinin; CK, casein kinas; ROR, retinoic acid receptor-related orphan receptor; REV-ERB, reverse erythroblastosis virus; RORE, ROR/REV-ERB response elements; HESCs, human endometrial stromal cells; ZT, Zeitgeber time; TLR4, toll-like receptor 4; MT2, melatonin receptor type 2; siRNA, small interfering RNA; StAR, steroidogenic acute regulatory protein; CYP19A1, cytochrome p450 family 19 subfamily a member 1; Erβ, estrogen receptor β; ICR, Institute of Cancer Research; MT1, melatonin receptor type 1a; UESCs, uterine endometrial stromal cells; SOD, superoxide dismutase; MDA, malondialdehyde; PKC-α, protein kinase C-α; LLD, long-duration light exposure; AANAT, arylalkylamine N-acetyltransferase; EMS, endometriosis; EC, endometrial cancer; TIM, TIMELESS; miRNA, microRNA; lncRNA, long non-coding RNA

*Key words:* circadian rhythm, uterine-related diseases, suprachiasmatic nucleus, clock genes, melatonin

adipose tissue and skeletal muscle (3). At the molecular level, circadian rhythms depend on transcription-translation feedback loops driven by core clock genes (4), primarily including circadian locomotor output cycles kaput (CLOCK), brain and muscle ARNT-like 1 (BMAL1), period (PER)-1, 2 and 3, as well as cryptochrome (CRY)-1 and 2 (5).

Circadian rhythm disruption can be induced by numerous factors, including acute or chronic diseases, shift work or night shifts, misaligned eating or exercise schedules and circadian sleep-wake disorders (5,6). A previous study indicated that circadian rhythm disorders are associated with reproductive dysfunction and menstrual irregularities (7). The uterus, a key organ in menstruation, embryo implantation and pregnancy maintenance, may have its functional stability influenced by circadian clock regulation (8,9). Further research has demonstrated that core circadian clock genes are expressed in the uterine tissues of humans, rats and mice (10-12). Mutations or abnormal expression of these clock genes can disrupt uterine decidualization and endometrial receptivity, thereby increasing the risk of miscarriage and even causing infertility (13-16). Furthermore, circadian rhythm disruption may contribute to certain uterine disorders, including endometriosis (EMS), endometrial cancer (EC) and menstrual irregularities (17-19). Therefore, elucidating the mechanisms by which circadian rhythm-related clock genes regulate uterine function and influence disease progression is important. The present review systematically outlines circadian rhythm regulatory mechanisms and their impact on uterine-related diseases, identifies key research questions and challenges, whilst discussing potential therapeutic strategies and future research directions. The aim was to provide a theoretical foundation for the clinical prevention and treatment of uterine-related disorders.

## 2. Regulatory mechanisms of circadian rhythms

*Structure and function of the central clock*. Through neural circuits connecting numerous hypothalamic nuclei and subcortical regions, the SCN serves a pivotal role in rhythm generation, synchronization and output (19). Essentially, the SCN serves as the central pacemaker regulating circadian rhythms. The function of the SCN manifests primarily through three aspects. First, it synchronizes endogenous rhythms with external light-dark cycles through afferent and efferent neural circuits (20). Second, it maintains the endogenous rhythm of the central clock and systematically integrates and coordinates the autonomous transcription-translation feedback loops (TTFLs) across cells throughout the body. Third, it synchronizes the clock phase of peripheral tissues through signals such as neurotransmitters, hormones (including melatonin, glucocorticoids and catecholamines), metabolic factors and body temperature fluctuations (21-24).

With regard to light signal input, light stimuli are captured by retinal melanocytes and transmitted through retinal ganglion cells of the retinohypothalamic tract to the SCN, triggering and outputting clock-modulating signals. Subsequently, the SCN transmits clock-modulating signals to regions of the brain, including the paraventricular nucleus, subperiventricular zone, dorsomedial hypothalamus, medial preoptic area, paraventricular thalamic nucleus, lateral habenula and bed nucleus of the stria terminalis (Fig. 1).

The SCN comprises ~20,000 heterogeneous neurons, each containing an intrinsically generated circadian oscillator. These neurons are interconnected through a stable coupling network that ensures synchronized rhythmic oscillations between cells (20). Nearly all SCN neurons express g-aminobutyric acid and may co-express neuropeptides such as arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) (25,26). Neurons within the SCN can be further classified into distinct subtypes, including AVP, VIP, cholecystokinin (CCK) and gastrin-releasing peptide neurons (27,28). These subtypes exhibit differences in spatial distribution, clock gene expression profiles and responsiveness to light signals (19,29).

### *Key neurons in the SCN*

*AVP neurons*. Within the SCN, a large population of neuropeptide-rich neurons are present, primarily comprising AVP neurons and VIP neurons. Both AVP-positive and VIP-positive neurons are key in synchronizing circadian rhythms within the SCN network. AVP neurons are primarily localized in the shell region of the SCN, which exhibits robust rhythmic expression of clock genes and serves a key role in the generation and regulation of circadian timing within the SCN. The intrinsic circadian oscillations of AVP neurons are important not only for intra-SCN intercellular communication but also for conveying circadian signals to other brain regions. Importantly, targeted deletion of the core clock gene BMAL1 in AVP neurons leads to reduced rhythm amplitude and lengthened circadian periodicity within the SCN (30). In addition, mice deficient in AVP receptors V1a and V1b demonstrate a markedly impaired ability to reset circadian rhythms in response to changes in photoperiod, underscoring the importance of AVP signaling in circadian adaptability (31).

*VIP neurons and CCK neurons*. Compared with AVP neurons distributed throughout the shell region, VIP neurons are primarily located in the SCN core and can directly receive light signals from the retina (Fig. 1). VIP influences the rhythms of daily motor activity and the release of hormones such as gonadotropin-releasing hormone, corticosterone and prolactin, thereby helping to coordinate physiological activities with the central clock (32-35). A previous study demonstrated notably heightened VIP neuron activity during the nighttime, which may be associated with suppression of nocturnal activity and sleep maintenance (36). In addition, a recent study revealed that CCK neurons also participate in robust circadian rhythm maintenance, particularly influencing the recovery rate of circadian rhythms following jet lag. While CCK neurons do not directly respond to light stimuli, their activation induces phase advancement and can counteract light-induced phase delay mediated by VIP neurons (27), suggesting they have a potential role in circadian resynchronization within the SCN network.

*Reproductive function of the peripheral clock in the uterus*. The central biological clock coordinates with peripheral biological clocks through a feedback network comprising humoral signals, neural signals and body temperature rhythms, thereby maintaining the stability and synchrony of circadian rhythms at both systemic and molecular levels (37).

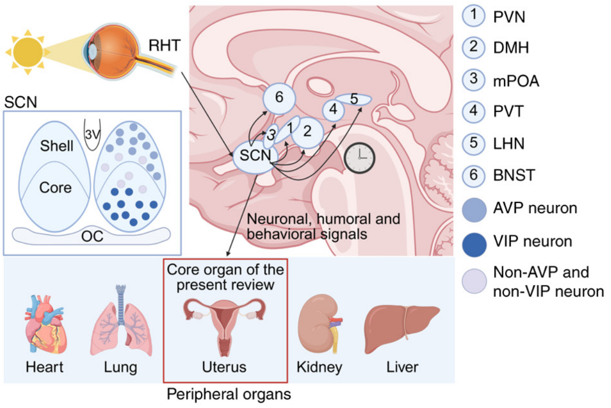

Figure 1. Schematic diagram of SCN-mediated light signal input and peripheral clock synchronization mechanism. The SCN receives light signals from the retina through the RHT and outputs rhythm-modulating signals, thereby influencing numerous downstream brain regions. It coordinates circadian rhythms in peripheral organs (such as the heart, lungs, liver, kidneys and uterus) through neuronal, humoral and behavior-related pathways. Neurons within the SCN exhibit regional distribution: AVP neurons (light blue circles) are primarily located in the shell region, while VIP neurons (dark blue circles) are predominantly found in the core region. SCN, suprachiasmatic nucleus; RHT, retinohypothalamic tract; 3V, third ventricle; OC, optic chiasm; PVN, paraventricular nucleus; DMH, dorsomedial hypothalamus; mPOA, medial preoptic area; PVT, paraventricular thalamus; LHN, lateral habenula nucleus; BNST, bed nucleus of the stria terminalis; AVP, arginine vasopressin; VIP, vasoactive intestinal peptide.

Peripheral clocks are present in nearly all tissues, including the heart, lungs, liver, kidneys and uterus, all of which are regulated by the central clock SCN (Fig. 1). The uterine clock, as a peripheral circadian oscillator, is key in maintaining reproductive function (38). A previous study indicated that the SCN influences hormone secretion by regulating the pineal gland and the hypothalamic-pituitary-gonadal axis, thereby promoting phase synchronization of clock genes in peripheral tissues including the uterus (39). Beyond responding to hormonal changes, the uterine clock may also participate in temporal regulation of pregnancy and fertility by influencing endometrial regeneration and cyclical remodeling (40). In animal models, disruption of uterine circadian rhythms has been shown to lead to physiological dysfunction and alter pregnancy outcomes in mice (41), underscoring the importance of the uterine clock in maintaining normal reproductive function.

*Molecular clock of circadian rhythms*. As aforementioned, the molecular clock governing circadian rhythms primarily consists of a TTFL system driven by core clock genes. Genes such as CLOCK, BMAL1, PER1/2/3 and CRY1/2 collectively maintain the periodicity and stability of the rhythm through numerous interconnected feedback loops (4,42) (Fig. 2).

In the first feedback loop, BMAL1 and CLOCK (or its homolog NPAS2) form heterodimers that recognize E-box elements, thereby activating transcription of PER1/2/3 as well as CRY1/2 (43). PER and CRY proteins gradually accumulate in the cytoplasm and form new heterodimers. Upon interaction with casein kinase (CK1)-δ or ε, they translocate to the nucleus, where they inhibit CLOCK/BMAL1-mediated transcriptional activity. Subsequently, PER/CRY proteins are degraded through E3 ubiquitin ligase complexes, releasing CLOCK/BMAL1 inhibition and initiating the next cycle (44,45).

In the second feedback loop, retinoic acid receptor-related orphan receptor (ROR)-α, β or γ, and reverse erythroblastosis virus (REV-ERB)-α and β regulate BMAL1 transcription by competitively binding to the ROR/REV-ERB response elements (RORE). Specifically, ROR promotes BMAL1 expression, while REV-ERB inhibits it (46). The third feedback loop involves members of the proline- and acid-rich basic leucine zipper transcription factor family, including transcription enhancer factor, hepatic leukemia factor and the repressor nuclear factor IL-3 regulated. These factors competitively bind to D-box elements and are regulated by the CLOCK/BMAL1 and REV-ERB/ROR circuits, respectively (45). Furthermore, CLOCK/BMAL1 regulates gene expression of REV-ERB and ROR, forming a complex negative feedback network. It influences cellular and tissue functions through epigenetic regulation mechanisms such as phosphorylation, acetylation and ubiquitination (47).

*Other regulatory factors of circadian rhythms*. Regulation of circadian rhythms involves complex and diverse factors. Beyond the SCN and clock genes, it is influenced by a number of external cues and endogenous factors. Among environmental factors, light exposure is one of the most important synchronizing signals, regulating clock gene expression and rhythm synchronization through the retinal/SCN pathway. Studies have indicated that prolonged exposure to artificial light environments can disrupt the TTFL of clock genes and induce rhythm disorders (48,49). Furthermore, temperature fluctuations can affect the period and amplitude of circadian rhythms. In both homeothermic and poikilothermic animals, daily temperature cycles of just a few degrees are sufficient to disrupt circadian clocks, driving free-running behaviors and molecular rhythms (50-52). Beyond light and temperature, magnetic field changes, social behavioral rhythms (such as shift work) and dietary habits (such as meal timing) also exert regulatory effects on circadian rhythms. Additionally, genetic factors contribute to the formation of rhythmic phenotypes. Research has indicated that maternal circadian disruption prior to conception can influence offspring rhythmic characteristics (53). Genetic variations, such as single nucleotide polymorphisms or functional mutations in clock genes, may alter circadian rhythm parameters-including period, amplitude and phase-by modifying clock gene expression and function, leading to interindividual circadian rhythm differences (54,55).

*Physiological effects of circadian rhythms*. Circadian rhythms participate in regulating numerous physiological functions, including sleep quality, metabolic homeostasis, immune function and mental health. In sleep-wake regulation, the SCN maintains the rhythmicity of the sleep-wake cycle by influencing specific mechanisms, including the neuronal activity of AVP and VIP neurons and the secretion of melatonin (37,56,57). Liver clock genes play a crucial role in the circadian regulation of lipid metabolism. Animal studies indicate that hepatocyte-specific knockout of REV-ERBα/β disrupts the rhythmicity of *de novo* lipid synthesis, leading to dysregulation of cholesterol and triglyceride metabolism (58). Furthermore, PER2 modulates the metabolic enzyme CYP2B10

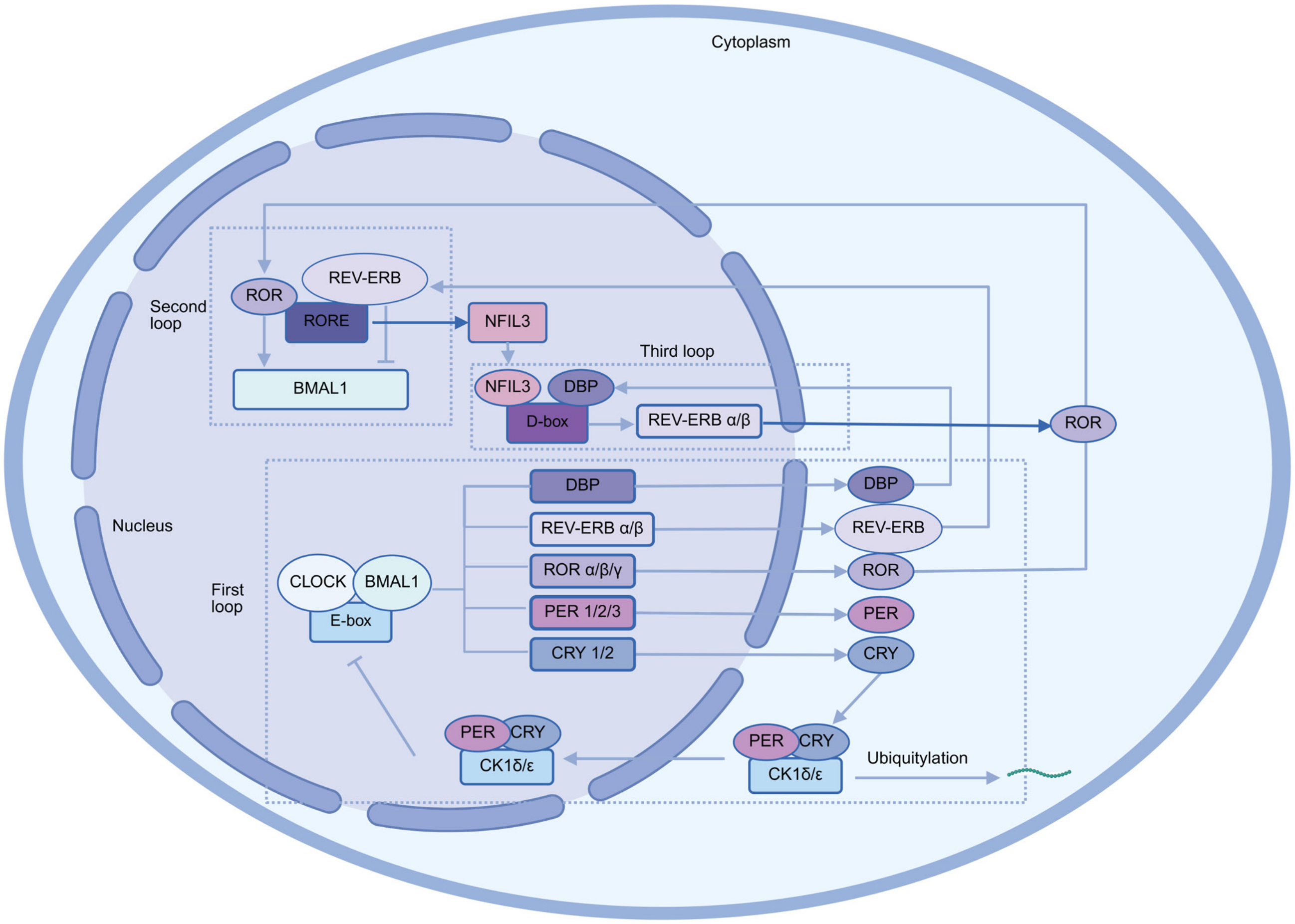

Figure 2. Key transcription-translation feedback loops regulating circadian rhythms in living organisms. The first feedback loop involves the core clock genes BMAL1 and CLOCK, which bind to form a CLOCK-BMAL1 heterodimer. This heterodimer binds to the E-box element, thereby activating the expression of other core clock genes PER1/2/3 and CRY1/2. PER and CRY proteins form new heterodimers in the cytoplasm, bind to CK1δ/ε and subsequently translocate to the nucleus to negatively regulate CLOCK and BMAL1 expression. Concurrently, PER and CRY protein levels decline through ubiquitination-mediated degradation, simultaneously relieving inhibition of CLOCK-BMAL1. In the second feedback loop, REV-ERBα/β and RORα/β/γ regulate BMAL1 expression by competitively binding to the RORE. ROR activates BMAL1, while REV-ERB inhibits it. In the third feedback loop, DBP and NFIL3 competitively bind to the D-boxes driven by either the CLOCK-BMAL1 circuit or the REV-ERB-ROR circuit. The dashed boxes represent the three circuits. BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; PER, period; CRY, cryptochrome; CK1, casein kinase 1; REV-ERB, reverse erythroblastosis virus; ROR, retinoic acid receptor-related orphan receptor; RORE, ROR/REV-ERB response element; NFIL3, nuclear factor IL-3 regulated; DBP, D-site binding protein.

through a REV-ERBα-dependent mechanism (59), while the core complex CLOCK:BMAL1 regulates the rhythmic expression of bile acid synthesis genes (60). These hierarchical transcriptional regulatory mechanisms collectively establish a systemic circadian regulatory framework for hepatic metabolic networks. Concurrently, clock proteins participate in glucose metabolism-related processes, thereby synchronizing energy metabolism with circadian rhythms (61,62).

Circadian rhythms are also associated with cardiovascular homeostasis (63). The SCN modulates circadian fluctuations in adrenocorticotropic hormone and cortisol synthesis, thereby influencing diurnal blood pressure variations (63,64). Notably, phenomena such as the morning blood pressure surge are associated with SCN-mediated body temperature changes (65). Circadian rhythm disruption promotes the development of numerous cardiovascular diseases, as impaired molecular clocks in rodents have been shown to induce phenotypes such as cardiomyopathy (66). Furthermore, circadian rhythms influence heart rate, pulmonary circulation, glomerular filtration rate, skeletal muscle metabolism, bone development and neuro-immune functions (67). Within the reproductive system, circadian rhythms are implicated in regulating key processes including sex hormone secretion, gametogenesis and fertilization (68,69). Due to the central role of the uterus in reproduction and pregnancy maintenance, the present review will further focus on the potential impact of circadian rhythms on uterine functional homeostasis and uterine-related disorders.

## 3. Effects of clock genes on the uterus

*Effects of clock genes on the endometrium*. Both animal studies and clinical research indicate that clock genes are widely expressed in the endometrium and myometrium, participating in uterine function maintenance and reproductive processes by regulating the local uterine microenvironment (13,70,71). As the foundational tissue for embryo implantation and development, the endometrium undergoes notable cyclical changes in cellular structure and functional state throughout the menstrual cycle. Correspondingly, a number of studies have detected certain circadian rhythm-related genes in the endometrium (12,13,72), exhibiting specific rhythmic patterns throughout the menstrual cycle, suggesting clock genes may participate in the cyclical regulation of the endometrium. Clinical research has further indicated that during the secretory phase, the expression of BMAL1, CRY2, NPAS2 and RORA markedly increases; PER2 shows an upward trend during the early and mid-secretory phases but decreases markedly in the late secretory phase; conversely, CLOCK and PER3 decrease markedly during the secretory phase, particularly in the late phase (12). These findings suggest notable clock gene expression differences across distinct phases of the human endometrial secretory phase, indicating stage-specific regulation of clock genes.

Notably, uterine clock gene expression patterns in different species do not always align with those in humans. A previous study indicated that in Small-tail Han sheep, CLOCK expression in the endometrium was markedly higher during the luteal phase compared with the follicular phase (73), contrasting with the decline observed in the human secretory phase (equivalent to the luteal phase). This discrepancy may be associated with differences in reproductive cycle characteristics and endometrial morphology between species. The human menstrual cycle lasts ~28 days, whereas the estrous cycle in Small-tail Han sheep spans 16-17 days; conversely, the human endometrial functional layer undergoes typical cyclic shedding and regeneration, whereas the Small-tail Han sheep endometrium primarily undergoes proliferation and resorption without a distinct 'shedding phase' (Table I) (12,13,73-76). Therefore, caution should be exercised when directly comparing the rhythmic characteristics and functions of uterine clock genes across different species.

At the cellular level, the expression patterns of clock genes in the endometrium vary markedly across different stages. A study has demonstrated that in undifferentiated human endometrial stromal cells (HESCs), clock genes CLOCK, BMAL1, CRY1/2 and PER1/2 exhibit pronounced circadian rhythmic expression. Following decidualization induction, this rhythmicity notably diminishes or even disappears, accompanied by changes in the post-translational modification patterns of corresponding clock proteins (76). By contrast, an additional study using immortalized HESCs reported that under undifferentiated culture conditions, CLOCK, BMAL1, CRY1/2 and PER1/2/3 did not exhibit pronounced rhythmicity and no further attenuation of rhythmicity was observed after decidualization treatment (13). These inconsistencies may stem from intrinsic differences between primary and immortalized cells. Cell cycle and metabolic reprogramming in immortalized cells may disrupt circadian oscillators; simultaneously, alterations in steroid hormone receptor expression and signaling pathways may weaken responses to decidualization stimuli. Furthermore, immortalized cell lines often exhibit phase dispersion due to weakened intercellular coupling, obscuring rhythmic gene expression patterns at the population level, whereas primary HESCs maintain superior synchrony (Table I) (12,13,73-76).

Current evidence supports a key regulatory role for PER1 and PER2 in uterine decidualization. A study has indicated that PER1 is rapidly upregulated and maintained at high levels following induction of decidualization in human endometrium (13). The progesterone receptor activates PER1 transcription by directly binding its promoter. Knockout of PER1 markedly reduces expression of the progesterone receptor and FOXO1, thereby inhibiting endometrial decidualization (13). This suggests PER1 primarily participates in the early initiation phase of decidualization. In response, PER2 knockdown induces $G_2$/M cell cycle arrest and inhibits mitotic proliferation of HESCs. Concurrently, it impairs decidualization and disrupts circadian rhythm oscillations (76). An *in vitro* study further revealed that PER2 gene knockdown in HESCs may impair endometrial receptivity and lead to recurrent implantation failure by regulating shootin 1, kruppel like factor 5 and six transmembrane epithelial antigen of the prostate 4 (12). In summary, PER1/2 may jointly maintain endometrial functional homeostasis by coordinating proliferation-differentiation (decidualization) processes. It should be noted that this understanding is primarily based on *in vitro* cell models and its regulatory role in the *in vivo* environment remains to be further validated.

CLOCK and BMAL1 may also be associated with female reproductive outcomes. An animal study indicates that mutations in the CLOCK gene reduce embryo implantation capacity and reproductive output in mice (77). Clinical research further suggests that genetic variations in the CLOCK gene are notably associated with increased miscarriage rates, implying the potential involvement of CLOCK in pregnancy maintenance (78,79). Furthermore, studies on BMAL1 similarly demonstrate its importance, in uterine and ovarian steroid-producing cells, conditional knockout of BMAL1 does not affect mouse embryo implantation but impairs placental vascularization, ultimately leading to pregnancy loss (74,80). This highlights the key role of BMAL1 in pregnancy maintenance.

BMAL1 deficiency also modulates other clock gene expression levels. In the mouse uterus, conditional BMAL1 knockout has exhibited distinct effects on clock genes at different Zeitgeber time points (ZT). At ZT 0, BMAL1 knockout markedly downregulated REV-ERBβ expression while upregulating CRY1/2 as well as RORα and RORγ. Conversely, at ZT 12, BMAL1 reduced REV-ERBα/β and PER3 expression while increasing CRY1, NPAS2 and RORγ (81). Furthermore, as a direct upstream transcriptional repressor of BMAL1, activation or knockout of REV-ERBα can influence inflammatory responses in HESCs by regulating the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway (82). These findings indicate that BMAL1 participates in maintaining endometrial microenvironment homeostasis by regulating both the clock gene network and inflammation-related signaling pathways. In summary, clock genes exhibit phasic expression patterns in the endometrium throughout the menstrual cycle, while their rhythmicity is markedly attenuated or even lost in decidualized endometrium.

*Effects of clock genes on the uterine myometrium*. As a key component of the uterus, the expression of core circadian clock genes in the myometrium also exhibits pronounced circadian rhythmicity. High expression of BMAL1 and PER2 was detected in primary myometrial cells from both non-pregnant and pregnant donors and BMAL1 was also stably expressed in the mouse myometrium (72). An *in vitro* experiment further determined that BMAL1 and PER2 exhibit stable rhythmic oscillations with opposite phases in immortalized human

Table I. Comparison of uterine clock gene expression and sources of variation across different research models.

| First author, year | Key findings | Sample sources | Reasons for the difference | (Refs.) |
|---|---|---|---|---|
| Zhai *et al,* 2021 | CLOCK expression is markedly reduced during the luteal phase. | Normal ovulating women endometrium | The discrepancy may stem from species-specific physiological differences in reproductive cycling and endometrial morphology. First, the human menstrual cycle (~28 days) differs markedly in length from the estrous cycle of Small-tail Han sheep (16-17 days). Second, the human endometrium undergoes cyclic shedding and regeneration of the functional layer, whereas in Small-tail Han sheep, the endometrium primarily undergoes proliferation and resorption, without a canonical shedding phase. | (12) |
| Han *et al,* 2021 | CLOCK expression is markedly elevated during the luteal phase. | Endometrium of the Small-tail Han Sheep | | (73) |
| Muter *et al,* 2015 | CLOCK, BMAL1, CRY1/2 and PER1/2 exhibit distinct circadian rhythmicity in undifferentiated cells, but this rhythmicity notably weakens or even disappears following decidualization treatment. | Primary HESCs | The discrepancy may be attributable to immortalized cells undergoing reprogramming of cell-cycle progression and metabolic programs, accompanied by alterations in the epigenetic landscape and hormone responsiveness. In addition, immortalized cells may exhibit reduced responsiveness to phase-synchronizing cues, leading to greater phase dispersion across the cell population. | (76) |
| Zhang *et al*, 2019 | CLOCK, BMAL1, CRY1/2 and PER1/2/3 did not exhibit distinct rhythmicity during the undifferentiated stage and no notable reduction in rhythmicity was observed following decidualization treatment. | Immortalized HESCs | | (13) |
| Ratajczak *et al*, 2012 | Conditional knockout of BMAL1 in uterine myometrial smooth muscle cells increases the probability of premature or delayed delivery. | Conditional BMAL1 knockout mice in uterine myometrial smooth muscle cells | The discrepancy may arise because myometrium-specific knockout primarily disrupts uterine contractile rhythms, thereby altering the timing of parturition. By contrast, whole-uterus knockout also compromises numerous processes key in the establishment and maintenance of pregnancy, including endometrial receptivity, decidualization, inflammatory homeostasis and vascular remodeling, ultimately rendering pregnancy difficult to sustain as early as the early-to-mid gestational period. | (75) |
| Ono *et al*, 2022 | Mice with conditional knockout of BMAL1 in the entire uterus exhibit impaired placental vasculature formation after embryo implantation, resulting in pregnancy loss. | Whole-uterus BMAL1 conditional knockout mice | | (74) |

CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle ARNT-like 1; PER, period; CRY, cryptochrome; HESC, human endometrial stromal cells.

uterine myometrial smooth muscle cells. Compared with primary cells from non-pregnant donors, BMAL1 rhythms in uterine myometrial cells from pregnant donors were more pronounced and sustained across a longer duration, suggesting pregnancy enhances the rhythmic output of clock genes in the myometrium. Further experiments demonstrated that overexpression of the BMAL1/CLOCK complex in uterine myometrial smooth muscle cells activated transcription of the melatonin receptor type (MT)2 (83), suggesting a potential functional association between clock genes and the MT2 receptor in human uterine myometrium. However, this finding requires further validation in intact uterine tissue.

Clock genes in the uterine myometrium also participate in regulating the timing of pregnancy and labor, causing delivery to predominantly occur during periods of bodily rest (84). The nocturnal delivery pattern observed in primates is associated with heightened uterine sensitivity to oxytocin and melatonin during late pregnancy, with their respective receptors synergistically promoting uterine contractions during labor (85,86). In mouse models, conditional deletion of BMAL1, specifically in uterine smooth muscle cells, leads to abnormal delivery timing (75), supporting the role of the myometrial clock in regulating labor timing. Notably, as aforementioned, whole-uterine BMAL1 knockout in mice has been shown to impair pregnancy maintenance (74). This discrepancy may arise as myometrial-specific knockout, primarily affecting uterine contraction rhythms and thereby influencing delivery timing. However, whole-uterine knockout simultaneously disrupts key processes for pregnancy establishment and maintenance, including endometrial receptivity, decidualization, inflammatory homeostasis and vascular remodeling-resulting in early-to-mid pregnancy failure (Table I) (12,13,73-76). In summary, the circadian rhythmicity of clock genes in the uterine myometrium during pregnancy is not only more pronounced but may also influence parturition timing by regulating uterine contractile activity.

## 4. Effects of circadian rhythms on estrogen and progesterone

Clinical studies indicate that the synergistic effects of estrogen and progesterone promote the establishment of uterine receptivity and serve an important regulatory role in embryo implantation (87,88). A previous study indicated that both hormones exhibit circadian fluctuations synchronized with clock gene expression across a 24 h period. Estrogen levels typically peak during the night, while progesterone rises during specific periods in the day (89). Growing evidence indicates that these rhythmic hormonal changes are regulated by the circadian rhythm system (90-92).

Estrogen, primarily secreted by ovarian granulosa cells, serves a central role in ovulation and embryo implantation. A study has indicated that estrogen receptors are expressed in the rat SCN and its afferent and efferent regions (including the lateral hypothalamus, medial preoptic area and paraventricular nucleus), providing a structural basis for the involvement of estrogen in circadian rhythm regulation (93). Further studies have revealed that estrogen influences circadian rhythms of feeding and behavioral activity through the SCN and that the timing of ovulation during the estrous cycle depends on precise synchronization between estrogen and SCN rhythmic signals (94,95). In ovarian granulosa cells, small interfering (si)-RNA knockdown of BMAL1 or CLOCK downregulates the expression of steroidogenic acute regulatory protein (StAR), cytochrome p450 family 11 subfamily a member 1 and cytochrome p450 family 19 subfamily a member 1 (CYP19A1), accompanied by decreased estrogen content within granulosa cells (96). Conversely, PER2 knockdown enhances StAR expression and promotes estrogen production (97). Furthermore, the nuclear receptor REV-ERBα directly binds to the RORE element on the CYP19A1 or BMAL1 promoter, thereby inhibiting estrogen synthesis in granulosa cells (98,99). Collectively, these findings indicate that clock genes participate in the rhythmic regulation of estrogen secretion through the steroid synthesis pathway.

Estrogen receptor β (ERβ), a key receptor mediating estrogen actions, exhibits clock protein-regulated expression. The CLOCK/BMAL1 heterodimer activates ERβ transcription through the E-box enhancer, a process inhibited by PER proteins. siRNA-mediated depletion of CLOCK or PER1 increases ERβ expression. In BMAL1 knockout mice, rhythmic oscillations of ERβ disappear (100). Concurrently, the rhythmic expression of PER2 and CLOCK is directly regulated by estrogen response elements (94). Estradiol treatment in ovariectomized rats altered the expression rhythm of PER1/2 in the uterus but did not affect the PER2 expression rhythm in the SCN and cortex (101-103). This demonstrated bidirectional and tissue-specific regulation between estrogen and circadian rhythms.

Furthermore, progesterone is the primary steroid hormone secreted by the *corpus luteum*. Increasing evidence has indicated that circadian rhythms participate in regulating progesterone signaling pathways. Studies have revealed that circadian rhythm disruption induced by continuous light exposure markedly reduces serum progesterone levels in Institute of Cancer Research (ICR) mice and ruminants (92,104). At 3.5 days post-conception, BMAL1 knockout mice also exhibited decreased serum progesterone (105). This phenomenon may be associated with circadian regulation of luteinization and luteolysis processes (87). Conversely, progesterone level fluctuations can also reciprocally influence clock gene expression. In ovariectomized mice, progesterone administration upregulated CLOCK, NPAS2, CRY1 and PER1 while downregulating REV-ERBβ, peroxisome proliferator-activated receptor γ coactivator 1-α and RAR-related orphan receptor C, a process mediated by the progesterone receptor (106). During pregnancy, the sharp rise in progesterone also shortens the oscillation period and reduces the amplitude of the PER2::Luciferase ratio in cultured uterine tissue (107). Overall, estrogen and progesterone exhibit bidirectional regulatory interactions with the circadian rhythm system, jointly influencing endometrial receptivity and decidualization during embryo implantation.

## 5. Effects of melatonin on the uterus

Melatonin is a key output hormone of the circadian rhythm system, regulated by neuroendocrine processes mediated by the SCN. It participates in regulating circadian phase and physiological rhythms by binding to MT1 and MT2. Additionally, melatonin serves a notable role in the female reproductive endocrine system (108). Studies have demonstrated that nighttime serum melatonin levels in postmenopausal women are markedly lower compared with perimenopausal women. Long-term oral melatonin supplementation improves psychosomatic symptoms in postmenopausal women (109,110), suggesting an association between melatonin levels and reproductive aging. Therefore, investigating the role of melatonin and its receptors in the uterus may help elucidate their importance in female reproductive health.

*Melatonin and uterine cell proliferation, apoptosis and inflammatory response*. Research has determined the expression of MT1 and MT2 receptors in the female uterus (111), providing a structural basis for the direct regulation of uterine cell function by melatonin. In uterine endometrial stromal cells (UESCs), MT1 knockdown inhibits cell proliferation and promotes apoptosis by activating the Bax/Bcl-2 pathway to inhibit cell proliferation and promote apoptosis, whereas exogenous melatonin reverses these changes by activating JNK/p38 MAPK signaling pathway (112). In mice, reduced MT1 expression in endometrial cells due to abnormal light exposure also promotes apoptosis and inhibits proliferative activity, a phenotype partially alleviated by melatonin supplementation (112). Furthermore, a study indicates that melatonin exerts a protective effect on the uterus during pregnancy by inhibiting the activation of lipopolysaccharide-induced inflammatory, autophagic, and apoptotic pathways via MT2 in an N6-methyladenosine-dependent manner (113). These findings indicate that MT1 and MT2 receptors synergistically regulate uterine cell proliferation and apoptosis.

Notably, the effects of melatonin on apoptosis exhibit cell-type dependence. In rat uterine leiomyoma ELT3 cells, melatonin induced apoptosis and autophagy, inhibited proliferation and downregulated the AKT/ERK1/2/NFκB signaling pathway, suggesting its specific regulatory effects in tumor tissues (114). Furthermore, melatonin participates in endometrial repair through immunomodulation. In a mouse model of intrauterine adhesions, melatonin promoted endometrial regeneration and improved pregnancy outcomes by enhancing macrophage recruitment, modulating macrophage polarization and suppressing local inflammatory responses (115). Thus, melatonin influences uterine cell proliferation, apoptosis and inflammatory responses through receptor-mediated signaling and immunomodulation.

*Melatonin and uterine oxidative stress, autophagy and mitochondrial function*. Melatonin, as a classical antioxidant and mitochondrial protective factor, has been reported to improve the uterine environment and enhance fertility in a number of animal models. In mice, melatonin reduced uterine oxidative stress levels while increasing litter size and fertility. These effects are associated with elevated total antioxidant capacity and superoxide dismutase (SOD) levels, alongside decreased malondialdehyde (MDA) content (116). In a uterine thermal ischemia-reperfusion injury model, melatonin combined with other drugs mitigated oxidative stress-induced cellular damage (117). Concurrently, melatonin treatment markedly reduced collagen deposition in mouse endometrium, increased glandular number and improved pinopode architecture, ultimately enhancing endometrial receptivity and promoting embryo implantation (118). In a rat model of continuous light exposure, melatonin also inhibited uterine apoptosis, further demonstrating its protective effect on uterine tissue (119). In large animal models, the protective effects of melatonin exhibit a degree of conservation.

In porcine endometrial epithelial cells, melatonin was shown to enhance endometrial receptivity and embryo implantation rates by reducing lipid accumulation, inflammation and endoplasmic reticulum stress through the MT2/PI3K/leukemia inhibitory factor signaling pathway, while promoting cell proliferation and migration. This process may be associated with melatonin-mediated upregulation of sirtuin 1, which improves maternal uterine-embryo interactions (120). In bovine and dairy endometrial epithelial cells, melatonin enhanced cell viability by alleviating mitochondrial dysfunction, upregulating autophagy levels and reducing oxidative stress (121). Concurrently, melatonin improves endometrial receptivity by suppressing reactive oxygen species production and reducing IL-6 expression through inhibition of the TLR4/NF-κB pathway (122). This multi-species evidence collectively demonstrates that melatonin improves the uterine environment and promotes embryo implantation by regulating oxidative stress, autophagy, inflammation and apoptosis-related signaling pathways.

*Melatonin and pregnancy maintenance*. During pregnancy, melatonin not only participates in endometrial receptivity and embryo implantation but also contributes to pregnancy maintenance by influencing placental vascularization and uterine spiral artery remodeling. In early pregnancy, melatonin promotes spiral artery remodeling and placental vascularization. Abnormalities in this process can induce pre-eclampsia-a hypertensive disorder of pregnancy characterized by placental hypoperfusion due to impaired spiral artery remodeling (111). In patients with pre-eclampsia, oral melatonin supplementation enhances embryo quality and prolongs gestation duration by activating the upstream antioxidant transcription factor nuclear factor erythroid 2-related factor 2 and suppressing NF-κB-mediated inflammatory responses (123). This suggests melatonin holds promise as a potential adjunctive intervention for pre-eclampsia during pregnancy.

Human births primarily occur at night or in the early morning, which may be associated with melatonin secretion rhythms in late pregnancy (124). A clinical study reported a notable positive linear association between salivary melatonin concentrations and uterine contraction frequency in late-pregnancy women (125). Synergistic interactions between melatonin receptors and oxytocin receptors jointly promote uterine contractions (83). In late pregnancy, MT2 receptor and oxytocin receptor levels in the uterine myometrium of parturients are markedly higher compared with that of non-parturients, suggesting that the melatonin signaling pathway is activated in preparation for labor as delivery approaches. A mechanistic study further proposed that melatonin enhances human uterine myocyte sensitivity to oxytocin by activating protein kinase C-α (PKC-α) and ERK1/2-mediated calmodulin phosphorylation. This may explain the increased uterine contractility during late pregnancy nights and the concentration of labor onset during this period (126).

A previous animal study similarly confirmed melatonin's regulatory role in uterine contraction rhythms. In female rats, pinealectomy-induced loss of endogenous melatonin did not markedly affect estrous cycles or fertility, but did shift parturition from predominantly daytime to occur at any time of the day or night. Supplementing melatonin at night restored the normal daytime parturition pattern (127). This concept suggests melatonin may be one of the key circadian signals regulating parturition timing in rats.

## 6. Effects of circadian rhythm disorders on the uterus

Common triggers of circadian rhythm disorders include irregular sleep patterns such as prolonged inconsistent sleep schedules, shift work, staying up late and time zone travel, as well as abnormal light exposure (78,87). These factors can disrupt uterine clock gene expression, causing desynchronization between the uterine clock and the central clock. This, in turn, reduces endometrial receptivity, affecting embryo implantation and pregnancy outcomes (12). Research has revealed that long-duration light exposure (LLD) can cause desynchronization in the expression rhythms of clock genes BMAL1, CLOCK, PER1/2 and CRY1/2 in the SCN and uterus during both pregnancy and non-pregnancy states. Notably, in pregnant women, this asynchrony in central and peripheral uterine clock gene expression can lead to pregnancy abnormalities. The mechanism may involve downregulating downstream clock gene regulators such as arylalkylamine N-acetyltransferase (AANAT), progesterone-induced blocking factors HOXA10 and HOXA11, alongside activating the AKT/FOXO1 pathway (128). A mouse study also reached similar conclusions (41). Prolonged exposure to artificial light causes desynchronization of circadian rhythms in Swiss albino mice, affecting clock genes (BMAL1, CLOCK, PER1/2 and CRY1) and their downstream regulator, hepatocyte growth factor, in the SCN and uterus. This is accompanied by endometrial thickening, decreased serum progesterone and reduced progesterone-dependent HOXA10 protein levels, ultimately lowering pregnancy success rate (41). Furthermore, LLD increases endometrial thickness while decreasing myometrial thickness in hamsters (128), suggesting widespread adverse effects of abnormal light exposure on uterine structure and function.

Beyond light exposure, feeding timing also influences uterine clock gene expression. A study has shown that compared with mice fed *ad libitum*, restricted feeding (8 h feeding and 20 h fasting) markedly reduces uterine expression levels of CRY2, REV-ERB$\alpha$/$\beta$, PER3 and ROR$\alpha$/$\beta$ at ZT 12 (81). In addition, time-restricted feeding disrupts the uterine circadian oscillation system in mice, eliminating the circadian rhythms of clock genes (129).

Numerous epidemiological studies have suggested that circadian rhythm disruption is associated with certain female reproductive issues. These include increased risks of menstrual irregularities (130), infertility (131), recurrent implantation failure (12), spontaneous abortion (132), preterm birth (133), polycystic ovary syndrome, EMS and EC (134,135) associated with shift work. These associations may stem from circadian rhythm disruption-induced abnormalities in hormone secretion, cell cycle imbalance and dysregulation of cell proliferation and apoptosis (112,136-138). Therefore, targeting the correction of circadian rhythm disruption or enhancing rhythmic homeostasis may represent novel approaches in the prevention and treatment of reproductive system disorders.

## 7. Association between circadian rhythm disorders and uterine-related diseases

*EMS and circadian rhythm disorders.* EMS is a chronic inflammatory gynecological disorder characterized by the ectopic presence of endometrial glands and stroma outside the uterine cavity. It commonly involves the pelvic peritoneum, ovaries, rectovaginal septum amongst other structures and may also occur in tissues beyond the abdominal and pelvic cavities. Clinically, EMS primarily manifests as chronic pelvic pain and fatigue (139,140), accompanied by anxiety and emotional disorders, metabolic abnormalities, infertility and gastrointestinal and urinary system-related symptoms. EMS is also associated with an increased risk of cardiovascular diseases (such as atherosclerosis) and various cancers (such as ovarian cancer and melanoma) (141,142).

Sleep disorders represent one of the primary manifestations of circadian rhythm disruption (143). Current epidemiological evidence suggests that sleep disorders are associated with EMS risk and disease progression. Systematic reviews have indicated a notable positive association between sleep disorders and EMS risk (144,145), while Mendelian randomization analyses further identified insomnia as an adverse factor for EMS, with prolonged sleep duration potentially offering protective effects (146). At the molecular level, microarray analyses have also suggested that the transcription factor CLOCK contributes to disease pathogenesis by regulating inflammation-related pathways, particularly the NF-κB pathway and downstream pro-inflammatory cytokine responses (16). Concurrently, PER2 and PER3 expression is markedly downregulated in stromal cells of endometriotic lesions compared with normal UESCs (147). This suggests that CLOCK and PER2/3 may be implicated in the pathogenesis and progression of EMS, although the precise mechanisms require further elucidation.

Decreased melatonin levels due to circadian rhythm disruption are considered a key factor elevating EMS risk, making exogenous melatonin a potential intervention strategy (148). Previous studies have demonstrated that melatonin reduces ectopic lesion volume and adhesion formation, alleviates chronic pelvic pain and lowers recurrence rate (136,149). Mechanistic studies have further indicated that melatonin may influence numerous pathways including cell migration/invasion, oxidative stress and angiogenesis (Fig. 3) (150-152). Melatonin inhibits PI3K/AKT and ERK1/2 signaling pathways as well as the mitochondrial-related processes, thereby suppressing migration of ectopic epithelial and stromal cells. Additionally, melatonin may block 17β-estradiol-induced migration, invasion and epithelial-mesenchymal transition in endometrial epithelial cells by upregulating Numb and inhibiting Notch signaling (150). In EMS rats, melatonin elevated SOD and catalase activity in peritoneal fluid while increasing SOD and tissue inhibitor of metalloproteinase-2 levels in ectopic lesions; while simultaneously reducing MDA, MMP-9 and vascular endothelial growth factor expression. This alleviates oxidative stress in ectopic lesions, inhibits angiogenesis, weakens invasive and migratory capabilities and promotes lesion regression (151,152).

In addition, melatonin reduces proteolysis and tissue remodeling by inhibiting MMP-3 and its transcription factor activator protein-1 DNA-binding activity. It promotes endometrial

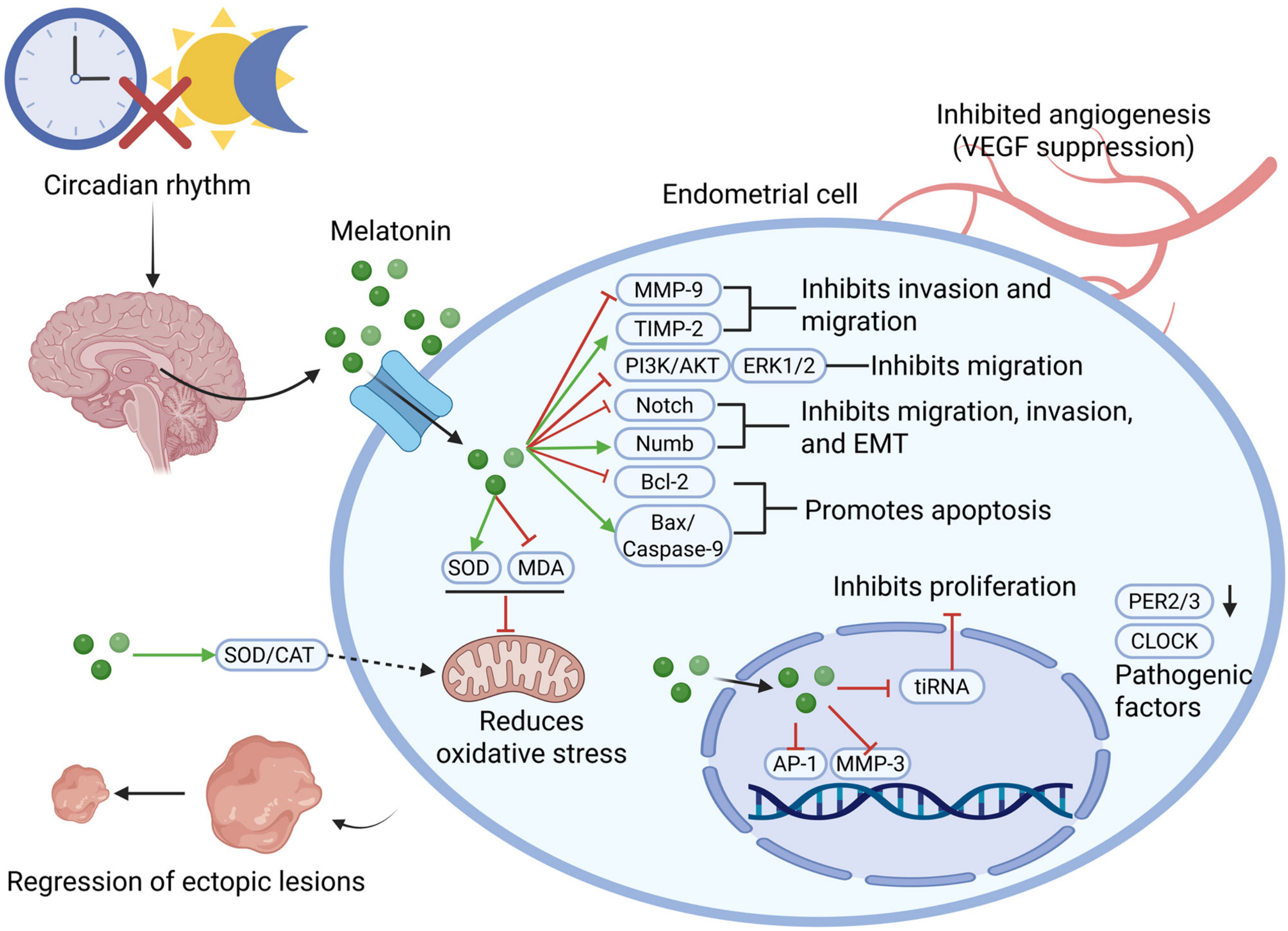

Figure 3. Schematic diagram of the potential mechanism of circadian rhythm disruption in EMS. The circadian rhythm system participates in the onset and progression of EMS by regulating melatonin levels secreted by the pineal gland. Melatonin enhances the activity of SOD and CAT in peritoneal fluid while increasing SOD levels in ectopic lesions and reducing MDA content, thereby mitigating oxidative stress damage. Within ectopic lesions, melatonin inhibits invasion and migration of endometrial cells by downregulating MMP-9 and upregulating TIMP-2. Concurrently, melatonin suppresses migration of ectopic endometrial cells by inhibiting PI3K/AKT and ERK1/2 signaling pathways. Furthermore, melatonin blocks migration, invasion and EMT of endometrial cells by upregulating Numb and inhibiting Notch signaling. It also promotes apoptosis in ectopic endometrial cells by downregulating Bcl-2 and upregulating Bax and caspase-9. Simultaneously, melatonin attenuates proteolysis and tissue remodeling by inhibiting MMP-3 and DNA-binding activity of its transcription factor AP-1. It suppresses cell proliferation by inhibiting tiRNA expression within lesions. Furthermore, melatonin downregulates VEGF expression to inhibit angiogenesis, ultimately promoting regression of ectopic lesions. The transcription factors CLOCK and PER2/3 are key pathogenic factors in EMS. EMS, endometriosis; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; TIMP, tissue inhibitor of metalloproteinase; EMT, epithelial-mesenchymal transition; AP-1, activator protein 1; tiRNA, tRNA-derived stress-induced RNA; CLOCK, circadian locomotor output cycles kaput; PER, period.

apoptosis through downregulating Bcl-2, upregulating Bax and facilitating caspase-9 activation, leading to notable degeneration of glandular epithelium in ectopic lesions (153). In mouse models, melatonin has been shown to inhibit proliferation by suppressing transfer RNA-derived stress-induced RNA expression in primary EMS stromal cells and lesions (154). However, the majority of the aforementioned data originate from rodent models or *in vitro* cell experiments, which differ markedly from patients with EMS in terms of immune microenvironment, endocrine status and disease progression. Furthermore, clinical studies exhibit limited sample sizes which are insufficient to determine the optimal dosage of melatonin, therapeutic timing and long-term safety (149,155,156). Therefore, although melatonin is recognized as a promising adjunctive therapeutic strategy, its clinical application still requires further robust evidence-based medical support.

*EC and circadian rhythm disorders*. EC is one of the most common gynecological malignancies, typically presenting with abnormal uterine bleeding, often accompanied by increased vaginal discharge and secondary infection. Currently recognized risk factors include obesity, metabolic abnormalities and genetic susceptibility (157). Previous epidemiological studies have further suggested that circadian rhythm disruption caused by night shift work and nocturnal chronotype (such as delayed peak activity) may increase EC incidence and disease severity (158,159). However, existing research primarily stems from observational studies, making it difficult to fully exclude confounding factors such as occupational stress, lifestyle and metabolic status. The causal relationship remains to be further validated.

Animal models and *in vitro* experiments have further indicated that altered clock gene expression contributes to EC pathogenesis. A previous study demonstrated that PER1 and PER2 exert tumor-suppressive effects in EC by promoting apoptosis and inhibiting tumor invasion through regulating tumor markers such as tubulin β-2B chain and R-sphingosine receptor 4 (160). Furthermore, prolonged light exposure disrupts the circadian rhythms of BMAL1, AANAT and melatonin in female hamster uterine tissue, activating the PKC-α/AKT signaling pathway and inducing endometrioid adenocarcinoma development (161). In human EC tissue, NPAS2 overexpression was associated with clinical stage, poor prognosis and myometrial immune cell infiltration, promoting tumor cell proliferation and colony formation while inhibiting apoptosis (161). Furthermore, TIMELESS (TIM) has been implicated in EC malignant transformation, with its knockdown suppressing tumor cell proliferation and migration. Notably, a previous study suggested that high mobility group box 1 can upregulate TIM, which in turn activates the Wnt ligand WNT8B and promotes EC progression through activation of the Wnt/β-catenin signaling pathway (162).

At the epigenetic level, methylation-specific PCR and sequencing results have revealed frequent DNA methylation in the promoter regions of clock genes in patients with EC, suggesting these genes may undergo epigenetic suppression (17). Concurrently, non-coding RNAs, as key post-transcriptional regulatory molecules, influence EC cell activity. Studies have indicated that microRNAs (miRNAs) associated with clock genes can regulate the proliferation, migration, and invasion of EC cells, while also influencing cell death (163,164). For example, miRNA-576-5p promotes the proliferation and metastatic potential of EC cells by suppressing the expression of zinc finger and BTB domain-containing protein 4 (163). By contrast, overexpression of miRNA-1271-5p suppresses EC cell proliferation, migration and invasion and induces apoptosis by targeting its downstream gene catenin delta 1 (164). Long non-coding RNA (lncRNA) OIP5-AS1 regulates the phosphatase and tensin homolog/AKT pathway by competitively binding to miRNA-200c-3p, thereby inhibiting proliferation and invasion in EC cells (Fig. 4) (165). In summary, the onset, progression and prognosis of EC is associated with circadian rhythm disruption, a process potentially mediated through clock gene expression, epigenetic abnormalities and post-transcriptional regulation through miRNAs/lncRNAs. However, current findings primarily stem from correlational studies and experimental models. The causal role of circadian gene alterations in EC development and their clinical translational potential require further clarification through large-scale prospective cohort studies and multi-omics integrated analyses.

*Menstrual irregularities and circadian rhythm disorders.* Menstrual irregularities refer to abnormalities in the menstrual cycle, menstrual flow or duration of menstruation. Common symptoms include irregular cycles, delayed or early periods, excessive or insufficient flow and periods that are too long or too short (166). Extensive epidemiological studies have indicated an association between circadian rhythm disruption and menstrual abnormalities in women. Women engaged in shift work, particularly night-shift nurses, exhibit a notably elevated risk of menstrual irregularities (167). Shift frequency is markedly associated with shorter menstrual cycles, while the interaction between individual chronotype and shift patterns further exacerbates menstrual cycle disruption (130,167). Shift work often involves nighttime light exposure and disrupted sleep rhythms, potentially increasing physiological stress responses and disrupting endocrine homeostasis. This can lead to abnormal levels of hormones including estrogen, progesterone, cortisol, luteinizing hormone, follicle-stimulating hormone and melatonin, thereby elevating the risk of menstrual irregularities (168,169). Furthermore, studies have identified a positive association between sleep disorders and the risk of menstrual irregularities, a relationship potentially further associated with reduced melatonin secretion and the development of mood disorders such as emotional instability, irritability, depression and anxiety (18,170).

Although epidemiological evidence supports the association between circadian rhythm disruption and menstrual irregularities, the underlying molecular mechanisms remain incompletely elucidated (18,171,172). At the genetic level, a study has reported that the CLOCK 3111T > C gene polymorphism may be an independent risk factor for menstrual irregularities, highlighting its potential as a molecular biomarker for gynecological diseases (173). However, further validation in larger samples and diverse populations is required. Additionally, altered expression of clock genes has been observed in other uterine-related disorders. For example, decidual macrophages in patients with spontaneous abortion predominantly exhibit an M1 phenotype, accompanied by downregulation of REV-ERBα expression (174), suggesting an association between reproductive immune homeostasis and circadian rhythm regulation. Overall, notable gaps remain in current mechanistic research and clinical studies predominantly rely on cross-sectional data, making it challenging to determine the causal direction between circadian rhythm disruption and menstrual disorders. Future prospective cohort and mechanism-oriented studies are warranted, along with further evaluation of the clinical utility of non-pharmacological interventions based on rhythm regulation (such as light therapy and sleep management) in preventing or improving menstrual irregularities.

## 8. Crosstalk between the uterine clock and the ovarian clock

As important organs in the female reproductive system, the uterus and ovaries jointly regulate female reproductive function and physiological state. Estrogen and progesterone secreted by the ovaries control the proliferation, secretion and shedding of the endometrium, forming the basis of the menstrual cycle. Conversely, the local state of the uterus and peripheral hormone levels promote the maintenance of ovarian function. Circadian rhythm disruption can cause the loss of synchrony between the SCN and the rhythmic oscillations of the peripheral biological clocks in the ovaries and uterus. For example, circadian rhythm disruption can cause desynchronized expression of clock genes BMAL1, CLOCK, PER1/2 and CRY1 in the SCN, ovaries and uterus, accompanied by abnormal progesterone levels (41). Furthermore, circadian disruption resulting from skipping breakfast disrupts the hypothalamic-pituitary-ovarian axis, impairs reproductive rhythms and leads to ovarian and uterine dysfunction (175). Animal studies have further demonstrated that estrogen and progesterone serve central roles in maintaining synchrony between the uterine and ovarian clocks. In a controlled superovulation rat model, elevated ovarian estrogen and progesterone levels significantly reduced endometrial receptivity, which correlated with decreased mRNA levels of

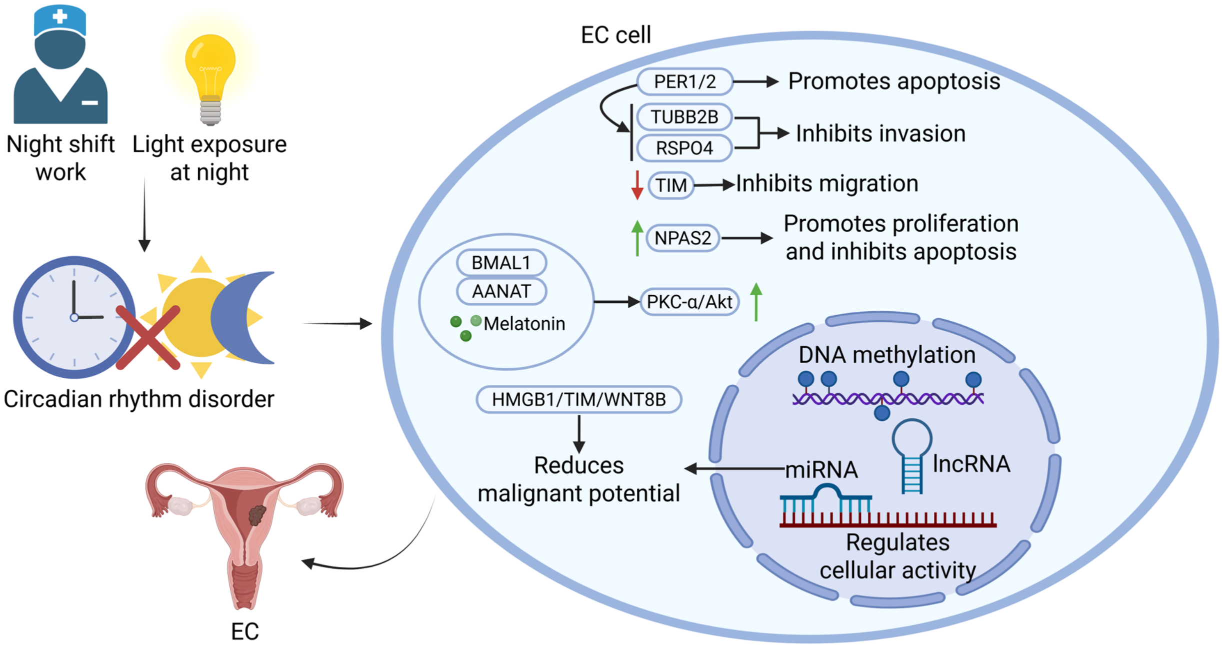

Figure 4. Schematic diagram of the potential mechanisms of circadian rhythm disruption in EC. Night shift work and nocturnal light exposure can induce circadian rhythm disruption, thereby contributing to the onset and progression of EC. At the molecular level, circadian rhythm disruption leads to abnormal expression of BMAL1, AANAT and melatonin, activate the PKC-α/AKT signaling pathway and induces EC development. The clock genes PER1/2 promote apoptosis and inhibit tumor cell invasion by regulating TUBB2B and RSPO4 expression. Furthermore, TIM knockdown inhibits tumor cell migration, while abnormal activation of the HMGB1/TIM/WNT8B signaling axis is implicated in regulating the malignant phenotype of EC cells. At the post-transcriptional level, DNA methylation occurs in the promoter regions of numerous clock genes in patients with EC and clock gene-associated miRNAs and lncRNAs can influence tumor cell activity. EC, endometrial cancer; PKC-α, protein kinase C-α; BMAL1, brain and muscle ARNT-like 1; AANAT, arylalkylamine N-acetyltransferase; PER, period; TUBB2B, tubulin β-2B chain; RSPO4, R-sphingosine receptor 4; NPAS2, neuronal PAS domain protein 2; TIM, TIMELESS; HMGB1, high mobility group box 1; miRNA, microRNA; lncRNA, long non-coding RNA.

the clock gene Bmal1 at ZT 12 (176). In mice, treatment of UESCs on gestational day 4 with progesterone and estradiol induced PER2:luciferase ratio oscillation phase shifts and increased amplitude, while upregulating BMAL1 and PER2 expression (177). Thus, circadian rhythms jointly ensure normal hypothalamic-pituitary-ovarian-uterine axis function by regulating clock gene expression and hormonal timing.

Research has also revealed a reciprocal influence between ovarian and uterine clock gene expression. Ovarian circadian abnormalities can alter uterine receptivity through steroid hormone output. A study has indicated that BMAL1 deficiency in ovarian steroid-producing cells leads to failed embryo implantation, while supplementation with progesterone or ovarian implantation can partially improve implantation success rates (178). Conversely, maternal circadian rhythm disruption also affects offspring ovarian clock and function. Research has indicated that female offspring of ICR mice with pre-pregnancy circadian disruption exhibit impaired follicular development, oocyte quality and pre-implantation embryo development, accompanied by downregulation of ovarian CLOCK, CRY1, REV-ERBβ and PER2 expression. This phenomenon may be associated with alterations in inflammation-related signaling pathways, particularly IL-17-mediated inflammatory responses and abnormal regulation of chemokine signaling axes (e.g., Cxcl1-Cxcr2, Ccl2/Ccl7-Ccr2) (53). Furthermore, CLOCK knockdown induces apoptosis and inhibits proliferation in mouse embryonic stem cells, leading to reduced oocyte release and decreased litter size (179). These findings collectively underscore the importance of uterine-ovarian circadian clock crosstalk in reproductive health. Therefore, elucidating the mechanisms of these mechanisms holds promise for improving reproductive health and treating infertility.

## 9. Limitations

Although existing research contributes towards elucidating the regulatory mechanisms of uterine circadian rhythms, the present review must still consider a number of limitations. First, the majority of existing evidence comes from nocturnal rodents, whereas humans are diurnal species. There are fundamental differences between the two in activity-rest patterns under light-dark cycles, as well as in hormone secretion and metabolic rhythms. Therefore, conclusions drawn from animal studies cannot be directly extrapolated to humans. Second, animal experiments are typically conducted under strictly controlled conditions of light exposure and feeding schedules, whereas clinical populations exhibit more complex lifestyles, increasing translational uncertainty. Third, circadian patterns vary across species. For example, during the luteal phase, CLOCK expression decreases in the human endometrium but markedly increases in the endometrium of Small-tail Han sheep (12,73), suggesting that physiological differences such as reproductive cycle length and endometrial shedding mechanisms may limit the extrapolation of mechanisms. Fourth, the reproducibility of *in vitro* studies is insufficient. For example, marked differences in circadian rhythm alterations of clock genes exist between primary and immortalized HESCs before

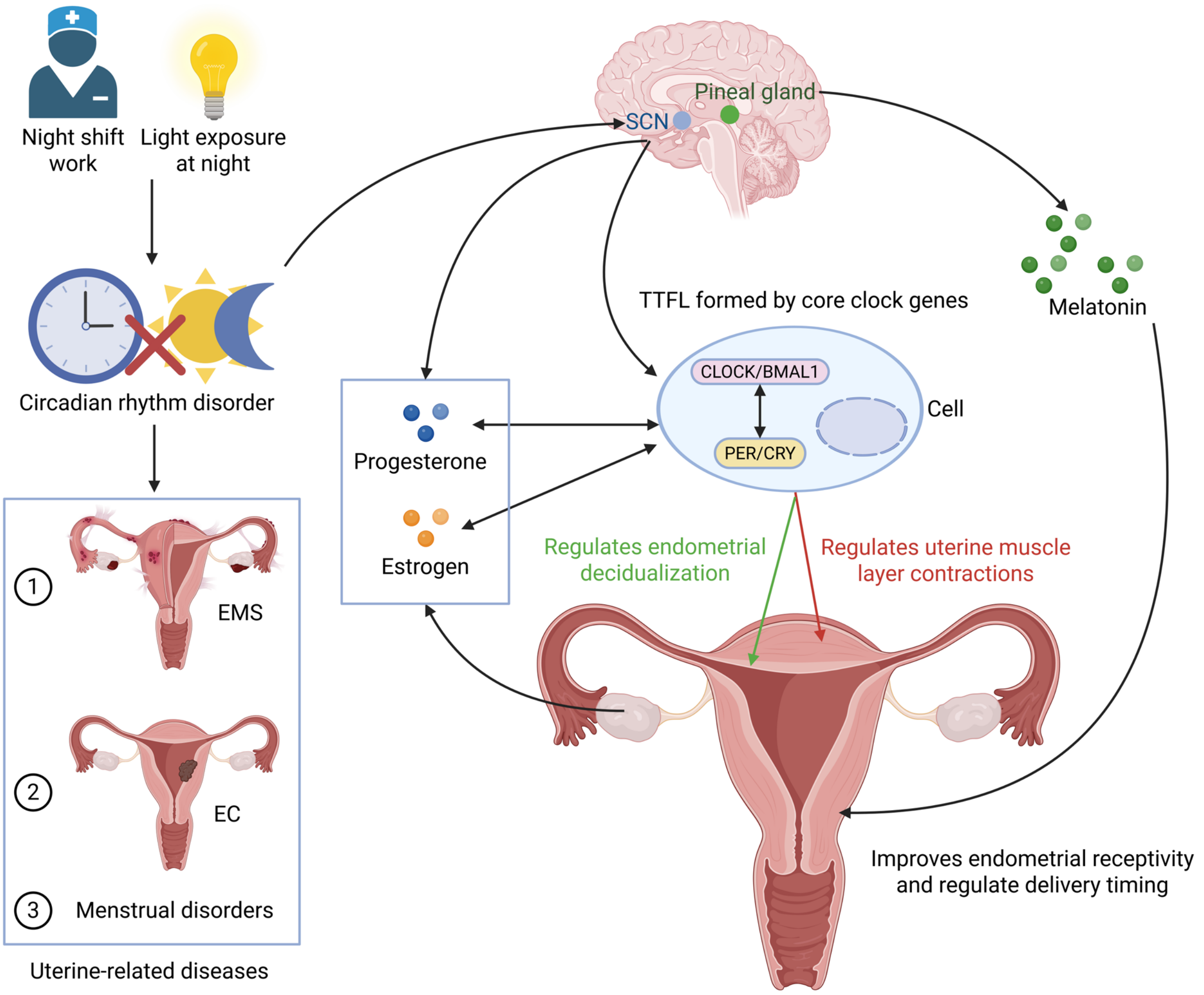

Figure 5. Schematic diagram illustrating the role of circadian rhythms in uterine-related diseases. Factors such as night shift work and nocturnal light exposure can disrupt circadian rhythms, subsequently affecting the central clock SCN and pineal melatonin secretion, thereby further disturbing the circadian rhythms of uterine clock genes and sex hormone levels. These alterations may regulate endometrial decidualization and rhythmic contractions of the uterine myometrium, thereby affecting endometrial receptivity and timing of labor. Ultimately, they contribute to the development and progression of uterine disorders including EMS, EC and menstrual irregularities. EMS, endometriosis; EC, endometrial cancer; CLOCK, circadian locomotor output cycles kaput; SCN, suprachiasmatic nucleus; BMAL1, brain and muscle ARNT-like 1; PER, period; CRY, cryptochrome.

and after decidualization treatment (13,76), indicating that the high sensitivity of results stems from model type and intervention method. Future studies should aim to enhance physiological relevance and clinical translational potential by utilizing diurnal animal models, uterine organoids and 3D co-culture systems, combined with human cohort studies and *in vivo* monitoring research.

## 10. Future research directions

As shift work-related circadian rhythm disruption is associated with increased risks for numerous uterine disorders, it is recommended that rhythm assessment and intervention be incorporated into comprehensive management strategies. First, outpatient systems should aim to evaluate sleep-wake schedules, night shift history, light exposure and meal timing to identify high-risk individuals with circadian rhythm disorders. Second, non-pharmacological interventions centered on regular sleep should be prioritized. This includes optimizing shift schedules for shift workers (reducing consecutive night shifts and limiting the number of night shifts) and ensuring adequate recovery sleep after night shifts to reduce cumulative exposure to circadian rhythm disruption. Finally, individualized melatonin use may be explored for select patients (particularly EMS personnel) (180). Previous studies regarding melatonin for sleep disorders have commonly employed oral doses of 2-4 mg/day taken 3 h before sleep, with treatment durations ranging from a number of weeks to ≥6 months (181,182). However, to the best of our knowledge, no unified evidence-based dosing regimen currently exists for uterine disorders and its efficacy and long-term safety require systematic evaluation. Future clinical trials should aim to clarify the dose-response relationship of melatonin, optimal administration window, treatment duration and combination strategies with existing therapies.

Pharmacological targeting of key circadian rhythm regulators holds potential translational value. REV-ERB agonists selectively target and destroy cancer cells, potentially enhancing mouse survival by regulating autophagy and inducing apoptosis (183). In the uterus, REV-ERBα activation modulates inflammatory responses in HESCs (82). Notably, uterine REV-ERBα expression is markedly reduced in circadian rhythm-disrupted mouse models (81). This suggests that REV-ERB-targeted therapeutics may be applicable not only for EC but also warrant further investigation in inflammatory conditions such as EMS.

Chronotherapy-optimizing drug administration or intervention timing based on endogenous rhythms to enhance efficacy and reduce adverse effects has demonstrated advantages in certain cancer types (such as metastatic colorectal cancer and metastatic adenocarcinoma), rheumatology, cardiovascular and allergic diseases (184). For example, administering chemotherapy drugs such as oxaliplatin and cisplatin at specific times can enhance their efficacy and reduce drug toxicity (185). However, research on uterine-related disorders remains relatively scarce, necessitating rigorous clinical trials to compare the effects of different treatment timings on disease progression and efficacy. Hormone therapy may also be coordinated with menstrual cycles and melatonin secretion rhythms to develop more personalized, time-dimensioned treatment strategies.

## 11. Conclusions

Existing research indicates that circadian rhythms participate in key reproductive processes such as uterine decidualization, pregnancy maintenance and timing of delivery by regulating reproductive hormones, the uterine environment and endometrial remodeling. Circadian rhythm disruption is associated with uterine-related disorders including EMS, EC and menstrual irregularities (Fig. 5). Notably, the majority of the current evidence has been derived from *in vitro* experiments and animal models, whereas clinical studies in humans remain limited. Differences between research models and human rhythms limit clinical translation potential. Consequently, future research should aim to focus on enhancing physiological relevance by incorporating diurnal animal models, uterine organoids and multidimensional co-culture systems, combined with *in vivo* rhythm monitoring in human cohorts. Concurrently, systematic advancement is required in clinically validating rhythm assessment, lifestyle interventions, pharmacologic rhythm modulation and chronotherapy for uterine disorders. This will further accelerate the translation of mechanistic research into precise, actionable clinical intervention strategies.

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## Availability of data and materials

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## Authors' contributions

TM contributed towards conducting the investigation and writing the manuscript. JL and YF collected the literature and revised the manuscript. TX, QL and LX provided guidance and revised the manuscript. YX contributed markedly to the intellectual content of the review and participated in drafting and finalizing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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