

The Role of Circadian Rhythms in Polycystic Ovary Syndrome

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Abstract. Polycystic ovary syndrome (PCOS), as a most common metabolic disrupted disease, has several main symptoms, including ovarian insufficiency, hyperandrogenism, insulin resistance, etc., which may lead to female infertility. Many studies on the processes of PCOS have been done throughout the years, but unfortunately, the pathophysiology of PCOS is still not fully figured out. The circadian rhythm is the metronomic adjustment of the organisms to the external environment at all levels, from the molecular to the individual. It is revealed in multiple studies that there is a clear association between the progression of PCOS and the disturbance of circadian rhythms. Numerous studies have demonstrated that circadian rhythms can influence the development of PCOS by altering the Wnt/ β -catenin, GPCR/cAMP/PKA, PI3K/AKT, and MAPK signaling pathways of the hypothalamic-pituitary-ovarian/hypothalamic-pituitary-adrenal axis, which result in abnormal hormone expression, receptor resistance, and metabolic disorders. The circadian rhythm misalignment may contribute to the formation and development of PCOS through the expression of certain genes that control the canonical signaling pathway. It is foreseeable that more preventive and targeted treatment for PCOS is the hot zone of clinical research in the future. This article aimed to review the state regarding the link between circadian rhythm disorder and PCOS, focus on the pathophysiology of PCOS, explore the pathways of circadian rhythm in the process of PCOS, and seek to offer a clear direction and practical approach for the prevention and treatment of PCOS.

Keywords: polycystic ovary syndrome (PCOS); circadian rhythms; signaling pathways.

1. Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent endocrine condition that affects 8% to 15% of women of childbearing age [1]. The female body has not only an obvious circadian rhythm but also an obvious monthly rhythm, which is modulated by the central-peripheral circadian clock [2]. Under the influence of the hypothalamus-pituitary-ovarian (HPO) /hypothalamic-pituitary-adrenal (HPA) axis, it regulates the rhythm of the reproductive system and even the whole body in a neuroendocrine way, affecting diverse physiologic processes. It is generally recognized that the circadian rhythm may be greatly impacted by exogenous conditions such as light, sleep, food, and other etiological risks. PCOS is brought on by an irregular contemporary lifestyle, and the disruption of lifestyle can lead to the disruption of circadian rhythm in females' bodies. For instance, the strong correlation has been found that between working nights and PCOS, and this condition affects a much larger proportion of people than other groups [3]. These phenomena suggest that the circadian rhythm in PCOS patients is disrupted.

It is known that PCOS symptoms like insulin resistance will appear when the expression of circadian rhythms-related genes is changed or eliminated. The transcript loop operates transcript controllers, also known as clock genes, as the basis of circuit rhythms. The core programmer consists of the BMAL1 transcript factor, its CLOCK binding component, and the PER and CRY components. Equivalent activity ROR of the transcription factor and REV-ERB of the compressor, controlled by both the BMAL1-CLOCK interfaces, maintain the rhythms of BMAL1 expression. The ovary disrupting ovulation in PCOS, especially BMAL1, the expression of the clock gene altered or eliminated at different degrees [4]. In the pituitary gland and ovary, the physiological role of the HPO axis has been well defined, despite each tissue being made up of cell-autonomous circadian oscillators.

Insulin resistance can directly or indirectly induce the excess of androgen production. Hyperandrogenism can positively promote the further deterioration of insulin resistance. Additionally, dysfunction in the HPO axis is the main reason cause hyperandrogenism the disorder of the endocrine system will lead to the dysfunction of other systems in the body, especially in the reproductive system, cardiovascular system, and urinary system, causing excessive weight or obesity, type II diabetes. Some clinical observational studies have shown that in patients with PCOS, the incidence of sleep disorders (e.g. Obstructive sleep apnea) [5], and abnormal expression of circadian genes [3], is higher than in other groups. It suggests that the occurrence of endocrine disorders in PCOS may lead to circadian rhythm disorder from hormonal and neurological dysfunction.

This paper aims to introduce the symptoms and pathophysiology of PCOS, the mechanism of the circadian rhythm regulating PCOS, and focus on the role of the circadian rhythm regulating in the pathophysiology of PCOS from the organ and cell level to the molecular biology level. Ultimately, given that the regulation of circadian rhythms is the treatment target, it is likely that future research hotspots will be circadian-related therapy strategies that will benefit PCOS patients by reestablishing the homeostasis of the body.

2. The symptoms and pathophysiology of PCOS

The current diagnosis of PCOS is mainly based on two international diagnostic criteria: the diagnostic criteria of the National Institutes of Health proposed in 1990 and the Rotterdam diagnostic criteria proposed in 2003. It is generally agreed that, the endocrine disorder of PCOS is mainly characterized by these symptoms in clinical practice: hyperandrogenism, insulin resistance, and abnormal follicular development. The complex combination of genetics, lifestyle, environment, and other factors leads to endocrine disorders, women's original strong circadian rhythm is broken, and the regulation of the circadian rhythm is disrupted. Endocrine disorder increases the frequency and amplitude of the pituitary gland releasing not only luteinizing hormone (LH) but also another sex-related hormone: gonadotropin releasing hormone (GnRH) in the same time, which is caused by a dysfunction of the HPO/HPA axis. This is the main pathophysiology of PCOS. Excessive secretion of LH and insufficient secretion of FSH in PCOS patients cause follicular atresia and premature luteinizes, related to amenorrhea, absent menstruation, and excess androgen production, increasing pregnancy complications. It leads to chronic anovulation, which is the main cause of clinical infertility. Previous studies have shown that dysfunction of the HPO/HPA axis also contributes to PCOS [6].

Under normal circumstances, to regulate the secretion of pituitary gonadotropins like FSH and LH, GnRH secreted by the arcuate nucleus of the hypothalamus is transported to the pituitary gland, in a pulsed manner, through the pituitary portal system. The pulsed release of GnRH can regulate the ratio of LH to FSH. The concentration of FSH in blood rises while the blood level of LH falls when the frequency of GnRH secretion pulses decreases, resulting in a decline in the LH/FSH ratio. On the other hand, the LH/FSH ratio rises as the frequency of GnRH secretion pulses rises. GnRH secretion pulses have been seen to occur more frequently in PCOS. Furthermore, the pituitary gland exhibits heightened sensitivity to GnRH, resulting in an increase in GnRH receptors induced by GnRH. This, in turn, increases the frequency and amplitude of LH secretion by the pituitary gland. Therefore, patients with PCOS typically exhibit the increase of the LH/FSH ratio. It has been demonstrated that the concentration of LH in PCOS patients increased by 40% to 60% than the control group proven previously [7].

2.1. Hyperandrogenism

Androgens are steroid hormones that are present in women. All steroid hormones are synthesized by the enzyme cytochrome P450 cholesterol side chain lyase, which is encoded by CYP11A1. The main rate-limiting enzyme in the ovary and adrenal cortex's production of androgens is cytochrome P450 17-hydroxylase (CYP17A1). Increased CYP17 activity and increased androgen synthesis in

ovarian theca cells are two direct effects of high LH levels on the ovary. Further evidence that the ability of steroid hormones to inhibit the activity of GnRH pulse generators is impaired comes from the fact that PCOS patients require higher concentrations of estradiol and progesterone to prevent the release of LH pulses. This further suggests that PCOS patients have a disorder of the hypothalamic GnRH neuron and an imbalance in the HPO axis [8].

Androgens in women are mainly produced in the adrenal glands and ovaries. Where the ovaries mainly secrete testosterone (T) and androstenedione (A4), the adrenal glands mainly secrete dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). CYP17A1 is substantially expressed in PCOS and catalyzes the activity of 17-hydroxylase reactive and possesses the activity of 17,20-lyase. The mechanism of pregnenolone converted to DHEA is CYP17A1 mediates the conversion through 17-hydroxylation to synthesize 17-hydroxypregnenolone, which is based on the 17,20-lyase activity. DHEA changes through 3 β - Hydroxysteroid Dehydrogenase (3 β - HSD) into A4. Additionally, 3 β - HSD is another mediator of the possessors of progesterone synthesis. This progression is then converted to A4 through CYP17A1. The 17-hydroxysteroid dehydrogenase (17-HSD) is the catalytic enzyme, for the final step of androgen biochemical synthesis, mainly expressed in the ovary, whose activity is required, the biosynthesis of T.

2.2. Insulin Resistance

Insulin Resistance (IR) can directly regulate the secretion of androgen and further aggravate the occurrence of T2DM and cardiovascular disease in cooperation with IR. PCOS associated with obesity can also worsen IR and increase the prevalence of CVDs, such as atherosclerosis [9]. Hyperandrogenism and IR are associated with each other and jointly promote the occurrence and progression of PCOS.

Insulin promotes the formation of hyperandrogenism in the following aspects: At the adrenal level, insulin can interfere with the HPA axis by affecting the central nervous system, especially in PCOS, where the insulin system interferes with the LH secretion pattern. Moreover, high insulin levels can enhance the sensitivity of the adrenal gland to adrenocorticotrophic hormones, causing the adrenal gland to produce excessive DHEA and DHEAS. In addition, Abnormal phosphorylation of insulin receptors can increase the expression and activity of CYP17A1 mRNA in the adrenal gland, and insulin can upregulate steroid production of rapid regulatory factor protein (StAR), thereby promoting androgen production in the adrenal gland. At the ovarian level, insulin stimulates the development of atrial follicles through the action of granulosa cells of FSH, resulting to a rise in both the growth and quantity of antral follicles. Insulin also stimulates the synthesis of excessive androgens in both theca cells and interstitial cells in PCOS. Furthermore, in the anterior pituitary, high concentrations of insulin stimulate the insulin receptor, promoting the secretion of LH and increasing the concentration of T [10]. Insulin also has a synergistic effect with human chorionic gonadotropins, increasing the levels of CYP17 and p450_{scc}, leading to hyperandrogenism [11].

3. Circadian rhythms

Mammals display periodic changes in their internal environment and behavior to adapt to the repeated environmental conditions caused by the Earth's rotation. Numerous biological cells and creatures have these periodic changes, known as circadian rhythms, which share comparable characteristics and reaction patterns to variations in light. The endogenous circadian rhythms of mammals, by sensing 24-hour cues in light in the environment, reset the internal clock every day and keeps the oscillation around 24 hours. Almost all physiological functions of living organisms can be affected by the endogenous circadian rhythm. Physiological parameters like blood pressure and body temperature, biological processes like clock gene and protein expression, and behavioral changes like cognitive ability and sleep-wake cycle all exhibit regular circadian shifts [12].

3.1. The suprachiasmatic nuclei and the molecular clock

The timing of metabolism is managed by the circadian rhythm. The suprachiasmatic nuclei (SCN), which are found in the anterior hypothalamus, a region at the base of the brain, serve as the primary pacemaker of circadian rhythms in mammals.

Intrinsically photosensitive retinal ganglion cells (ipRGCs), a kind of photoreceptor cell seen in mammals, are involved in circadian phototransduction [13]. When exposed to the particular spectrum of light that activates ipRGCs, ipRGCs transmit neural impulses directly through the retinohypothalamic fibers to the SCN, which is regarded as the circadian master clock [14]. The SCN receives signals of the light and dark cycle, causing Ca^{2+} influx and activation of intracellular signaling cascades [14]. This eventually leads to gene expression in the corresponding cells to coordinate the biological rhythm of peripheral organs and tissues through the neuroendocrine system to synchronize it with the light and dark phase changes of the external environment.

The expression of two transcription factors, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), formed the positive limb of the core transcriptional-translational feedback loops (TTLs) that regulate the circadian rhythm at the molecular level [15]. The BMAL1/CLOCK heterodimer will induce the expression of period and cryptochrome genes [16]. When the PER1, PER2, PER3, CRY1, and CRY2 proteins in the cytoplasm reach a certain level, a heterodimer will be formed and transpose to the nucleus, restricting the activity of BMAL1/CLOCK, thereby reducing the concentration of PER/CRY heterodimer where the process is considered as a negative feedback regulation [15]. Other feedback loops exist to adjust the expression of genes relevant to the circadian rhythm in addition to the fundamental loops of CLOCK-BMAL1 and PER-CRY. For instance, CLOCK-BMAL1 also directly targets Rev-erba (Nr1d1), which suppresses the transcription of BMAL1 causing an antiphase oscillation of BMAL1 [17]. By regulating pertinent downstream elements, the molecular clock in mammals controls the functioning of organs and tissues. These molecular feedbacks have a periodicity of about 24 hours, which can link the expression of downstream genes to clock genes, driving endogenous circadian rhythms in vivo to operate normally.

3.2. Peripheral clocks

With the SCN being on the master clock, those tissues that generate self-sustaining circadian rhythms are peripheral clocks [12]. Circadian oscillations can be observed in peripheral tissues, supporting the hypothesis that circadian oscillators in peripheral tissues control local physiology. Many endocrine factors are known to display diurnal rhythms. For example, the secretion of TSH follows a well-defined daily pattern, and the hypothalamus-pituitary-thyroid (HPT) axis is regulated by the central circadian pacemaker in the SCN [18]. Like this, circadian oscillators in the hypothalamic-pituitary-gonadal (HPG) axis, which is likewise governed by the SCN, are crucial in controlling female reproductive rhythms [19].

4. The Mechanism of circadian rhythm regulating PCOS

The regulation of corticotropin-releasing hormone (CRH) secretion through melatonin by the SCN in the hypothalamus is a significant finding. It highlights the complex interplay between the circadian rhythm and hyperandrogenism, and sheds light on the potential therapeutic applications of melatonin in PCOS [3]. Another important related discovery is about the regulation of ACTH secretion and the release of androgen from the adrenal gland by the SCN. It underscores the role of the circadian rhythm in regulating the endocrine system and the production of hormones, and may have implications for the treatment of PCOS [3].

In gene level, the finding that specific knockout of the BMAL1 can disrupt the sensitivity rhythm to LH, leading to ovulation disorders in the ovary of female mice [4], is a significant contribution to our understanding of the circadian clock regulating reproductive system at different level. The circadian rhythm gene regulating the pathways produced by PCOS-related hormones such as

androgens, FSH, and LH is a promising area of the research between circadian clock and PCOS. This is based on the results of the circadian rhythm gene regulating the pathways produced by PCOS-related hormones such as androgen, FSH, and LH. Therefore, this section highlights how circadian rhythm regulates the progress of PCOS by following signaling pathway.

4.1. The Wnt/ β -catenin signaling pathway

As a conserved evolutionary mechanism involved in procedural progression growth, death, proliferation, and migration of the biochemical phenomena in cells. The Wnt/ β -catenin signaling pathway has been studied in recent years. The cycle of circadian clock is controlled by the complex CLOCK-BMAL1, which stimulates this pathway by both increasing the transcription and decreasing the degrading progression of β -catenin. BMAL1 also inhibits the activity of GSK-3 β in the Wnt/ β -catenin signaling pathway [20]. Another circadian gene: PER2, the depletion of it stimulates β -catenin expression [21].

The promotion of β -catenin expression and nuclear accumulation, as well as its mRNA, occurs because of CRY1 reduction [22]. The identification of CRY1 as a key regulator of lipid metabolism and its potential impact on the Wnt/ β -catenin pathway sheds new light on the complex pathogenesis of obesity in individuals with PCOS. The interplay between these two pathways represent a potential therapeutic target for PCOS-related obesity. Moreover, the Wnt/ β -catenin signaling pathway involving in PCOS, emphasizes its multifaceted role in the regulating the biochemical synthesis and secretion androgen and female reproductive function. The discovery of Wnt4's paracrine impact on female sexual development and ovarian function further highlights the intricate interplay between different signaling pathways in the regulation of reproductive physiology. These findings have significant implications for the development of targeted therapies for PCOS and related disorders. Overall, these findings represent a significant step forward in the pathophysiology of PCOS, especially with it associated the complex metabolic and reproductive dysfunctions [23]. Likely, boosting the expression of the CYP Family, especially CYP11A1 and CYP17, 17-HSD1, and StAR, which control the biochemical synthesis of androgen, is how the Wnt4 mutation increases androgen production [24]. In granulosa cells (GCs), cell apoptosis coexists with high Wnt4 levels [25]. Circadian rhythm genes could induce androgen secretion in the HPO/HPA axis through these molecular mechanisms, which cause hyperandrogenism in PCOS patients.

4.2. The GPCR/cAMP/PKA signaling pathway

In the cell membrane, the G protein-coupled receptor (GPCR) expresses the most frequently has already been proven. In the SCN, the cAMP-responsive element, located in the promoter of the GPCR/cAMP/PKA pathway, can induce circadian transcription. GPCR can downregulate to inhibit BMAL1, which typically peaks during the night in circadian rhythm [26]. CRY1 was observed in the accumulation of cAMP in the cytoplasm when the GPCR activated, which is an activator of adenylyl cyclase, directly. CRY1 also modulates GPCR activity in the same role. During the transition from night to day, CRY1 expression was elevated, and it reduced the expression of fasting gluconeogenic genes by inhibiting the glucagon-mediated increase in PKA-mediated phosphorylation of crab and intracellular cAMP concentrations. In mice with IR, the hepatic overexpression of CRY1 causes the reduction of glucose levels in the blood, which shows in insulin sensitivity improved [27]. The GPCR/cAMP/PKA pathway can be a signaling target for improving IR in PCOS by adjusting the expression of CRY1.

Most studies are aware of the cAMP/PKA pathway as the main signaling pathway controlling steroidogenesis and as a master mechanism inducing several downstream signals. There are two primary categories of G protein-coupled receptors (GPCRs) that are involved in steroidogenesis. One of these categories includes the specific receptor for an adrenocorticotrophic hormone, known as the melanocortin 2 receptor (MC2R) [28]. The demonstrated potential of ACTH to trigger steroidogenesis in the adrenal gland is noteworthy. This process involves the production of cAMP, which occurs when ACTH enhances MC2R binding. Subsequently, protein kinase A (PKA) is

activated, further promoting the activation of androgen synthesis. It is worth noting that additional receptors, which are sensitive to LH and FSH, respectively, are also involved in this process. Besides the camp/PKA pathway, via the cAMP/PKC pathway, the FSH receptor and LH receptor also facilitate steroid production in the gonads, which causes the dysfunction of the HPO/HPA axis.

4.3. The PI3K/AKT signaling pathway

One important non-gonadotropic signaling system is the PI3K/AKT signaling pathway. According to a previous study, PER1 overexpression drastically reduced the PI3K/AKT signaling pathway, proliferation, glucose absorption, glycolysis, and cell growth [29]. Another study has demonstrated that the hypothalamus and pituitary is controlled by the expression of the circadian rhythm, through the PI3K/AKT signaling pathway, which controls the release of sex-related hormones, especially estrogen secretion [30]. Decreased estrogen secretion can also exacerbate the progression of PCOS, as an important cause of abnormal ovulation. PTEN plays a crucial role as a molecular controller for PI3K signal transduction. It has previously been found that the activation of mTOR signal transduction and BMAL1, as the core protein in circadian clock are caused by the oxidant driven loss of PTEN function [31]. The use of small interfering RNA targeting PTEN and PTEN depletion from the epidermis in vivo further confirmed the PTEN-induced upregulation of BMAL1. The accumulation of BMAL2 caused by the deletion of PER2 is also saved [32].

Overactivation of the PI3K/AKT signaling pathway strongly associated with female reproductive disorders, including PCOS, has been verified. Additionally, excessive androgen production and ovarian dysfunction may result from overactive PI3K/AKT signaling in theca cells. CYP17A1, as the essential enzyme for the control of the biochemical synthesis of androgen mentioned previously, is significantly accelerate the progress of hyperandrogenism. Its stimulation is facilitated by LH, which activates the AC in this signaling pathway of the PCOS ovary by inhibiting with LH receptor. Moreover, the testosterone production in an insulin-induced way is mediated by the insulin receptor substrate co-activating both the PI3K signaling and the cAMP signaling, which also engages CYP17A1 and 17-hydroxylase, leading to hyperandrogenism. Furthermore, hyper-concentrated steroidogenic acute regulatory protein and CYP11A1 are positively associated with the activation of PI3K/AKT signaling [33].

4.4. The MAPK signaling pathway

The MAPK signaling pathway has been implicated in various diseases, making it a promising target for therapeutic interventions. The three possible routes of the MAPK pathway, namely MEK1/2/ERK1/2, p38MAPKs, and JNK/SAPKs, have been extensively studied for their role in regulating the endocrine system and circadian rhythm. However, the precise role of JNK/SAPKs signaling in the MAPK pathway remains to be fully elucidated. The involvement of CREB as a significant endpoint in the circadian rhythm, controlling the expression of PER in the MAPK signaling pathway, highlights the importance of this pathway in regulating the body's internal clock. Additionally, the phosphorylation of CLOCK, BMAL1, and the family of CRY by ERK and MAPK further emphasizes the intricate relationship between the MAPK pathway and the circadian rhythm system. The finding that the decrease in BMAL1, through the p38 MAPK phosphorylation, exacerbates pathological circadian disruption underscores the potential of targeting the MAPK pathway for the treatment of circadian rhythm disorders [34]. Moreover, the MAPK signaling pathway represents a promising avenue in the circadian regulating therapeutic strategies for PCOS.

In hormone disorders, as the MAPK signaling pathway is a pivotal part of the metabolism of androgen and estrogen, ERK1/2 is more closely associated with the progression of PCOS than the others. ERK1/2 is highly involved in the metabolism of androgens and estrogens, which is more closely associated with the pathophysiology of PCOS. The mitogen-activated protein kinase kinase 4 (MAP3K4) and phosphorylated-ERK1/2 are downregulated in PCOS-affected GCs, which will lead to GCs dysfunction, suggesting that it is highly associated with androgen overproduction. The inhibition of MAPK signaling in GCs has been detected that promotes the expression of CYP17.

This signaling pathway provides valuable insights into the regulation of androgen synthesis through the MAPK signaling pathway. The downregulation of StAR and CYP17A1 expression by this pathway highlights its crucial role in maintaining normal reproductive system function. The identification of the cAMP and MEK/ERK interaction as a key regulator of androgen synthesis further emphasizes the complexity and diversity of this process. These findings have significant implications for the development of novel therapeutic approaches for diseases related to androgen synthesis [35].

5. Treatment

Clinical guidelines for a variety of illnesses point out that dietary and lifestyle changes are the essential methods for the precaution and remedy of metabolic diseases, as well as for females with PCOS, whereas drug treatment cannot be replaced. At present, there are a great number of methods that alleviate basic symptoms of PCOS by regulating circadian rhythm disorders, such as weight control strategies, improving sleep quality, taking metformin and melatonin, etc.

Epidemiological data indicate that 38%–88% of PCOS-afflicted women are overweight or obese [36]. According to research, weight growth in these patients can increase the activity of the HPO and HPA axis, which contributes to more extreme hyperandrogenism. This effect is caused by the weight gain's impact on IR. Therefore, it is of great clinical significance that maintaining a healthy weight can be helpful to attenuate hyperandrogenism and relieve metabolic symptoms of PCOS patients. From the correlation between IR and PCOS, insulin sensitizers, such as metformin, are commonly used to treat PCOS to their effectiveness and safety, especially in overweight or obese patients to relieve ovulation and metabolic dysfunction and reduce androgen levels [22].

Melatonin is a circadian rhythm-related hormone that is produced and secreted by the pineal gland and is ubiquitous throughout the body, including the female reproductive cells [37]. Studies have shown that the lipid peroxides in PCOS patients' serum and follicular fluid are increased, which will lead to the degeneration of oocyte organelles, the decrease of mitochondrial function, DNA damage, and the apoptosis of oocytes [37]. As a free radical scavenger, melatonin can protect the body from oxidative stress and reduce mitochondrial dysfunction and damage, thus it improves hyperandrogenism-related symptoms, oocyte maturation, and folliculogenesis, in the clinical therapy of PCOS patients, therefore, can improve the success rate of chemical pregnancy [38].

In addition to the therapies related to circadian rhythm regulation described above, there are other symptomatic therapies to treat PCOS. Combined oral contraceptives (COCs) are the main treatment for patients who do not plan to give birth temporarily, to regulate menstruation. Moreover, spironolactone can act against PCOS through direct effects on ovarian and adrenal androgen synthesis for its multiple antiandrogenic effects [22].

Some PCOS treatments are inadequate since the pathogenesis of the disease has not been thoroughly investigated, and the phenotype of the condition is variable and highly heterogeneous. Hence, fundamental and clinical research is still desperately needed to develop preventative and targeted treatments.

6. Conclusion

The current study suggests that circadian rhythm is crucial to the emergence and progression of PCOS. The association between PCOS and circadian clock is introduced along with the description of the symptoms of PCOS, such as hyperandrogenism, insulin resistance, ovarian insufficiency, as well as the disruption of the HPO/HPA axis. The circadian clock can alter the LH level in the body before ovulation, insulin sensitivity, and androgen level via controlling the expression of particular clock genes to modulate the activities of the HPA/HPO axis, which eventually contributes to the pathophysiology of PCOS. The treatment by regulating circadian rhythm misalignment has a special status in the adjuvant treatment of PCOS, for example, lifestyle intervention, improving sleep quality, taking metformin and melatonin, etc. Due to the complexity and heterogeneity of PCOS, targeted and

more effective treatments have not been discovered. Therefore, to have greater and wider clinical significance and prospects, it is of instant need to carry out clinical trials for more preventative and targeted treatment of PCOS.

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