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Narrative Review

A NARRATIVE REVIEW OF ADDRESSING FEMALE REPRODUCTIVE DISORDERS: THE POTENTIAL ROLE OF MELATONIN.

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ABSTRACT

Disorders pertaining to the female reproductive system, encompassing conditions related to hormone regulation, fertility, and fetal well-being, are of significant global apprehension. In recent times, the utilization of melatonin supplementation has emerged as a potential therapeutic modality within the field of gynecology. In various animal models as well as in female subjects, the administration of melatonin has demonstrated potential therapeutic and preventive effects. These effects are primarily attributed to the antioxidant properties of melatonin and its ability to modulate hormone activity. The primary objective of this comprehensive literature review is to delve deeper into the existing body of evidence pertaining to the impact of melatonin supplementation in both animal and human studies. The specific focus of this investigation is to explore the potential utility of melatonin supplementation in the field of gynecology. Melatonin-containing supplements are readily available for purchase through online and brick-and-mortar retailers. Although these supplements are generally considered safe for supplementation, there remains a lack of consensus regarding the optimal dosage and duration of supplementation. In the context of short-term supplementation investigations, typically spanning a duration of no more than six months, preliminary findings indicate that the administration of melatonin at a daily dosage ranging from 2 to 18 mg exhibits promising prospects in enhancing fertility rate, oocyte quality, maturation, and the quantity of embryos produced. The current body of evidence regarding the impact of melatonin supplementation on gestational age and gestational outcomes is notably limited. Further investigation is warranted to evaluate the potential clinical implications of melatonin supplementation within the realm of gynecology. This necessitates the implementation of clinical trials and extended supplementation studies to ascertain any discernible clinical outcomes.

Keywords: *Melatonin supplementation, Gynecology, Hormone regulation, Fertility, Antioxidant properties*
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INTRODUCTION

The circadian clock, which is the body's internal clock, is essential to many biological processes, including reproduction. There are particular genes that control this clock; these genes are commonly called "clock genes." The reproductive system's ability to function depends on these genes [1].

The reproductive system can be harmed by circadian rhythm disruptions, such include those brought on by night shift work, jet lag, or sleep deprivation. Numerous chemicals in the bloodstream aid in the regulation of this circadian clock. One such material is the hormone melatonin, which is primarily generated at night [2].

The pineal gland is not the only tissue in the body that produces melatonin. It can shield the neurological system and has antioxidant qualities. By altering the body's equilibrium of reactive chemicals, melatonin can potentially have an impact on the reproductive system.

In addition to lifestyle choices and stress, gynecological and reproductive health can also be impacted by age-related declines in the quality and viability of reproductive cells. Research has indicated that night work can have an adverse effect on fetal development and be a contributing factor to metabolic and gynecological problems [3, 4].

Safe and effective therapies are required to enhance gynecological and reproductive health. Melatonin pills are widely accessible and purportedly beneficial for conditions such as jet lag, sporadic sleep disturbances, sleep disorders caused by stress, mood, and general health. On the appropriate dosage, length of treatment, or if melatonin actually improves gynecological and reproductive health, there is disagreement.

Although melatonin is known to affect the hormone system that regulates reproduction, nothing is known about how it can affect the health of women. In the context of gynecology and reproduction, this review intends to investigate the usage of melatonin supplements and explore their therapeutic significance.

The review covers many melatonin supplement gynecological and reproductive health subjects. First, it examines how melatonin supplementation affects hormone balance, fertility, and fetal health in women. Melatonin supplementation to improve fertility, oocyte quality, maturation, and embryo development is also reviewed in gynecology. Also examined are how melatonin supplementation impacts pregnancy outcomes and gestational age. The review also explores if 6-sulfatoxymelatonin levels might predict gynecological and reproductive health. Gynecology: melatonin doses, duration, risks, and interactions, especially during pregnancy. The review concludes by assessing the consensus and agreement among studies on melatonin's use in gynecology and emphasizing the necessity for future research to completely understand its therapeutic effects

METHODOLOGY

A systematic literature review examined the effects of melatonin supplementation on hormone regulation, fertility, and fetal well-being in women. The papers in this research were rigorously evaluated to determine their relevance and quality to provide a complete grasp of the topic area. Experimental, observational, and clinical trials are covered in this review. PubMed, Google Scholar, and academic databases were searched for relevant literature for this review. To find further relevant studies, the reference lists of the discovered papers were meticulously searched.

This review focused on English-language articles and studies. The review included published and unpublished studies and articles that met relevant criteria. The review analyzes animal and human studies thoroughly. Animal research was used to examine how melatonin administration affects reproductive parameters. Melatonin supplementation in gynecology was studied in humans.

REDUCTION-OXIDATION MODULATION IN THE OVARY

Melatonin has been researched for its potential to protect several physiological systems because of its well-known antioxidant qualities. It increases the activity of antioxidant enzymes and aids in the elimination of dangerous free radicals [5]. Melatonin helps protect mitochondria in the ovaries and lowers indicators of cell death.

The hormonal system in charge of reproduction may benefit from melatonin's antioxidant properties. It might increase progesterone synthesis, lessen oxidative damage to follicles, and promote oocyte maturation. The ovaries synthesize and absorb melatonin, indicating a major significance for this hormone in the reproductive system of women.

Melatonin's capacity to suppress tumor growth, lower inflammation, and alter the immune system has led to its application in the treatment of ovarian cancer, in addition to its antioxidant qualities. There is evidence that melatonin therapy reduces the expression of some markers linked to metastasis and tumor growth. It also works by interfering with specific receptors to lessen ovarian inflammation [6].

To sum up, melatonin is a potentially useful therapeutic agent for ovarian cancer treatment and reproductive health due to its antioxidant and protective properties.

THE EFFECTS OF MELATONIN ON REPRODUCTION – ANIMAL MODELS

Mammals' reproductive systems are impacted by various signals, environmental cues (such as variations in light and temperature), and the availability of food.

The suprachiasmatic nucleus of the brain is influenced by light and darkness, which has an effect on sexual behavior and reproduction. Though the effects differ depending on the species, greater exposure to light improves rat reproductive [7], whereas shorter exposure has the opposite effect. Certain species, such as mares, on the other hand, benefit from shorter exposure to light [8].

In this mechanism, melatonin is involved. It influences the reproduction-related hormone system directly and indirectly by promoting the synthesis of several chemicals that support the development of follicles and the maturation of eggs.

In addition to influencing the release of hormones crucial for reproduction, melatonin also lessens the damage done to ovarian follicles, which increases fertility. Greater melatonin levels during pregnancy promote healthy placental and fetal growth.

Melatonin is essential for both ovulation and preserving the health of the uterus, according to research on rats lacking a pineal gland (referred to as pinealectomized rats) [9]. Treatment with melatonin substitutes lessens the effects of pinealectomy.

The endometrium's melatonin receptors highlight the hormone's importance in reproduction. Long-term melatonin administration in mice results in higher litter sizes and better egg quality and quantity [10].

Fish are among the other animals whose reproductive systems are impacted by melatonin. increased melatonin levels in zebrafish subjected to constant darkness result in increased rates of reproduction.

Genes like Kiss-1 and Kiss-2, which stimulate gonadotropin secretion and support reproductive maturation and function, are likewise influenced by melatonin. These genes affect the reproductive system in a number of ways, including hormone cycles and puberty [11].

THE EFFECTS OF MELATONIN ON REPRODUCTION – HUMAN STUDIES

Women with polycystic ovarian syndrome (PCOS) may experience irregular menstrual periods, metabolic disorders, and an elevated risk of miscarriage. 40 women with PCOS were included in a study that discovered using melatonin pills for six months helped them return to normal hormone levels and menstrual cycles [12].

Because melatonin has anti-androgenic qualities, it can lessen the generation of hormones that are problematic in diseases like PCOS. Additionally, it may help with ailments like endometriosis, which can cause discomfort and problems with conception. Supplementing with melatonin can help with pain management, menstruation issues, and even preserve developing embryos by lowering oxidative stress.

In women with reproductive problems, melatonin supplements have demonstrated promise in increasing fertility rates as well as the quantity and quality of eggs produced. Melatonin supplementation has also been shown to boost hormone levels, happiness, and general well-being in studies on menopausal women [13].

All things considered, melatonin is important for the female reproductive system, and as we age, it starts to diminish, which is related to menopause and hormonal changes.

6-SULFATOXYMELATONIN CONCENTRATION: A RELIABLE BIOMARKER ON GYNECOLOGY?

Urine contains a chemical called 6-sulfatoxymelatonin, which is a useful indication of melatonin activity. It's been applied to evaluate gynecological problems.

Women who work night shifts have been found to have higher amounts of progesterone and estradiol in their urine when their 6-sulfatoxymelatonin levels are lower than those of day shift workers [14]. Its link to the female reproductive system is demonstrated by the lower levels of this chemical in girls going through early onset puberty.

Conversely, compared to women without PCOS, women with PCOS typically have greater urine levels of 6-sulfatoxymelatonin during their periods. The hormonal abnormalities linked to PCOS are linked to this increase [15]. This material, however, is not a trustworthy indicator of endometriosis.

MELATONIN IN PREGNANCY

Pregnancy care has been found to benefit with the inclusion of melatonin supplements. Melatonin may shield the developing embryo's brain, placenta, and general development when consumed during pregnancy, according to research on animals [16]. Melatonin modulates the baby's internal clock, which affects its development, immune system, and defense against dangerous substances. It also crosses the placenta with ease.

The antioxidant qualities of melatonin are advantageous to the placenta because they boost the synthesis of protective enzymes and have an impact on the formation of the baby's internal clock. This protects the developing baby's brain from oxygen level fluctuations and oxidative damage.

Supplemental melatonin has demonstrated potential advantages in managing specific pregnancy-related issues. Fetal growth restriction (FGR), for example, can have major repercussions and affects 5–10% of pregnancies [17]. Melatonin supplementation has been shown in studies to be safe for both mother and child and to lower markers of placental oxidative stress.

Another pregnancy disorder that affects 3 to 10% of pregnancies is called pre-eclampsia, and it is characterized by elevated blood pressure and proteinuria [18]. Pre-eclampsia has been linked to decreased levels of enzymes and melatonin receptors. The injection of melatonin has demonstrated preventive effects in averting pregnancy-related issues by preserving the baby's mitochondria and placental DNA and lowering indicators of oxidative stress and inflammation [19]. Furthermore, supporting melatonin's safety during pregnancy, certain human research indicate that it helps lengthen gestation and lessen the requirement for hypertension medications.

APPROACHES TO POSOLOGY

Based on available data, using melatonin supplements may improve a woman's gynecological health, particularly for those who aspire to become pregnant [20]. It not only raises reproductive parameters but also promotes general well-being. In addition to its beneficial benefits on mental health, melatonin appears to have advantages for bones and muscles.

Since melatonin is a well-researched and safe sleep aid, its application in gynecology also seems promising. Despite the paucity of trials, the majority have employed daily dosages between 2 and 18 mg.

However, more extensive and long-term research is required to fully understand potential dangers and interactions with other medications before melatonin is advised for pregnant women. To be safe, it's also critical to look at the health of those whose moms used melatonin pills while they were pregnant.

DISCUSSION

The narrative review offers a comprehensive overview of melatonin supplementation's potential impact on gynecology and reproductive health. Key findings highlight melatonin's role in hormone regulation, potential benefits for fertility enhancement, and positive implications during pregnancy. These findings suggest that melatonin supplementation could be considered as an adjunct therapy for gynecological conditions and fertility treatment, pending further clinical trials to determine optimal dosages. Additionally, monitoring 6-sulfatoxymelatonin levels may aid in diagnosing circadian-related gynecological disorders, although more research is needed to confirm its clinical utility. The review underscores the necessity for future research and evidence-based guidelines to guide clinical practice in gynecology.

Policy implications are also evident, as regulatory agencies and healthcare organizations should support and facilitate research into melatonin's gynecological applications. As the evidence continues to evolve, it is essential to align policy development with emerging findings to ensure safe and effective gynecological care, especially when considering melatonin supplementation during pregnancy. In conclusion, while the review presents promising prospects for melatonin in gynecology, further research and careful clinical consideration are essential to harness its full potential and provide evidence-based care to women with reproductive disorders.

CONCLUSION

Melatonin's antioxidant qualities and hormone-modulating abilities make it a possible therapeutic and preventive option in the fields of obstetrics and gynecology. A daily dosage of 2 to 18 mg of melatonin has been shown to boost fertility rate, oocyte quality, maturation, and embryo quantity in melatonin supplementation studies that have lasted anywhere from a few days to up to six months. Daily dosages of 8 to 30 mg appeared to be safe for both the mother and the fetus in cases of gestational abnormalities, and they also had a significant therapeutic effect. In the field of obstetrics and gynecology, however, a clear agreement regarding the appropriate dose and duration of supplementation has not yet been obtained. Even though melatonin supplements seem to be useful and safe, long-term clinical trials are necessary to evaluate further clinical effects, especially during the pregnant period.

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List of abbreviations
PCOS- Polycystic ovarian syndrome
FGR- Fetal growth restriction

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REFERENCES
1. M.H. Johnson, A. Lim, D. Fernando, M.L. Day, Circadian clockwork genes are expressed in the reproductive tract and conceptus of the early pregnant mouse, Reproductive biomedicine online, 4 (2002) 140-145.
2. D.X. Tan, L.C. Manchester, L. Fuentes-Broto, S.D. Paredes, R.J. Reiter, Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity, Obesity reviews, 12 (2011) 167-188.
3. J.L. Zhu, N.H. Hjollund, J. Olsen, Shift work, duration of pregnancy, and birth weight:: the National Birth Cohort in Denmark, American Journal of Obstetrics and Gynecology, 191 (2004) 285-291.
4. L.J. Stocker, N.S. Macklon, Y.C. Cheong, S.J. Bewley, Influence of shift work on early reproductive outcomes: a systematic review and meta-analysis, Obstetrics & Gynecology, 124 (2014) 99-110.
5. E. Miller, A. Morel, L. Saso, J. Saluk, Melatonin redox activity. Its potential clinical applications in neurodegenerative disorders, Current Topics in Medicinal Chemistry, 15 (2015) 163-169.
6. L.G.A. Chuffa, L.A. Lupi Júnior, F.R.F. Seiva, M. Martinez, R.F. Domeniconi, P.F.F. Pinheiro, L.D. dos Santos, F.E. Martinez, Quantitative Proteomic Profiling Reveals That Diverse Metabolic Pathways Are Influenced by Melatonin in an in Vivo Model of Ovarian Carcinoma, Journal of Proteome Research, 15 (2016) 3872-3882.
7. T. Mousa-Balabel, R.A. Mohamed, Effect of different photoperiods and melatonin treatment on rabbit reproductive performance, Journal Veterinary Quarterly, 31 (2011) 165-171
8. G. Williams, J. Thorson, L. Prezotto, I. Velez, R. Cardoso, M. Amstalden, Reproductive seasonality in the mare: neuroendocrine basis and pharmacologic control, Domestic Animal Endocrinology, 43 (2012) 103-115.
9. W.Y. Chan, T.B. Ng, Effects of pineal indoles on ovarian response to gonadotropin-induced ovulation in mice, Journal of Neural Transmission/General Section JNT, 100 (1995) 239-246.
10. C. Song, W. Peng, S. Yin, J. Zhao, B. Fu, J. Zhang, T. Mao, H. Wu, Y. Zhang, Melatonin improves age-induced fertility decline and attenuates ovarian mitochondrial oxidative stress in mice, Scientific Reports, 6 (2016) 35165.
11. M. Tena-Sempere, KiSS-1 and reproduction: focus on its role in the metabolic regulation of fertility, Neuroendocrinology, 83 (2006) 275-281
12. V. Tagliaferri, D. Romualdi, E. Scarinci, S.D. Cicco, C.D. Florio, V. Immediata, A. Tropea, C.M. Santarsiero, A. Lanzone, R. Apa, Melatonin Treatment May Be Able to Restore Menstrual Cyclicity in Women With PCOS: A Pilot Study, Reproductive Sciences, 25 (2017) 269-275.
13. O. Vakkuri, A. Kivelä, J. Leppäluoto, M. Valtonen, A. Kauppila, Decrease in melatonin precedes follicle-stimulating hormone increase during perimenopause, European journal of endocrinology, 135 (1996) 188-192.
14. E.S. Schernhammer, B. Rosner, W.C. Willet, F. Laden, G.A. Colditz, S.E. Hankinson, Epidemiology of urinary melatonin in women and its relation to other hormones and night work, Cancer Epidemiology Biomarkers and Prevention, 13 (2004) 936-943.
15. R. Luboshitzky, G. Qupti, A. Ishay, Z. Shen-Orr, B. Futerman, S.J. Linn, Increased 6-sulfatoxymelatonin excretion in women with polycystic ovary syndrome, Fertility and sterility, 76 (2001) 506-510.
16. S. Aversa, S. Pellegrino, I. Barberi, R.J. Reiter, E. Gitto, Potential utility of melatonin as an antioxidant during pregnancy and in the perinatal period, The Journal of Maternal-Fetal & Neonatal Medicine, 25 (2012) 207-221.
17. L.M. Nardozza, A.C. Caetano, A.C. Zamarian, J.B. Mazzola, C.P. Silva, V.M. Marcal, T.F. Lobo, A.B. Peixoto, E. Araujo Junior, Fetal growth restriction: current knowledge, Archives of gynecology and obstetrics, 295 (2017) 1061-1077.
18. B.W.J. Mol, C.T. Roberts, S. Thangaratinam, L.A. Magee, C.J.M. de Groot, G.J. Hofmeyr, Pre-eclampsia, Lancet, 387 (2016) 999-1011.
19. S.R. Hobson, S. Gurusinghe, R. Lim, N.O. Alers, S.L. Miller, J.C. Kingdom, E.M. Wallace, Melatonin improves endothelial function in vitro and prolongs pregnancy in women with early-onset preeclampsia, Journal of pineal research, 65 (2018) e12508
20. K.M. Sharkey, L.F. Fogg, C.I. Eastman, Effects of melatonin administration on daytime sleep after simulated night shift work, Journal of sleep research, 10 (2001) 181- 192.

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