Review Article

LITERATUR REVIEW : MELATONIN AND GYNECOLOGIC DISORDERS~~: A REVIEW OF STUDIES PUBLISHED BETWEEN 2011 AND 2022~~

Comment [M1]: add this word to the title

ABSTRACT

The present review aimed to determine the clinical relevance of melatonin supplementation in the setting of gynecologic disorders. We searched the following databases for articles published between 2011 and 2022 that investigated the pathophysiology of the relationship between melatonin and gynecological pathologies in humans: PubMed, MEDLINE, and Embase databases.The 10 included studies primarily focused on the effects of melatonin on patients with polycystic ovarian syndrome (PCOS), as a treatment to reduce pain and improve sleep quality in gynecological pathologies, and as a treatment option for endometriosis. The findings of the present literature review suggested that melatonin can be beneficial in the treatment of PCOS, dysmenorrhea, and endometriosis. The effects of melatonin on MR1A and MR1B receptors, which are present in the epithelial cells of the endometrial gland, in addition to its known analgesic, anti-inflammatory, and antioxidant properties were also addressed. We concluded that there is a vast field of research on melatonin supplementation and its effects on gynecologic disorders. We also verified the prospects of its use as a therapeutic agent in the auxiliary treatment of gynecological diseases.

Comment [M2]: Write the aim/formulation of the literature review clearly and firmly

Keywords: melatonin, gynecologic disorders, treatment

Comment [M3]: sort alphabetically

INTRODUCTION

Comment [M4]: Sequence the introduction starting from the focus of the problem to solving the problem, namely:
1. The main problem is gynecological disorders. explain this first starting from the definition, signs, symptoms, causes, impacts, treatment.
2. Treatment of gynecological problems, explain in general, one of them is melatonin treatment
3. Explain melatonin in detail and how it relates to solving gynecological problems based on the literature you found

The hormone melatonin, responsible for the transformation of night and daylight intensity into chemical signals, is primarily produced in the pituitary gland by pineal cells; however, as it helps regulate the sleep cycle and circadian rhythm, melatonin is also involved in many functions and structures throughout the human body (1). It was demonstrated that melatonin plays a variety of physiological roles, including having antioxidant, anti-inflammatory, and bone metabolism (melatonin has an important relationship with osteoblast expression, which is responsible for the formation of bone tissue) properties, which are all important anti-aging factors (2) There is also a link between melatonin and reproduction, as melatonin influences the synthesis and secretion of reproductive hormones by acting on the hypothalamic-pituitary system, in which the pituitary hormone may reduce secretion of estradiol (melatonin reduces luteinizing hormone and follicle-stimulating hormone, hormones that are responsible for the elevation of estradiol levels), indicating that there is a possibility that melatonin inhibits ovarian function (3). Females experience a variety of physiological phases that change throughout life, such as reproduction, puberty, ovulation, luteinization, fertilization, implantation, pregnancy, parturition, and menopause, all of which involve the regulation of the hypothalamic-pituitary-gonadal system. This system is regulated by melatonin, which, therefore plays a role in the process of puberty and reproductive function (4).

Due to its lipophilic properties, melatonin is primarily released into the cerebrospinal fluid, from which it enters the bloodstream, and from there, various organs and tissues. The effects of melatonin are largely related to the action of the MT1 and MT2 membrane receptors (5), although hypothalamic neurons also express melatonin receptors that control the release of pituitary gonadotropins (4). Melatonin also plays a role in regulating many vital physiological processes, such as puberty, genital organ formation, the menstrual cycle, and the aging of the reproductive system. Additionally, abnormal melatonin levels have been found to be associated with malfunctions of the hypothalamus-hypophysis-ovary system (5).

As a result of its antioxidant properties and activity as a hormone modulator, melatonin supplementation may play a therapeutic and preventive role in women's health, gynecological pathologies in particular (6). These conditions include amenorrhea, endometriosis, polycystic ovary syndrome (PCOS), fibroids, infertility, ovarian cancer, miscarriage, ectopic pregnancy, and premature birth, among others, all of

which have a negative impact on quality of life, daily activities, and general well-being, resulting in increased anxiety and depression (7). Additionally, while some gynecological diseases are curable, unfortunately, others are chronic and/or fatal. Treatments for these conditions (medication and/or surgery) are effective, although not completely. Furthermore, some of these treatments are associated with adverse effects (8).

Melatonin plays a significant role in the female body; however, its use in the treatment of gynecological disorders requires further investigation (5). Although melatonin supplementation is believed to be safe, there is not, as of yet, a consensus regarding the optimal dosage or treatment period (6). Previous study investigated the effects of melatonin supplementation in humans (9) in patients with chronic pelvic pain associated with endometriosis. The results indicated that melatonin supplementation improved sleep quality, reduced the risk of analgesic use by 80%, and reduced brain-derived neutrophic factor (BDNF) levels, independent of its effect on pain.Mousavi et al. (2022) observed positive outcomes on hirsutism, serum tumor necrosis factor alpha (TNF-α), and total antioxidant capacity levels in women with PCOS from the co-supplementation of magnesium with melatonin for 8 weeks (11). Melatonin supplementation has also been shown to exert positive effects on psychosomatic symptoms in postmenopausal women (12).

Given the availability of studies regarding melatonin supplementation in women, the present study aimed to review the relevant literature for studies describing the treatment of gynecologic disorders with melatonin, and the clinical relevance of melatonin supplementation in the field of gynecology.

METHODS

Search strategy

We searched the following databases for articles published in English between 2011 and 2021 that involved studies investigating the pathophysiology of the relationship between melatonin and gynecologic disorders in humans: PubMed; MEDLINE; and Embase. The following keywords were used to perform our search: (‘melatonin’ AND ‘’ OR ‘chronic pelvic pain’ OR ‘candidiasis’ OR ‘urinary infection’ OR ‘vulvovaginitis’ OR ‘bacterial vaginosis’ OR ‘endometriosis’ OR ‘polycystic ovary’ OR ‘dysmenorrhea’). Each eligible article was reviewed by two researchers, and the following data were extracted: name of author(s); year of publication; purpose; sample; methods; and selection results.

Inclusion and exclusion criteria

The inclusion criteria for the present review were studies that evaluated the relationship between melatonin and gynecologic disorders, including randomized trials, observational, and experimental studies in humans.

Studies that did not meet the inclusion criteria, as well as those with no full text, reviews, case reports, conference abstracts, expert opinions, animal experiments, or incomplete clinical trials were excluded from the present review. Articles that were duplicated or unavailable in English were also excluded.

Data extraction

Each eligible article was reviewed by two researchers and the following data were extracted: (a) author name and year of publication, (b) purpose, (c) sample, (d) methods, and selected results.

Comment [M5]: explain how to synthesize all articles according to the intended criteria

RESULTS

Literature search

The initial search produced 2,957 articles; however, after screening the articles by title and abstract, 2,914 were excluded, leaving 33 for a full-text assessment. Studies that were inconsistent with the aforementioned inclusion criteria, or those with missing information, were then excluded. In total,10 articles were included in the present review. A summary of the data we extracted from the eligible studies is seen in Table 1, and as indicated by that data, the majority of the studies were clinical trials.

Table 1. Characteristics of the studies

Authors/ Year of publication	Purpose	Sample	Methods and selected results
Azade Shabani et al 2019 (13)	Evaluate the effect of melatonin supplementation on mental health, metabolic and genetic parameters in women suffering from polycystic ovary syndrome (PCOS)	58 subjects aged 18-40 years old	Randomized double blinded, placebo-controlled clinical trial. Subjects were randomly allocated to take either 10 mg melatonin (2 melatonin capsules, 5 mg each) ($n = 29$) or placebo ($n = 29$) once a day 1 h before bedtime for 12 weeks. Melatonin supplementation had beneficial effects on mental health parameters, insulin levels, HOMA-IR, QUICKI, total- and LDL-cholesterol levels, and gene expression of PPAR-γ and LDLR among women with PCOS.
André Schwertner et al 2013 (9)	This trial investigates the effects of melatonin compared with a placebo on Endometriosis associated chronic pelvic pain (EACPP), brain-derived neurotrophic factor (BDNF) level, and sleep quality.	40 females aged 18-45 years old	Randomized, placebo or melatonin 10mg treatment for 8 weeks. The treatment reduced daily pain scores by 39.80% (95% confidence interval [CI] 12.88–43.01%) and dysmenorrhea by 38.01% (95% CI 15.96–49.15%). Melatonin improved sleep quality, reduced the risk of using an analgesic by 80%, and reduced BDNF levels independently of its effect on pain.
Alessandro Pacchiarotti et al 2015 (14)	To test the synergistic effect of myo-inositol and melatonin in IVF protocols with PCOS (polycystic ovarian syndrome) patients.	526 women with PCOS	Randomized, controlled, double-blind trial. The sample were divided into three groups: Controls (only folic acid: 400 mcg), Group A (Inofolic plus, a daily dose of myo-inositol: 4000 mg, folic acid: 400 mcg, and melatonin: 3 mg), and Group B (Inofolic, a daily dose of myo-inositol: 4000 mg, and folic acid: 400 mcg). Myo-inositol and melatonin have shown to enhance, synergistically, oocyte and embryo quality.
Mi Kyoung Kim et al 2013 (15)	The present study evaluated the effects of melatonin	At phase I, PCOS patients ($n = 111$) were randomized	Melatonin concentrations in the culture media of granulosa cells (GC) or

	supplementation on IVM of human immature oocytes and the clinical outcomes of PCOS patients undergoing a IVM IVF-embryo transfer programme.	to the IVM medium supplemented with melatonin (MEL+) group or no melatonin (control) group. At phase II, PCOS patients (n = 132) were subjected to IVM IVF-embryo transfer using protocol 2, and aspirated oocytes matured *in vitro* in IVM medium containing melatonin (MEL+)	cumulus-oocyte-complexes (COC) were measured and the clinical outcomes after using IVM media with or without melatonin were analyzed. In the culture media of GC or COC, melatonin concentrations gradually increased. When human chorionic gonadotrophin priming protocols were used, implantation rates in the melatonin-supplemented group were higher than those of the non-supplemented control group.
Farahnaz Keshavarzi et al 2018 (16)	To discover whether and if so to what extent melatonin and meloxicam can improve subjective and objective sleep and reduce pain among women with primary dysmenorrhea (PD)	14 women with primary dysmenorrhea	Double-blind cross-over clinical trial lasting for three menstrual cycles. It used a visual analogue scale to rate pain and Pittsburgh Sleep Quality Index (PSQI). The participants were randomly assigned to one of two conditions, either melatonin during the second, and meloxicam during the third menstruation, or meloxicam during the second, and melatonin during the third menstruation. As a result objective sleep efficiency increased and objective sleep latency shortened. The efficacy of melatonin was superior to that of meloxicam. The present pattern of results suggested that both melatonin and meloxicam are suitable to treat pain and PD-related sleep complaints among women with primary dysmenorrhea.
Lin, Xiang et al 2020 (17)	Aim to illuminate the etiopathogenesis of endometriosis-associated infertility that involve excessive oxidative stress (OS) induced pathological changes of ovary cumulus granulosa cell (GCs).	258 infertile patients	Senescence-associated ß-galactosidase (SA ß-gal) activity in GCs from endometriosis patients, soluble isoform of advanced glycation end products receptor (sRAGE) expression in follicular fluid from endometriosis patients and differentially expressed

			senescence-associated secretory phenotype factors (IL-1ß, MMP-9, KGF and FGF basic protein) are all useful indexes to evaluate oocyte retrieval number and mature oocyte number. Moreover, melatonin administration rescued OS-enhanced ER stress, cellular senescence, and MMP and ATP abnormities of endometriosis GCs in vitro and in vivo. In conclusion, our results indicated excessive reactive oxygen species induces senescence of endometriosis GCs via arouse ER stress, which finally contributes to endometriosis-associated infertility, and melatonin may represent a novel adjuvant therapy strategy for endometriosis-associated infertility.
Alizadeh, Mohammad et al 2021 (18)	This study was designed to investigate the effects of melatonin and/or magnesium supplementation on metabolic profile and levels of sex hormones in PCOS women.	84 patients, aged 18 - 40 years old.	In an 8-week randomized double-blind placebo-controlled trial, 84 subjects with PCOS aged 18-40 years were randomly assigned based on the random block procedure to take magnesium, melatonin, magnesium plus melatonin, and placebo. Moreover, combined melatonin and magnesium supplementation was more effective in improving serum levels of cholesterol, LDL-C, HDL-C and insulin, and HOMA-IR
Jamilian, Mehri et al 2019 (19)	The aim of the current study was to evaluate the effect of melatonin administration on clinical, hormonal, inflammatory, and genetic parameters in women with polycystic	56 patients with PCOS, aged 18-40 years old.	The present randomized, double-blinded, placebo-controlled clinical trial was conducted among 56 patients with PCOS, aged 18-40 years old. Subjects were randomly allocated to take either 5 mg melatonin

	ovarian syndrome (PCOS).		supplements (n = 28) or placebo (n = 28) twice a day for 12 weeks. Overall, melatonin administration for 12 weeks to women with PCOS significantly reduced hirsutism, total testosterone, hs-CRP, and MDA, while increasing TAC and GSH levels. In addition, melatonin administration reduced gene expression of IL-1 and TNF-α.
Mosher A.A. et al 2019 (20)	The objectives of the current study were to investigate melatonin receptor expression in the eutopic endometrium of women (control group) and the eutopic and ectopic endometrium of women with endometriosis (cases) as well as document the effect of melatonin on estrogen-induced endometrial epithelial cell proliferation *in vitro*.	Women ($n = 46$)	Collection of endometrial and endometriotic tissue samples, gynecologic history and demographic information. Quantification of estradiol (1.0 nM) and melatonin (0.1 nM–1.0 μM) ± estradiol-induced endometrial epithelial cell proliferation in cultures of endometrial epithelial cells (CRL-1671) following 24 and 48 hours of culture. MR1A and MR1B were localized by immunohistochemistry in glandular epithelial cells of endometrial biopsies from women with and without endometriosis. Both receptors were expressed in eutopic and ectopic endometrial tissue. mRNA expression of MR1A and MR1B was significantly greater in peritoneal lesions than in either endometriomas or eutopic endometrium. However, protein expression of MR1A was decreased in peritoneal lesions compared to control eutopic endometrium, whereas MR1B expression did not differ between the groups. Melatonin (0.1 nM–1.0 μM) treatment inhibited estradiol (1.0 nM)-induced

			endometrial epithelial cell proliferation at 48 hours but not 24 hours of culture. Our data suggest that melatonin may be useful as an adjunct to current endometriosis treatments
Hongwanyu, Li et al. 2022 (21)	The study aimed to find whether the level of melatonin, a rhythm regulating hormone changed in the ovarian microenvironment in this disease.	The melatonin concentrations in follicular fluid (FF) were measured in 35 PCOS and 36 non-PCOS women undergoing in vitro fertilization (IVF) treatment.	The FF melatonin concentration was significantly lower in PCOS women than non-PCOS women ($p = 0.045$) and it was found positively correlated with serum basal FSH level ($r = 0.308$, $p = 0.013$). In IVF procedures, there was no significant difference in the fertilization rate of oocytes between the two groups, but the high-quality embryogenesis rate on the third day of the PCOS group was significantly lower than that of the control group ($p = 0.042$), which showed a weak positive correlation with the FF melatonin concentration ($rs = 0.240$, $p = 0.044$). Furthermore, there was no significant difference in overall pregnancy outcome. The PSQI questionnaire showed that sleep disorders were more likely to exist in the PCOS group, though there was no significant difference.

Melatonin in patients with PCOS

Of the 10 articles included in the present review (TABLE 1), 5 were related to melatonin supplementation in patients with PCOS (14,15,18,19,21).

Pacchiarotti et al. (2015) (14) aimed to elucidate the synergistic effects of myo-inositol and melatonin in enhancing oocyte quality in women with PCOS undergoing *in vitro* fertilization (IVF) by correlating oocyte quality with positive IVF outcomes. They found that the combination of myo-inositol and melatonin synergistically improved the ovarian response to gonadotropin stimulation, and that supplementation with oral melatonin improved oocyte quality.

Kim et al. (2013) (15) evaluated melatonin treatment in patients with PCOS who were undergoing IVF, through the analysis of the clinical outcomes of patients who did and did not receive melatonin supplementation. Clinical outcomes were the measured concentrations of melatonin in the culture medium of granulosa cells (GCs) or cumulus-oocyte complexes (COCs). Since follicular melatonin, secreted from luteinizing GCs and supplied from circulation, plays a role in oocyte maturation, melatonin supplementation may improve clinical outcomes, as evidenced by increased melatonin concentrations.

Alizadeh et al. (2021) (18) determined that reduced concentrations of the follicular hormone melatonin may be responsible for reduced oocyte quality in women with PCOS. Additionally, the mineral magnesium has been shown to be important in PCOS-associated dyslipidemias. The results of this study showed that the combined use of melatonin and magnesium improved participants' body mass index (BMI) and WC, in addition to improving sleep quality and decreasing dyslipidemia. Melatonin use was also found to lower testosterone levels and alleviate menstrual irregularities and biochemical hyperandrogenism.

Jamilian et al. (2019) (19) aimed to evaluate the effects of clinical, hormonal, inflammatory, and genetic parameters in women with PCOS who were candidates for IVF, and found that the use of melatonin for 12 weeks decreased hirsutism and total testosterone levels. Additionally, as melatonin influenced steroid production, it contributed to ovarian modulation, reducing insulin resistance and dyslipidemia. Treatment with melatonin lowered the levels of TAC and GHS, and reduces the gene expression of interleukin (IL)-1 and TNF-α. Additionally, melatonin mitigated the effects of oxidative stress by directly scavenging free radicals from inflamed tissues.

Azade et al. (2019) (13) evaluated the effects of melatonin supplementation on mental health, metabolic, and genetic parameters in women with PCOS, and found that melatonin supplementation significantly decreased the Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory, and Beck Anxiety Inventory indices compared with the placebo. Additionally, compared with the placebo, melatonin supplementation significantly reduced serum insulin, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score, and serum total and low-density lipoprotein (LDL)-cholesterol levels, and significantly increased the quantitative insulin sensitivity check index (QUICKI) score. Overall, the supplementation of melatonin for 12 weeks had beneficial effects on mental health parameters, the aforementioned indices, and gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and low-density lipoprotein receptor (LDLR) among women with PCOS.

Li et al. (2022) (21) aimed to determine whether or not melatonin levels changed the ovarian microenvironment in 35 women with PCOS. They observed that the concentration of melatonin in the follicular fluid was significantly lower in women with PCOS than those without PCOS, and occurred in conjunction with mild sleep disturbance.

Melatonin for the improvement of pain and sleep quality in gynecological pathologies

Two of the included studies evaluated the use of melatonin to treat pain and improve sleep quality in patients with gynecological pathologies. Keshavarzi et al. (2018) (16) compared the use of melatonin and meloxicam to improve sleep quality and reduce pain in patients with primary dysmenorrhea, using a visual analog scale to measure pain and the PSQI to assess sleep quality. The effects of melatonin and meloxicam use were compared, and the results indicated that while melatonin was superior at reducing pain, total sleep quality and efficiency showed better outcomes in both treatment groups, although melatonin use was superior in increasing sleep duration.

Schwertner et al. (2013) (9) aimed to determine the efficacy of melatonin as an analgesic, antioxidant, and anti-inflammatory agent in the treatment of endometriosis-associated chronic pelvic pain (EACP), and observed that melatonin both improved sleep quality and affected pain pathways. Melatonin supplementation was found to have an effect on dysmenorrhea, dysuria, dyspareunia, and dyschezia, while reducing daily pain and the use of analgesics and improving sleep quality.

The use of melatonin in the treatment of endometriosis

Two of the included studies investigated the effects of melatonin on endometrial cell proliferation in patients with endometriosis. Mosher et al. (2019) (20), who carried out an experiment involving melatonin supplementation in women with endometriosis, found that melatonin is an effective and safe treatment for

endometriosis, and concluded that it had low levels of BDNFs. Additionally, a relevant concentration of melatonin inhibited the estradiol-induced proliferation of cultured endometrial epithelial cells. The melatonin receptors MR1A and MR1B are present in the epithelial cells of the endometrial gland during the menstrual cycle, and it is possible, therefore, that melatonin modulates endometrial epithelial cell function and may subsequently have beneficial effects on the management of endometriosis, although the effects of the melatonin supplementation depend on the type of endometrial lesion.

Given that endometriosis is a significant cause of female infertility and seriously impacts patients' physical and psychological health, Xiang et al. (2020) (17) aimed to elucidate the etiopathogenesis of endometriosis-associated infertility involving excess oxidative stress (OS)-induced pathological changes of ovarian cumulus granulosa cells (GCs). Senescence-associated β-galactosidase (SA β-gal) activity in the GCs, soluble receptor of advanced glycation end product (sRAGE) expression in follicular fluid, and differentially expressed senescence-associated secretory phenotype factors (IL-1β, matrix metalloproteinase [MMP]-9, keratinocyte growth factor [KGF], and fibroblast growth factor [FGF] basic protein) are all useful indices with which to evaluate potential oocyte retrieval and mature oocyte numbers in patients with endometriosis. Ribonucleic acid (RNA) sequencing and bioinformatics analyses indicated a senescent phenotype of and aggravated endoplasmic reticulum (ER) stress in the GCs of patients with endometriosis. Targeting ER stress significantly alleviated OS-induced GC senescence and reduced the mitochondrial membrane potential (MMP) and adenosine triphosphate (ATP) reduction in the GCs of patients with endometriosis. Moreover, melatonin supplementation rescued the OS-enhanced ER stress, cellular senescence, and MMP and ATP abnormalities in both *in vitro* and *in vivo* GCs from patients with endometriosis. These results, therefore, indicate that an excess of reactive oxygen species induces GC senescence in patients with endometriosis via the arousal of ER stress, which, in turn, contributes to endometriosis-associated infertility; however, melatonin may represent a novel adjuvant therapeutic strategy for the treatment of endometriosis-associated infertility.

Comment [M6]: include it in the discussion section

DISCUSSION

Comment [M7]: Break it down into several discussion topics

The present review, which evaluated relevant English literature on the relationship between melatonin supplementation and gynecologic disorders, had the primary findings the beneficial melatonin treatment of PCOS, dysmenorrhea, and endometriosis; melatonin effects including analgesic, anti-inflammatory, antioxidant properties; and regulation of biological circadian rhythms.

Circadian rhythms are regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, via a complex network of self-regulating genes and proteins, and result in regular cycles of activity and inactivity that are repeated every 24 h (22). Light is the primary source of circadian rhythm synchronization with the external environment, accompanied by other environmental factors, such as food, physical activity, and body temperature. The NSQ is also responsible for the various bodily systems that function properly in regular circadian rhythms. When the body's internal circadian rhythm and the external environment become unsynchronized, symptoms of insomnia or excessive daytime sleepiness may occur (23).

The circadian timekeeping system, controlled by the pineal gland at night, and primarily during sleep, plays an important role in circadian rhythms, and is actively engaged in the maintenance of physiological homeostasis, not only in adults, but also during developmental stages (24). The peaks and troughs of rhythms vary per individual, occurring at various times during sleep, based on different physiological variables. In humans, for instance, under normal light-dark conditions, cortisol levels, body temperature, blood pressure, and heart rate drop until 8 am, or through the duration of the sleeping period (25). Melatonin, therefore, is controlled by sleep duration and is irreplaceable in humans (26).

Sleep disorders are associated with poor sleep quality, increased time to fall asleep, and early awakening, and are primarily related to the desynchronization of the circadian rhythm (26). These symptoms are present in a variety of diseases, although the biological clock is typically responsible for regulating various physiological processes, including metabolism, immune responses, and cell regeneration (27). Additionally, people with circadian rhythm disorders may experience an impairment of their daily tasks, and as their condition worsens, they may exhibit a greater predisposition to psychiatric conditions, including depression, anxiety, and substance abuse (28).

In circadian rhythm sleep-wake disorder (CRSWD), there is a reduction in the time between falling asleep and waking up, which occurs when the body's internal circadian rhythm and the external environment are not synchronized. This is primarily seen in people who use electronic devices that emit light when sleeping, indicating that overexposure to light or abrupt changes in the environment can lead to desynchronization of the circadian rhythm, resulting in low melatonin secretion (29). Sleep hygiene, relaxation training, and therapy are generally the most recommended non-pharmacological therapies used to address CRSWD; however, in some cases, medication is necessary to improve quality of life (30). There are a variety of medications used to treat sleep disorders; however, they have the potential to result in dependence and withdrawal, and can negatively interfere with cognition (31).

As a supplement, melatonin increases the hormone levels in the body at specific times of day, helping to adjust circadian rhythms (32). The use of exogenous melatonin, therefore, is an option for patients with diseases that affect the circadian rhythm, as it crosses the blood-brain barrier and is well-tolerated, with few adverse effects and no withdrawal symptoms. Melatonin has two forms – an immediate-release form, which primarily functions via chronobiotic action, and a prolonged-release form, which mimics the physiological rhythm of melatonin in cases of natural deficiency. Furthermore, in the case of rapid eye movement (REM) sleep behavior disorders, melatonin is very effective in treating clinical symptoms, and as seen on polysomnography (PSG) during REM sleep, without episodes of atonia (33).

Given the importance of circadian rhythm regulation for the proper production of melatonin, previous studies have suggested that both PCOS (34) and endometriosis (35) are affected by pituitary hormone production. In the case of PCOS, melatonin plays a significant role in steroidogenesis, folliculogenesis, and oocyte maturation in the ovary (34). Melatonin and its receptors can be detected in primordial and atretic follicles, and high concentrations of melatonin can suppress atresia and help reduce inflammation by regulating the nuclear factor kappa beta (NF-κB) factor pathway (36). Melatonin secretion patterns may be disrupted in in patients with PCOS; therefore, to investigate the mechanisms of the melatonin-based regulation of endogenous production and antioxidant damage in the GCs of patients with PCOS, Yu et al. (2019) (34), collected GCs and FFs from 15 patients aged 25–35 years with PCOS being treated with melatonin (10 -7M) every 24 h for 6 months. By inhibiting the apoptosis of GCs through the regulation of apoptotic genes, this treatment significantly decreased overall androgen levels, as well as melatonin levels in the FFs of patients with PCOS with hypoestrogenia and hyperandrogenia. Additionally, it was found that melatonin inhibited NF-kB expression and reduced IL-18 levels in patients with PCOS, while protecting GCs from oxidative damage. Disturbances in melatonin production also affected the pathogenesis of endometriosis, as melatonin can affect the expression of estrogen receptor genes in the endometrium, and a deficiency in melatonin production can increase the expression of these receptors, subsequently promoting an overgrowth of endometrial tissue (35). Furthermore, because melatonin is an anti-inflammatory hormone, a deficiency thereof may contribute to the formation of a pro-inflammatory environment, promoting chronic inflammation, which, in turn, promotes the development of endometriosis (37,38). It is important to note, however, that the relationship between melatonin and endometriosis has not yet been fully elucidated.

PCOS is a complex endocrine disorder, primarily characterized by polycystic ovaries, hyperandrogenism, hyperinsulinemia, and chronic anovulation. Beneath the tunica albuginea, polycystic ovaries contain numerous small antral follicles that stop growing and/or developing (39). High levels of oxidative stress can occur in patients with PCOS, as demonstrated by Yang et al. (2018), who exposed experimental rats to constant illumination, which resulted in a a deficiency in the production of melatonin by the pineal gland, causing damage to the reproductive system and an increase in oxidative stress (6). Oxidative stress, in turn, may cause damage to the GCs and oocytes through lipid peroxidation, protein oxidation, and deoxyribonucleic acid (DNA) damage in the follicle (40). Gupta et al. (2006) concluded, therefore, that oxidative stress may result in poor oocyte quality (40).

It has been reported that in the ovary, the oocytes, as well as the cells that constitute the cumulus oophorus, synthesize melatonin (41), which is produced for their own benefit or for neighboring cells as an antioxidant, or as an autocrine or paracrine agent (42). Melatonin concentrations in the ovarian follicular fluid have been reported to be three times higher than those in the serum in normal women (43). Moreover, the concentration of melatonin is higher in the fluid of larger, compared to smaller, follicles in women undergoing IVF embryo transfer (44). Elevated melatonin levels in pre-ovulatory follicles are likely to protect GCs and

oocytes from the free radicals that are created during ovulation (45). In contrast, the intrafollicular melatonin concentration was found to be significantly lower in patients with PCOS when compared to women undergoing IVF embryo transfer, possibly accounting for the anovulation and poor oocyte quality observed patients with in PCOS (46). In a recent study by Shreeve et al. (2013), serial urine collections over a 24 h period revealed novel observations that nighttime melatonin and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels are significantly elevated in women with PCOS, when compared with non-PCOS controls (FIGURE 1) (47). These elevated nighttime melatonin levels can potentially act as free radical scavengers in cases of increased oxidative stress, indicating that women with PCOS and increased 8-OHdG levels (FIGURE 1), in response to high oxidative stress levels, produce more melatonin, possibly in an attempt to neutralize excess reactive oxygen species. Jain et al. (2013) corroborated these results by demonstrating that the serum melatonin concentration in women with PCOS was higher than that in control women, indicating a feedback mechanism based on reduced melatonin concentrations at the level of the ovarian follicles (48) Oral supplementation with melatonin, therefore, increases its concentration in the follicular fluid, which defines a follicle containing high-quality oocytes (49). These findings indicate that melatonin behaves synergistically at the ovarian level, improving the ovarian response to gonadotropin stimulation, subsequently resulting in increased oocyte and embryo quality. Additionally, melatonin supplementation can significantly improve the nuclear maturation of oocytes in patients with PCOS and guarantee their fertilization potential (49).

Endometriosis is an estrogen-dependent, chronic inflammatory disease, characterized by the implantation and proliferation of endometrial tissue outside of the uterine cavity. It is a complicated gynecologic disease that affects approximately 5–15% of all women of reproductive age, and 20–50% of all women diagnosed with fertility issues. The pelvic fluid from women suffering from endometriosis has been found to have high concentrations of inflammatory cytokines, such as IL-6, IL-8, and TNFα (50). Oxidative stress in the peritoneal cavity is one cause of infertility, with detrimental effects on cells, via lipid peroxidation, protein oxidation, and DNA damage. The etiology and pathogenesis of endometriosis remain unclear, despite Sampson's most widely accepted theory, the theory of retrograde menstruation, which states that the dissemination of menstrual effluent stimulates oxidative stress and chronic inflammation under appropriate circumstances (51,53). Endometriosis is strongly associated with chronic pelvic pain, which presents as an intense inflammatory reaction, while endometrial lesions cause pain by compressing or infiltrating the nerves near the lesions (53). The presence of nerve growth factors (NGFs) in these lesions is correlated with hyperalgesia and the growth of sympathetic and sensory neurons during ectopic endometrial growths (53, 54).

Previous studies have shown the potential therapeutic effects of melatonin supplementation in facilitating the regression of endometrial lesions (55). Guney et al. (2008) found that melatonin supplementation effectively decreased the volume and weight of endometriosis explants in a rat model [55], while Paul et al. (2008 & 2010) found that the experimental group that received melatonin supplementation, the levels of malondialdehyde (MDA) and cyclooxygenase-2 (COX-2) in endometrial explants and tissues were significantly decreased, whereas the activation of superoxide dismutase (SOD) and catalase (CAT) was significantly increased in those same tissues (56,57). Paul et al. (2008 & 2010) also found that melatonin not only protected, but also caused regression of peritoneal EMS in mice by downregulating the activity and expression of MMP-9 and MMP-3 while increasing tissue inhibitor of metalloproteinase (TIMP)-1 expression. Additionally, it was observed that melatonin induced apoptosis and endometrial regression via a caspase-3 mediated pathway. Melatonin supplementation resulted in significant increases in SOD and CAT levels, and a decreased recurrence rate, compared to what was observed after the cessation of treatment in the experimental group treated with letrozole. In another study, two different doses of melatonin treatment of endometrial implants (10 or 20 mg/kg/day) both resulted in the regression of endometrial lesions by improving histological scores in oophorectomized experimental rat models (58).

Another observed effect of melatonin supplementation decreased growth of ectopic uterine tissue in cases of surgically induced endometriosis, through the modulation of DNA codes. At the conclusion of the study, it was found that melatonin significantly decreased the volume, weight, and histopathologic score of endometrial implants, which subsequently affected chronic pelvic pain, progressive dysmenorrhea, dyspareunia, and infertility, all of which reduce quality of life, stressing the importance of this disease (21).The aim of current pharmacological treatments for endometriosis is to promote the cessation of therapy, which does not provide any benefit in cases of endometriosis-associated infertility. However, in the present study, melatonin

supplementation was evaluated as a new therapeutic agent, as new blood vessel formation plays a pivotal role in the development of endometriosis, and the prevention of angiogenesis may present a new alternative for the treatment of this chronic disease. Elevated MMP-9 secretion, increased MMP-2 concentrations, and decreased TIMP-2 concentrations were observed in the eutopic endometrial tissue of women with endometriosis, when compared to healthy women. Melatonin also inhibits MMP-9 activity by binding to its active site. Guney et al. (2008) showed that melatonin effectively decreased the volume and weight of endometrial explants in an experimental rat model, as the endometrial explant levels of MDA and tissue COX-2 positivity were significantly decreased the rats in the melatonin-treated group, whereas SOD and catalase activity were significantly increased (55). Additionally, Paul et al. (2008) demonstrated that melatonin protected mice from while causing the regression of peritoneal endometriosis by downregulating the activity and expression of MMP-9 while increasing TIMP-1 expression (56). They also identified a novel diagnostic marker, the MMP-9/TIMP-1 expression ratio, for assessing disease progression and severity. Furthermore, Paul et al. (2010) investigated the activity of MMP-3 and its relationship with MMP-9 during the onset of endometriosis in an experimental mouse model, and showed that MMP-3 plays a role in the early phases of endometriosis, while MMP-9 plays a role in the later phase. Melatonin, therefore, should be considered a potential therapeutic agent for the treatment of endometriosis (57).

Yildirim et al. (2010) evaluated the effects of melatonin supplementation in an experimental rat model of endometriosis. Melatonin supplementation resulted in a larger regression of endometrial foci, as well as a statistically significant increase in SOD and catalase levels (59). Koc et al. (2010) studied the effects of pinealectomy and melatonin supplementation on endometrial explants in an experimental rat model after the cessation of treatment, and found that the pinealectomy was associated with significant growth of the endometrial explants and decreased antioxidant activity (60). They also found that exogenous melatonin supplementation decreased the growth of endometrial explants and oxidative stress by reducing the MDA levels of the explant while increasing the levels of SOD and catalase. Similar findings regarding the SOD and MDA levels were observed in the present review. A Phase II, randomized, double-blind, placebo-controlled trial demonstrated the efficacy of melatonin supplementation in the treatment of endometriosis, with results suggesting that melatonin may reduce oxidative stress. Melatonin supplementation reduced the daily pain scores and dysmenorrhea symptoms of patients with endometriosis. Melatonin supplementation has been found to improve sleep quality, reduce the risk of analgesic use, and reduce BDNF levels, independent of its effect on pain. Cetinkaya et al. (2014) investigated the effects of varying doses of melatonin on endometrial implants (10 vs. 20 mg/kg/day), and at the conclusion of their study, reported that melatonin supplementation resulted in the regression of endometrial lesions, as evidenced by improved histologic scores as well as implant levels of SOD, MDA, and vascular endothelial growth factor (VEGF) in an oophorectomized experimental rat model (58).

Melatonin inhibits steroidogenesis by altering cAMP levels via direct action on the theca or GCs of the follicles (61). It decreases the luteinizing hormone surge and increases progesterone levels, without affecting follicle-stimulating hormone or estrogen levels (62). The treatment of experimental rats with supplemental melatonin resulted in reduced plasma levels of luteinizing hormone and 17 beta-estradiol, and promoted the differential regulation of estrogen, progesterone, and androgen receptors in the reproductive tissues (63). Melatonin may act directly on the MT1 receptors in rat uterine antimesometrial stromal cells to inhibit their proliferation (64), and its action may be mediated through a pertussis toxin-sensitive adenylate cyclase-coupled Gi-protein (65).

CONCLUSION

In the present review, we searched various databases for studies regarding the supplementation of melatonin, a hormone produced by the pineal gland during sleep, primarily at night, to validate the importance of its effects in women, and more specifically in relation to gynecologic disorders.

We also verified the feasibility of using supplemental melatonin as a therapeutic agent in the auxiliary treatment of diseases involving the female gynecological tract. Based on the results of the present review, we concluded that there is a vast field of research on melatonin supplementation and its effects on gynecologic disorders. We also verified the prospects of its use as a therapeutic agent in the auxiliary treatment of gynecological diseases.

Comment [M8]: should be submitted for further research based on the findings of this literature review

Ethical approval

The authors report that ethics approval was not required for this narrative review.

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