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REVIEW

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# The impact of mitochondrial dysfunction on ovarian aging

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## Abstract

**Importance** Ovarian aging has become a focal point in current research on female aging and refers to the gradual decline in ovarian function as women age. Numerous factors influence ovarian aging, among which mitochondrial function is one because it plays a crucial role by affecting oocytes and granulosa cells. Mitochondrial deterioration not only leads to a decrease in oocyte quality but also hinders follicle development, further impacting women's reproductive health and fertility.

**Objective** This review summarizes and integrates research on the impact of mitochondrial function on ovarian aging, outlining the mechanisms by which mitochondria regulate the functions of oocytes and granulosa cells. This study aims to provide potential therapeutic directions to mitigate mitochondrial decline and support female reproductive health.

**Evidence review** According to a 2023 study published in *Cell*, factors such as oxidative stress, mitochondrial dysfunction, chronic inflammation, and telomere shortening collectively drive ovarian aging, directly affecting female fertility. Among these factors, mitochondrial dysfunction plays a key role. This study reviewed literature from databases such as PubMed, Google Scholar, and CNKI, using keywords such as "mitochondrial dysfunction", "decline in oocyte quality and quantity", and "ovarian aging", aiming to summarize current research on the mechanisms of the impact of mitochondrial dysfunction on ovarian aging and provide theoretical support for future exploration of related therapeutic strategies.

**Findings** The main characteristics of ovarian aging include a decline in oocyte quantity and quality, fluctuations in hormone levels, and a reduction in granulosa cell function. Studies have shown that mitochondria affect fertility by regulating cellular energy metabolism, exacerbating oxidative stress, causing mitochondrial DNA (mtDNA) damage, and impacting the physiological function of granulosa cells within the ovary, gradually diminishing the ovarian reserve.

**Conclusion** This review focuses on analyzing the effects of mitochondrial decline on energy production in oocytes and granulosa cells, the accumulation of reactive oxygen species (ROS), and the calcium ion ($Ca^{2+}$) concentration, which all contribute to the ovarian aging process, and understanding them will provide new insights into the mechanisms of ovarian aging.

**Relevance** Therapeutic interventions targeting mitochondrial dysfunction may help delay ovarian aging and improve female reproductive health.

**Keywords** Mitochondrial dysfunction, Mitochondrial DNA, Ovarian aging, Oocyte function

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## Introduction

Current research suggests that women possess a reserve of primordial follicles as early as the fetal period or early postnatal stage, which progressively decreases with age after puberty. By the seventh week of female embryonic development, primordial germ cells (PGCs) differentiate into oogonia and undergo mitotic proliferation [1]. At approximately the 11th to 12th week of embryonic development, oogonia enter meiosis and develop into primary oocytes [2]. Primary oocytes are subsequently surrounded by granulosa cells, which form primordial follicles. Before puberty, the oocytes within these primordial follicles remain arrested in the diploid stage of prophase I of meiosis. These primordial follicles have three possible developmental paths: remaining quiescent, undergoing direct atresia, or being recruited into the growing follicle pool [3]. Baker et al. reported that most follicle reserves undergo atresia, reducing follicle numbers from around 7 million at birth to 2 million. The remaining follicles are recruited and undergo further growth and differentiation after puberty to contribute to the formation of mature gametes [4]. With increasing age, more follicles are recruited into the follicle pool, and the number of primordial follicles gradually decreases. However, the probability of aneuploidy in oocytes increases with age, leading to a marked decline in the quality of oocytes and the follicle pool, which has a substantial effect on pregnancy rates and live birth rates [5]. Based on these findings, researchers have further analyzed factors influencing ovarian aging and discovered that mitochondrial dysfunction can lead to ROS accumulation, the activation of apoptotic mechanisms, mtDNA mutations, calcium ion oscillations, and reductions in adenosine triphosphate (ATP) synthesis, ultimately affecting meiosis and oocyte quality.

## Mitochondrial structure and function

Mitochondria are among the most abundant organelles in most human cells and play crucial roles in cellular metabolism and energy production. Mitochondria have a double-membrane structure, with the inner membrane forming cristae that increase surface area [6]. This membrane is rich in protein complexes that form the respiratory chain, playing a key role in ATP synthesis, the cell's primary energy source for various physiological processes [7]. The mitochondrial matrix contains mtDNA, ribosomes, tRNA, and other molecules closely related to protein synthesis and metabolism [8–10]. Mitochondria are not static organelles; rather, they are highly dynamic structures [11]. They can adjust their shape and number through continuous fusion and fission to adapt to the cell's energy demands and functional changes [12]. This dynamism plays a critical role in cellular stress responses, programmed cell death, and various other physiological processes [13].

MtDNA is the genetic material of mitochondria, and it is independent of the cell nucleus [14]. This double-stranded circular genome is approximately 16.6 kilobases (kb) in length and encodes 37 genes, with each mitochondrion containing approximately 2 to 8 copies of mtDNA [15]. MtDNA plays a key role in many hereditary diseases, aging processes, metabolic disorders and neurodegenerative diseases. As a unique marker of mitochondria, the amount of mtDNA is often closely related to the number of mitochondria. In human cells, different types of cells contain varying amounts of mitochondria and mtDNA.

In addition, the mitochondrial matrix is rich in ions such as calcium ($Ca^{2+}$) and magnesium ($Mg^{2+}$), which participate in multiple cellular activities to maintain normal cellular function. Mitochondria not only are a primary source of free radicals within cells [such as reactive oxygen species (ROS)] but also play an important role in regulating the cellular antioxidant defense system. When the cellular oxidative phosphorylation system is imbalanced, large amounts of ROS may accumulate within mitochondria [16]. Excessive ROS production can lead to oxidative stress and damage biomolecules such as DNA, proteins, and lipids, ultimately inducing apoptosis [17]. Therefore, mitochondria are essential not only for ATP production but also for maintaining homeostasis, generating ROS, and regulating cell growth and apoptosis (Fig. 1A).

## Mitochondrial dysfunction and ovarian aging

### Characteristics of mitochondria in oocytes

The morphology, quantity, and distribution characteristics of mitochondria in oocytes play crucial roles in their development [18]. Compared with those in somatic cells, the mitochondria in oocytes exhibit distinct morphological features, a unique adaptation to meet the energy demands of oocyte maturation [19]. The quantity of mitochondria in oocytes significantly changes throughout development, which is important for optimizing mtDNA and minimizing mutation risk [20]. The distribution of mitochondria not only affects the metabolic activity of oocytes but also plays a key role in the energy supply during the maturation process [21]. The following sections explore these three aspects in detail.

The mitochondria in oocytes are typically round or oval, whereas in most somatic cells, they are often elongated or branched. Oocyte mitochondria are smaller and more compact, which correlates with their specific functional requirements [22]. Studies have shown that oval or spherical mitochondria may be better suited for rapid ATP generation, meeting the metabolic demands of

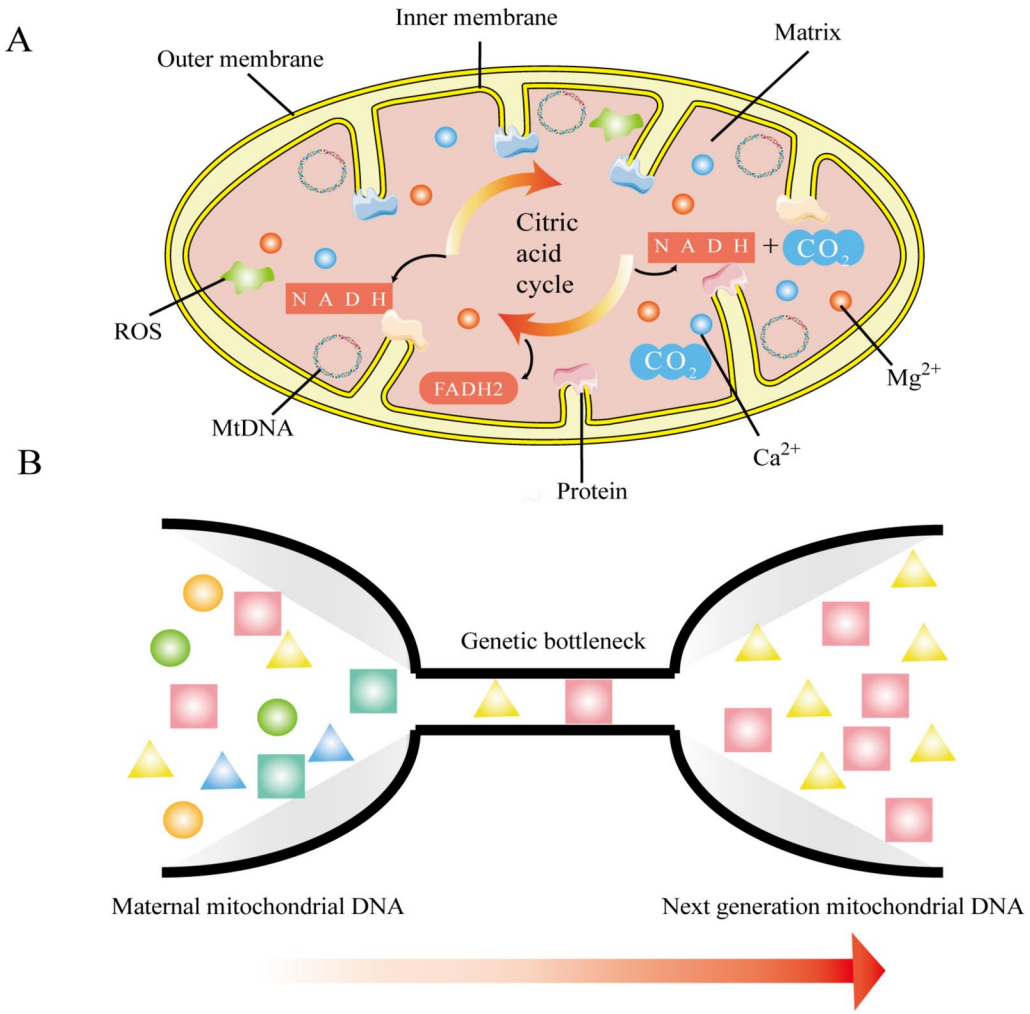


**Fig. 1** **A** The structure and function of mitochondria, encompassing the mitochondrial outer membrane, inner membrane, cristae, membrane proteins, circular mitochondrial DNA (mtDNA), ions within the mitochondrial matrix (such as calcium ions, magnesium ions, etc.), reactive oxygen species (ROS) generation, and energy metabolism. **B** The mitochondrial genetic bottleneck mechanism, in which oocytes selectively transmit a small subset of mitochondrial DNA (mtDNA) to offspring, thereby reducing the risk of inheriting mutations

oocytes during these stages. In contrast, elongated mitochondria, common in somatic cells, primarily support a steady energy supply rather than the rapid, high-energy demands seen in oocytes [18]. Anastasia Kirillova et al. noted that mitochondrial distribution and morphology in oocytes are closely linked to function, with significant changes occurring as oocyte development progresses. During different stages of oocyte development, mitochondria transition from the original round or oval shape to more complex forms. Notably, in the early stages of embryonic development, mitochondria need to provide rapid energy to support cell division and development. This morphological change may be an adaptation to meet the requirements for rapid replication, thus generating a large amount of energy [18]. Additionally, the oval shape of mitochondria may be related to their distribution within oocytes. Bahety et al. found that oval-shaped mitochondria are more easily mobilized and positioned when concentrated around the nucleus or other key regions, compared to elongated mitochondria. This distribution pattern helps ensure that the energy supply is concentrated where needed, especially during oocyte maturation and fertilization [23].

The quantity of mitochondria in oocytes significantly changes during development, resulting in a "bottleneck effect" (Fig. 1B) during fertilization and early embryonic development. This effect refers to the reduction in the number of mitochondria from millions to thousands during oocyte maturation [24]. As embryonic development progresses, these mitochondria replicate

extensively, gradually increasing in number to maintain the energy supply needed for further development. This mechanism helps reduce the incidence of mtDNA mutation, providing an effective selection process to optimize oocyte quality [25]. This phenomenon has been observed in oocyte development across different species. In a mouse model, Anastasia Kirillova et al. measured mtDNA copy numbers using quantitative PCR, revealing a sharp decline during oocyte development, followed by subsequent replication [18]. A similar bottleneck effect has been observed in human oocytes. In studies on in vitro maturation (IVM) of oocytes, Anastasia Kirillova et al. noted that changes in mitochondrial quantity closely correlate with mtDNA copy number changes. The existence of the bottleneck effect may explain why, in certain cases, abnormal amplification of mtDNA can lead to embryonic developmental failure or mitochondrial diseases [18].

The spatial and temporal specificity of mitochondrial distribution in oocytes directly impacts their metabolic activity and developmental potential. In mammalian oocytes, mitochondria typically concentrate in specific regions of the cytoplasm and redistribute uniformly as the oocyte matures. This dynamic change supports the energy needs of oocyte maturation and further development [26]. Van Blerkom et al. studied mouse oocytes and found that during the germinal vesicle (GV) stage, mitochondria are evenly distributed, while during germinal vesicle breakdown (GVBD), they migrate to the perinuclear region [27]. With polar body extrusion, mitochondria move toward the periphery of the cell, subsequently redistributing evenly. This observation suggests that GVBD and chromosome relocation require a mitochondrial ATP supply [27]. Mitochondrial redistribution and aggregation are crucial for supporting the maturation and differentiation processes of oocytes. By efficiently generating and supplying energy, mitochondria ensure that oocytes have adequate energy reserves during maturation and early embryonic development [28].

The morphology, quantity, and distribution characteristics of mitochondria in oocytes closely influence their developmental processes. The oval or round morphology of mitochondria enables rapid ATP production, meeting the high-energy demands of oocyte development [29]; the "bottleneck effect" in terms of mitochondrial quantity reduces the risk of mutation transmission, increasing embryo quality [20]; and the dynamic distribution changes ensure that oocytes can efficiently access energy during maturation and fertilization [30]. These characteristics collectively ensure that oocytes have sufficient metabolic capacity to support normal early embryonic development.

### Mitochondrial DNA and oocytes

The maternally inherited nature of mtDNA plays a crucial role in the selection of oocytes [31]. Since mtDNA is inherited exclusively through the maternal line, offspring inherit all their mtDNA from the mother's oocyte [32]. During oocyte development and maturation, mitochondrial function is crucial for oocyte quality, especially proteins related to the oxidative phosphorylation (OXPHOS) system encoded by mtDNA, which directly impact mitochondrial energy metabolism [33]. As mtDNA mutations can impair mitochondrial function, oocytes undergo a "quality control" mechanism to select oocytes with optimal mitochondrial function, a process known as oocyte selection [34]. Studies have shown that during the mitochondrial bottleneck phase, oocytes selectively eliminate mitochondria with high levels of mutated mtDNA, ensuring mtDNA quality and function in offspring. This selection mechanism reduces heteroplasmy (the proportion of mutated to normal mtDNA), thereby enhancing mitochondrial functional integrity [24, 35]. Oocytes with a high mtDNA mutation load may be eliminated through apoptosis or other mechanisms, whereas oocytes with relatively normal mtDNA have greater developmental potential and fertility. This selection process is crucial for maintaining genetic stability across generations, ensuring that healthy mtDNA is passed to the next generation. However, as women age, mtDNA mutations accumulate, and the efficiency of mitochondrial selection decreases. This leads to the retention of more oocytes with mtDNA mutations, reducing fertility and increasing the risk of hereditary mitochondrial diseases. Additionally, studies have shown that maternally inherited mtDNA mutations affect oocyte function in the current generation and may be passed on, impacting mitochondrial function and health in offspring [36, 37]. This transgenerational inheritance effect highlights the regulatory role of mtDNA mutations in reproductive processes. Therefore, maternally inherited mtDNA not only regulates oocyte energy metabolism but also establishes the genetic foundation for mitochondrial function in future generations. This mechanism helps explain why mtDNA mutations play a significant role in research related to reproduction and fertility.

As genetic material independent of nuclear DNA, mtDNA possesses unique characteristics, enabling it to play a critical role in oocyte aging and fertility [38]. Specifically, mtDNA has the following features (Fig. 2A): 1. Polyploidy: Mature oocytes contain thousands of mtDNA copies, providing a robust genetic basis for maintaining mitochondrial function [39]. However, as age increases, mtDNA copy numbers decline, potentially impairing mitochondrial function and affecting oocyte quality and fertility [40]. 2. High Mutation Rate:

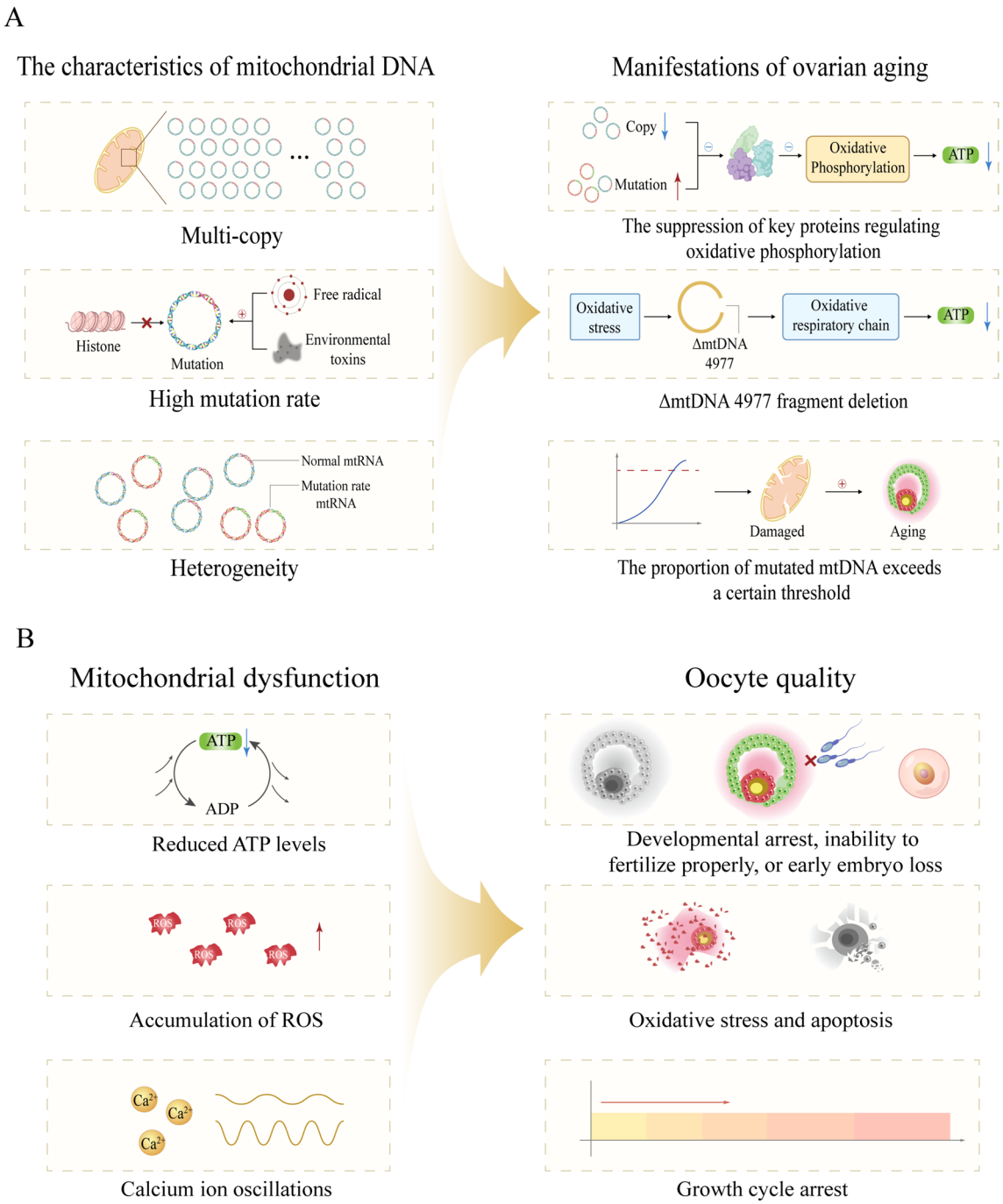


**Fig. 2** **A** Characteristics of mitochondrial DNA (mtDNA) and mechanisms leading to mitochondrial dysfunction. **B** Mitochondrial dysfunction results in decreased ATP synthesis, accumulation of reactive oxygen species, and calcium ion oscillations in oocytes, thereby impairing oocyte function

mtDNA is more susceptible to damage than nuclear DNA is, primarily due to the lack of histone protection. Additionally, mtDNA lacks a complete DNA repair mechanism, which increases the risk of mutations [41]. Due to its vulnerability, mtDNA is more susceptible to external factors like free radicals and toxins, leading to a higher mutation rate than nuclear DNA [42]. These mutations may accumulate over time, eventually leading to mitochondrial dysfunction and impairing oocyte vitality and quantity. 3. Heteroplasmy: In a single cell,

mutated mtDNA is often mixed with normal mtDNA, a phenomenon known as heteroplasmy [43]. The level of heteroplasmy varies among cells or individuals and can fluctuate across generations. When the proportion of mutated mtDNA exceeds a certain threshold, mitochondrial function is significantly impaired, further accelerating oocyte aging. mtDNA encodes 13 proteins related to the OXPHOS system, including complexes I, III, IV, and V in the oxidative respiratory chain [40]. These proteins are essential for mitochondrial energy metabolism. A decrease in mtDNA copy numbers or accumulation of mutations inhibits key protein expression, disrupting oxidative phosphorylation and leading to insufficient energy production. This metabolic disorder not only affects oocyte growth and differentiation but also weakens oocyte fertilization and decreases the capacity for early embryonic development.

Furthermore, mitochondrial transcription factor A (TFAM) plays an important role in maintaining mtDNA structure and function [44]. Unlike histones, TFAM does not provide effective DNA repair protection, increasing the susceptibility of mtDNA to mutations caused by external factors such as oxidative stress [45]. The ΔmtDNA 4977 deletion is one of the most common mtDNA mutations and is considered a hallmark of mitochondrial aging [46]. This mutation disrupts electron transfer in the oxidative respiratory chain, significantly reducing energy efficiency and ultimately lowering oocyte quality. In summary, a reduction in mtDNA copy number and accumulation of mutations are major factors influencing oocyte function [47]. Studies indicate that with increasing age, the mtDNA mutation rate significantly increases, whereas the copy number tends to decrease [48]. These changes are closely related to decreases in oocyte quality and quantity. Therefore, assessing the integrity and quantity of mtDNA is crucial not only for understanding the mechanisms of oocyte aging but also for identifying important molecular markers for predicting fertility [49].

Research by Read et al. indicates that mtDNA replication and quantity are essential for oocyte developmental competence. During oocyte maturation, the number of mitochondria increases significantly, especially during the transition from the immature germinal vesicle (GV) stage to the mature metaphase II (MII) stage. Data show that GV oocytes have approximately 490,799 mtDNA copies, and that increases to 1,087,127 at the MII stage [28]. This substantial increase highlights the critical role of mitochondria in meeting increased energy demands as oocytes mature. However, Pawlak et al. concluded from extensive research that mtDNA copy numbers exhibit high variability among different oocytes [50]. Overall, mtDNA copy number is positively correlated with oocyte vitality and volume [51].

#### The impact of mitochondrial function on granulosa cells

Granulosa cells and oocytes interact closely, forming bidirectional communication and gap junctions, including homotypic and heterotypic connections between granulosa cells and oocytes [52]. Oocytes regulate granulosa cell activity by releasing specific factors, while granulosa cells play a crucial role in constructing the follicular microenvironment necessary for oocyte maturation [53].

Under normal physiological conditions, granulosa cells convert glucose into energy through oxidative phosphorylation, whereas oocytes convert the products of glycolysis into energy via oxidative phosphorylation [54]. This metabolic shift plays an important role in regulating mitochondrial function and maintaining the level of oxidative phosphorylation. Research by Alberico and Woods suggests that in elderly women and animal models of ovarian aging, markers of mitochondrial function, such as mitochondrial structure and mtDNA mutations, are reflected in granulosa cells [55].

According to Liu et al., mitochondria in young granulosa cells are typically round or oval, with intact parallel tubular cristae and uniform matrix density. However, in aged granulosa cells, the mitochondria appear elongated or vacuolated, with numerous cristae and high-density granules in the matrix [56]. Elongated mitochondria typically represent a mature state that is capable of generatin more ATP. In granulosa cells from older women, highly differentiated mitochondria suggest a compensatory mechanism to cope with the decline in physiological function [56].

Alberico and Woods reported that ultrastructural changes in aged granulosa cells may be associated with the accumulation of ROS in follicular fluid. They reported that the level of the ROS scavenger superoxide dismutase 1 (SOD1) in granulosa cells decreases with age, affecting mtDNA damage, mutations, and steroid hormone production [55]. As mentioned, the ΔmtDNA 4977 deletion is a common mutation, and studies show its frequency increases in granulosa cells with age [56].

In summary, changes in mitochondrial function in granulosa cells significantly impact ovarian aging and fertility [57]. Interventions targeting mitochondrial dysfunction—such as enhancing biogenesis, improving function, or using antioxidants—may offer new strategies to delay ovarian aging and improve oocyte quality [58]. These studies provide a new theoretical basis for the development of reproductive medicine and warrant further exploration.

**The impact of mitochondrial dysfunction on ovarian aging**

Mitochondrial function is closely related to oocyte quality, a relationship widely confirmed in reproductive medicine research. Studies have shown that mitochondrial dysfunction is associated with a decline in oocyte quality, which is clinically manifested in various forms. For example, mtDNA mutations are common in oocytes from older women, and research has shown that these mutations are significantly related to oocyte maturation and fertilization rates. In one study, the mtDNA mutation frequency was as high as 60% in low-quality oocytes, whereas the mutation frequency in high-quality oocytes was only 20% [59]. Furthermore, reduced mitochondrial ATP production typically coincides with decreased oocyte developmental potential, while elevated oxidative stress and calcium ion fluctuations are closely linked to lower oocyte quality. High oxidative stress often triggers apoptosis, further reducing oocyte quality, while abnormal calcium ion fluctuations exacerbate oxidative stress, accelerating apoptosis. In assisted reproductive technology (ART), particularly in vitro fertilization (IVF) treatments, a decline in oocyte quality is one of the main reasons for low success rates. Data show that the implantation rate of high-quality oocytes can reach 50%, whereas the implantation rate of low-quality oocytes is only 10% [60]. These clinical manifestations and data further emphasize the importance of mitochondrial function in oocyte quality and reproductive success.

Normal oocyte development relies on mitochondrial health and efficient ATP production, as ATP is the main energy source within the cell. Mitochondria generate ATP through oxidative phosphorylation, supplying energy for cellular metabolism, division, and other processes, particularly during oocyte maturation and early embryonic development. When mitochondria are damaged or dysfunctional, their energy production capacity is reduced, directly leading to an insufficient energy supply. Studies have shown that when ATP levels in oocytes drop below 100 ng/μl, fertilization rates significantly decrease to less than 30% [60]. This energy deficit can impair oocyte developmental potential and quality, leading to developmental arrest, fertilization failure, or early embryonic loss [61]. (Fig. 2B).

ROS play key roles in regulating oocyte and ovarian function, but mitochondrial dysfunction can lead to excessive ROS accumulation, causing cell damage, apoptosis, and accelerating ovarian aging, which impacts fertility [62]. ROS are byproducts of cellular metabolism and are primarily produced during mitochondrial oxidative phosphorylation. The major forms of ROS include superoxide anions ($O2\cdot-$), hydroxyl radicals (·OH), peroxy radicals (ROO·), and hydrogen peroxide (H2O2) [63]. Moderate ROS levels play a key role in maintaining normal physiological functions, participating in the regulation of cellular energy metabolism, signal transduction, and cell proliferation [64–66]. These processes are closely linked to key physiological activities in the ovary, such as primordial follicle formation, oocyte maturation, ovulation, corpus luteum formation, and follicular atresia [67]. However, mitochondrial dysfunction or aging disrupts the balance between oxidative and antioxidative systems, leading to excessive ROS production. Excessive ROS can cause lipid peroxidation and oxidatively damage proteins and DNA, especially mtDNA, which is highly susceptible to ROS due to the lack of histone protection and weak repair mechanisms [68]. The accumulation of oxidative damage worsens mitochondrial dysfunction, creating a vicious cycle of ROS generation and mitochondrial damage, ultimately leading to oxidative stress and apoptosis. Research has shown that with the intensification of oxidative stress, excess ROS not only damage oocytes but also affect the ovarian reserve, leading to a decline in oocyte quality and quantity [69, 70]. As women age, the balance between the oxidative and antioxidative systems gradually decreases, and the accumulation of ROS intensifies. ROS not only disrupt the oxidative phosphorylation process on the mitochondrial membrane, leading to decreased ATP production but also reduce calcium ion storage in the mitochondrial matrix [71]. Excessive ROS accumulation activates mitochondrial apoptotic pathways, disrupting calcium ion homeostasis, causing mitochondrial dysfunction, and ultimately halting oocyte growth and triggering apoptosis. In the long-term, ROS accumulation is a key driver of ovarian aging, accelerating the degeneration of ovarian function and subsequently affecting female fertility [72]. (Fig. 2B).

Normal intracellular calcium ion levels and fluctuations are crucial for oocyte development, ovulation, and fertilization. Mitochondria, as key regulators of calcium ion levels, play critical roles in calcium homeostasis and apoptosis [73]. Mitochondria maintain a dynamic calcium ion balance by participating in calcium ion release and uptake. When mitochondrial function is abnormal, intracellular calcium ion fluctuations are affected, which may lead to apoptosis and accelerate ovarian aging [74]. Abnormal calcium ion fluctuations due to mitochondrial dysfunction disrupt redox homeostasis and increase mitochondrial outer membrane permeability (MOMP), creating an imbalance between intracellular and extracellular environments and worsening oxidative stress. This environmental change is a key inducer of apoptosis, particularly during follicular loss, where the intensification of apoptosis is a major feature of ovarian aging [75]. In this process, Bcl-2 family

proteins, key regulators of apoptosis, control MOMP and apoptosis through complex interactions among their members. This family includes both proapoptotic and antiapoptotic members, which determine cell survival or death by either activating or inhibiting MOMP [76]. Anti-apoptotic Bcl-2 family members (such as Bcl-2 and Bcl-xL) maintain mitochondrial membrane integrity by inhibiting MOMP, preventing the release of apoptotic factors, and protecting cells from apoptosis [77]. In contrast, proapoptotic proteins (such as Bax and Bak) promote MOMP, leading to the release of apoptotic factors such as cytochrome C from mitochondria and initiating a cascade of apoptotic reactions [78]. Studies have shown that Bcl-2 family proteins play crucial roles in regulating MOMP, particularly in maintaining mitochondrial membrane stability and calcium ion balance. Research also indicates that cytochrome C, a key apoptotic factor in mitochondria, is usually contained within the mitochondrial inner membrane. Abnormal calcium ion fluctuations due to mitochondrial dysfunction disrupt redox homeostasis and increase mitochondrial outer membrane permeability (MOMP), creating an imbalance between intracellular and extracellular environments and worsening oxidative stress [78]. Therefore, regulating calcium ion fluctuations and apoptotic pathways caused by mitochondrial dysfunction may provide new research directions for preventing and treating ovarian aging. An in-depth study of mitochondrial function and calcium ion dynamics, particularly the regulation of MOMP and Bcl-2 family proteins, may reveal effective therapeutic strategies to delay ovarian aging and related diseases. (Fig. 2B).

In summary, mitochondrial dysfunction and its impact on oocyte quality have been widely confirmed by reproductive medicine research. Studies show that reduced mitochondrial ATP production, mtDNA mutations, excessive ROS generation, and abnormal calcium ion fluctuations are closely linked to a decline in oocyte quality. These changes not only reduce the developmental potential and fertilization rates of oocytes but also accelerate apoptosis and ovarian aging. In ART, maintaining mitochondrial function is considered key to improving oocyte quality and reproductive success rates. Future research should focus on regulating mitochondrial function and related processes to develop strategies for delaying ovarian aging, improving fertility, and enhancing treatment success rates.

### The relationship between mitochondrial dysfunction and ovarian aging-related diseases

Ovarian aging can be divided into two main categories: physiological ovarian aging and pathological ovarian aging. Physiological ovarian aging refers to the gradual decline in ovarian function with age under normal physiological conditions [79]. Pathological ovarian aging includes conditions such as diminished ovarian reserve (DOR), primary ovarian insufficiency (POI), and poor ovarian response (POR) [80]. DOR refers to an abnormal decrease in the number and/or quality of ovarian follicles, which may be caused by natural aging, genetic factors, diseases, or treatments, leading to reduced fertility. POI refers to a decline in ovarian function before the age of 40, which may cause menstrual irregularities, infertility, and other issues [81]. POR refers to a poor ovarian response to ovulation-stimulating drugs in ART treatments, resulting in fewer or lower-quality follicles and reduced pregnancy success rates. The fertilization and developmental capacity of human embryos are closely related to mitochondrial metabolic function. Genetic abnormalities, hypoxia, oxidative stress, and other internal and external factors can impair mitochondrial function in embryos, leading to decreased ATP production within oocytes. This energy deficiency may cause abnormal chromosomal separation or embryo developmental arrest, ultimately affecting fertility outcomes. Studies have shown that mitochondrial function is significantly lower in patients with POI, DOR, or physiological ovarian aging than in normal individuals [82]. As the energy center of the cell, mitochondria play a key role in these cases of ovarian aging. The decline in mitochondrial function leads to insufficient energy supply, affecting normal cellular metabolism and further exacerbating the decline in ovarian function [83].

Recent studies have shown that the ovarian aging caused by DOR is closely related to the expression of Sirtuin 3 (SIRT3). SIRT3 is a mitochondrial protein that plays a critical role in maintaining mitochondrial function and maintaining the cellular metabolic balance. Yan et al. reported that, compared with women with a normal ovarian reserve (NOR), women with DOR presented significantly lower mRNA levels of SIRT3 and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) in granulosa cells [80]. Additionally, the mtDNA content in granulosa cells and oocytes also tended to decrease. These findings further support the associations between ovarian aging, mitochondrial dysfunction, and abnormal SIRT3 expression. Abnormal expression of SIRT3 may lead to mitochondrial dysfunction, thus affecting the normal function of the female reproductive system [84]. In DOR patients, the reduction in SIRT3 levels not only affects mitochondrial energy metabolism but also exacerbates the decrease in oocyte quality by disrupting the oxidative stress balance. Moreover, studies have shown that abnormal regulation of granulosa cells (GCs) may be closely related to the decline in oocyte function in DOR women [85]. Li et al. reported

that miR-484 expression in the follicular fluid of DOR women was significantly higher and negatively correlated with serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC). Further experiments showed that miR-484 affects ovarian reserve by influencing mitochondrial function in GCs and inducing their apoptosis [86]. These findings provide new clues for exploring the molecular mechanisms of ovarian aging and reveal the important role of GCs and SIRT3 in maintaining ovarian function [84]. More importantly, these studies provide a theoretical basis for developing treatment strategies for ovarian aging. By regulating the expression levels of SIRT3 and miR-484 in GCs, it may be possible to restore mitochondrial function, delay ovarian aging, and improve the fertility potential of DOR women. This research direction offers new hope for the treatment of ovarian aging.

Several pathogenic genes related to primary ovarian insufficiency (POI) participate in the regulation of mitochondrial function in oocytes and granulosa cells. These genes play key roles in mtDNA replication, gene expression, and protein synthesis and transcription, and they include MRPS22, POLG, TWNK, LARS2, HARS2, AARS2, CLPP, and LRPPRC [87]. Abnormal function of these genes may impair mitochondrial function, leading to the occurrence and development of POI. In addition to the pathogenic effects of single genes, chromosomal abnormalities are also potential causes of POI. Tiosano et al. summarized studies related to X chromosome defects and noted that Turner syndrome (TS) and fragile X syndrome (FXPM) are the main examples [87]. Both conditions result in certain types of mitochondrial dysfunction. Turner syndrome is an important genetic factor leading to POI, which is caused primarily by X chromosome monosomy. Alvarez-Nava et al. reported that DNA methylation in TS patients may affect mitochondrial biogenesis [88]. Additionally, a study analyzing the mitochondrial genome of a TS patient identified four specific mutations related to Turner syndrome, suggesting that there may be interactions between X chromosome abnormalities and mtDNA. Fragile X syndrome (FXPM) is another potential genetic cause of POI. Tassone et al. noted that the triplet repeat mutation in the FMR1 gene is the primary pathogenic mechanism leading to FXPM [89]. The loss of the FMR protein encoded by the FMR1 gene affects multiple physiological processes, including altering mitochondrial gene expression, impairing mitochondrial function, and increasing oxidative stress [90]. Conca Dioguardi et al. revealed the close association between FXPM and mitochondrial dysfunction in a mouse model, further emphasizing the importance of mitochondria in ovarian aging [91]. In FXPM mice, researchers found significant reductions in mtDNA and corpus luteum contents, increased follicular atresia, and ultimately decreased fertility. These findings not only highlight the severity of mitochondrial dysfunction in FXPM patients but also increase our understanding of the relationship between ovarian aging and mitochondrial function. This research provides valuable insights for further exploration of ovarian aging and related diseases.

Recently, Liu et al. reported that the dysregulated expression of Epg5, a homolog of P-granule autophagy protein 5, in GCs can trigger the pathogenesis of POI. They reported that knocking out Epg5 induced GC aging and apoptosis, leading to follicular development defects [92]. As we deepen our understanding of mitochondria's role in ovarian health, we can better grasp the pathophysiological mechanisms of these diseases and develop more effective treatments, offering improved options and quality of life for patients with POI and related conditions.

Chia-Jung Li et al. studied granulosa cells from POR patients and normal individuals, finding significantly impaired mitochondrial function and lower mitochondrial quality in the POR group [93]. These findings highlight the key role of mitochondria in oocyte maturation and corpus luteum formation. Furthermore, this study suggested that dehydroepiandrosterone (DHEA) could be a potential treatment for POR. DHEA is an androgen primarily secreted by the adrenal glands, central nervous system, and ovarian follicular cells. It is widely distributed in tissues and organs and can be converted into active sex hormones in peripheral tissues. As women age, DHEA levels gradually decline, suggesting that it may be associated with ovarian aging [93]. To verify this hypothesis, Chia-Jung Li et al. used GnRH antagonists and immunofluorescence techniques, confirming that DHEA supplementation improved mitochondrial quality, reduced mitochondrial division, and cleared dysfunctional mitochondria through enhanced mitochondrial autophagy [93]. In addition, Cai et al. reported that differences in the expression levels of the follicle-stimulating hormone receptor (FSHR) in GCs could lead to varying ovarian responses. Low expression of FSHR in GCs may be a key factor contributing to POR [94]. These findings provide an innovative treatment strategy for ovarian aging caused by POR, suggesting new hope and treatment options for patients with ovarian dysfunction.

## Outlook

As scientific research continues to advance, our understanding of the impact of mitochondrial dysfunction on ovarian aging has increased. Mitochondria are the energy centers of the cell and key sites for redox reactions

within oocytes [95]. Mitochondrial dysfunction leads to a series of biological effects, including energy supply deficiency, increased oxidative stress, and DNA damage, all of which affect normal ovarian function. Therefore, in-depth research on the effects of mitochondrial dysfunction on ovarian aging is of great academic and clinical importance.

Mitochondria play crucial roles in ovarian aging, and exploring their molecular mechanisms can help reveal the multifaceted mechanisms of ovarian aging. Mitochondrial dysfunction may affect various processes, such as redox reactions, ROS generation and clearance, and mtDNA mutation and repair [96]. These studies will not only help comprehensively elucidate the biological processes of ovarian aging but may also reveal new therapeutic targets and methods, providing more effective strategies for treating related diseases. The development of therapeutic strategies and drug targets that target mitochondria is crucial, particularly for delaying ovarian aging and treating related diseases. By promoting mitochondrial biogenesis, enhancing mitochondrial membrane stability, and increasing mitochondrial autophagy, it is possible to regulate mitochondrial function while effectively slowing the aging process of the ovary [97]. The progress of these strategies will offer clinicians more personalized and effective treatment options. Gene editing and repair technologies provide new possibilities for treating ovarian aging. Advanced gene editing tools such as CRISPR/Cas9 may allow for the direct repair of mitochondrial DNA or the regulation of mitochondrial-related genes, restoring their normal function [87]. Through these precise gene repair technologies, mitochondrial function in the ovary can be effectively improved, ultimately providing more personalized and accurate treatment plans.

The impact of environmental factors and lifestyle on mitochondrial function and ovarian health should not be overlooked. In-depth studies on how factors such as diet, sleep, exercise, and psychological stress regulate mitochondrial function can help elucidate the mechanisms underlying ovarian aging [98]. For example, a healthy diet supports the maintenance of normal mitochondrial function [99]; Good sleep and moderate exercise can reduce oxidative stress damage to mitochondria; and psychological stress may affect mitochondrial function through the neuroendocrine system [100]. By studying these factors, we hope to discover new strategies to delay ovarian aging and provide practical lifestyle recommendations to improve quality of life.

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