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Melatonin's Role in Female Fertility: Molecular Insights and Therapeutic Implications

Benedikta Diah Saraswati[1*]
[1]Faculty of Medicine, IPB University, Bogor, West Java, Indonesia
*Email: benediktadiah@apps.ipb.ac.id

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Abstract

Background: *This narrative review examines how melatonin enhances reproductive health functions. Melatonin has established itself as a multifaceted neurohormone with pivotal roles in female reproductive health. Through its potent antioxidant properties, melatonin protects oocytes and orchestrates hormonal regulation and ovarian function, with melatonin receptors strategically located in key reproductive tissues, including ovarian granulosa and luteal cells.*

Method: *This narrative review examines how melatonin preserves and enhances female fertility by analyzing clinical outcomes and molecular pathways. It compiles research on the effects of melatonin on ovarian function, oocyte quality, hormone regulation, and assisted reproductive technologies from major databases published between 2015 and 2025. The study consistently shows how melatonin works and its potential benefits, offering broad insights without strict limits.*

Result: *Melatonin operates through multiple receptor-mediated pathways to regulate reproductive functions. Clinical evidence shows melatonin supplementation improves assisted reproductive technology (ART)'s success rates by enhancing oocyte maturation and embryo quality, restoring menstrual regularity in PCOS patients, and protecting reproductive tissues from oxidative stress-induced damage.*

Implication: *These findings support melatonin's therapeutic potential in assisted reproductive technologies and treating reproductive disorders. Healthcare providers should consider melatonin supplementation as an adjuvant therapy for women undergoing fertility treatments or experiencing reproductive dysfunction while establishing standardized protocols for optimal dosing and timing.*

Novelty: *This comprehensive review reveals melatonin's multifaceted role as a fertility regulator, providing molecular insights into its therapeutic mechanisms and clinical applications in women's reproductive health across the reproductive lifespan.*

INTRODUCTION

Female fertility is a highly complex and finely controlled biological process involving sophisticated interactions between hormonal, cellular, and molecular components that must be precisely synchronized to enable successful reproduction (Olcese, 2020). In addition to dietary habits and stress, gynecology and female reproductive health can be influenced by age-related reductions in both the viability and quality of reproductive cells (Pervez, 2023). Recently, knowledge about what factors influence female reproductive health and fertility has expanded rapidly, highlighting the essential functions of many regulatory molecules that produce reproductive hormones. Among these emerging authorities, melatonin is a particularly intriguing and diverse neurohormone that has attracted the attention of reproductive biologists and clinicians worldwide (Gelen et al., 2022).

Originally known as a “sleep hormone” because of its ability to control circadian rhythms, melatonin has since been recognized as a master controller of many physiological processes that are sensitive to the sleep-wake cycle (Amaral & Cipolla-Neto, 2018). Therefore, melatonin is one of the most studied reproductive endocrinologies that gives a deeper insight into normal reproductive physiology and the etiology of various fertility problems (Gelen et al., 2022). Melatonin is well-known for its capacity to protect and control the reproductive system. Melatonin regulates essential reproductive functions such as ovulation, menstrual cycle management, and fertility, in addition to its well-known role in regulating circadian rhythms (Parua et al., 2024). Its ability is probably due to its complex hormonal and ovarian function control and its antioxidant properties that protect the delicate oocyte from oxidative damage. Melatonin receptors are found in key reproductive organs, like ovarian luteal and granulosa cells, showing strong proof that melatonin works directly in these areas, boosting its overall effects in the body (Fang et al., 2019).

Current literature reveals gaps in understanding melatonin's clinical applications for female fertility enhancement. Standardized protocols for melatonin supplementation are lacking, with inconsistent dosing and timing across studies (Bao et al., 2022; Y. Li et al., 2022). This review addresses rising infertility rates and increasing interest in natural adjuvant therapies. The analysis synthesizes molecular discoveries of melatonin's receptor-mediated pathways in reproductive tissues and integrates clinical evidence from diverse populations. This narrative review examines the mechanisms and clinical applications of melatonin in female fertility, spanning from molecular pathways to therapeutic uses.

The objective of this review is to synthesize recent findings regarding molecular mechanisms and clinical applications of melatonin in female fertility modulation. This analysis aims to inform evidence-based approaches for incorporating melatonin into fertility treatment protocols and establish foundations for future therapeutic applications in reproductive medicine. The analysis covers melatonin synthesis, receptor systems, genetic polymorphisms, and therapeutic applications in reproductive medicine and assisted reproductive technologies. The review addresses melatonin's potential impact on future research and clinical practice in reproductive medicine.

METHOD

Type and Design

This review presented a conceptual synthesis of various relevant studies to answer the question of melatonin's role in female reproductive systems. This review focuses on exploring the protective mechanisms of melatonin on female fertility, encompassing both

clinical effectiveness and underlying biological mechanisms. This approach enables a broader and deeper understanding of diverse research findings within a more flexible context without being bound to systematic review protocols.

Literature Selection Process

The literature search was conducted through multiple high-reputation databases including PubMed, Google Scholar, Science Direct, and Cochrane Library using relevant keyword combinations focusing on melatonin's effects on the female reproductive system. The search strategy employed systematic combinations of terms such as 'melatonin AND female fertility enhancement,' 'melatonin AND ovarian function improvement,' 'melatonin AND oocyte quality,' 'melatonin AND reproductive hormone regulation,' and 'melatonin AND assisted reproductive technology outcomes.'

Inclusion Criteria:

- Articles published in English or Indonesian language
- Publications published between 2015–2025, except when earlier studies are needed to strengthen or provide foundational statements
- Studies conducted on female subjects
- Full-text availability
- Relevance to melatonin's role in female fertility
- Type of studies: Experimental studies, including laboratory investigations and clinical trials; comprehensive reviews and meta-analytical studies; Epidemiological research with longitudinal and case-control designs

Exclusion Criteria:

- Animal studies
- Studies focusing exclusively on male reproductive function
- Research primarily addressing other body systems or diseases
- Articles with incomplete or inaccessible data
- Duplicate publications

Following the initial database searches, a three-stage screening process was implemented. First, titles and abstracts of retrieved articles were screened to identify potentially relevant studies. Second, full-text articles were obtained and evaluated against the predetermined inclusion and exclusion criteria listed above. After applying these criteria through rigorous full-text evaluation, a final corpus of articles was selected and subjected to comprehensive descriptive and comparative analysis to synthesize current understanding of melatonin's protective role in female fertility."

Data Collection Technique

The data collection process began with initial searches using predetermined keyword combinations for each database. Besides, initial screening was also conducted by screenin on titles and abstracts, followed by the content review of the article to ensure compliance with inclusion criteria. The selection process was done recording to the number of articles obtained, screened articles, and exclusion reasons for every reject articles for each stage.

Data analysis

Data obtained from selected studies were analyzed using descriptive and comparative approaches. Descriptive analysis was used to summarize general study characteristics, while comparative analysis was conducted to evaluate differences and similarities in findings

across studies. Emphasis was placed on identifying recurring patterns of biological mechanisms, melatonin dosage and treatment duration effects, and contextual variables such as age, hormonal status, and other individual risk factors. Synthesis was performed narratively to construct comprehensive understanding regarding the protective effectiveness of melatonin on female fertility.

Following the comprehensive screening and selection process described above, 40 articles that met the inclusion criteria were thoroughly reviewed and analyzed in this narrative synthesis. These articles formed the evidence base for examining melatonin's role in female reproductive systems and fertility enhancement.

RESULT AND DISCUSSION

Melatonin Synthesis and Regulation

Tryptophan is one of the most important amino acids, precursor to synthesize melatonin. Naturally, the pinealocytes of the pineal gland produce this neurohormone, especially to regulate a circadian rhythm (Tsui et al., 2024). The biosynthesis of melatonin begins when the enzyme tryptophan hydroxylase transforms tryptophan into 5-hydroxytryptophan. The amino acid decarboxylase then produces serotonin (Espino et al., 2019). After that, N-acetyl transferase converts serotonin to N-acetyl serotonin. N-acetyl serotonin is finally changed into melatonin by methyltransferase, which is released into the circulation (Hu et al., 2020).

Although melatonin is probably produced in many cells, only the pineal glandecretes it, following a strict daily schedule linked to the light-dark cycle, releasing melatonin only at night (Rai and Gosh 2021).Melatonin is not just a chemical made and work in the dark. It also plays an important role in treating sleep disorders linked to circadian rhythm problems like delayed sleep phase syndrome, non-24-hour sleep-wake disorder, and jet lag. While it naturally acts at night, it can also be used during the day when melatonin levels are low, if administered properly (J & A, 2022).

The suprachiasmatic nucleus (SCN), which resides in the brain, is the main regulator of this time. It gets light signals from the retina and sends them to other parts. When light is detected, the SCN releases gamma-aminobutyric acid (GABA), which stops neurons in the paraventricular nucleus (PVN) from sending signals to the pineal gland and stops melatonin production (Ma & Morrison, 2023). When there is no light, the SCN turns on and releases glutamate, which helps the PVN send signals to the pineal gland to make melatonin. There are multiple steps involved in linking light exposure to hormone release. Retinal cells see light and send it to the suprachiasmatic nucleus through the retinohypothalamic tract (Arendt & Aulinas, 2022). After that, the SCN sends signals through the hypothalamus to the lateral horn of the spinal cord. After that, the preganglionic nerve fibers join to the superior cervical ganglia. The sympathetic nerves from these ganglia connect to the pineal gland and make noradrenaline, which produces melatonin by turning on the enzyme N-acetyltransferase in pinealocytes (Rai and Gosh 2021).

Furthermore, the bioavailability and metabolism of melatonin in humans exhibit considerable individual variation, influenced by genetic polymorphisms in metabolizing enzymes and age-related changes in synthesis capacity. A recent randomized controlled trial in women undergoing IVF demonstrated that melatonin supplementation significantly improved clinical pregnancy rates and reduced miscarriage rates compared to placebo controls. Additionally, circadian disruption in shift-working women has been associated with altered melatonin synthesis patterns and decreased fertility outcomes, highlighting the

importance of maintaining physiological melatonin rhythms for optimal reproductive health (Q. Li et al., 2025). Understanding these human-specific regulatory mechanisms is essential for developing personalized melatonin therapy protocols that account for individual differences in synthesis, metabolism, and reproductive health requirements (Koonrungsesomboon et al., 2018).

Molecular Mechanisms in Reproductive Systems

The regulation of melatonin synthesis involves complex molecular mechanisms that extend beyond the classical pineal pathway. Recent clinical research has identified extrapineal melatonin production in human reproductive tissues, including ovarian granulosa cells and cumulus cells, suggesting local autocrine and paracrine functions in human fertility (Asma & Marc-André, 2022). These peripheral sites of melatonin synthesis operate independently of circadian control and respond to local tissue demands, particularly during oxidative stress conditions in human oocytes. Human follicular fluid melatonin concentrations have been demonstrated to correlate significantly with oocyte quality and embryo development outcomes in assisted reproductive technology cycles (Cheng et al., 2020).

Certain receptors on membranes and in the nucleus are responsible for the physiological effects of melatonin. These nuclear sites are part of the RZR/ROR nuclear receptor superfamily since they are nuclear receptors (Marco et al., 1999). There are melatonin receptors in the cells of mammals, including humans. There are three groups: MT1, MT2, and MT3. According to Parua et al. 2024, MT1 and MT2 are part of a G protein-coupled receptor (GPCRs) with seven-transmembrane proteins. The third type, MT3, is like quinone reductase 2, an enzyme in the cytoplasm that acts like a receptor (Parua et al., 2024).

The GPCR family changes how cells communicate with one other through heterotrimeric G proteins. So, the receptors greatly affect how the mitogen-activated protein kinase (MAPK) family, which includes c-Jun N-terminal kinase (JNK), is regulated downstream. When turning JNK on, it adds a phosphate group to the transcription factor c-Jun, making the AP-1 complex work better. The AP-1 complex is a crucial gene regulator that controls growth, differentiation, and death (Chan et al., 2002; Hu et al., 2020). Melatonin can change the MAPK/JNK pathway in either direction, depending on the cell type and the body's needs. It might stop JNK from working, preventing cells from dying from stress and growing too quickly, protecting gonadal cells (Jing et al., 2017). Melatonin may also turn on JNK, which helps cells become different and grow normally, which is important for gonadal growth. This dual modulation keeps reproductive tissues growing and working properly by carefully controlling JNK signals. Melatonin also controls ESR1 by changing how much of it is made or by engaging with signaling pathways that affect estrogen receptor pathways. This controls how estrogen works, which is important for keeping reproductive tissue healthy and for sexual development (Figure 1) (Chan et al., 2002) .

Melatonin controls several functions in addition to its role in regulating reproduction. These include synchronizing circadian rhythms, modulating the immune system, regulating endocrine function, and brain development. G protein-coupled signaling pathways are what the MT1 and MT2 receptors mostly use to do these things. MT3 is a cytoplasmic quinone reductase 2 that helps melatonin have its effects on the body (Amaral et al., 2018; Liu et al., 2016). When MT1 or MT2 is activated, it stops adenylate cyclase (AC), which lowers the levels of cyclic AMP (cAMP). In human reproductive systems, the hormone stops cAMP from building up by activating GPCR receptors. This suggests that there is a complicated signaling

network that affects reproductive outcomes (Nikolov et al., 2022). Melatonin also interacts with MT1 and MT2, which starts a number of signaling cascades, including the MAPK-ERK pathway, the PI3K/Akt (protein kinase B) route, the ERK1/2, JNK1/2, and Akt pathways. This allows cells to respond in many different ways (Guo et al., 2021).

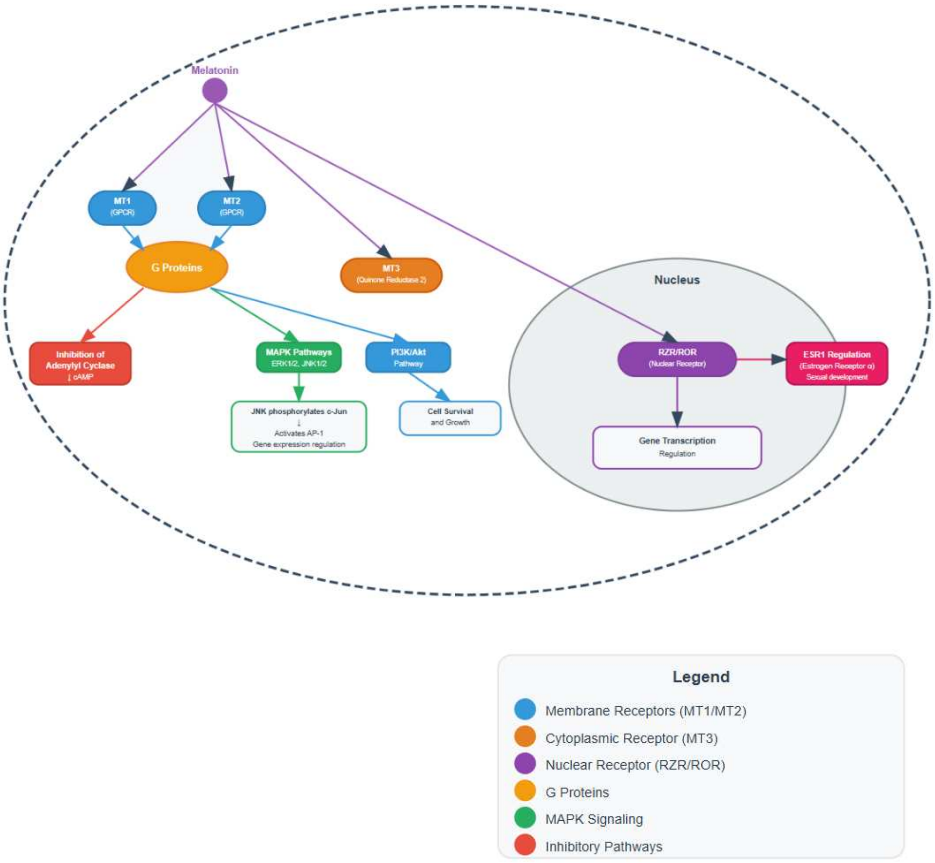

Figure 1. Melatonin signaling pathways in reproductive physiology. Melatonin regulates reproductive functions through membrane receptors (MT1/MT2 GPCRs, MT3 quinone reductase) and nuclear receptors (RZR/ROR), activating G protein-coupled pathways, MAPK signaling, and gene transcription, including ESR1 (Chan et al., 2002; Hu et al., 2020; Parua et al., 2024).

Antioxidant Properties and Cellular Protection of Melatonin

Melatonin's primary benefit for female fertility stems from its potent antioxidant properties. Reactive oxygen species (ROS) accumulation commonly causes poor oocyte quality and adverse reproductive outcomes. ROS readily attack mitochondria, with free oxygen radicals damaging mitochondrial DNA in oocytes and reducing mitochondrial functionality, significantly affecting fertility aging (Jiang et al., 2021).

Melatonin effectively scavenges reactive oxygen species and other free radicals, playing crucial roles in reproduction. Present in ovarian follicular fluid and oocytes, melatonin enhances oocyte maturation, fertilization, and embryo formation while protecting these cells from oxidative damage (Tamura et al., 2017). Melatonin protects granulosa cells from oxidative stress through antioxidant action (Parua et al., 2024). Reducing oxidative stress closely relates to restoring regular ovulation, a primary goal for women seeking pregnancy.

Melatonin combats oxidative stress by elevating superoxide dismutase (SOD) and total antioxidant capacity (TAC) levels in ovaries while simultaneously reducing malondialdehyde (MDA) levels. Melatonin preserves mitochondrial membrane potential through the MT1/AMPK pathway and regulates autophagy levels by reducing autophagy-related gene expression, minimizing oxidative stress damage (Jiang et al., 2021). The hormone can activate intracellular antioxidant enzymes without using receptors and directly chelate reactive oxygen and nitrogen species (Amaral et al., 2018).

Additionally, melatonin protects against environmental toxins. Lead (Pb), a common environmental metal pollutant, demonstrates harmful effects on female reproductive system (Yang et al., 2025). Melatonin reduces Pb-elevated nucleus-encoded proteins like SDHA, mitofilin, and MTCO2, while decreasing Pb-elevated mitochondrial dynamic-related proteins including OPA1, MFN, and FIS1. Melatonin maintains stable mitochondrial membrane potential levels and reduces anti-mitochondrial fission factor (MFF) antibody expression connected to mitochondrial dynamics, successfully reducing Pb-induced P38 signaling pathway phosphorylation blockage (Jiang et al., 2021).

Melatonin Roles in Hormonal Functions and Menstrual Cycle Effects

Melatonin regulates the hypothalamic-pituitary-gonadal axis, affecting the release of gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone. The steroidogenic effects of melatonin are driven by specific biochemical mechanisms. The steroidogenic acute regulatory protein (StAR) promotes the rate-limiting phase of ovarian steroidogenesis and progesterone synthesis. Melatonin and its receptors influence basal progesterone synthesis in human granulosa cells, with melatonin boosting StAR expression in initial cultures of hGL cells from IVF patients. Melatonin's stimulatory activity on StAR expression is supported by both the MT1 and MT2 melatonin receptors, which activate the PI3K/AKT signaling pathway (Fang et al., 2019).

Melatonin stimulates progesterone synthesis by luteal cells, essential for healthy pregnancy maintenance (Rai et al., 2021). Consequently, melatonin enhances progesterone secretion and affects the balance between luteotrophic and luteolytic components. Melatonin expression and MT2 receptor identification substantiate this indoleamine's direct influence on the Corpora Lutea. Melatonin significantly influences corpus luteum function regulation and early pregnancy initiation and maintenance, serving as a potential therapeutic agent for enhancing ovarian and luteal function during early pregnancy phases, creating new treatment avenues for ovarian-luteal and pregnancy-related disorders (Scarinci et al., 2019).

Human reproduction differs from that of other mammals in that it lacks seasonal patterns; however, environmental factors do influence conception, with photoperiod and temperature being the most relevant. Melatonin plays a crucial role in human reproduction and influences conception. Increased light exposure at planned ovulation times helps women with severely irregular menstrual cycles manage ovulation and encourage ovulation. Since melatonin alters pituitary and gonadal hormone production and secretion, gonadotropins and gonadal steroid hormones change dramatically during human menstrual cycles (Jiang et al., 2021).

Therapeutic Role of Melatonin in Assisted Reproductive Technology (ART)

Clinical trials demonstrate melatonin's improvement of assisted reproductive technology outcomes, particularly in vitro fertilization and embryo transfer (IVF-ET) for infertility patients. Clinical evidence suggests that melatonin supplementation enhances

ART outcomes through multiple mechanisms, including improved oocyte quality, enhanced fertilization rates, and improved embryo development (Tamura et al., 2020).

Melatonin demonstrates promising ART benefits by significantly increasing clinical pregnancy rates and improving egg and embryo quality. Studies reveal that melatonin treatment increases retrieved egg numbers, mature egg quantities, and the number of good-quality embryos, while also raising biochemical pregnancy rates, indicating positive early pregnancy signals. However, despite encouraging effects, melatonin does not significantly improve live birth rates or affect miscarriage rates. The hormone's antioxidant properties likely protect eggs and embryos from oxidative stress, a known infertility factor (Hu et al., 2020).

Immature oocyte use represents a key ART element. However, excessive ROS from in vitro culture poses serious problems for oocyte quality and developmental capability. Oxidative stress injuries increase cell apoptosis and decrease oocyte developmental potential. Melatonin presence in follicular fluid suggests usefulness in managing human fertility, with reduced melatonin levels associated with marked oxidative imbalance in patients' follicular fluid (Espino et al., 2019).

Melatonin plays important roles in oocyte maturation, fertilization, and embryonic development. Concurrent melatonin use increases mature oocyte numbers, fertilization rates, and high-quality embryos, improving ART clinical outcomes (Jiang et al., 2021). Exogenous melatonin supplementation helps IVF processes by promoting oocyte maturation, primarily through oxidative damage suppression. Melatonin can increase granulosa cell progesterone production, associated with follicle growth and maturation stages. This proves crucial since granulosa cells often reach advanced development stages in women undergoing IVF (Q. Li et al., 2024).

Melatonin Supplement Recommendation

Clinically, melatonin is most appropriately given to women undergoing ART procedures, especially those with repeated IVF failures, poor oocyte quality, or oxidative stress-related infertility. It is also considered in patients with PCOS who experience irregular menstrual cycles, where circadian regulation and antioxidant support can improve reproductive outcomes. Melatonin is considered an adjuvant rather than a primary treatment for fertility issues, recommended as a supplement alongside conventional therapies (Hu et al., 2020). Evidence suggests benefits for women with poor oocyte quality, advanced maternal age, repeated IVF failures, and fertility problems related to oxidative stress (Hu et al., 2020; Tsui et al., 2024). It may also support women with irregular menstrual cycles associated with PCOS by helping regulate circadian rhythms and hormonal balance (Espino et al., 2019).

The optimal dosage ranges from 1.0 to 5.0 mg of oral melatonin for treating melatonin-responsive reproductive disorders (Jing et al., 2017). However, individual dosage must be customized based on symptom response and potential side effects like nocturnal nightmares or daytime somnolence (Amaral et al., 2018). The evolution of melatonin dosing in fertility treatments tells a fascinating story of scientific discovery and clinical refinement. The evolution of melatonin dosing in fertility treatments tells a fascinating story of scientific discovery and clinical refinement. A daily dose of 3 mg was established as the foundational standard and later validated across diverse patient populations, ranging from general IVF cases to women with low ovarian reserve (Nishihara et al., 2014; Tamura et al., 2017; Unfer et al., 2011). As confidence in melatonin’s role increased, higher doses were tested, 4 mg twice daily, 3 mg versus 6 mg daily, and even 2 to 8 mg twice daily, though these approaches produced contradictory results, suggesting that more is not always better (Espino et al., 2019; Fernando et al., 2014, 2020). A major paradigm shift occurred when much lower

doses proved effective in combination strategies, where just 1 mg daily, one-third of the standard, improved fertility outcomes when paired with complementary supplements such as vitamin D and myo-inositol (Bezerra Espinola et al., 2021). Mechanistic studies further supported these findings by providing cellular-level insights into therapeutic concentrations and antioxidant mechanisms underlying melatonin's reproductive benefits (Hu et al., 2020; Q. Li et al., 2024; Tsui et al., 2024).

Melatonin supplementation requires medical supervision, particularly for reproductive applications. Healthcare providers should evaluate individual patient needs, monitor treatment responses, and adjust protocols accordingly. Long-term safety profiles in women of reproductive age require further investigation to establish comprehensive treatment guidelines (Bao 2022). Research indicates that melatonin administration at doses of 3 mg daily or higher can dramatically elevate melatonin levels in serum and follicles, potentially improving oocyte and embryo quality and subsequent pregnancy outcomes (Hu et al. 2020). Timing considerations prove crucial for therapeutic effectiveness. The melatonin phase-response curve indicates that evening or nighttime administration best mimics natural hormone synthesis (Bao et al., 2022; Jing et al., 2017). For circadian regulation without phase alteration, melatonin should be taken one hour before to four hours after regular bedtime (Jing et al., 2017). Late afternoon or early evening administration helps advance circadian clocks, while late-night or early-morning dosing may cause rhythm phase delays.

Melatonin Effects on Reproductive Disorders

Reproductive disorders seriously affect female fertility by disrupting hormonal balance, anatomy, and ovulation necessary for conception. Polycystic ovary syndrome (PCOS) particularly disrupts hormone levels, causing irregular or absent ovulation (Patel et al., 2023). Endometriosis leads to painful inflammation and scar tissue formation that blocks or distorts the fallopian tubes, making egg and sperm meeting difficult and preventing fertilization (Y. Li et al., 2022).

Genetic aspects of melatonin function in reproduction reveal important insights into individual variability. Limited information exists regarding potential associations between reproductive system clinical syndromes and melatonin production or receptor polymorphisms (Olcese 2020). Research identifies significant gene polymorphism differences in the melatonin type 1 receptor (MTNR1a) regions between women with PCOS, though no associated phenotypic differences appear (Song et al., 2015).

Meta-analysis of two single-nucleotide polymorphisms (rs10830963 C>G in *MTNR1B* and rs2119882 T>C in *MTNR1A*) in large Chinese women populations reveals substantial relationships in several genetic models. *MTNR1B* rs10830963 and *MTNR1B* rs2119882 polymorphisms link to increased PCOS risk, requiring validation through larger multi-ethnic investigations (Yi et al., 2020).

Melatonin's antioxidant and anti-inflammatory qualities improve ovarian function and fertility in reproductive illness pathophysiology, including polycystic ovarian syndrome (PCOS) and endometriosis (Parua et al., 2024). Melatonin impacts PCOS patients' clinical, endocrine, and metabolic characteristics. Granular cell androgen-estrogen conversion inhibition by melatonin reduces estrogen levels, causing hypothalamus-pituitary axis negative feedback and increasing FSH secretion through pituitary stimulation. PCOS patients' serum androgen and anti-Mullerian hormone (AMH) levels significantly reduce after six months of melatonin treatment, while FSH levels significantly elevate (Guo et al., 2021).

Endometriosis represents abnormal endometrial conditions where endometrial-like tissue grows outside the endometrium, usually in pelvic regions (Y. Li et al., 2022). Endometriosis demonstrates abnormal hormone profiles, cell survival, migration, invasion, angiogenesis, oxidative stress, immunology, and inflammation. The mammalian pineal gland produces and releases melatonin primarily at night, with mounting evidence showing melatonin production and secretion from various extra-pineal organs, locally controlling inflammation, angiogenesis, and immune responses. Uterine melatonin receptor expression and reported therapeutic benefits for endometriosis and other reproductive conditions demonstrate melatonin's pleiotropic properties and potential for endometriosis treatment (Y. Li et al., 2022).

Melatonin combats ovarian cancer by fighting free radicals that harm cells and promoting cellular natural defense efficacy to prevent DNA damage (Zare et al., 2019). It disrupts survival signals while enhancing tumor suppressor genes like p53 and other pro-apoptotic genes, inducing regulated cancer cell apoptosis. Melatonin inhibits critical inflammatory molecules, including TNF-α and NF-κB, preventing cancer cell proliferation. It also inhibits cancer proliferation by reducing VEGF levels, diminishing angiogenesis, and disrupting hypoxic signals essential for tumor growth (Reiter et al., 2017). Melatonin enhances chemotherapeutic agent efficacy, like cisplatin, while protecting healthy ovarian cells from damage, representing a safe, natural ovarian cancer treatment option (González et al., 2018; Zare et al., 2019).

Challenges and Future Directions

Although studies on melatonin look promising, many problems still need to be addressed before it can be used in real life. When studying how melatonin affects the reproductive system (or any other system) in clinical settings, it's important to remember things like when melatonin is given (day or night) and how long the plasma melatonin levels stay high after melatonin is given from outside sources (Hu et al., 2020). There are several reasons why studying human reproduction is hard, such as the fact that people are different, there are ethical constraints on experimenting with people, research expenditures are high, and the right tools are needed. It has been hard to come to clear conclusions about melatonin's natural physiological involvement in human reproduction so far because of the quality of clinical data, its statistical power, reproducibility, suitability of controls, treatment differences, and other factors. In the same way, the purported medical uses for melatonin or its analogs in the treatment of puberty, infertility, menopause, and other conditions have not yet been proven because there isn't enough published scientific research on the subject (Olcese 2020).

CONCLUSION

Melatonin is a hormone that influences women's fertility through various mechanisms, including hormone regulation and cellular protection from damage. Melatonin may influence ovarian function in individuals with many reproductive diseases that cause infertility, such as PCOS. Besides, with the property of being a potent antioxidant, it is also able to improve oocyte quality and embryo development in ART and mitigate age-related fertility decline. This suggests that melatonin may be beneficial for women's reproductive health. Clinical applications demonstrate potential for enhancing IVF success, restoring regular menstrual cycles, and mitigating oxidative stress-induced damage to reproductive organs. Further investigation is required to determine optimal melatonin administration timings concerning menstrual cycles and fertility therapies, appropriate dosages for various reproductive diseases, and the long-term safety profiles in women of reproductive age. This

will enable melatonin to achieve its maximum therapeutic efficacy in safeguarding and enhancing female fertility during the reproductive lifespan.The findings from this review support the development of evidence-based practice guidelines for melatonin therapy in fertility treatments. Future research should focus on establishing standardized protocols to optimize melatonin's therapeutic benefits while ensuring patient safety across diverse reproductive health conditions.

REFERENCES

Amaral, F. G. do, & Cipolla-Neto, J. (2018). A brief review about melatonin, a pineal hormone. *Archives of Endocrinology and Metabolism, 62*(4), 472–479. https://doi.org/10.20945/2359-3997000000066

Arendt, J., & Aulinas, A. (2022). Physiology of the pineal gland and melatonin. In L. J. De Groot, G. Chrousos, K. Dungan, et al. (Eds.), *Endotext*. MDText.com. https://www.ncbi.nlm.nih.gov/sites/books/NBK550972/

Arjoune, A., & Sirard, M.-A. (2022). Melatonin signaling pathways implicated in metabolic processes in human granulosa cells (KGN). *International Journal of Molecular Sciences, 23*(6), 2988. https://doi.org/10.3390/ijms23062988

Bao, Z., Li, G., Wang, R., Xue, S., Zeng, Y., & Deng, S. (2022). Melatonin improves quality of repeated-poor and frozen-thawed embryos in human, a prospective clinical trial. *Frontiers in Endocrinology, 13,* 853999. https://doi.org/10.3389/fendo.2022.853999

Bezerra Espinola, M. S., Bilotta, G., & Aragona, C. (2021). Positive effect of a new supplementation of vitamin D3 with myo-inositol, folic acid and melatonin on IVF outcomes: A prospective randomized and controlled pilot study. *Gynecological Endocrinology, 37*(3), 251–254. https://doi.org/10.1080/09513590.2020.1760820

Chan, A. S. L., Lai, F. P. L., Lo, R. K. H., Voyno-Yasenetskaya, T. A., Stanbridge, E. J., & Wong, Y. H. (2002). Melatonin MT1 and MT2 receptors stimulate c-Jun N-terminal kinase via pertussis toxin-sensitive and -insensitive G proteins. *Cellular Signalling, 14*(3), 249–257. https://doi.org/10.1016/S0898-6568(01)00240-6

Cheng, J. C., Fang, L., Li, Y., Wang, S., Li, Y., Yan, Y., Jia, Q., Wu, Z., Wang, Z., Han, X., & Sun, Y. P. (2020). Melatonin stimulates aromatase expression and estradiol production in human granulosa-lutein cells: Relevance for high serum estradiol levels in patients with ovarian hyperstimulation syndrome. *Experimental & Molecular Medicine, 52*(8), 1341–1350. https://doi.org/10.1038/s12276-020-00491-w

Espino, J., Macedo, M., Lozano, G., Ortiz, Á., Rodríguez, C., Rodríguez, A. B., & Bejarano, I. (2019). Impact of melatonin supplementation in women with unexplained infertility undergoing fertility treatment. *Antioxidants, 8*(9), 338. https://doi.org/10.3390/antiox8090338

Fang, L., Li, Y., Wang, S., Yu, Y., Li, Y., Guo, Y., Yan, Y., & Sun, Y. P. (2019). Melatonin induces progesterone production in human granulosa-lutein cells through upregulation of StAR expression. *Aging, 11*(20), 9013–9024. https://doi.org/10.18632/aging.102367

Fernando, S., Osianlis, T., Vollenhoven, B., Wallace, E., & Rombauts, L. (2014). A pilot double-blind randomised placebo-controlled dose-response trial assessing the effects of melatonin on infertility treatment (MIART): Study protocol. *BMJ Open, 4*(8), e005986. https://doi.org/10.1136/bmjopen-2014-005986

Fernando, S., Wallace, E. M., Rombauts, L., White, N., Hong, J., Vollenhoven, B., Lolatgis, N., Hope, N., Wong, M., Lawrence, M., Lawrence, A., Russell, C., Leong, K., Thomas, P., & da Silva Costa, F. (2020). The effect of melatonin on ultrasound markers of follicular development: A double-blind placebo-controlled randomised trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 60*(1), 141–148. https://doi.org/10.1111/ajo.13074

Gelen, V., Şengül, E., & Kükürt, A. (2022). An overview of effects on reproductive physiology of melatonin. In *Melatonin - Recent Updates*. IntechOpen. https://doi.org/10.5772/intechopen.108101

González, A., González-González, A., Alonso-González, C., Menéndez-Menéndez, J., Martínez-Campa, C., & Cos, S. (2018). Complementary actions of melatonin on angiogenic factors, the angiopoietin/Tie2 axis and VEGF, in co-cultures of human endothelial and breast cancer cells. *Oncology Reports, 39*(1), 433–441. https://doi.org/10.3892/or.2017.6070

Guo, Y. M., Sun, T. C., Wang, H. P., & Chen, X. (2021). Research progress of melatonin (MT) in improving ovarian function: A review of the current status. *Aging, 13*(13), 17930–17944. https://doi.org/10.18632/aging.203231

Hu, K. L., Ye, X., Wang, S., & Zhang, D. (2020). Melatonin application in assisted reproductive technology: A systematic review and meta-analysis of randomized trials. *Frontiers in Endocrinology, 11,* 160. https://doi.org/10.3389/fendo.2020.00160

Jiang, Y., Shi, H., Liu, Y., Zhao, S., & Zhao, H. (2021). Applications of melatonin in female reproduction in the context of oxidative stress. *Oxidative Medicine and Cellular Longevity, 2021,* 6668365. https://doi.org/10.1155/2021/6668365

Jing, T., Shile, S., Sun, Y., Li, H., Li, W. P., Cong, Z., & Chen, Z. J. (2017). Melatonin levels in follicular fluid as markers for IVF outcomes and predicting ovarian reserve. *Reproduction, 153*(4), 443–451. https://doi.org/10.1530/rep-16-0641

Koonrungsesomboon, N., Khatsri, R., Wongchompoo, P., & Teekachunhatean, S. (2018). The impact of genetic polymorphisms on CYP1A2 activity in humans: A systematic review and meta-analysis. *Pharmacogenomics Journal, 18*(6), 760–768. https://doi.org/10.1038/s41397-017-0011-3

Li, Q., Zheng, T., Chen, J., Li, B., Zhang, Q., Yang, S., Shao, J., Guan, W., & Zhang, S. (2024). Exploring melatonin's multifaceted role in female reproductive health: From follicular development to lactation and its therapeutic potential in obstetric syndromes. *Journal of Advanced Research, 70,* 223–242. https://doi.org/10.1016/j.jare.2024.04.025

Li, Y., Hung, S. W., Zhang, R., Man, G. C. W., Zhang, T., Chung, J. P. W., Fang, L., & Wang, C. C. (2022). Melatonin in endometriosis: Mechanistic understanding and clinical insight. *Nutrients, 14*(19), 4087. https://doi.org/10.3390/nu14194087

Liu, J., Clough, S. J., Hutchinson, A. J., Adamah-Biassi, E. B., Popovska-Gorevski, M., & Dubocovich, M. L. (2016). MT1 and MT2 melatonin receptors: A therapeutic perspective. *Annual Review of Pharmacology and Toxicology, 56,* 361–383. https://doi.org/10.1146/annurev-pharmtox-010814-124742

Ma, M. A., & Morrison, E. H. (2023). Neuroanatomy, nucleus suprachiasmatic. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK546664/

Marco, M., Plazzi, P. V., Spadoni, G., & Tarzia, G. (1999). Melatonin. *Current Medicinal Chemistry, 6*(6), 501–518. https://doi.org/10.2174/0929867306666220330190146

Nikolov, G., Konakchieva, R., Nikolaev, G., & Marinova, E. (2022). Molecular mechanisms of melatonin action in human reproductive system – Implications for assisted reproduction. *Human Reproduction, 37*(Suppl. 1). https://doi.org/10.1093/humrep/deac107.200

Nishihara, T., Hashimoto, S., Ito, K., Nakaoka, Y., Matsumoto, K., Hosoi, Y., & Morimoto, Y. (2014). Oral melatonin supplementation improves oocyte and embryo quality in women undergoing in vitro fertilization-embryo transfer. *Gynecological Endocrinology, 30*(5), 359–362. https://doi.org/10.3109/09513590.2013.879856

Olcese, J. M. (2020). Melatonin and female reproduction: An expanding universe. *Frontiers in Endocrinology, 11,* 85. https://doi.org/10.3389/fendo.2020.00085

Parua, S., Roy Choudhury, G., Bhattacharya, S., Hazra, A., Dutta, S., Sengupta, P., & Bhattacharya, K. (2024). Melatonin in female fertility: Multifaceted role from

reproductive physiology to therapeutic potential in polycystic ovary syndrome, endometriosis, and ovarian failure. *Chronobiology in Medicine, 6*(4), 145–162. https://doi.org/10.33069/cim.2024.0022

Patel, A., Dewani, D., Jaiswal, A., Yadav, P., & Reddy, L. S. (2023). Exploring melatonin's multifaceted role in polycystic ovary syndrome management: A comprehensive review. *Cureus, 15*(6), e48929. https://doi.org/10.7759/cureus.48929

Pervez, A. (2023). Addressing female reproductive disorders: The potential role of melatonin. *Student's Journal of Health Research Africa, 4*(12), 5. https://doi.org/10.51168/sjhrafrica.v4i12.897

Rai, S., & Gosh, H. (2021). Modulation of human ovarian function by melatonin. *Frontiers in Bioscience - Elite, 26*(1), 140–157. https://doi.org/10.2741/875

Reiter, R. J., Rosales-Corral, S. A., Tan, D.-X., Acuña-Castroviejo, D., Qin, L., Yang, S.-F., & Xu, K. (2017). Melatonin, a full service anti-cancer agent: Inhibition of initiation, progression and metastasis. *International Journal of Molecular Sciences, 18*(4), 843. https://doi.org/10.3390/ijms18040843

Scarinci, E., Tropea, A., Notaristefano, G., Arena, V., Alesiani, O., Fabozzi, S. M., Lanzone, A., & Apa, R. (2019). "Hormone of darkness" and human reproductive process: Direct regulatory role of melatonin in human corpus luteum. *Journal of Endocrinological Investigation, 42*(10), 1191–1197. https://doi.org/10.1007/s40618-019-01036-3

Song, X., Sun, X., Ma, G., Sun, Y., Shi, Y., Du, Y., & Chen, Z. J. (2015). Family association study between melatonin receptor gene polymorphisms and polycystic ovary syndrome in Han Chinese. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 195,* 108–112. https://doi.org/10.1016/j.ejogrb.2015.09.043

Tamura, H., Jozaki, M., Tanabe, M., Shirafuta, Y., Mihara, Y., Shinagawa, M., Tamura, I., Maekawa, R., Sato, S., Taketani, T., Takasaki, A., Reiter, R. J., & Sugino, N. (2020). Importance of melatonin in assisted reproductive technology and ovarian aging. *International Journal of Molecular Sciences, 21*(3), 1135. https://doi.org/10.3390/ijms21031135

Tamura, H., Kawamoto, M., Sato, S., Tamura, I., Maekawa, R., Taketani, T., Asada, H., Takaki, E., Nakai, A., Reiter, R. J., & Sugino, N. (2017). Long-term melatonin treatment delays ovarian aging. *Journal of Pineal Research, 62*(2), e12381. https://doi.org/10.1111/jpi.12381

Tsui, K. H., Li, C. J., & Lin, L. T. (2024). Melatonin supplementation attenuates cuproptosis and ferroptosis in aging cumulus and granulosa cells: Potential for improving IVF outcomes in advanced maternal age. *Reproductive Biology and Endocrinology, 22*(1), 30. https://doi.org/10.1186/s12958-024-01311-w

Unfer, V., Raffone, E., Rizzo, P., & Buffo, S. (2011). Effect of a supplementation with myo-inositol plus melatonin on oocyte quality in women who failed to conceive in previous in vitro fertilization cycles for poor oocyte quality: A prospective, longitudinal, cohort study. *Gynecological Endocrinology, 27*(11), 857–861. https://doi.org/10.3109/09513590.2011.564687

Yang, Z., Du, X., Wang, A., Zhao, Y., Xia, Y., Shi, L., Ding, S., Yue, X., Xing, F., Ji, D., Liang, D., Zha, Z., Liang, C., Cao, Y., & Liu, Y. (2025). Melatonin ameliorates Pb-induced mitochondrial homeostasis and ovarian damage through regulating the p38 signaling pathway. *Ecotoxicology and Environmental Safety, 292,* 117937. https://doi.org/10.1016/j.ecoenv.2025.117937

Yi, S., Xu, J., Shi, H., Li, W., Li, Q., & Sun, Y. P. (2020). Association between melatonin receptor gene polymorphisms and polycystic ovarian syndrome: A systematic review and meta-analysis. *Bioscience Reports, 40*(6), BSR20200824. https://doi.org/10.1042/bsr20200824

Zare, H., Shafabakhsh, R., Reiter, R. J., & Asemi, Z. (2019). Melatonin is a potential inhibitor of ovarian cancer: Molecular aspects. *Journal of Ovarian Research, 12*(1), 65. https://doi.org/10.1186/s13048-019-0502-8