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Review

An in-depth overview of the molecular mechanisms governing ovarian aging and the corresponding preventative and therapeutic strategies

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ABSTRACT

Ovarian aging is a progressive and dynamic process closely related to age, in which ovarian function gradually declines until exhaustion; this process is influenced by a combination of factors, including genetics, lifestyle, environment, psychosocial factors, and iatrogenic factors. It is closely related to the quantity and quality of follicles in the ovaries and is characterized by changes in female hormone levels and fertility. Therefore, understanding the factors influencing ovarian aging, its molecular mechanisms, and strategies for prevention and intervention is of significant importance for comprehending and addressing the challenges posed by ovarian aging.

KEYWORDS

ovarian aging, molecular mechanisms, preventative and therapeutic strategies

1 Introduction

Since the beginning of the 21st century, declining global fertility rates, population aging, low birthrates, and shrinking labor force sizes have increasingly threatened sustainable economic and social development. The situation in China is particularly acute; from 2016 to 2020, the number of births decreased dramatically from 17.86 million to 12 million. The total fertility rate among women of childbearing age reached 1.3, which is significantly below the replacement-level fertility rate of 2.1 which is necessary for maintaining societal population size. A key contributing factor to this decline is the decreased fertility and increasing incidence of adverse pregnancy outcomes associated with delayed childbearing. At the heart of these issues lies ovarian aging, which has emerged as a major challenge impacting national population security, social/familial stability, and offspring health [1].

As a vital reproductive organ in women, the ovary plays dual roles in facilitating reproduction and maintaining hormonal homeostasis, thus influencing both personal and offspring health. With advancing female age, the ovary gradually ages, with studies indicating a more pronounced decline in function starting at the age of 35 [2]. Therefore, ovarian aging occurs earlier than in other organs and progresses at a much faster pace. Currently, the average age at menopause for women is approximately 51 years [3], and as overall life expectancy increases, postmenopausal life spans account for approximately one-third of a woman's lifetime [4]. Ovarian aging primarily manifests as a decrease in both the quantity and quality of oocytes, leading to a decrease in female fertility and reproductive quality. Following ovarian exhaustion, not only does reproductive capacity cease, but women also experience perimenopausal symptoms such as hot flashes, night sweats, worsening sleep quality, and emotional anxiety. Moreover, ovarian dysfunction contributes to systemic imbalances, including an increased risk of cardiovascular diseases, osteoporosis, Alzheimer's disease, cancers, and diabetes [5]. Research has shown that transplanting young mouse ovaries into older mice can extend

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the latter's lifespan [6]. For this reason, ovarian aging is often referred to as the pacemaker of overall female body aging [5]. Ovarian aging represents a unique form of organ aging that, in addition to impacting reproductive capacity, causes bodily and psychological discomfort due to changes in hormone levels, such as hot flushes, excessive sweating, insomnia, vivid dreams, and irritability. More importantly, ovarian aging triggers and accelerates aging in multiple organs, such as the brain, heart, and bones, leading to dysfunction across various systems. Hence, combating ovarian aging has become a central focus of attention within the biomedical and pharmaceutical sectors.

In summary, the array of issues stemming from ovarian aging profoundly impacts household happiness indices, women's healthy life expectancy, and the well-being of future generations. Therefore, to gain a proper understanding of the factors influencing ovarian aging and its detrimental effects, exploring therapeutic strategies and medications to delay ovarian aging, as well as preventing subsequent multiorgan aging, has become an urgent necessity in today's aging society.

2 Factors influencing ovarian aging

Ovarian aging is a multifactorial and dynamic process influenced by both irreversible biological genetic patterns and modifiable lifestyle and environmental factors. Among intrinsic factors, genetic elements play a critical role. Studies have demonstrated that specific gene variations and altered expression, such as those of Forkhead Box O3 gene (*FOXO3*) and *Klotho*, are tightly linked to ovarian aging processes. These genes might influence ovarian aging through the regulation of antioxidant defense mechanisms, DNA repair, and cell cycle progression [7,8]. As women age, the gradual depletion of primordial follicles within the ovaries constitutes the physiological foundation for ovarian aging. Hormonal changes, particularly decreases in estrogen and progesterone levels, further exacerbate the rate of ovarian aging [9]. Externally, environmental pollution, such as prolonged exposure to harmful chemicals and radiation, can damage the structural integrity and functional capability of ovarian cells, thereby triggering premature ovarian failure (POF) [10]. Due to their direct cytotoxic effects on ovarian cells, medical interventions, including chemotherapy, radiotherapy, and certain medications used to treat chronic illnesses, may also contribute to the onset of ovarian aging [11]. Thus, ovarian aging is a complex phenomenon involving intricate interactions among genetic, physiological, environmental, and iatrogenic factors. Identifying these contributing factors and developing corresponding preventive and intervention strategies are of paramount importance for enhancing women's quality of life, extending healthy lifespans, and safeguarding population health. Future research should continue to deepen our understanding of the mechanisms underlying ovarian aging and actively explore effective prevention and treatment measures.

2.1 Genetic factors

Epidemiological studies have convincingly demonstrated that the genetic contribution to the age at menopause in populations is remarkably high, ranging from 30% to 85%, underscoring the pivotal role of genetic factors in the development of ovarian aging [12]. Ovarian aging exhibits remarkable heterogeneity at the genetic level, encompassing chromosomal number and structural abnormalities, chromosomal segment anomalies, single nucleotide polymorphisms (SNPs), and telomere and mitochondrial gene variations. Previous research has focused extensively on chromosomal karyotypes and SNPs in patients with POF, an extreme phenotype of ovarian aging. In patients with POF, the detection rate of chromosomal abnormalities ranges from 10% to 30%, with approximately 10%–13% of these located on the X chromosome, suggesting that the X chromosome is a critical regulator of ovarian function. To date, numerous mutated genes associated with ovarian aging have been identified; these genes are primarily involved in processes such as oocyte meiosis, follicle development, hormone synthesis and secretion, DNA damage, and repair. However, currently known ovarian aging-related mutated genes can only explain 15% of inherited causes of ovarian aging, leaving a vast area of unknown factors yet to be explored [13].

Researchers have leveraged the normal variation in the age at natural menopause (ANM) to evaluate nearly 200,000 women of European ancestry, pinpointing 290 genetic determinants of ovarian aging. These common alleles were found to be associated with clinical extremes of ANM; women in the top 1% of genetic susceptibility had a comparable risk of POF to those carrying X mental retardation 1 gene (*FMR1*) mutations. This study identified genetic loci implicated in a wide range of DNA damage response (DDR) processes, including functional loss-of-function variants in key DDR-related genes. Integrative studies with experimental models have suggested that these DDR processes operate throughout life, shaping the ovarian reserve and the rate at which it is depleted [14].

2.2 Age factor

Age is closely related to ovarian function. In females, menstruation typically commences around the ages of 13–14 years, although it can begin as early as 11 years or as late as 16 years. Upon entering puberty, women develop reproductive capabilities and, following a period of ~ 5–7 years, establish regular cyclical ovulation. During this time, the ovaries secrete estrogen and progesterone hormones, leading to peak ovarian function and optimal fertility levels between the ages of 20 and 30 years [15]. With advancing age, ovarian function declines, and concomitantly, fertility decreases. On average, this descent starts showing a month-to-month reduction from the age of ~ 30 years old, eventually resulting in hormonal imbalances. When menstrual irregularities occur, women enter the perimenopausal stage, characterized by the worsening of ovarian function. During this phase, fluctuating and declining estrogen levels lead to a series of adverse changes in various bodily systems, causing symptoms such as menstrual disturbances, hot flashes, night sweats, mood swings, insomnia, and vivid dreams. Ultimately, menopause is characterized by the complete deterioration of ovarian function following the last menstrual period.

Research on healthy populations reveals that the age at which natural fertility is lost (defined as the age when the last child is born without strict contraception) ranges from 23 to 51 years, with an average age of 41 years [16]. In healthy

Chinese women, the average age at natural menopause is approximately 52 years. Thus, ovarian function progresses from weak to strong, to peaking, and then to declining in tandem with age-related milestones such as menarche, sterilization, menstrual irregularities, and menopause. The number of ovarian follicles steadily diminishes with increasing age, accelerating after the age of 37.5 years, until fewer than 1000 follicles remain by the time of menopause. Moreover, follicle quality also declines with advancing age. It is estimated that, on average, follicle quality starts to rapidly deteriorate at the age of approximately 37.5 years, consequently leading to a significant decrease in pregnancy and live birth rates [17]. Therefore, the number and quality of ovarian follicles in women are closely intertwined with age, making age a crucial factor in ovarian aging.

2.3 Environmental factors

Extensive epidemiological surveys and basic research indicate that environmental factors can exert detrimental effects on the degeneration of the ovarian germ cell niche, meiotic division of oocytes, folliculogenesis, steroid hormone synthesis, and fecundity; are closely associated with decreased ovarian reserve, premature ovarian failure, and early menopause; and, in some cases, play a decisive role in severely compromising women's reproductive health. A wide variety of environmental factors are implicated, including elevated concentrations of PM2.5 in the air, polycyclic aromatic hydrocarbons (PAHs) found in cigarette smoke and vehicle emissions, heavy metals (such as lead, mercury, and cadmium) in contaminated water sources, residual pesticides in fruits and vegetables, and plastic components in packaging materials such as bisphenol A (BPA) and phthalates [18]. Other potential environmental stressors may involve occupational exposure to anesthetic gases, electromagnetic radiation, and chronic noise pollution. For instance, air pollution from PM2.5 particles and chemical substances present in commonly used skincare products could impair ovarian function, leading to premature ovarian senescence [19].

In one particular study, female C57BL/6J mice were exposed systemically to either filtered air or urban air containing PM2.5 for a period of four months. The findings showed that PM2.5 exposure significantly altered the estrous cycle, reproductive capacity, hormone levels, and ovarian reserve. An increase in PM2.5 was found to exacerbate oxidative stress and inflammation in the ovaries of mice via the NF-κB/IL-6 signaling pathway [18]. Therefore, enhancing public awareness and understanding of the link between environmental factors and their impacts on human health is highly important.

2.4 Medical factors

In the clinical medical process, a multitude of healthcare-related factors can impact or damage ovarian function, such as chemotherapeutic drugs administered to cancer patients, radiation therapy, and surgical injuries [20]. These factors can lead to POF and reduced or even decreased fertility in female patients, ultimately resulting in a decrease in their quality of life. To protect or preserve ovarian function, clinical options include ovarian suspension, ovarian tissue cryopreservation, or transplantation; during surgery, efforts should be made to minimize thermal injury, such as reducing or preventing electrocoagulation during ovarian cystectomy, instead of prioritizing suturing for hemostasis.

Exploration and research are needed to identify the least damaging methods for managing ovarian injury among inevitable medical interventions, aiming to achieve maximum ovarian protection [21]. Data from the St. Marianna University School of Medicine and Tokyo Fertility Clinic suggest that among 827 patients with POI [22], 131 (15.8%) may have resulted from iatrogenic factors. Most healthcare-related ovarian injuries (64%) occurred following ovarian surgeries (excluding bilateral oophorectomy); ovarian endometrioma stripping, for instance, is a risk factor for ovarian dysfunction that may manifest several months postsurgery. Chemotherapy and radiation therapy are also common causes of ovarian toxicity; the risk of ovarian injury following radiation depends on the irradiation field size (pelvic vs. whole-body irradiation), radiation dose, and patient age. Chemotherapy-induced ovarian toxicity largely depends on the type and dosage of the drug used and is also age dependent.

Given that ovarian function cannot be reversed and tissue regeneration is not possible once damaged, current approaches for treating healthcare-related ovarian injury place greater emphasis on prevention and control. Examples include administering protective drugs during chemotherapy to shield ovarian tissue from gonadotoxic effects [23]; exercising stringent criteria for indications during surgery; adopting appropriate surgical techniques and hemostatic materials to avoid compromising the ovarian blood supply; and performing ovarian transposition before radiation therapy and accurately localizing ovarian tissue during radiation therapy—all of which can help protect the ovaries and prevent iatrogenic ovarian injury.

3 Molecular mechanism of ovarian aging

Ovarian aging is governed by a complex network of regulatory interactions both within and outside the ovary, fundamentally representing a progressive depletion of the primordial follicle pool. Extrinsic factors exert their influence through direct or indirect routes, affecting the ovarian microenvironment via mechanisms such as DNA damage, telomere attrition, and mitochondrial dysfunction. Ultimately, these external influences culminate in the establishment of a molecular regulatory network that operates reciprocally on the backdrop of chronological ovarian aging.

3.1 Depletion of primordial follicles

Oocytes develop from primordial follicles within the ovaries, where each follicle consists of a single oocyte surrounded by numerous smaller granulosa cells in the ovarian cortex. Women are endowed with approximately 2 million primordial follicles at birth, with most of them regressing during childhood; nonetheless, approximately 300,000 primordial follicles still remain by the time of adolescence [24]. These follicles are quiescent prior to puberty. However, upon entering puberty, the pituitary gland and hypothalamus produce hormones that stimulate the ovaries, promoting the secretion of sex hormones and controlling the menstrual cycle, a process that persists until approximately age 51 [25].

Maintaining normal ovarian function relies on the activation of primordial follicles at a controlled rate. This activation is subject to dual regulation by inhibitory and stimulatory factors; overactivation or excessive inhibition can both lead to ovarian dysfunction. Anti-Müllerian hormone gene (*AMH*), phosphatase and tensin homolog gene (*PTEN*), *FOXO3a*, tuberous sclerosis complex gene (*TSC*), and yes-associated protein gene (*YAP*) serve as inhibitory genes in primordial follicle activation, and their expression mainly involves participation in the PI3K–AKT–mTORC1–S6K1–rpS6 and PI3K–AKT–FOXO3 signaling pathways, which suppress excessive follicle activation [20]. Therefore, stimulatory factors targeting these genes and pathways can result in overactivation of primordial follicles, accelerating the depletion of the follicular pool.

Additionally, atresia is another means by which primordial follicles are consumed. In mammals, over 99% of follicles within the ovary will undergo atresia, with apoptosis currently recognized as a principal mechanism driving follicle atresia. The key players involved in apoptotic regulation include members of the Caspase family, the Bcl-2 family, and p53, among others. Emerging research also suggests that autophagy, ferroptosis, cellular senescence, and pyroptosis are all processes that participate in the atresia of follicles. Given these findings, regulating the activation and atresia of primordial follicles holds promise for developing potential therapeutic strategies to intervene in ovarian aging.

3.2 Telomere shortening

Reproductive senescence, the theory of telomere attrition, provides a contemporary explanation for the decline in fertility observed in older women [26]. Telomere shortening can trigger cellular senescence through p53-mediated cell cycle arrest. In slowly dividing cells, such as oocytes, a significant cause of telomere erosion is the accumulation of reactive oxygen species (ROS). ROS are believed to oxidize guanine-rich telomeric DNA and proteins required for telomere maintenance. Telomere length has been proven to be essential for accurate chromosome alignment and spindle function during meiosis, both of which are critical for preventing the production of aneuploid embryos [27].

Furthermore, recent research has suggested that alterations in telomere length and telomerase activity may be among the key mechanisms underlying ovarian aging [28]. Studies have shown that telomerase activity in ovarian tissue tends to decrease with advancing age, and in some cases, the telomeres in the ovarian cells of POF patients are shorter than those in the ovarian cells of age-matched women with normal ovarian function. Telomere length impacts the proliferation of granulosa cells and the quality of oocytes; researchers have discovered that the antioxidant N-acetylcysteine can protect telomeres within oocytes, thereby improving oocyte quality.

3.3 DNA damage

DNA damage prompts cells to initiate DNA repair mechanisms, depending on the severity of the damage, which may lead to cellular senescence or death. For oocytes, effective strategies for recognizing and repairing DNA damage are crucial for preventing premature aging and the loss of oocytes or for preventing the transmission of genetic mutations to offspring [29]. A robust DNA repair machinery is essential for maintaining metabolic balance and delaying aging phenotypes; genome-wide association studies suggest that genomic instability may be a factor in menopause, providing further evidence linking ovarian aging to DNA damage repair capabilities [30].

Research has illuminated how the functional regulation of genes involved in DNA damage response (DDR) processes governs ovarian reserve and depletion rates, determining the age at natural menopause. Furthermore, experiments have demonstrated that the modulation of key genes in the DDR pathway can enhance fertility and prolong the reproductive span in mice [14]. Another study revealed that compared to younger mice, older mice have more double-strand breaks (DSBs) in their oocytes. While only 33% of follicles in 1-month-old mice showed DSBs, this figure increased to 59% in 11-month-old mice. Several genes are responsible for repairing these DSBs, and the expression of some genes, including BRCA1, gradually decreases with age. Similar findings were observed in a study of oocytes from 24 healthy women of varying ages, where the expression of certain DNA repair genes, including breast cancer susceptibility gene 1 (*BRCA1*), decreased over time [31].

This illustrates that the DNA repair capacity of oocytes diminishes with advancing age. Consequently, the regulation of the DNA damage response process may represent a viable approach for slowing ovarian aging.

3.4 Mitochondrial dysfunction

Mitochondria, as crucial energy-producing organelles, play pivotal roles in the regulation of calcium homeostasis, oxidative phosphorylation, the cell cycle, aging, and apoptosis. They also serve as a major source of endogenous ROS, significantly impacting ovarian aging development [9]. Mitochondrial dysfunction can lead to follicular apoptosis and subsequent decreases in ovarian reserve through various pathways, including mitochondrial DNA (mtDNA) abnormalities, abnormal numbers of mitochondria, morphological defects, and oxidative stress damage. Multiple studies have confirmed that the mtDNA content in human oocytes is inversely correlated with age and positively correlated with ovarian reserve function. Additionally, the number of mitochondria is closely related to adenosine triphosphate (ATP) synthesis; research indicates that the quantity of mitochondria in granulosa cells from aged women is notably lower than that in granulosa cells from younger women.

Autophagy, a system that degrades and recycles unused or damaged cellular organelles and proteins, is vital for maintaining cellular homeostasis [32]. It has been proposed that the decrease in autophagy levels with advancing age is associated with the activation of the mammalian target of rapamycin (mTOR) kinase, which inhibits autophagy and contributes to the regulation of the senescence-associated secretory phenotype (SASP) in aging cells [33]. Recently, it has been speculated that age-related increases in methylation changes of autophagy-associated genes could lead to decreased autophagy levels, subsequently causing an accumulation of defective proteins and increased numbers of mitochondria within cells.

In the ovary, oxidative damage occurs during the long dormant period preceding follicle formation. Higher ATP levels in human oocytes are positively correlated with in vitro fertilization success rates; thus, a reduction in mitochondrial energy in oocytes is considered a significant factor contributing to age-related chromosomal abnormalities [34].

4 Strategies for the prevention and management of ovarian aging

Current efforts to explore and implement strategies for preserving ovarian function have gained increasing attention, with researchers endeavoring to investigate protective measures across multiple fronts. Notable reported interventions aimed at countering ovarian aging encompass several aspects, including lifestyle adjustments, pharmacological interventions (Table 1), and gene therapies.

4.1 Lifestyle modifications

Adopting a healthy lifestyle includes maintaining a balanced diet, engaging in regular exercise, and cultivating good sleep habits. Smoking and excessive alcohol consumption may accelerate the progression of POF; hence, smoking cessation and limiting alcohol intake are recommended to mitigate the negative impact of these factors on the body. Obesity can disrupt hormonal balance within the body, thereby negatively affecting ovarian function; therefore, weight should be managed to maintain a body mass index (BMI) within the range of 18.5–24.9 kg/m^2. Moreover, sufficient sleep promotes metabolic processes and hormonal equilibrium in the body, contributing to the prevention of POF.

4.2 Drug therapy

4.2.1 Anthocyanin

Proanthocyanidins are a class of polyphenolic compounds primarily found in fruits, vegetables, wines, and teas. Structurally, they are formed by the polymerization of catechins or epicatechins. Experimental evidence has demonstrated that PAs possess strong antioxidant capabilities, effectively protecting against tissue damage induced by free radicals and oxidative stress [35].

In 2017, Liu et al. established an ovarian aging model in hens using D-gal (2.5 mg/mL). *Ex vivo* ovarian tissues were treated with 5 μg/mL proanthocyanidins for 72 h to investigate the inhibitory effect of the compounds on ovarian aging. The results showed that proanthocyanidins could enhance antioxidant enzyme activities and gene expression, maintain the balance between cell proliferation and apoptosis, and alleviate D-gal-induced chromatin condensation in ovarian granulosa cells, thereby improving the antioxidant capacity of D-gal-induced and naturally aged ovaries [45].

4.2.2 Curcumin

Curcumin, an active component of turmeric rhizomes (containing 3%~5% curcuminoids), exhibits antioxidant, anti-inflammatory, and antiapoptotic properties [46]. It has been demonstrated that curcuminoids can mitigate the detrimental effects of factors such as ionizing radiation, environmental mutagens, oxidative stress, and ischemia-reperfusion injury on ovarian function. Curcuminoids and their analogs also preserve ovarian function; studies have shown that they promote proliferation, inhibit apoptosis, and facilitate folliculogenesis and hormone synthesis in ovarian cells [36]. In 2018, Yan et al. used a D-gal-induced mouse model of ovarian aging and administered curcumin (100 mg/kg/day) intraperitoneally for 42 days. The results revealed that curcumin could effectively suppress D-gal-induced oxidative stress, apoptosis, and ovarian damage via the NRF2/HO-1 and PI3K/AKT signaling pathways. Thus, curcumin may be a promising candidate for preventing ovarian aging [47].

4.2.3 Hesperidin

Hesperidin, a flavonoid compound widely present in citrus fruits, has garnered attention for its antioxidant and anti-inflammatory properties. Many studies have focused on its potential protective effects on ovarian function. Research has shown that hesperidin can ameliorate cyclophosphamide-induced ovarian damage in rats by suppressing oxidative stress [48] and alleviating ovarian injury caused by ischemia-reperfusion [49]. *In vitro*, hesperidin promotes the growth and maturation of murine follicles during three-dimensional (3D) culture, enhancing the rate of *in vitro* fertilization and embryonic development [37].

4.2.4 Quercetin

Quercetin, a prominent member of the flavonoid family, is ubiquitously distributed in plants such as *Ginkgo biloba*,

Table 1 Medications for retarding ovarian aging and preserving ovarian function

Category	Drug	Function	Refs.
Plant extract	Proanthocyanidins	Antioxidation	[35]
	Curcumin	Foster follicle formation and hormone synthesis	[36]
	Hesperidin	Foster the growth and maturation of mouse follicles	[37]
	Quercetin	Enhance the vitality of granulosa cells to improve subsequent fetal development	[38]
Compound	Metformin	Improving age-related ovarian fibrosis	[39]
	Resveratrol	Improve the quantity and quality of oocytes	[40]
	Rapamycin	Increase the number of follicles	[41]
	Melatonin	Protecting ovarian function damage in mice caused by cisplatin by reducing oxidative stress	[42]
Chinese medicine	American ginseng (ginsenoside)	Delaying the onset of premature ovarian failure in mice induced by D-gal	[43]
	Epimedium	Promote the repair of DNA damage to effectively mitigate ovarian injury	[44]

Forsythia suspensa, apples, and berries [50]. Characterized by a wide range of biological activities, including antioxidant, anti-inflammatory, and antiapoptotic properties, quercetin has recently gained increasing attention for its potential application in the treatment of ovarian aging. Animal studies have demonstrated that quercetin administration can increase ovarian volume, primordial follicle counts, and growing follicle numbers while concurrently reducing granulosa cell apoptosis [51]. Moreover, quercetin intervention has been shown to enhance granulosa cell viability, decrease the percentage of early apoptotic cells, alleviate deterioration in oocyte quality, and improve subsequent embryonic development [38,52].

4.2.5 Metformin

Currently, there is a substantial body of evidence from both basic research and clinical trials indicating the significant potential of metformin in combating cancer, slowing aging, reversing pulmonary fibrosis, protecting cardiovascular health, and modulating the gut microbiota. When 28-week-old female C57BL/6 mice were fed a diet for six months, researchers observed that compared to the control group, the metformin-treated group displayed a greater number of primordial follicles within their ovaries and significantly reduced levels of ovarian senescence markers. These findings suggest that metformin can enhance ovarian function, retard primordial follicle activation, and effectively delay ovarian aging in mice [53].

4.2.6 Melatonin

Melatonin is a hormone secreted by the pineal gland that is regulated by the light cycle and is released only at night. On the one hand, melatonin can protect mitochondria by increasing the activity of uncoupling proteins (UCPs), promoting mitochondrial synthesis, and regulating mitochondrial homeostasis, thereby reducing the production of free radicals and improving ovarian function. On the other hand, melatonin can also promote DNA damage repair, ensuring the accuracy of gene translation and the stability of protein synthesis, playing a role in preventing POF [54]. Research has shown that melatonin is present in the follicular fluid and oocytes of the ovaries and has strong antioxidant capabilities; it is capable of eliminating ROS and reactive nitrogen species (RNS) and counteracting oxidative stress in ovarian cells, and its scavenging effect is direct and does not require receptor mediation [55]. Therefore, melatonin may play multiple beneficial roles in the maturation of oocytes, fertilization, and embryonic development and in preventing the rapid progression of POF.

4.2.7 Rapamycin

Rapamycin is a serine/threonine protein kinase that regulates cell growth and metabolism and modulates nutritional and hormonal signaling. Mechanistic target of rapamycin kinase gene (mTOR) functions in two different complex forms, mTORC1 and mTORC2, with varying sensitivities. As an inhibitor of mTORC1, rapamycin has been shown to extend the lifespan of yeast, fruit flies, and mice and improve the health span and metabolic function of nonhuman primates [56,57]. However, its application is limited due to the adverse effects of long-term treatment on follicle development and ovulation. In 2017, Dou et al. shortened the duration of rapamycin treatment to 2 weeks and applied this regimen to young mice (8 weeks old) and middle-aged mice (8 months old). The results showed that all animals regained normal fertility two months after treatment. These data suggest that short-term rapamycin intervention can preserve primordial follicles, improve oocyte quality, and improve the ovarian microenvironment [58].

4.3 Gene therapy

Currently, some genes have been proven to be associated with POF, and researchers are exploring the use of RNA interference (RNAi) technology and gene editing technology (such as CRISPR-Cas9 gene editing technology) to regulate the expression of aging-related genes and even replace abnormal genes, with the aim of slowing aging and extending lifespan.

Recent studies have shown that Sirtuin 1 gene (*SIRT1*) plays an important role in various physiological processes, such as cell proliferation and differentiation, energy metabolism, autophagy, apoptosis, and homeostatic regulation. An increasing number of studies have shown that *SIRT1* can participate in the development of oocytes and delay the progression of POF through multiple pathways. FoxO, p53, and NF-κB, among others, can participate in the regulation of inflammation and apoptosis by binding with certain factors. In the nucleus, SIRT1 acts as a hub for deacetylation, reducing the transcriptional level of the aforementioned factors and inhibiting apoptosis [59]. In ovarian tissue, SIRT1 may induce granulosa cells to resist apoptosis by activating the ERK1/2 signaling pathway, directly inhibiting follicular atresia. Studies have shown that treating animal cells with substances that can produce ROS can upregulate the expression of SIRT1 in the nucleus and inhibit apoptosis [60]. The above studies indicate that SIRT1 may play a protective role in the body by reducing the production of ROS, participating in the regulation of the cellular survival environment under oxidative stress, and inhibiting the apoptosis of reproductive cells, playing a potential protective role in POF.

Recent research suggests that the activity and expression levels of the *IDO1* and *QRT* genes may also be related to POF [61]. NAD+ plays an important role in POF, and the knockout of *IDO1* and *QRT*, two key genes involved in the *de novo* biosynthesis of NAD+, can lead to a decrease in the level of NAD+ in the ovaries of mice, causing menstrual cycle disorders, a reduction in ovarian reserves, and the induction of POF [62]. By regulating the expression of the above genes, it may be possible to improve the ovarian function of POF mice effectively, providing a potential method for the prevention and treatment of POF. In addition, the *FOXO3a* gene and the *BCL2* gene have also been confirmed to be correlated with POF.

These methods have achieved certain effects in animal models, but more research is needed to determine whether they are safe and effective, and further research is required before they can be applied to humans. It should be emphasized that gene therapy, as a promising method, has certain potential, but it is still in the research stage. The specific application still requires more research and experiments to verify its effectiveness and safety, and it must

strictly follow relevant laws, regulations, and ethical guidelines. Maintenance of a healthy lifestyle and drug intervention should be the main means of delaying ovarian aging.

5 Conclusion and perspectives

Ovarian aging is a pathophysiological process involving multiple factors and mechanisms, where internal and external factors influence the course of ovarian aging through a complex network of regulation. Throughout a woman's life, the rate at which follicles are consumed varies at different stages, and precise regulation ensures that the menopausal age for most women is approximately 50 years. Therefore, understanding the factors influencing ovarian aging, molecular mechanisms, and intervention methods is important for understanding and preventing ovarian aging. Currently, there is a lack of sufficiently sensitive and specific biomarkers in this field for the early detection and prediction of ovarian aging, especially in the clinical practice of accurately assessing ovarian reserve function. The process of ovarian aging is gradual, and long-term follow-up research is needed to understand its dynamic changes. However, due to the difficulty and cost of this research, large cohort studies with long follow-up periods are rare. In summary, more basic scientific and clinical research is needed to fill the existing gaps in the field of ovarian aging research to better understand and address the health and social issues associated with ovarian aging.

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Conflict of interests

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