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REVIEW ARTICLE

Melatonin in Female Fertility: Multifaceted Role From Reproductive Physiology to Therapeutic Potential in Polycystic Ovary Syndrome, Endometriosis, and Ovarian Failure

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Melatonin, synthesized by the pineal gland, plays a pivotal role in female reproductive physiology. In addition to its established function in regulating circadian rhythms, melatonin influences critical reproductive processes, such as ovulation, menstrual cycle regulation, and fertility. Recent studies underscore melatonin's regulatory effects on the hypothalamic-pituitary-gonadal axis, influencing the secretion of gonadotropins, including follicle-stimulating hormone and luteinizing hormone. Furthermore, melatonin has been implicated in the pathophysiology of reproductive disorders, such as polycystic ovary syndrome and endometriosis, where its antioxidant and anti-inflammatory properties may enhance ovarian function and fertility. Melatonin also plays a protective role against oxidative stress in granulosa cells, thereby improving oocyte quality and increasing the potential for successful fertilization. These effects position melatonin as a promising therapeutic agent in assisted reproductive technologies, such as in vitro fertilization. Studies demonstrate that melatonin supplementation mitigates the harmful effects of reactive oxygen species on ovarian cells, enhancing embryo development and improving pregnancy outcomes. By counteracting oxidative stress and apoptosis in reproductive tissues, melatonin emerges as a crucial factor in promoting reproductive health.

Keywords: Female reproductive health; Infertility; Melatonin; Menstrual cycle; Ovulation

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INTRODUCTION

Melatonin is a hormone produced by the pineal gland in the brain that plays a crucial role in regulating circadian rhythm, sleep-wake cycles, and mood [1]. Recent research has shed light on the impact of melatonin on female reproductive physiology [2]. Studies have shown that melatonin influences the menstrual cycle, ovulation, and fertility [3-5]. The hormone has been shown to impact the secretion of other hormones involved in the regulation of reproductive functions, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [6]. Additionally, melatonin has been linked to menstrual irregularities, polycystic ovary syndrome (PCOS), and infertility [7-9]. This highlights the need for further research to fully understand the role of melatonin in female reproductive physiology and its potential as a therapeutic target for reproductive disorders.

Disruptions to the normal production and secretion of melatonin, such as exposure to artificial light at night or disruptions to the sleep-wake cycle, have been linked to menstrual irregularities, changes in ovulatory function, and infertility [10,11]. Moreover, melatonin has a regulatory effect on the onset of puberty [12,13]. It acts on the hypothalamic-pituitary-gonadal (HPG) axis, which is the primary hormonal control system that regulates reproductive function [2,13]. During puberty, the pineal gland becomes less active, leading to a decrease in melatonin levels. This decrease in melatonin levels allows for an increase in gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, which stimulates the pituitary gland to release LH and FSH [14-16]. LH and FSH then stimulate the gonads (ovaries in females, testes in males) to produce and secrete sex hormones, such as estrogen and testosterone, respectively. The sex hormones then act on the HPG axis, leading to the onset of puberty, the maturation of the reproductive organs, and the development of secondary sexual characteristics [17]. It is important to note that melatonin is just one of several factors that regulate the onset of puberty, and its exact role may vary between individuals and populations. Nevertheless, melatonin plays a key role in the regulation of the HPG axis and the onset of puberty.

Additionally, research has shown that melatonin supplementation may have therapeutic benefits for certain reproductive health conditions, such as PCOS and endometriosis, which are both associated with female infertility [9,18]. Thus, the purpose of this article is to thoroughly review and present the association between melatonin and female reproductive functions, which has been largely neglected and remains elusive, unlike the numerous studies conducted on other endocrine factors and hormones.

PROPERTIES AND PHYSIOLOGICAL EFFECTS OF MELATONIN

Epiphysis cerebri or "pineal gland" is situated near the cortex of the brain, between two hemispheres join which is also known as the diencephalon. This pineal gland releases a serotonin-derived hormone called "melatonin" hormone, also known as N-acetyl-5-methoxytryptamine. Lerner, one of the renowned skin specialists, had done an experiment in the year of 1958 on a frog and had observed a change in the complexion of the frog skin and assumed the action of melatonin [19]. A few years later, approximately in the year 1960, Lerner and his colleagues described the chemical formulae of melatonin [19]. Previously, more concisely from the last 50 to 60 years back, it was believed that melatonin has effects only on various physiological processes. For example, pubertal attainment [6], aging process [20], circadian rhythms [21], sleep-wakefulness cycle [22], etc. Melatonin also has its effects on other parts of the human body, as it regulates neuroendocrine functions [23], and functions of the cardiovascular system [24], besides its oncostatic effects [25]. Intake of exogenous melatonin not only as medicine but also in other forms also very crucially acts on the sleep cycle and body temperature controlling mechanism in humans. The sleep-inducing effect of melatonin expands by heat loss due to more body temperature at the time of sleeping [26-28]. The sleep-inducing effects of melatonin have been observed with oral doses ranging from 0.3 mg to 1.0 mg in healthy individuals [29]. While often termed "hypnotic," melatonin is more accurately described as a "soporific," as it induces dizziness and modulates circadian rhythms, making it a chronobiotic [30,31].

THE PHOTONEUROENDOCRINE SYSTEM

The duration of the diurnal and nocturnal rhythms can be received at the level of retina in mammals which is also known as the photoperiodic effect. This rhythm or periodical surge has occurred through a multisynaptic neural pathway for the melatonin hormone secretion to the epiphysis cerebri also known as the pineal gland [32]. The suprachiasmatic nucleus of the hypothalamus mainly controls the biological clock by regulating the release of pineal melatonin [33]. The production of melatonin internally is been reduced by exposing it to bright light naturally or artificially. After sunset, melatonin is released in adults between 19:30 and 21:30 hrs, and in children aged 6 to 12 years, between 19:00 and 21:00 hrs [34]. The hormonal depiction of the photoperiod varies according to the daytime or the diurnal period by the duration of the secretion of the melatonin hormone [35]. During the daytime, the administration of melatonin creates a half-life of 35−45 minutes [36].

MELATONIN AND FEMALE REPRODUCTIVE PHYSIOLOGY

Melatonin and its role in sexual maturation

In a transverse study, melatonin level was tested from serum during the nighttime among 367 individuals starting from the age of 3 days to 90 years of age [37]. After close observation, these researchers have inferred that between 1 and 3 years of age the children have the highest level of nighttime serum melatonin concentration. On the other hand, the researchers examined individuals from childhood through puberty and into young adulthood, observing a gradual reduction averaging 80% during these stages. This study can be related to a previous study where it explained the gradual reduction of 75% in the nighttime serum melatonin concentration as analyzed between children aged of 1 years to 5 years up to young adults [37]. Pubertal maturation development is related to the few signs and symptoms of the reduction in the nighttime serum melatonin concentration [37]. Conversely, the expansion of tanner stages is also correlated with this nocturnal serum concentration of melatonin [38]. These observations suggest that external melatonin sources may suppress GnRH secretion, potentially affecting pubertal maturation in children [39,40]. Additionally, melatonin use has become prevalent in diagnosing sleep disorders in children and adolescents, raising questions about

its impact on pubertal onset due to altered nocturnal serum melatonin concentrations.

Physiological crosstalk between melatonin and puberty

The development of children into an adult capable of maintaining the normal human reproductive cycle is allied with proper magnification and maturation of accessory sex organs. The journey from childhood to adulthood needs to follow some proper steps, which are still unknown, fully [41,42]. The hormonal changes occur in a rhythmic manner which indicates the onset of puberty. The onset of puberty is related to the release of GnRH [43]. The GnRH neuronal axons are extended from the hypothalamic preoptic area up to the arcuate nucleus [17,42]. The hypothalamus maintains the gonadal hormone functions via the pituitary (known as the HPG axis). It helps to keep the hormonal milieu when a child is in his mother's womb, i.e., from the embryonic stage, the hormonal axis becomes organized, and after parturition to puberty onset this hormonal axis remains hibernated [44]. The exact mechanisms that trigger the onset of puberty remain unclear. However, the activation of GnRH secretion, along with the suppression of GnRH inhibitors, is thought to play a key role in pubertal maturation. In addition to GnRH activators and inhibitors, neurotransmitters and neuropeptides also play a crucial role. These signals, originating from the hypothalamus, are influenced by peripheral or gonadal signals. Several studies have identified various factors influencing the initiation of puberty [45], including 1) sex-specific differences, 2) genetic inheritance, 3) nutritional status, 4) circadian rhythm patterns, 5) endometrial conditions, 6) hormonal influences such as leptin, ghrelin, IGF-I, and sex steroids, and 7) environmental disruptions affecting hormonal regulation. Hershey (1996) identified the Kiss-1 gene, named after Hershey's Kisses, which encodes kisspeptins that act via the GPR54 receptor (KISS1R) [46]. Kisspeptin-10 was recognized in 2005 as a major regulator of GnRH neuronal activity [47], critically linking kisspeptin to reproductive and electrophysiological functions [48-50]. Other regulatory molecules also contribute to the onset of puberty [17].

Based on a few animal studies, exposure to a specific photoperiod condition leads to the suppression of kisspeptin following melatonin administration [51]. The expression of kisspeptin can be affected to some extent by the diminishing effect of decreased photoperiod due to reduced melatonin levels internally, which can also be referred to as surgical pineal gland abolition [52]. A relevant study explained that the first administration of melatonin decreases the level of the outcome of kisspeptin gene expression, whereas extended administration will lead to an uplift in the level of kisspeptin gene expression [53]. This will excite the gonadal axis. Therefore, it can be inferred that melatonin impacts the functions of the reproductive system depending on the administration in different phases. The above-mentioned findings are based on the review of some collected research studies, exploring the outcome of melatonin on adolescence and the frequent changes of kisspeptin gene expression.

Animal studies

Exogenous melatonin administration delays sexual maturation in children, and long-term use is prohibited. Seasonal breeding models, including sheep and hamsters (Syrian and Siberian), have shown that the pulsatile release of melatonin is regulated internally. This mechanism parallels the transition from the nonbreeding to breeding season, similar to adolescence [54-57]. Several homogeneities could be put out within adolescence and transformation to nonbreeding season. For example, one experiment performed on female sheep which is at the age before puberty and seasonally nonbreeding showed that the LH surge which is the main reason for ovulation, does not happen, even though inborn ability and the neuronal connection are as normal as compared with other mammals [58,59]. Then, the LH level becomes reduced. Before adolescence, secretion of LH becomes rhythmical but at the time of nonbreeding season the LH release is tremendously lesser [58]. However, these uniformities are exciting but the total hormonal and neuronal regulation that controls the reproductive system is still an uncertainty [41]. Several studies have explored the effect of melatonin on puberty and its modulation by photoperiod. One study found that administering melatonin for 10 days during the pre-pubertal stage delayed puberty in male hamsters, normally reaching puberty at 25 days [60,61]. However, similar treatment in prepubertal gilts yielded no significant effects [62]. In ewe lambs, melatonin delayed puberty by about four weeks compared to controls [62], while in Suffolk ewe lambs, it advanced puberty by three weeks [63]. Pinealectomy in ewe lambs also delayed puberty [62]. In Soay ewes, changes in kisspeptin levels correlated with altered melatonin secretion and reproductive development [64]. The Soay ewe typically breeds during autumn and winter when longer nights correspond with increased melatonin secretion. In contrast, male Syrian hamsters, as long-day breeders, show reduced melatonin levels during shorter nights in spring and summer. However, whether kisspeptin cells activate melatonin receptors under these conditions remains unclear [60]. Simonneaux et al. [65] suggested that RFRP-3, part of the RF-amid peptide family, inhibits GnRH release, potentially influencing reproductive timing.

Human studies

Very few studies have been done only on human beings and primarily are based on the dosage of melatonin and secondarily on the onset of puberty. An arbitrarily controlled trial also known as meldos trial where the children and youth experienced the maximum dosage of melatonin for their uncontrollable insomnia [66]. A total strength of 69 participants who were in the age between 6 to 12 years had experienced the meldos trial. Out of those 69 subjects only 59 of them had enclosed the datasheet of the first report [66]. The study involved children who had been taking melatonin for at least six months. They were asked questions about puberty, such as the Tanner scaling for male and female subjects, and their parents' experiences of their first menstrual cycle or ejaculation. However, only 19 participants had reached puberty with-

in the normal age range. The same cohort from the initial study was reassessed after 9 or 12 years. Of the 33 participants in the follow-up, pubertal timing was compared to general population data. The study revealed that 31.3% of participants experienced delayed puberty, compared to 17% in the control group [67]. In a long-term study, children with developmental disorders related to their neurological or biological sleep patterns, which were untreatable, were treated with melatonin [68]. The study had specific criteria, including a double-blind, placebo-controlled crossover trial of sustained-release melatonin. The participants were interviewed by phone every three months for up to 3.8 years. Of the five children with major neuro-developmental disorders, which were observed before the melatonin treatment, puberty was observed at the age of 12 to 15 years. The remaining children completed puberty within normal limits, with an average age of 13.4± 1.4 years. Overall, very few studies have investigated the timing of puberty in young children and adolescents who received prolonged melatonin treatment. The three studies available have a small sample size, limited scope, and poor measures of puberty timing, making it difficult to draw any definitive conclusions.

Magee et al. [69] recommended the probability of the vulnerability of humans to light in puberty. Given one observation, menarche was found to be more susceptible among the blind girls before their usual age but this information was not accepted [45]. According to other studies as recommended in the winter season than in the summer females are more prone to menarche [70,71] implying that light can be an obstruction at the beginning of puberty. Colder regions such as the Arctic region are correlated with decreased pituitary-gonadal function at a less frequent rate of conception which can be an opposite phenomenon in comparison with earlier findings [72]. According to the studies, it was found that melatonin level decreases at a speed-up rate at the time of adolescence in humans [73,74] and after a close observation, so, as an inference, the beginning of puberty (among the adolescents in between Tanner stage II and III) followed by the reduction in melatonin synthesis and secretion [73].

Evidence of melatonin receptor expression in ovarian cells

The physiological functions of melatonin are interceded not only by definite membrane-bound receptors but also through the nuclear binding sites. Nuclear binding sites relate to the members of the nuclear receptor superfamily of RZR/ROR [75]. Researchers have identified three different types of melatonin receptors that are located on the membrane of mammalian cells, and they have replicated three corresponding proteins. Among these three subtypes, MT1 and MT2 are two of the receptors that belong to the seven transmembrane G-protein coupled receptor family [76].

The third subtype of melatonin receptors is known as MT3, which is also identified as quinone reductase 2. In some animals, this subtype serves as both an enzyme and a receptor for melatonin [77,78]. When MT1 or MT2 receptors are stimulated in target cells, it can lead to the inhibition of adenylate cyclase activity. This is part of the signal transduction pathway [79]. The activation of MT1 and MT2 receptors typically results in a reduction of cyclic adenosine 3',5'-monophosphate (cAMP) production, which is typically triggered by forskolin. This, in turn, leads to a decrease in the activity of protein kinase A. These biochemical pathways are commonly involved in the functioning of MT1 and MT2 receptors [80]. These receptors can give rise to a signal transduction mechanism. Melatonin triggers various second messenger pathways by communicating with the same receptor subtype based on the tissue, organ, and species. MT1 and MT2 melatonin receptors are observed in different rodent tissues. Human melatonin receptors are found in a variety of organs, including the brain, skin, retina, cardiovascular system, immune cells, liver, gallbladder, intestine, mammary glands, fat cells, prostate, uterus, and kidney [81].

Ovarian function appears to be influenced by melatonin, with higher melatonin concentrations observed in human ovarian follicular fluid (FF) compared to plasma [81]. Melatonin modulates granulosa cell (GC) functions, including folliculogenesis and steroidogenesis, as demonstrated in hamsters [82] and humans [83]. MT1 and MT2 melatonin receptors are present in human GCs, luteal cells [84,85], and rat ovaries [86].

Functions of melatonin in the growth and development of follicles

Endocrine, paracrine, and autocrine mechanisms are the three different processes involved in follicular development within the ovary. The first stage of the folliculogenesis process involves the accumulation of several primordial follicles. The subsequent stages that the process of folliculogenesis involves are the primary, preantral, and antral stages. After these three stages, they follow the preovulatory and ovulatory stages where they become capable of releasing the ovum which is able for fertilization. Based on different species, the growth of preantral and early antral stages crucially becomes important on the level of circulating FSH. Out of the bulk amount, only a few of them had been allotted from the ovarian follicular reserve during the development of follicles in each reproductive cycle [87]. Individuals who are receiving in vitro fertilization (IVF) treatment typically have follicles that are filled with fluid and are larger in size. These large follicles have a high amount of melatonin concentration as compared to small fluid-filled follicles. Melatonin and its two precursors, serotonin and N-acetyl-serotonin along with their two synthesizing enzymes NAT and HIOMT can be observed in human ovaries and its homogenates [88], which may indicate a possibility of intraovarian synthesis of melatonin and its release into the FF. Nowadays, by current studies, it is observed that a huge quantity of melatonin which is identified in the ovary and from the circulation, the preovulatory FF can be derived. This observation has come to an end by observing the rat and cat ovaries which contain 3-H melatonin [89]. With this content, 3 mg of melatonin was administered in tablet form to the women receiving fertility treatment, FF contained a high concentration of melatonin as compared to control [90]. After the maturation of follicles, they

become dependent on LH rather than FSH, which may be a mechanism related to the selection of follicles for their development. The selection of follicles is related to the mRNA expression timing and LH receptor encoding in GCs [91]. The expression of LH has been observed in an increased version than FSH in GCs by administering a dosage of melatonin (10 pM to 100 nM) in human GCs [85].

The growth and differentiation of ovarian cells are significantly influenced by sex steroids. The theca cells and GCs of the ovary are essential for steroid biosynthesis, highlighting the interdependence of these two cell types in estrogen (E) production [92]. This mechanism is explained by the two-cell, two-gonadotropin model. Steroidogenic enzymes, such as P450-side chain cleavage enzyme (P450scc), P450 17-alpha-hydroxylase/C-17, 20-lyase (P450 c17), and P450 aromatase, regulate the biosynthesis of progesterone (P), androstenedione (A), and estradiol (E2). These enzymes are activated by cAMP within theca cells and GCs, which is modulated by FSH and LH through membrane-bound receptors [93]. In porcine theca cells, the key steroidogenic genes, CYP11A, CYP17, and CYP19, are regulated by cAMP. Alongside gonadotropins, estrogen drives the growth and differentiation of GCs [92]. Progesterone plays a limited yet crucial role in follicular development and ovulation, as shown by studies on progesterone receptor knockout mice, where ovulation was absent [94,95]. Androgens promote premature follicular growth but also induce atresia and apoptosis [96,97]. Melatonin influences sex steroid synthesis during follicular maturation. Notably, melatonin increases P and A production in mouse pre-antral follicles, while reducing CYP11A and CYP17 expression [98,99].

Following the separation of theca cells and GC, melatonin decreases the progesterone synthesis by theca cells, but it does not affect the GCs. Melatonin may directly repress follicular or thecal steroid synthesis pathway by cAMP regulation. The inferences are constant with information elaborating that melatonin clogs the expression of steroidogenic dreadful regulatory proteins [100]. It is trusted that steroidogenic acute regulatory protein determines the transfer of cholesterol through the intermembrane space into the inner membrane space, where P450scc converts cholesterol into pregnenolone. Melatonin (10 nM) administration for three hours decreased the steroidogenic regulatory protein expression (chronic) activated by human chorionic gonadotrophin (hCG) in mouse Leydig tumor cells. On the other hand, the undeviating effect of melatonin on the synthesis of follicular steroid is not so simple; it is dependent on the thecal cell and GC type, the length of treatment (acute or chronic), experimental model (cell culture or culture of follicles), species, and dosage. The growth factors that are synthesized regionally such as insulin-like growth factors (IGF), members of the transforming growth factor b (TGF-b) superfamily (inhibins, activins, and bone morphogenic proteins [BMP]), work together with gonadotropins across the total follicular growth. At the time of follicular development, the IGFs are synthesized by the GC [101]. IGFs are mitogenic as well as antiapoptotic peptides that ensure variation with the metabolic effect as insulin is conducted by attaching to specific high-affinity membrane receptors. The activation of DNA synthesis happens only by IGF-1 and IGF-2 with relation to the secretion of E2 and progesterone from human GCs and the granulose luteal cells [101].

IGF-1 acts as antiapoptotic in ovarian follicles but ovarian apoptosis is controlled by the IGF-binding proteins [102]. The cultured human GCs activate or enhance IGF-1 production by administration of melatonin (0.01 to 10 mg/mL) [103]. A recent study by Picinato et al. [104] elaborated that a melatonin dosage of 0.1 mM influences the IGF-1 receptor and initiates two intracellular signaling pathways: the p13K/AKT, which is majorly involved with cell metabolism, and the MEK/ERKs, which takes part in cell growth and development with the differentiation. The IGF-β superfamily was communicated by ovarian cells and oocytes in a developmental, step-related manner, and their functions between two ovaries regulate the follicular development. TGF-β is produced in case of humans by both the theca cells and GC [105]. The TGF-β also enhances the reveal of FSH receptors [106], which multiplies FSH stimulated aromatase activity along with the production of progesterone and the attraction of LH receptor by GC [107]. In human benign prostate epithelial cells, melatonin stimulates the production of TGF-β [108]. In the growth of antral follicles, members of the TGF-β superfamily, including BMPs and growth and differentiation factor-9 (GDF-9), play an important role. Oocytes can manufacture the BMP-15 and GDF-9 which may exert their controlling effect on gonadotropins. The BMP-15 had been observed to weaken the actions of FSH on rat granulose cells by suppressing the FSH receptor expression [109]. GDF-9 has another function of reducing the E2 and progesterone production by activating the FSH and has a major function in the weakening of FSH stimulated LH receptor construction [110]. Following the aforementioned findings, the relationship between melatonin, BMP-15, and GDF-9 in growing follicles has been studied. Atresia, which is an apoptotic process, is supposed to be controlled by the proapoptotic and antiapoptotic factors. It was elaborated previously the relationship between follicular atresia, apoptosis, and nitric oxide (NO) emergence in the development of follicles within different sized follicles. No variation regarding the concentrations between nitrite and nitrate has been observed. Small sized follicles contain more apoptotic cells compared with the large sized follicles [111]. Small sized follicles due to poor response regarding gonadotropins undergo degeneration through the programmed cell death. Zhang et al. [112] proposed that, oxidative stress also stimulate the process of apoptotic mechanism during atresia. At the time of follicular growth, phagocytic macrophages increase in their number [100]. Reactive oxygen species (ROS) are known to be generated or synthesized by the endothelial cells [113]. The ROS in GCs of antral follicles, which are steroidogenically active, deliver more amount of energy which is needed by the cells [114]. In atretic follicle, oxidative stress mediated apoptosis are being regulated by the reduced levels of few antioxidant enzymes like SOD, catalase, etc. [115].

Usually, aformentioned enzymes prevent the GCs from vandal-

ization and obstruct atresia [116]. The atretic degeneration is shown to be controlled by the members of BCl2 family. After comparing with wild-type (BCl2, p/p) ovaries, it had been observed that reduction of BCl2 family can affect the quantity of healthy follicle numbers rather increasing the numbers of abnormal follicles [117]. The over declaration of BCl2 on GCs of growing follicles can lead to decreased apoptosis of the aforementioned cells [118]. Casp3-/- follicles, another type of follicle, have shown not to be discarded as caspases or casps enhance follicular atresia [119]. Recent studies have explained that melatonin protects the attraction of the mitochondrial pathway of apoptosis by influencing BCl2 declaration and decreasing casps-3 activity. Melatonin (10 mg/kg) injection markedly protects hepatocyte apoptosis in mice infused at the time of malarial infection by obstructing the casps-3 activity [120]. Rats with more age express the changes within the apoptosis in the liver and moreover enhances cytochrome-c mitochondrial emancipation, relative declaration of Bax to BCl2, and activity of casps-3, but after the administration of melatonin by drinking water (20 mg/L) for nearly about 4 weeks or a month, the aforementioned changes were overridden [121].

The accumulation of signals other than ovary but internal follicular factors exhibits the gateway of the follicle either towards development or atresia. Melatonin also helps the growing follicle by rummaging the reactive nitrogen species (RNS) and ROS system as well as energizing the antioxidant enzyme activities. It also controls not only the antioxidant enzymes as well as the antiapoptotic/proapoptotic protein gene expression. The higher concentration of melatonin in the growing follicles can also be a major factor in inhibiting atresia. For this reason, a follicle before ovulation can be fully developed and will provide an oocyte for fertilization.

Melatonin and ovulation

A decrease in LH secretion and hindrance in oocyte release can be continuous ingestion of external melatonin along with progesterone in women. On the other hand, the aforementioned combination exaggerates the luteal phase of progesterone, not affecting at all the FSH or inhibiting the E2 secretion [122]. On the contrary, in the case of men, the LH level was severely decreased because of melatonin treatment [123]. These changes in the hormonal level are due to the activation of hypothalamic gonadotropin release supported by melatonin [123]. Melatonin can also do its work by attaching itself directly to granulose cells inside the ovary [84]. MT1 and MT2, the two types of melatonin receptors, are to be found in the human GCs, which can improve the LH mRNA receptor [85]. The LH is mostly required for the beginning of luteinization. The LH surge stimulates some structural and biochemical changes which promote the breakage of Graafian follicles resulting in the release of oocytes and followed by maturation of corpus luteum (CL). After the hCG administration, the hormonal regulation becomes shifted from E2 to progesterone by inhibiting 17α-hydroxylase-c17-20-lyase activity [124]. The drastic progesterone production is necessary for the maintenance of CL and ovulation. As compared melatonin with E2 and P, the concentrations of both are higher in large follicles than in small follicles. Importantly, there is a positive integrity between the progesterone and melatonin concentrations [81]. Increased concentration of melatonin in primary follicles before ovulation might be related to progesterone production which concludes in luteinization and ovum release.

The local increase in the concentration of ovarian prostaglandin (PG), angiotensin II [125], and NO synthase (NOS) [125] has been observed during ovulation. The above-mentioned substances play an important role in the process of ovulation. At the time of follicular rupture, the collagen that is observed in the follicular wall becomes damaged along with a huge amount of vascular dilatation and permeability [126]. The increased level of follicular PGE2 level is needed for a successful ovulation. Treatment with melatonin (20 mg/kg body weight) markedly elevates the PGE2 concentrations in the gastric mucosa of rats [127]. Melatonin treatment (20 mg/kg body weight) via intraperitoneal injection also elevates the PGE2 levels in the esophageal tissue of rats [128]. On the other hand, the physiological melatonin concentration will cease the nor-epinephrine-induced activation of PGE2 in the medial basal thalamus of rats [129]. The above-discussed relationship between melatonin and PGE2 could be a way to relate whether these two hormones are responsible for creating any change in the ovulation process or not. Ovulation can be likened to an inflammatory process, during which RNS and ROS are generated [130]. Oocytes and theca cells in mice express endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) [96]. During ovulation, macrophages and neutrophils in the ovary produce large quantities of ROS, facilitating apoptosis of ovarian cells [81,115]. Melatonin and its metabolites, known for their antioxidant properties, effectively scavenge ROS and RNS [131-134]. Elevated melatonin levels in follicles prior to ovulation protect GCs and oocytes from oxidative damage during ovulation.

Melatonin on oocyte quality and embryo

Poor oocyte quality is a primary cause of female infertility, often resulting from ROS produced during ovulation [135]. Specific ROS, including OH-, O_2-, and H_2O_2, cause lipid degradation, DNA damage, and apoptosis [136], leading to two-cell inhibition, programmed cell death, and impaired fertilization [137,138]. Reduction in antioxidant enzyme levels, such as GPX, was keenly observed in the FF of women with sterility which was unexplained [139]. Along with this, more levels of H_2O_2, a type of oxidant, had been observed in fragmented embryos in lieu of non-fragmented embryos, and oocytes that were not fertilized have also been reported [140]. More usage of antioxidants, which can be a reason for increased ROS levels at the time of incubation of embryos with poor quality, has been informed [141]. The comparison between ROS production and the rummaging ability of antioxidants has been considered an important factor for the development and maturation of oocytes and their fertilization. Medicines that protect the oocyte and its neighboring feeder cells from any destruc-

tion are of real importance. The observance of maximum melatonin receptors in GCs [83,85] expresses that indoleamine might be a molecule that is more helpful in the follicle. Intrafollicular levels of 8-hydroxy-2'-deoxi guanosine (8-OHDG, marker of destroyed DNA products) in women with poor quality oocytes are markedly more compared with normal quality of oocyte in patients with IFV transfer of embryos, and intrafollicular density of 8-OHDG and hexanoyl lysine adduct (HEL, a lipid peroxidation biomarker), are noticeably decreased by 3 mg melatonin/day or 600 mg Vit-E/day dosage [90]. Along with this, before the embryo transfer cycle, the fertility rate was around 50%, but, after melatonin treatment, the IVF embryo transfer cycle was improved [90]. On the other hand, melatonin also assertively influences both antioxidant enzyme activity and gene expression. The administration of 5 mg/kg body weight melatonin increases the SOD activity [142], whereas 1 nM of physiological serum level of melatonin influences the gene expression of all the three antioxidant enzymes (i.e., Cu-Zn-SOD; Mn-SOD; and GPx) [143]. Melatonin might be a boon to those women who were suffering from poor-quality oocytes. It also maintains the proper maturation of oocytes [98]. The pregestational steroid, 17α, 20β- dihydroxy-4-pregnen-3-one (17α, 20β-DP), is known to have an impact on oocyte maturation [144]. It works on receptors located on the membrane of the oocyte and enhances the activation factor for promoting maturation in the cytoplasm of the oocyte which can induce the final maturation [145]. The maturation-promoting factor of the oocyte goes through a significant morphological change in association with the meiotic cell cycle, where cleavage of the oocyte nuclear envelope or germinal vesicle appearing in between prophase and metaphase is normally regarded as a mask in the development of oocyte maturation [146]. A melatonin dosage of 50 to 500 pg/mL preceded the action of maturation-inducing hormone in both the maturation-promoting and factor and lysis of germinal vesicles of oocytes [147].

According to a few studies, melatonin is also responsible for inducing epigenetic moderation in oocytes [148,149]. The DNA methyl transferase inhibitory effects could be brought to apply by melatonin only after obscuring target sequences or by plugging the active site of the enzyme [150]. Epigenetic modifications can lead to the interaction of melatonin with nuclear melatonin receptors. Melatonin markedly enhances the effects of trans-activation of these receptors [151]. The nuclear melatonin receptors have an important function in the bending of DNA [152]. The epigenetic modification induced by melatonin and affected by the nuclear melatonin receptors, can on the other hand alter the superstructure of DNA. As per the above discussion, melatonin plays the role of a mediator that passes the environmental stimulus to oocytes interconnections within environmental factors and epigenetic inheritance system. The presence of melatonin in the culture medium carries through not only in the fertilization of mice but also premature development of embryonic tissue [153] apparently by working as a non-compelling radical rummager. Presently, Rodriguez-Osorio et al. [154] informed that 10 nM melatonin administration has an assertive effect on cleavage rates in porcine embryos. In addition to this, in the culture medium, melatonin has changed the rate of progression of thawed blastocysts with a maximum hatching rate after a close observation of 24 hours [155]. Within 1 pM to 100 nM dosage of administration, no nullative effects of melatonin on the development of embryos were seen [156], even after administration of high dosage also at the time of pregnancy [157].

Melatonin in pregnancy outcome and fetal development

Several studies have demonstrated the role of melatonin in pregnancy. Maternal melatonin crosses the placenta, exposing the fetus to daily rhythms of low and high concentrations, contributing to the circadian regulation of fetal organ function. Melatonin also supports embryo development, as observed by increased blastocyst formation in mouse embryos cultured with melatonin [153]. Additionally, melatonin positively influences in vitro development in rodent embryos at the 2-cell stage [158] and facilitates ovine blastocyst maturation [159]. Suppression of the maternal plasma melatonin circadian rhythm by continuous exposure to light during the second half of the gestation period showed several effects on fetal development. Firstly, it generated intrauterine growth retardation. Secondly, in the fetal adrenal gland in vivo, it distinctly affected the mRNA expression level of the clock genes and clock-controlled genes, as well as it reduced the content and modified the rhythm of corticosterone. Thirdly, a revamped in vitro fetal adrenal response to adrenocorticotropic hormone (ACTH) of both corticosterone production and relative expression of clock genes and steroidogenic genes was observed. All these changes were reversed when the mother received a daily dose of melatonin during the subjective night [160].

Torres-Farfan et al. [161] reported that maternal melatonin influenced a reduced cortisol production in the fetal adrenal gland of the capuchin monkey. In another study on sheep, it was found that melatonin had direct inhibitory effects on the noradrenalin-stimulated fetal cerebral artery contraction, the release of glycerol by brown adipose tissue, and on ACTH-induced secretion of cortisol by the fetal adrenal gland. Low levels or a deficient circadian rhythm of the fetal corticosterone may be the cause of the intrauterine growth retardation that has been previously reported. The deficiency of maternal melatonin (induced by pinealectomy) during the early stages of gestation was found to disturb the drinking behavior of rat pups, an effect that was reversed by the administration of exogenous melatonin to the dam [162]. Melatonin is crucial in normal placental development and function, a function supported by the placenta melatonin receptor expression during early pregnancy [90].

Moreover, an oral dose of 75 mg of melatonin was shown to inhibit the release of gonadotrophin hormones, which has enlightened the experimental works on melatonin-based contraception methods [122] previously, like intrauterine device, levonorgestrel-releasing intrauterine system methods of the recent era [163].

Melatonin and luteal function

Progesterone (P) plays a pivotal role in implantation and pregnancy regulation by modulating GC functions and follicular rupture during ovulation [94,164]. LH receptor activation in follicular cells due to the LH surge induces ovum release and initiates luteinization, transforming the follicle into the CL [165]. Theca interna and GC undergo biochemical and morphological changes, rapidly differentiating into luteal cells [165]. These structural and genetic alterations culminate in follicular cells' terminal differentiation into P-producing cells. LH surge also influences PR and cyclooxygenase-2 (cox-2) gene expression in GCs [166,167]; absence of PR or cox-2 results in infertility in mice. They bring up pre-ovulatory follicles, but they are unable to ovulate [167]. In the luteal phase, there is a higher level of melatonin rather than the proliferative or follicular phase of the menstrual cycle [168]. The cells of GC-luteal phases contain melatonin binding sites in humans [83,85], and the release of progesterone from human luteal cells is been directly stimulated by melatonin [85]. Melatonin can change or improve luteal functions. This melatonin not only stimulates to production of progesterone by GCs-luteal cells [83] but also, at dosages of 10 pM to 100 pM, markedly increases the expression of mRNA of LH receptor in the GCs-luteal cells of humans and inhibits the expression of GnRH receptor [85]. Melatonin elevates progesterone secretion, stimulated by hCG, probably by the enhanced expression of the LH receptor. On the other hand, few results or reports imposed a nullified expression of melatonin in the growing and luteinized GCs [81,103] on account of progesterone production. In another study [169], it has been documented that GCs, isolated from porcine ovaries, when administered 1 ng/mL to 100 mg/mL dosage of melatonin, showed inhibition of progesterone production and secretion by GC cells. cAMP, a second messenger, plays an important role in the steroidogenesis process and can be inhibited by the action of melatonin. Short-term incubation of 48 hours inferred the negative effect of melatonin on the release of progesterone whereas long-term incubation led to an assertive effect. It is been hypothesized that at the beginning, melatonin plays an inhibitory role on cAMP. However, as it proceeds further, the inducing effect of melatonin on LH receptor mRNA expression and cooperative effect on GCs become prominent. The cytotoxicity, which occurs by the free radicals within long-term cultured GCs, may be prevented by melatonin by its antioxidant ability, which may be direct or sometimes indirect. ROS production may repress progesterone production and can prompt CL regression [170]. Melatonin apparently prevents CL from ROS production and thus maintains the functional physiology of CL. Presently, a recent study [171] has imposed a mandatory effect of melatonin on the morphology of the endometrium and the implantation of the embryo.

The researchers elaborated on the speed or rate of implantation and the level of progesterone in the serum was been reduced in the rats whose pineal glands were atomized, whereas on the other hand, the decreased serum progesterone levels were consolidated to the normal level by administering day to day melatonin intravenously in the dosage of 2 mg/kg body weight. Enhanced melatonin in the luteal phase and early pregnancy may increase progesterone production by the luteal cells, which is essential for the desired and healthy pregnancy. Several biochemical and endocrine factors are related to excessive information and create an impact on the production of progesterone by luteal cells. hCG, LH, PRL [172], cytokines [173], and growth factors [91] induce the production of progesterone, whereas PGF-2α [174], oxytocin [175], cytokines [176], and ROS [170] reduces progesterone production. PGF-2α is of major importance because of its strong autocrine/paracrine actions that conclude the suppression of CL. A 10 mM dose of melatonin can insulate the secretion of PGF-2α from the uterus of a rat [177]. Melatonin in the range of 0.1 to 1 mm has been observed to inhibit the expression of the Cox-2 gene, which is responsible for producing the PGF-2α synthesizing enzyme, in a murine macrophage cell line [178]. Melatonin also enhances PRL secretion [178,179] and plugs the release of oxytocin from the hypothalamohypophyseal system of the rat [180], representing the necessity of indoleamine for the maintenance of progesterone synthesis and the function of luteum by making the better usage of different mechanisms.

Melatonin and parturition

Melatonin is an endocrine signal of nighttime duration [181] and was certainly expected to have regulatory effects on the timings of parturition. Takayama et al. [182], regarding female rats subjected to pinealectomy resulting in the loss of endogenous, showed that their estrous cycles or their ability to get impregnated were not perturbed. However, a failure in the delivery of young ones in the daytime was observed (dawn being the normal birthing phase for nocturnal animals such as rodents). Moreover, delivery was noted randomly across a 24-hour light-dark cycle. Interestingly, administration in the evening (when the endogenous levels would normally increase) had impressive effects in the regeneration of normalcy in the daytime birth, whereas morning administration of melatonin was ineffective, which sharply hints that melatonin may discharge the role of a circadian "gating" signal in this event of birth of rats being under circadian control. This insinuates the significant role of the clock in the entire reproductive process. However, we must be cautious while generalizing this data to humans, considering we are dominantly diurnal whereas the majority of animals are nocturnal.

The mode of action of melatonin on the mammalian uterus remains unclear and appears to be species-specific. Studies in rodents have shown that pharmacological doses of melatonin inhibit uterine contractility and interact with melatonin-specific binding sites in the uterus [183-185]. Additionally, melatonin inhibits prostaglandin synthesis in rodent tissues [177,178] and regulates calcium signaling, including in vascular smooth muscle [186]. However, caution is required when extrapolating these findings to humans, as they are primarily derived from nocturnal species with different parturition physiology. Human labor predominantly occurs during the night phase, contrary to the pattern ob-

served in nocturnal rodents [187,188]. The nocturnal secretion of melatonin and its effects on uterine contractions in other mammals suggest that melatonin may act as a temporal regulator in the process of uterine contractions during human parturition. Studies have shown that melatonin and oxytocin have a significant positive synergistic effect on the contraction of human myometrial smooth muscle cells, resulting in enhanced IP3 signaling and an increase in contraction induced by oxytocin. These results may explain the high frequency of uterine contractions that occur during the night in the later stages of pregnancy, which can ultimately lead to labor at night [189,190]. Recently, it has been identified the synergistic action of melatonin and oxytocin on myometrial smooth, muscle cell induction of the core circadian gene hbMAL1 [191]. BMAL1 is the transcription factor at the core of the circadian system [192,193] as its basic function is the modulation of expression of the genes whose promoters contain the E-box motif which includes the melatonin receptors. Oxytocin (OT) analogs serve as pivot tools in obstetric practices. Uninterrupted infusions of OT antagonists are now being used for the induction of labor and prolonging pregnancy in case of preterm labor. However, only very high amounts of hormones are shown to be effective in case of prolonged labor induction due to receptor desensitization [194]. Unfortunately, high dosage of oxytocin is often accompanied by serious side effects including fetal distress, uterine rupture, and postpartum atony and bleeding. Tracing a synergism between melatonin and oxytocin could lead to the development of new melatonin combined with OT medical dosage for labor induction without considerable side effects of high levels of administered oxytocin. Conversely, the studies accounting for the popular inhibitory effect of light on the circulating melatonin levels have provided substantial evidence that nocturnal uterine contractions common to later pregnancy are under melatonin control [195,196].

The regulation of melatonin receptor MTNR1B in the myometrium of laboring pregnant women, compared to non-pregnant women, has been observed, showing suppression during most of gestation and de-suppression near parturition [189]. Similar patterns were noted for MTNR1A and MTNR1B expression, with increased melatonin binding towards the end of pregnancy [196]. While progesterone maintains uterine dormancy during pregnancy [197,198], changes in its signaling due to melatonin receptor activation in the myometrium remain unclear. Melatonin receptor proteins were detected in women entering preterm labor, suggesting potential sensitivity to contraction and preterm labor via premature receptor expression [199,200].

MELATONIN AND FEMALE REPRODUCTIVE PATHOPHYSIOLOGY

Melatonin and PCOS

PCOS is a type of hormonal disease that results in sterility because of anovulation in a woman at her reproductive age. Not only sterility but women with PCOS can also have some other features like hyperandrogenism, hyper-insulinemia, insulin resistance, hirsutism, obesity, chronic anovulation, and polycystic ovaries. Reduced quantity of oocytes along with the quality of the embryo might be a reason for sterility in women with PCOS [201]. Any type of stress may reduce the quality of female reproductive as well as endocrine functions. In PCOS, the ROS produced by oxidative stress might be responsible for the reduced quality of oocytes. The oxidative stress induced by ROS might be a reason ROS for the low quality of oocytes. The generation of ROS from the cells that are mononuclear is enhanced in women who are suffering from PCOS [202]. It significantly increased serum lipid peroxidation has been proven by few studies [203]. Malondialdehyde, a product developed due to lipid peroxidation, is enhanced in the FF of women with PCOS [204]. On the other hand, the apoptotic GC ratio is also higher in women with PCOS [205]. Due to oxidative stress GCs and oocytes can be damaged by the peroxidation of lipids, protein oxidation, and damage of DNA inside the follicle. The most important enzymatic metabolite of melatonin, urinary 6-sulfatoxymelatonin, is enhanced significantly in PCOS women compared with non-PCOS women [206]. Enhanced melatonin increased LH release [86,207], the amplitude of LH [207], and the response of LH to GnRH [208]. Along with this, melatonin might decrease peripheral tissue sensitivity to insulin [209]. On the other hand, the suppression in melatonin levels due to pinealectomy and exposure to intermittent light enhances the upliftment of a few features of PCOS in rats [210].

Women with PCOs have less amount of indoleamine in their follicles, while also having higher concentrations of serum level. An elevated level of serum melatonin indicates a lower level of melatonin in the ovary. An enhanced level of melatonin in the FF is necessary for the growth and proliferation of the follicle, ovulation, and maintaining the quality of the oocyte. Decreased serum melatonin levels might be a reason for anovulation and reduced quality of oocytes in the case of PCOS women. The 16 kDa hormone named leptin is majorly synthesized in the adipose tissue and gets elevated in obese persons [211]. Amidst circulation, leptin gets attached to protein(s) [212], which might change its physiological activity [213]. Leptin maintains metabolic balance and intake of food and gets attached to specific cellular receptors by affecting the reproductive system [214]. The disbalance in the leptin system is concerned with the pathological conditions in the reproductive organs with PCOS [215]. The function of the leptin hormone is to promote the process of steroidogenesis and maturation of follicles. On the other hand, the concentration of leptin higher than the normal level might produce adverse effects [216]. The level of leptin in the serum of PCOS women is remarkably higher than compared to normal women [217]. In addition, the FF has the same concentration of leptin as in the serum level [218], cells of the ovary along with GCs, thermal cells, and interstitial cells that expose a particular leptin receptor [219]. Leptin modifies the production of steroids by action on GCs and theca cells in vitro [220], which represents a straight intraovarian effect that happens in vivo. Women who see with PCOS have been re-

ported with elevated levels of leptin in FF [217]. Supplementation of melatonin daily to rats represses body weight, plasma leptin levels, and adiposity [221]. However, two factors, such as pinealectomy and melatonin administration, have been observed to influence serum leptin levels. Specifically, melatonin has been shown to enhance leptin expression in adipocytes of rats in the presence of insulin [222,223]. Through a few specific receptors like G-protein coupled receptors, MT1 and MT2 receptors act straightly on melatonin [224]. The stimulation of these receptors may release a changing effect on the synthesis of heparin by decreasing cAMP levels. Furthermore, the correlation between reduced melatonin and elevated leptin in the FF of women with PCOS is not expressed yet. More studies and research are required to explain the proper relationship between the aforementioned two conditions, which may be major in acknowledging the pathophysiology of PCOS.

Melatonin and endometriosis

A persistent provoking disease that is specified by implantation and growth of the endometrial tissue at the out-sided line within the uterine cavity. It is a usual gynae-related disorder that contains an increasingly repeated nature and has been diagnosed to affect 21% to 44% of sterile and 4%–22% of non-sterile women [225,226]. It is related to persistent pelvic pain, continuous dysmenorrhea, dyspareunia, and sterility. Usually, the extrauterine implantation location is in the reliant parts of the pelvis, most importantly, the ovaries, the pelvic walls, and the posterior cul-de-sac. The reason for endometriosis is not known still. It is trusted to be a multifarious disease related to a usual proactive response in the peritoneal cavity. One of the theories explains that at the time of menstruation, the release of endometrial fragments may pass within the oviduct or fallopian tubes and repetitively arriving the peritoneal cavity. These fragments of endometrium may attach on the serosal surfaces of the peritoneal cavity and with every monthly followed menstrual cycle they may go through development and bleeding. At this location, the oxidative stress inducers contain erythrocytes, apoptotic cells of the endometrium with not digested endometrial cells in the menstrual effluent [227]. The ROS has a close relation to the process of proliferation and pathophysiology of a disorder. Peritoneal fluid (PF) volume in women who have endometriosis has been enhanced with the elevated number of macrophages in the PF compared with control women. Stimulated macrophages increase oxidative stress, the formation of lipid peroxide, and other by-products resulting in the relation of peroxides with apolipoprotein. PF macrophages synthesize more amounts of ROS in the case of endometriosis patients [228]. The ROS reaches a centralized pelvic inflammatory reaction, which results in elevated concentrations of cytokines, growth factors, PGs, and other inflammatory products. Non-attached iron and heme play a significant role in the synthesis of ROS. Their sedimentation is elevated in the vicinity of the peritoneum where the endometrial implants are done [227]. Persistently, the activity of iNOS and the production of NO by the macrophages of the peritoneum are markedly increased in women with endometriosis [229]. The decrease of adhesions is done by melatonin, a powerful free radical scavenger [230]. However, the importance of melatonin in endometriosis is still not known but two interesting research articles have explained the participation of melatonin in maintaining the pathogenicity of endometriosis. Güney et al. [231] have proved the antioxidant, anti-inflammatory, and immune-modulatory results of melatonin on endometrial explants in the model of rat endometriosis. Melatonin administration (10 mg/kg) each day intraperitoneally, markedly decreased the explant volume in correlation with the control group. On the other hand, after the endometrial transfer COX-2-positive cells were remarkably reduced in rats treated with melatonin (91% vs. 18.1%). On the contrary, in melatonin-treated rats, the transfer of endometrial malondialdehyde was markedly suppressed, whereas the work of SOD and catalase (CAT) were enhanced in the rats with melatonin treated. This administered that melatonin is a reason for regression and withering of the endometrium lesions by reducing the oxidative stress [231]. According to a study by Paul et al. [232], it was approved that melatonin also plays a significant role in the protection and suppression of endometriosis in mice. They had pointed out a pioneered diagnostic marker, matrix metalloproteinases (MMP-9)/tissue blockers of metalloproteinase (TIMP-1), pronouncing ratio in determining disease succession and seriousness and melatonin treatment intraperitoneally 48 mg/kg with accumulation of lipid peroxidation and oxidation of protein in the peritoneal endometriosis. Melatonin also reduces the composition and activity of pro-MMP-9 and enhances TIMP-1 expression. The outcome determines a role for melatonin in protecting and elevating the suppression of endometriosis through the maintenance of MMPs.

Melatonin and premature ovarian failure

Premature ovarian failure (POF) is diagnosed in women under 40 years, when elevated gonadotropins, sex steroid deficiency, and amenorrhea are observed [233]. POF may arise from a genetically determined low ovarian follicle count at birth, proliferative follicular depletion (atresia), or follicular dysfunction [234]. The etiology of POF includes chromosomal and genetic abnormalities, autoimmune disorders, viral infections, and iatrogenic factors such as pelvic surgery, chemotherapy, and radiotherapy. Chemotherapy and radiotherapy, commonly used for malignancy treatment, are well-established causes of POF, contributing to follicular depletion and dysfunction through cytotoxic effects on ovarian tissue. However, changed chemotherapy and radiotherapy regimens for malignancy in youth have proceeded to be enhanced for long-term existence. One situation has been a curtailment in ovarian storage and therefore an enhanced prevalence of POF. The danger diagnosis proceeding to POF elevates, with age after adolescence, with different strong chemotherapy subjugation with accumulated chemotherapy and radiation therapy [235]. The demonizing effects of ionizing radiation are turnabout by direct and indirect mechanisms. The straight action synthesizes delicate molecules

inside the cells and leads to the genesis of disorders; however, the unintended actions of ionizing radiation come out when it reacts with water molecules in the cells, concluding in the production of vigorously reactive free radical, like OH-, H- with aqueous electron. An approximate 60% to 70% of tissues and cellular DNA vandalism influenced by ionizing radiation is trusted to be an out-turn of OH- [236]. If the toxicity present in both the ovaries due to radiation exposure should be known as gonadotoxicity [237]. A dose-dependent damage of the primary follicles was observed after enhancing the doses of radiation, according to Gosden et al. [238]. In contrast other studies have assured the high efficiency of melatonin against ionizing radiation effects [236]. When melatonin acts on OH-, it will be turned into a halfway indolyl (melatonyl) radical which is less reactive as well as less harmful too. Therefore, when melatonin combines with OH-, a highly reactive harmful substance is converted into a less harmful substance through a radical transformation, resulting in complete acquisition [239]. This intermediate molecule then binds with a second hydroxide (OH-) molecule to form cyclic 3-hydroxy melatonin, which demonstrates its effectiveness as a radioprotective molecule by scavenging the free radicals produced by ionizing radiation [240]. The prior treatment with melatonin decreases the plasma and red blood cell levels which can be an inference malondialdehyde influenced oxidative entire body from the condition of being exposed to radiation. On the other hand, melatonin also enhanced the levels SOD and GPx [241]. Thus, due to its scavenging effects, melatonin may prevent molecular damage caused by radiation by increasing the activity of antioxidant enzymes. The administration of melatonin effectively mitigates the detrimental effects of radiation when administered prior to exposure. However, it does not confer protective benefits if administered after radiation exposure has occurred [240]. When anticancer drugs are given in various malignant diseases in young women, there is marked loss of primordial follicles and reduce the function of GCs and oocytes [241]. The cytotoxic effect of chemotherapy is mostly drug, dose, and age-dependent [242]. Generation of ROS in mitochondria induced by anticancer medication, such as alkylating agents (like cyclophosphosphamide, ifosfamide, etc.), platinum agents (such as cisplatin), and antitumor antibiotics (like doxorubicin, daunorubicin, bleomycin, etc.), also contribute to cytotoxicity [243,244]. Melatonin antagonizes this ROS-induced cytotoxicity by acting as an antioxidant agent and it also promotes apoptosis of cancer cells. The administration of melatonin at the dose of 10 mg/kg of body weight with a chemotherapeutic agent reduces the occurrence of thrombocytopenia, neurotoxicity, cardiotoxicity, and asthenia [245]. Studies have proven that melatonin is highly effective in protecting against doxorubicin-induced cardiotoxicity by reducing glutathione and malondialdehyde levels in cardiac tissue [244]. Melatonin is also expected to protect the cell damage due to autoimmune disorders like premature ovarian failure in which ovarian autoantibodies are produced against GCs, theca cells, and zona pellucida leads to autoimmune lymphocytic oophoritis. Autoimmune mechanisms are mostly involved in the pathogenesis of likely 30% of cases of POF [246]. Many other autoimmune disorders like Addison's disease, diabetes mellitus, hypothyroidism, myasthenia gravis, systemic lupus erythematosus, and rheumatoid arthritis are also caused by increased activity of peripheral T-lymphocytes [234,247]. The melatonin is a widely known immune modulator [248]. There are specific melatonin binding sites on lymphocytes and monocytes [249]. After binding at these sites, melatonin regulates the functions of lymphocytes and monocytes [250] and th1/th2 balance cytokine [251]. It acts as an anti-inflammatory and anti-apoptotic effect [252]. A study conducted in mice showed that when melatonin was given in the dose of 5 mg/kg body weight via IV injections 1 hour before antibodies administration, then melatonin restored the oocyte meiotic maturation and survival [253]. Thus, melatonin may be a promising agent with beneficial effects on immune-mediated ovarian pathology.

MELATONIN IN REPRODUCTIVE AGING

In contrast to early childhood, where elevated melatonin levels are associated with suppressed gonadotropin secretion, low melatonin levels in elderly individuals are linked to reproductive aging, marked by increased gonadotropin secretion [254]. Research shows that plasma melatonin levels decline with age, and the nocturnal melatonin peak shifts earlier [255,256]. The onset of menopause, characterized by diminished ovarian follicular reserve and altered hormonal secretion, signifies the end of reproductive fertility. This process results in menstrual cycle cessation and is clinically associated with increased gonadotropin secretion from the anterior pituitary due to the loss of ovarian function. A previous report indicated mitigation of depression, along with improved mood and sleep quality following melatonin administration to perimenopausal and postmenopausal women [257]. However, this was not confirmed in a study by Amstrup et al. [258], which found no significant effect on quality of life or sleep quality in 81 postmenopausal women who were given pharmacological melatonin nightly for a year. However, the authors did mention a non-significant trend toward improved sleep quality in a subgroup of melatonin-treated women who had sleep disturbances at the initial baseline. Toffol et al. [259] showed that postmenopausal women have reduced night-time serum melatonin levels than perimenopausal women; however, no correlations were found between serum melatonin and FSH or estradiol levels, Beck Depression Inventory score, State-Trait Anxiety Inventory score, Basic Nordic Sleep Questionnaire (BNSQ) insomnia score, BNSQ sleepiness score, subjective sleep score, climacteric vasomotor score, or quality of life. The apparent inconsistency in the aforementioned studies is probably reconcilable, since, in the Bellipanni and Amstrup investigations [257,258], pharmacological levels of melatonin (3 mg/night for 6–12 months) were administered, while the Toffol study [259] analyzed physiological and psychological correlations with the naturally reduced endogenous melatonin levels. Lately, however, long-term pharmacological melatonin administration

was shown to decrease psychosomatic symptoms in postmenopausal women after 12 months of treatment in a double-blind, placebo study [260].

This is consistent with numerous previous studies on the use of pharmacological melatonin in the treatment of sleep disturbances in elderly men and women [261]. Some studies have proposed a role for melatonin in ovarian aging, given the supportive and pleiotropic effects of melatonin on ovarian activities, including the suppression of oxidative stress, protection of mitochondrial integrity, etc. [262]. However, as most of the research to date has been in rodents, neither a clear etiological connection between declining endogenous melatonin levels and human menopause has not been adequately demonstrated, nor have sufficiently powered clinical trials with melatonin administration to premenopausal women been reported [263,264].

MELATONIN AND IVF

One of the important causes of female infertility is the poor quality of oocytes. The ROS are normally generated inside the ovarian follicle, during ovulation, and an increased production could serve as a cause of impaired oocyte maturation. Considering its well-established role in foraging free radicals, treatment with melatonin during human pregnancy may help reduce the high oxidative stress. Therefore, it could be a possible treatment for some forms of infertility. Melatonin has been studied in assisted reproductive technology aiming to enhance the oocyte quality and conception rates following IVF. Administering melatonin, which was started before IVF cycles and continued during pregnancy, was found to improve pregnancy outcomes. Successful fertilization and pregnancy rates were improved due to melatonin treatment. The fertilization rate was 50% higher in the melatonin treatment regimen as compared to the previous melatonin-free cycle (20.2%) [265,266].

Moreover, maternal melatonin treatment has been observed to significantly improve placental antioxidant enzyme gene expression [267]. Maternal and/or embryo-fetal toxicity effects, due to melatonin treatment, have never been reported as such. A median lethal dose in mice could not even be confirmed because no increased mortality rate was observed, even after following the administration of extremely high doses of up to 800 mg/ kg melatonin [268].

CONCLUSION

Melatonin significantly impacts female reproductive physiology, from ovulation to overall fertility regulation, suggesting its potential as a therapeutic intervention for conditions such as PCOS and endometriosis. Its potent antioxidative effects reduce oxidative stress in ovarian cells, enhancing oocyte quality and fertility. Melatonin supplementation holds promise for infertility management, particularly in assisted reproductive technologies, where its application has been linked to improved pregnancy outcomes. Continued research is essential to fully understand melatonin's multifaceted role in reproductive health and its therapeutic potential in broader clinical settings.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Author Contributions

Conceptualization: Suparna Parua, Gargi Roy Choudhury, Pallav Sengupta, Koushik Bhattacharya. Methodology: Suparna Parua, Gargi Roy Choudhury, Soumita Bhattacharya. Project administration: Pallav Sengupta, Koushik Bhattacharya. Resources: all authors. Supervision: Pallav Sengupta, Koushik Bhattacharya. Validation: Pallav Sengupta, Koushik Bhattacharya. Writing—original draft: all authors. Writing—review & editing: all authors.

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