Journal of Medical Sciences

ISSN 1682-4474

science alert

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OPEN ACCESS Journal of Medical Sciences

ISSN 1682-4474
DOI: 10.3923/jms.2026.37.50

Review Article
Unlocking the Secret of Oocyte Ageing: The Role of SIRT1

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Abstract

Background and Objective: Oocyte aging is a natural biological process that has remained a significant challenge in reproductive biology. As women age, the quality of their oocytes declines, leading to reduced fertility rates and increased risks of pregnancy complications. This review provides an understanding of the ageing process of oocytes and the molecular mechanisms underlying SIRT1's influence on oocyte quality. **Materials and Methods:** Information used in this review was sourced from various databases, including PubMed, EMBASE, African Journal Online and Google Scholar. **Results:** While the underlying mechanisms of oocyte aging are complex and not fully understood, recent studies have implicated the involvement of Sirtuin 1 (SIRT1), a key regulator of cellular aging and stress response. Despite the growing body of evidence, the precise role of SIRT1 in oocyte aging and its potential as a therapeutic target remains unclear. **Conclusion:** A deeper understanding of the molecular mechanisms underlying SIRT1's influence on oocyte quality is essential for developing effective interventions to mitigate the effects of oocyte aging and improve fertility outcomes.

Key words: Sirtuin 1, oocytes, ageing, humans

Citation: Adenuga M.A. and M.A. Emokpae, 2026. Unlocking the secret of oocyte ageing: The role of SIRT1. J. Med. Sci., 26: 37-50.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Approximately 1 in 6 people (about 17.5% of the global adult population) experience infertility at some point during their reproductive years. In recent years, socioeconomic advancements, evolving career paths and changing family planning practices have resulted in significant delays in childbearing. This phenomenon has notably raised the number of individuals seeking to conceive during periods of reduced reproductive capability, thereby increasing the global demand for Assisted Reproductive Technologies (ART). In contrast to other organ systems, female reproductive organs experience a rapid physiological decline starting in the third and fourth decades of life. This deterioration is marked by a gradual loss of the non-renewable primordial follicle pool (ovarian reserve), heightened meiotic spindle abnormalities, mitochondrial dysfunction, oxidative stress and chromosomal aneuploidy in aging oocytes, all of which contribute to decreased fertilization rates and an increased likelihood of spontaneous miscarriage[1,2].

Oocyte aging means the natural decline in the quality of eggs (oocytes) as a woman ages. This decline is associated with a decrease in fertility and an increased risk of pregnancy complications and genetic abnormalities in offspring. As is widely known, oocyte aging correlates with a simultaneous decline in both quality and quantity of these cell types with advancing maternal age. A biological process is another key component of total female reproductive potential, which is determined mostly by older ovaries. In contrast to the situation in women, sperm production in men is a continuous process that begins at puberty and persists throughout most of their lives, effectively indicating that they do not deplete their supply[1,2].

As women grow older, the ovarian reserve and the pool of available oocytes progressively deplete, leading to fewer eggs for fertilization[2]. A reduction in oocyte quality also occurs. Inevitable genetic deterioration from diminishing ovarian reserve and augmented oxidative stress, DNA lesions and mitochondrial malfunction-induced chromosomal damage will lead to poor-quality oocytes[3].

While the underlying mechanisms of oocyte aging are complex and not fully understood, recent studies have implicated the involvement of Sirtuin 1 (SIRT1), a key regulator of cellular aging and stress response. Despite the growing body of evidence, the precise role of SIRT1 in oocyte aging and its potential as a therapeutic target remains unclear. A deeper understanding of the molecular mechanisms underlying SIRT1's influence on oocyte quality is essential for developing effective interventions to mitigate the effects of oocyte aging and improve fertility outcomes. This review therefore provides an understanding of the ageing process of the oocyte and the molecular mechanisms underlying SIRT1's influence on oocyte quality. This review summarizes the current understanding of oocyte aging, with particular emphasis on the molecular mechanisms by which SIRT1 regulates oocyte quality, mitochondrial function, oxidative stress and genomic stability, while highlighting its potential as a therapeutic target for preserving female fertility.

MATERIALS AND METHODS

A thorough search of the literature was conducted using electronic databases such as Google Scholar, PubMed, EMBASE, CINAHI (EBSCO) and African Journals Online (AJOL). The search encompassed peer-reviewed studies published from January 1, 2010, to May 31, 2026, with no geographic restrictions applied. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords using Boolean operators (AND, OR). The following terms and combinations were utilized: "Impact of Oocyte aging on fertility, Biology of Oocytes, SIRT1 and Oocyte quality". Human clinical trials, prospective/retrospective cohort studies, case-control studies, cross-sectional studies and mechanistic translational studies focusing on human reproductive tissue or oocytes. Pure animal models or non-human *in vitro* assays without translational correlation and studies focusing exclusively on male-factor infertility without female-specific outcome stratification were excluded. Two independent reviewers screened titles and abstracts against the predefined eligibility criteria and full texts of potentially eligible articles were retrieved and independently reviewed. Research articles, review papers and meta-analyses that addressed these topics met the inclusion criteria. The gathered data were synthesized and analyzed to uncover common themes, discrepancies and gaps within the literature. A critical evaluation was performed to assess the methodological rigor, limitations and potential biases of the included studies. The clinical relevance of the findings from the included research was also assessed.

IMPACT OF OOCYTE AGING ON FERTILITY

It is well established that the effects of oocyte aging on female fertility are among, if not the clearest and most dramatic, events that impair fecundity. It not only diminishes the ability to conceive (diminished ovarian reserve), but also reduces the capability to sustain a healthy pregnancy and was directly correlated to advancing maternal age[4]. The major

outcomes of oocyte aging are reduced fertility, increased risk of chromosomal abnormalities, higher miscarriage rates, decreased success of Assisted Reproductive Technologies (ART), delayed embryo development and implantation failure[5].

The decline in oocyte number and quality leads to decreased fecundity (the ability to conceive). As women approach the end of their reproductive lifespan, the likelihood of natural conception decreases significantly. Studies have shown that a woman's fertility decreases substantially in her late 30s and early 40s, mainly due to aging oocytes and the associated decline in ovarian function[4,5].

As oocytes age, they are more prone to chromosomal segregation errors during meiosis, particularly aneuploidy, where the oocytes contain an abnormal number of chromosomes. This is the primary cause of genetic disorders such as Down syndrome (trisomy 21). Older oocytes also have a higher incidence of chromosomal abnormalities like misaligned chromosomes during meiosis, which leads to conditions like miscarriages or failed implantation[6].

Oocyte aging is associated with an increased risk of spontaneous miscarriage. Research has shown that older women are more likely to experience pregnancy loss due to chromosomal abnormalities and oocyte dysfunction[7]. Also, *in vitro* fertilization (IVF) success rates decline with age, particularly after the age of 35. Women who undergo ART treatments using their own oocytes tend to have lower success rates as oocyte quality diminishes with age. To overcome this, donor eggs from younger women are often used in ART, which can result in higher pregnancy rates in older women[7]. Oocytes from older women may result in slower embryo development post-fertilization, impacting the embryo's ability to implant in the uterus and establish a successful pregnancy.

SIRT1 (Sirtuin 1): It is a member of the sirtuin family of proteins, which are highly conserved NAD+-dependent deacetylases. SIRT1 has gained considerable attention for its role in regulating cellular aging, stress response and metabolic homeostasis. As cells age, they accumulate DNA damage due to various intrinsic and extrinsic factors. SIRT1 promotes genomic stability by enhancing DNA repair mechanisms. It deacetylates and activates proteins involved in DNA repair, such as Ku70, which helps repair double-strand breaks and p53, which is a key regulator of the cell cycle and apoptosis[8].

By modulating these factors, SIRT1 prevents the accumulation of DNA damage, which is a hallmark of aging and age-related diseases. This protein acts as a master regulator of various physiological pathways by deacetylating key transcription factors and enzymes involved in aging, inflammation, metabolism and apoptosis. The activity of SIRT1 is closely linked to cellular energy status, making it a crucial mediator in processes like caloric restriction and cellular longevity[9].

ROLE OF SIRT1 IN CELLULAR AGING AND LONGEVITY

SIRT1 plays an essential role in regulating various processes that contribute to cellular aging and longevity. Its involvement in energy metabolism, DNA repair, oxidative stress response and mitochondrial function helps to slow down age-related cellular decline and promote healthy aging. Several mechanisms have been proposed through which SIRT1 influences ageing and longevity. They include regulation of DNA repair and genomic stability, Oxidative stress resistance, maintenance of mitochondrial function, caloric restriction and metabolic regulation, regulation of inflammation and immune response and apoptosis and cell survival[10].

SIRT1 enhances the ability of cells to resist oxidative stress, which is a major contributor to aging. It does this by deacetylating and activating FOXO transcription factors (FOXO1, FOXO3), which regulate the expression of antioxidant enzymes like superoxide dismutase (SOD) and catalase. These enzymes neutralize reactive oxygen species (ROS), reducing oxidative damage to cellular components such as DNA, proteins and lipids[11]. This oxidative stress resistance is particularly important for longevity, as excessive ROS production accelerates cellular aging.

Mitochondrial dysfunction is another hallmark of aging and SIRT1 plays a critical role in maintaining mitochondrial health. By deacetylating peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), SIRT1 promotes mitochondrial biogenesis and improves mitochondrial function. Enhanced mitochondrial activity helps meet the energy demands of cells and reduces the production of ROS, contributing to overall cellular longevity[12].

One of the most well-established roles of SIRT1 is its mediation of the beneficial effects of caloric restriction (CR), a dietary regimen that has been shown to extend lifespan in various organisms. CR activates SIRT1 by increasing the cellular NAD+ levels, which in turn deacetylates and activates metabolic regulators like PGC-1α and AMP-activated protein kinase (AMPK)[12]. These factors promote enhanced fatty acid oxidation, improved glucose metabolism and reduced fat storage, contributing to metabolic health and longevity[12].

SIRT1 negatively regulates the activity of NF-κB, a transcription factor involved in the inflammatory response. By deacetylating the p65 subunit of NF-κB, SIRT1 suppresses the expression of pro-inflammatory cytokines, reducing chronic inflammation, which is a common feature of aging (termed inflammaging). This anti-inflammatory effect contributes to the prevention of age-related diseases, such as cardiovascular disease and neurodegeneration[9].

Lastly, SIRT1 regulates apoptosis, or programmed cell death, by modulating the activity of p53, a protein that induces apoptosis in response to DNA damage and cellular stress. By deacetylating p53, SIRT1 reduces its pro-apoptotic activity, allowing cells to survive longer and avoid premature cell death. This function is crucial in preventing excessive cell loss during aging and maintaining tissue integrity[9].

SIGNIFICANCE OF UNDERSTANDING OOCYTE AGING FOR IMPROVING REPRODUCTIVE OUTCOMES

The significance of understanding Oocyte aging includes advancing reproductive medicine by formulating fertility treatments based on individual factors, such as oocyte age and quality that will improve outcomes[13]. With increased knowledge of oocyte aging, more women can opt for fertility preservation at a younger age through egg freezing. Cryopreserving oocytes when they are of higher quality allows women to defer childbearing until later in life, thus preserving their reproductive potential despite the effects of aging[14]. For women facing medical conditions that may affect their fertility, such as cancer treatments, ovarian tissue cryopreservation is an emerging fertility preservation option. Understanding how oocyte aging and preservation technologies interact is essential for optimizing the outcomes of these techniques[14]. By unraveling the mysteries of oocyte aging, scientists can pave the way for innovative treatments and strategies to help women achieve their dream of parenthood[13].

A deep understanding of oocyte aging is crucial for improving IVF protocol and improve oocyte selection. By understanding the molecular mechanisms of oocyte aging, researchers can develop more effective IVF protocols, including timing of hormone treatments and oocyte retrieval. Identifying biomarkers for oocyte quality can help select the best quality oocytes for fertilization, thereby increasing the chances of successful pregnancy[15].

It will help in targeting of specific molecular pathways involved in oocyte aging that will enable the development of therapies to delay or reverse the aging process. Also, for the formulation of strategies needed to improve mitochondrial function in oocytes which will enhance their developmental potential. Understanding of Oocyte ageing will help to modify epigenetic factors that contribute to oocyte aging and may offer new therapeutic avenues[5]. Understanding Oocyte ageing will lead to the prevention of pregnancy complications by identifying factors that contribute to early pregnancy loss and minimizing birth defects. If Oocyte quality is improved, it will enable the reduction of the risk of genetic abnormalities and birth defects[16].

BIOLOGY OF OOCYTE AGING

Molecular and cellular mechanisms underlying oocyte aging: Oocyte aging is a complex process driven by both molecular and cellular factors that affect the quality and functionality of oocytes over time. As women age, the aging of their oocytes becomes a key contributor to the decline in fertility, characterized by reduced oocyte quantity and quality, increased rates of chromosomal abnormalities and lower chances of successful fertilization and embryo development. Understanding the molecular and cellular mechanisms of oocyte aging is crucial for developing interventions to mitigate these age-related declines. The following highlights the key molecular and cellular mechanisms underlying oocyte aging.

Chromosomal segregation errors and aneuploidy: One of the most significant consequences of oocyte aging is the increased occurrence of chromosomal segregation errors during meiosis, the process by which oocytes undergo division to reduce their chromosomal number. As oocytes age, they exhibit reduced spindle assembly checkpoint (SAC) efficiency and cohesion loss between sister chromatids, resulting in nondisjunction (failure to separate chromosomes properly)[17]. This results in aneuploidy, where oocytes contain an abnormal number of chromosomes, increasing the likelihood of miscarriages and chromosomal disorders such as Down syndrome[17].

Mitochondrial dysfunction: Mitochondria play a vital role in oocyte quality by providing the energy required for meiotic spindle formation, chromosome segregation and early embryo development. As oocytes age, mitochondrial function declines, which leads to reduced ATP production, increased oxidative stress and accumulation of damaged mitochondria[18]. Aged oocytes often have mitochondrial DNA (mtDNA) mutations and decreased mitochondrial membrane potential, impairing their ability to support fertilization and early embryonic development. This mitochondrial dysfunction is one of the leading causes of reduced oocyte competence and compromised fertility in older women[18].

Oxidative stress and accumulation of reactive oxygen species (ROS): Oxidative stress plays a central role in the aging of oocytes. As oocytes age, the balance between ROS production and the capacity to neutralize them with antioxidant defenses is disrupted, leading to the accumulation of ROS. These reactive molecules damage cellular components, including DNA, proteins and lipids[19]. Increased oxidative stress in aging oocytes results in the formation of DNA double-strand breaks, cross-linking of proteins and damage to mitochondria. This contributes to reduced oocyte quality, impaired meiotic division and increased risk of apoptosis[19].

Telomere shortening and genomic instability: Telomeres, the protective caps at the ends of chromosomes, shorten with each cell division and are markers of cellular aging. Oocytes are particularly sensitive to telomere shortening because of their extended period of arrest in prophase I of meiosis, lasting from fetal development until ovulation decades later. In aged oocytes, telomere shortening leads to genomic instability, which increases the risk of chromosomal abnormalities and contributes to reduced oocyte viability. This shortening is exacerbated by oxidative stress and the diminished activity of telomerase, the enzyme responsible for maintaining telomere length[20].

Altered epigenetic regulation: Epigenetic modifications, such as DNA methylation and histone acetylation, play crucial roles in oocyte development and competence. These modifications are essential for maintaining genomic integrity and regulating gene expression in oocytes. However, as oocytes age, their epigenetic landscape becomes altered. DNA methylation patterns are disrupted in aged oocytes, leading to inappropriate gene expression and impaired developmental potential. Additionally, histone modifications, such as acetylation and methylation, are altered, impacting chromatin structure and oocyte maturation[21].

Dysregulation of the spindle assembly checkpoint (SAC): The spindle assembly checkpoint (SAC) ensures proper chromosome alignment and segregation during meiosis. In aged oocytes, SAC function declines, leading to increased rates of chromosome misalignment and segregation errors during meiotic division. This dysfunction is primarily due to the weakening of microtubule-kinetochore attachments, which are essential for correct chromosome alignment. As a result, aged oocytes are more prone to producing aneuploid embryos[3].

ROLE OF DNA DAMAGE, OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN OOCYTE AGING

Oocyte aging is a key contributor to female infertility and is driven by several interconnected molecular mechanisms, including DNA damage, oxidative stress and mitochondrial dysfunction. These processes contribute to the decline in oocyte quality, decreased fertilization rates and increased chromosomal abnormalities with advancing maternal age.

DNA damage in oocyte aging: DNA integrity is critical for oocyte function. As oocytes age, they accumulate DNA damage due to both intrinsic factors (e.g., oxidative stress) and external environmental factors. Oocytes are particularly vulnerable because they remain in a prolonged state of meiotic arrest for decades before ovulation. Double-strand breaks are a major form of DNA damage that accumulates in aging oocytes. It can arise due to replication stress, oxidative damage, or impaired DNA repair mechanisms and its persistence can lead to chromosomal abnormalities such as aneuploidy (incorrect chromosome numbers) during meiosis. In aging oocytes, the efficiency of the DNA repair mechanisms, such as homologous recombination and non-homologous end joining, declines. This impaired repair leads to an increased accumulation of unrepaired DNA damage, contributing to the decline in oocyte quality[22].

Oxidative stress in oocyte aging: Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, is a major driver of oocyte aging. As oocytes age, the production of ROS increases, while the oocytes' ability to neutralize these reactive molecules diminishes. This leads to widespread damage to cellular structures, including lipids, proteins and nucleic acids. ROS-induced damage in oocytes leads to DNA fragmentation, protein oxidation and lipid peroxidation. This cellular damage impairs key processes such as spindle formation during meiosis, chromosome segregation and ultimately, oocyte viability[23]. Antioxidant defenses, such as superoxide dismutase (SOD) and glutathione, are crucial in preventing oxidative damage. However, aging oocytes exhibit a reduction in antioxidant capacity, which exacerbates the harmful effects of oxidative stress[23].

Mitochondrial dysfunction in oocyte aging: Mitochondria are critical to oocyte health and function, as they supply the energy (ATP) required for various cellular processes, including meiotic spindle assembly, chromosome segregation and early

embryonic development. Mitochondrial dysfunction is one of the hallmark features of oocyte aging, contributing to reduced fertility and compromised embryo development. Aging oocytes often exhibit mitochondrial DNA (mtDNA) mutations, which impair the function of the mitochondrial electron transport chain. This leads to decreased ATP production and increased ROS generation, creating a vicious cycle of mitochondrial damage and oxidative stress[24].

In addition to decreased ATP production, aged oocytes display mitochondrial membrane potential loss, which disrupts mitochondrial function. The impaired energy supply and the accumulation of dysfunctional mitochondria in aging oocytes compromise their ability to complete meiotic divisions and support fertilization[25].

INTERCONNECTEDNESS OF DNA DAMAGE, OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

The processes of DNA damage, oxidative stress and mitochondrial dysfunction are intricately linked in aging oocytes. Whereas oxidative stress can directly damage both nuclear DNA and mitochondrial DNA, leading to mutations and reduced mitochondrial function, mitochondrial dysfunction can result in increased ROS production, which further accelerates oxidative damage to cellular components, including DNA. Consequently, DNA damage, particularly in mitochondrial DNA, thus impairs the mitochondrial energy supply, which is essential for oocyte viability and meiotic division. These processes compound with age and contribute to the overall decline in oocyte quality, leading to decreased fertility, higher rates of chromosomal abnormalities and reduced success rates in assisted reproductive technologies[26].

IMPACT OF OOCYTE AGING ON FERTILIZATION, EMBRYO DEVELOPMENT AND IMPLANTATION

Oocyte aging significantly affects reproductive outcomes, including fertilization, embryo development and implantation. This decline is associated with various cellular and molecular alterations that reduce the fertility potential of women and increase the risk of adverse reproductive outcomes.

Impact on fertilization: As oocytes age, their ability to undergo successful fertilization declines due to chromosomal abnormalities, spindle and cytoskeleton defects and zona pellucida hardening. Aged oocytes are more prone to chromosomal segregation errors during meiosis, leading to aneuploidy. This significantly reduces the likelihood of successful fertilization or results in early embryonic loss[2].

Spindle and cytoskeleton defects: Aged oocytes exhibit defects in meiotic spindle formation and cytoskeletal structures, leading to abnormal chromosome alignment and segregation. These defects can compromise the oocyte's ability to complete meiosis after fertilization[27].

Zona pellucida hardening: Oocyte aging is associated with changes in the zona pellucida, the outer layer of the oocyte, which may harden over time. This can reduce sperm penetration and lower fertilization success rates[27].

Impact on embryo development: Oocyte quality plays a crucial role in the early stages of embryo development. Aged oocytes often give rise to embryos with lower developmental potential. This can lead to increased rates of Aneuploidy. Embryos derived from older oocytes have a higher incidence of aneuploidy due to meiotic errors in chromosome segregation. Aneuploid embryos often fail to develop beyond the blastocyst stage or result in early miscarriage. Embryos originating from aged oocytes frequently show compromised morphological quality, with irregular cell division and fragmentation. These abnormalities reduce the likelihood of achieving a viable pregnancy[19]. Mitochondria in aging oocytes often exhibit decreased function, leading to lower ATP production. This energy deficit compromises critical processes during early embryonic development, such as cell division and differentiation[22].

Impact on implantation: Oocyte aging also affects the ability of the embryo to successfully implant in the uterus. Factors contributing to implantation failure include reduced endometrial receptivity. Although endometrial receptivity is influenced by multiple factors, the quality of the embryo plays a critical role. Aged oocytes produce embryos that are less capable of signaling the maternal endometrium to support implantation. Embryos derived from aged oocytes are more likely to be chromosomally unstable. Such embryos, even if they reach the blastocyst stage, may fail to implant due to an inability to generate the required molecular signals for endometrial interaction. Even if implantation occurs, embryos from aged oocytes have a higher chance of resulting in biochemical pregnancies or early miscarriage due to genetic abnormalities and compromised developmental potential. Oocyte aging significantly compromises the processes of fertilization, embryo development and implantation. The cumulative effects of chromosomal abnormalities, mitochondrial dysfunction and oxidative stress contribute to poor reproductive outcomes as women age. By understanding

the impact of oocyte aging, researchers and clinicians can develop targeted interventions, such as improving mitochondrial function or utilizing preimplantation genetic screening, to enhance fertility outcomes[20].

KEY ROLES PLAYED BY SIRT1 IN OOCYTE AGING

Structure and function of SIRT1: SIRT1 plays a pivotal role in regulating cellular processes, particularly in the context of cellular aging, metabolism and stress resistance. This family of proteins, particularly SIRT1, has gained significant attention in studies related to longevity, metabolic regulation and age-related diseases[9]. The structure of SIRT1is critical to its function as a deacetylase and regulator of various cellular pathways. SIRT1 is composed of a conserved catalytic core, which uses NAD+ as a cofactor for its deacetylation activity. This NAD+-dependency links SIRT1 activity to cellular energy status and metabolic processes. In addition to the catalytic core, SIRT1 contains N-terminal and C-terminal extensions that regulate its interactions with various protein substrates and cellular localization. These regions are more variable across sirtuin family members, contributing to their unique functional roles[10]. The core domain of SIRT1 consists of a Rossmann fold, a structural motif used to bind NAD+ and perform enzymatic activities.

SIRT1 catalyzes the deacetylation of lysine residues on target proteins by transferring the acetyl group from the substrate to NAD+, producing nicotinamide, 2′-O-acetyl-ADP-ribose and the deacetylated substrate. This activity modulates the function of key proteins involved in transcription, apoptosis and metabolism[12].

Function of SIRT1: SIRT1 is a master regulator of cellular homeostasis, responding to environmental stresses and metabolic cues. It is involved in several critical pathways related to aging, stress resistance and metabolic regulation. It participates in delaying Cellular Aging and improves Longevity. These it does by carrying out DNA repair, Telomere maintenance and regulation of apoptosis.

It carries out metabolic regulation to maintain energy homeostasis and glucose and lipid metabolism. SIRT1 enhances insulin sensitivity by deacetylating and activating FOXO1, a transcription factor involved in glucose metabolism. It also regulates lipid metabolism by modulating the activity of liver X receptor (LXR) and sterol regulatory element-binding proteins (SREBPs), which control cholesterol and fatty acid synthesis[12].

SIRT1 plays some roles in Stress Resistance and Antioxidant Defense as well as regulation of inflammation and immune response. It promotes autophagy, a cellular process that removes damaged organelles and proteins. This is achieved through the deacetylation of autophagy-related proteins, such as LC3 and Atg5, contributing to cellular cleaning and rejuvenation[10].

SIRT1 and apoptosis: SIRT1 modulates cell survival under stress conditions by regulating key proteins involved in apoptosis which include p53 Pathway, BCL-2 and apoptosis regulation. SIRT1 deacetylates and inactivates p53, a key regulator of apoptosis in response to DNA damage. By doing so, SIRT1 promotes cell survival under moderate stress, allowing cells time to repair damage instead of undergoing premature apoptosis. It also interacts with the anti-apoptotic protein BCL-2 and pro-apoptotic factors like BAX to control the balance between cell survival and death, particularly under oxidative stress conditions. By fine-tuning these pathways, SIRT1 prevents unnecessary cell death and maintains tissue function during aging[12].

EXPRESSION AND LOCALIZATION OF SIRT1 IN OOCYTES AND OVARIES

SIRT1, a key NAD-dependent deacetylase, is expressed in various tissues, including the ovaries, where it plays a crucial role in the regulation of reproductive function, particularly in oocytes. The expression and localization of SIRT1 in oocytes and ovaries provide significant insight into its involvement in processes such as folliculogenesis, oocyte maturation and ovarian aging[1,2].

SIRT1 is abundantly expressed in both primordial and growing oocytes, suggesting its essential role in the early stages of oocyte development. As oocytes mature, SIRT1 continues to be present, indicating its involvement in maintaining oocyte quality and function during the entire process of oogenesis. SIRT1 expression is detected in the nucleus and cytoplasm of primordial oocytes, suggesting its role in the early regulation of cellular metabolism, redox balance and protection against DNA damage during early follicular development. As oocytes develop into growing follicles, SIRT1 maintains its expression. It is involved in regulating mitochondrial function and protecting against oxidative stress, which are critical for the maintenance of oocyte quality[1,2].

SIRT1 is predominantly localized in the granulosa cells of ovarian follicles and the oocyte nucleus, highlighting its role in regulating follicular development and oocyte maturation. Granulosa cells provide the essential microenvironment for oocyte growth and maturation and SIRT1 helps maintain the cellular homeostasis of these support cells. SIRT1 is strongly expressed in the granulosa cells surrounding the developing

follicles, where it modulates the redox environment, inflammation and apoptosis. This localization is critical for follicle survival and oocyte development, as granulosa cells play a key role in nourishing the oocyte and supporting its growth. SIRT1 is found in the oocyte nucleus, where it deacetylates and activates transcription factors involved in stress responses, such as FOXO3a. This activation helps protect the oocyte from oxidative damage and promotes longevity by regulating gene expression related to cell survival, DNA repair and mitochondrial function[1,2].

SIRT1's expression declines with ovarian aging, which is associated with reduced oocyte quality, mitochondrial dysfunction and increased oxidative stress. This reduction in SIRT1 is linked to the diminished ability of oocytes and granulosa cells to counteract oxidative damage and maintain energy homeostasis, leading to decreased fertility in aging females.

The expression and localization of SIRT1 in both oocytes and ovarian granulosa cells underscore its critical role in regulating ovarian function, oocyte quality and protecting against oxidative stress. SIRT1 maintains cellular homeostasis and promotes longevity in oocytes, which is crucial for female reproductive health. A better understanding of SIRT1's role in these processes may open avenues for developing therapies to combat ovarian aging and improve reproductive outcomes in aging women[2].

SIRT1 AND OOCYTE QUALITY

Relationship between SIRT1 expression and oocyte quality: The expression of SIRT1 has been shown to play a pivotal role in the maintenance of oocyte quality, primarily through its regulation of oxidative stress, mitochondrial function, DNA repair and apoptosis. A decline in SIRT1 expression, particularly with aging, is associated with decreased oocyte quality and reduced fertility outcomes[27]. Oxidative stress is one of the major factors influencing oocyte quality. SIRT1 helps mitigate oxidative damage by regulating antioxidant enzymes such as superoxide dismutase (SOD) and catalase. By maintaining a balance between reactive oxygen species (ROS) production and antioxidant defense, SIRT1 ensures the protection of oocytes from oxidative damage, which is critical for preserving their quality and viability. Decreased SIRT1 expression leads to the accumulation of ROS in oocytes, resulting in oxidative damage to cellular structures such as DNA, lipids and proteins. Oocytes from aging females typically exhibit higher oxidative stress levels due to a decline in SIRT1 expression, which further exacerbates age-related infertility. Restoration of SIRT1 expression has been suggested as a potential therapeutic strategy to improve oocyte quality in aging women[27].

IMPACT OF SIRT1 ON DNA REPAIR, OXIDATIVE STRESS AND MITOCHONDRIAL FUNCTION IN OOCYTES

Sirtuin 1 (SIRT1) plays an essential role in multiple cellular processes related to aging, metabolism and stress responses. In oocytes, SIRT1 is critical in mitigating the adverse effects of DNA damage, oxidative stress and mitochondrial dysfunction, which are major contributors to reproductive aging. Here, we explore the impact of SIRT1 on DNA repair, oxidative stress and mitochondrial function in oocytes, highlighting its role in maintaining oocyte quality and fertility.

DNA damage in oocytes can arise due to aging, environmental factors, or oxidative stress, leading to a decline in fertility and an increased risk of chromosomal abnormalities in embryos. SIRT1 contributes to genomic stability in oocytes by promoting DNA repair mechanisms via regulation of DNA damage response, interaction with Ploy (ADP-Ribose) Polymerase[1,10]. Ageing women have less efficient DNA repair mechanisms in oocytes and because of decline expression of SIRT1 with age, contributing to the diminished capacity for DNA repair and the accumulation of genetic errors in oocytes. This decline in DNA repair capacity is linked to reduced oocyte quality and a higher incidence of infertility, miscarriage and birth defects in older women[26].

Oocytes are highly susceptible to oxidative stress due to their large size and metabolic activity. ROS accumulation in aging oocytes leads to lipid peroxidation, DNA mutations and mitochondrial dysfunction. By reducing ROS levels, SIRT1 plays a vital role in preserving oocyte quality and delaying reproductive aging. Studies have shown that activation of SIRT1 can reverse some of the age-related decline in oocyte quality by reducing oxidative stress[26,27].

Mitochondria are crucial for energy production in oocytes and their dysfunction is a hallmark of oocyte aging. SIRT1 supports mitochondrial health by promoting mitochondrial biogenesis and function. SIRT1 deacetylates and activates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis. PGC-1α promotes the transcription of genes involved in mitochondrial DNA replication and energy production. Through this mechanism, SIRT1 ensures that oocytes maintain a healthy population of functional mitochondria, essential for energy-intensive processes like oocyte maturation, fertilization

Table 1: The specific downstream targets of SIRT1 and their functional consequences, providing a mechanistic understanding of its protective roles

Pathway/Target	Cell type	SIRT1-mediated effect	Consequence for ovarian function
FOXO3a	Oocyte	Deacetylation and activation	Promotes resistance to oxidative stress and regulates quiescence[28,29]
p53	Granulosa cell	Deacetylation, inhibiting its activity	Suppresses apoptosis, promoting granulosa cell survival and follicle health[29,30]
Nrf2	Oocyte	Maintains protein stability and expression	Drives transcription of antioxidant enzymes (e.g., SOD2), reducing ROS[31]
NF-κB	Granulosa cell	Deacetylation, inhibiting its activity	Reduces inflammation and promotes cell homeostasis[31,32]
H4K16 (Histone)	Oocyte	Deacetylation	Maintains chromatin structure and meiotic cohesion, ensuring accurate segregation[33]
PGC-1α	Oocyte/Granulosa	Deacetylation and activation	Promotes mitochondrial biogenesis and function[34]

H4K16(Histone) (16th lysine residue on the histone H4 protein), PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha), NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), P53 (Tumor suppressor Protein p53), Nrf2 (Nuclear Factor Erythroid 2-Related Factor 2), SIRT1 (Sirtuin 1) and FOXO3 (Forkhead Box O Transcription Factor) pathways

and early embryonic development[19]. In addition to promoting mitochondrial biogenesis, SIRT1 helps preserve mitochondrial function by enhancing the removal of damaged mitochondria through mitophagy, a selective autophagy process. By preventing the accumulation of dysfunctional mitochondria, SIRT1 supports optimal energy production in oocytes, which is critical for maintaining oocyte quality and fertility[22]. Mitochondrial dysfunction, characterized by reduced ATP production and increased ROS generation, is a major contributor to oocyte aging. The decline in SIRT1 activity with age leads to impaired mitochondrial function, contributing to the decline in oocyte quality and fertility in older women. Studies have shown that activation of SIRT1 can improve mitochondrial function in aged oocytes, potentially reversing some of the age-related decline in reproductive potential[19].

SIRT1 plays a multifaceted role in protecting oocytes from the detrimental effects of aging. By enhancing DNA repair, reducing oxidative stress and preserving mitochondrial function, SIRT1 helps maintain oocyte quality and delay reproductive aging. These protective effects make SIRT1 a promising target for therapeutic interventions aimed at improving fertility and delaying oocyte aging, particularly in women of advanced reproductive age.

POTENTIAL ROLE OF SIRT1 IN PREVENTING OOCYTE AGING AND IMPROVING FERTILITY

SIRT1 has become a crucial modulator of stress response and cellular aging. It has a substantial and complex potential involvement in enhancing fertility and avoiding oocyte aging. Because of its antioxidant qualities, it can activate antioxidant enzymes that eliminate dangerous reactive oxygen species (ROS), such as catalase and superoxide dismutase (SOD). SIRT1 can shield oocytes from harm and preserve their quality by lowering oxidative stress[12]. SIRT1 is vital for preserving mitochondrial health, which is necessary for the function and generation of oocyte energy. SIRT1 can improve oocyte quality and developmental competence by enhancing mitochondrial biogenesis and activity. In order to assist oocytes in avoiding genomic instability and DNA damage, it also takes part in DNA repair, which can activate DNA repair pathways[19]. This can increase the likelihood that fertilization and embryo development will be successful while lowering the danger of genetic abnormalities. Gene expression is influenced by epigenetic changes like histone acetylation, which it may be modified. The correct programming of oocytes and early embryos can be facilitated by SIRT1 through the regulation of epigenetic patterns. A further crucial function of SIRT1 is cell cycle regulation. By controlling the course of the cell cycle, it can guarantee that oocytes mature and divide properly. In addition to enhancing oocyte quality, this can help avoid premature aging[19].

To increase oocyte quality and fertility, SIRT1 activation by pharmacological or nutritional means may be investigated. Treatments like mitochondrial antioxidants or some medications that target mitochondrial activity may be helpful. New treatment strategies may be available by focusing on the epigenetic variables that affect oocyte aging.

Table 1 shows the specific downstream targets of SIRT1 and their functional consequences, providing a mechanistic understanding of its protective roles.

EVIDENCE FROM ANIMAL STUDIES

Several animal studies have highlighted the role of SIRT1 in protecting against oocyte aging. In mouse studies, SIRT1 has been found to preserve ovarian function. For example, overexpression of SIRT1 in mice resulted in improved ovarian reserve and oocyte quality, even as the animals aged. In contrast, mice with reduced SIRT1 activity showed signs of premature ovarian aging, such as increased follicle loss and poor oocyte quality[33]. Caloric restriction (CR), a well-known intervention for extending lifespan, has been shown to activate SIRT1. In studies where caloric restriction was applied to aged mice, SIRT1 activity increased, resulting in improved oocyte quality and fertility[19]. This suggests that SIRT1 could mimic some of the beneficial effects of CR on fertility.

Resveratrol, a natural compound found in grapes and red wine, is a well-known activator of SIRT1. Animal studies suggest that resveratrol supplementation can improve ovarian function and delay oocyte aging by enhancing SIRT1 activity. Other SIRT1 activators, such as synthetic compounds like SRT1720, are also being explored as potential therapeutic agents to combat infertility and ovarian aging[21].

Gene therapies aimed at enhancing SIRT1 expression in ovarian tissue could be a promising approach to prevent oocyte aging. While still in its early stages, gene editing techniques such as CRISPR has been demonstrated to upregulate SIRT1 specifically in ovarian cells, leading to improved fertility outcomes[21]. Since oxidative stress plays a critical role in oocyte aging, combining SIRT1 activators with antioxidants could provide synergistic effects. This approach could offer a multifaceted strategy to protect oocytes from aging-related damage and enhance fertility, particularly in women of advanced reproductive age[26]. SIRT1 holds significant promise in preventing oocyte aging and improving fertility. By reducing oxidative stress, regulating apoptosis, supporting mitochondrial function and enhancing DNA repair, SIRT1 can help maintain oocyte quality and delay ovarian aging. Therapeutic approaches aimed at activating SIRT1, such as the use of resveratrol or gene therapy, offer potential avenues for treating age-related fertility decline in women[26].

THERAPEUTIC POTENTIAL OF TARGETING SIRT1

Potential benefits of targeting SIRT1 to improve oocyte quality and fertility: Targeting Sirtuin 1 (SIRT1) to improve oocyte quality and fertility has gained significant interest due to its roles in regulating key cellular processes such as oxidative stress response, DNA repair, mitochondrial function and metabolism. These processes are intimately linked to oocyte aging and reproductive health. Enhancing SIRT1 activity in oocytes may provide a therapeutic approach to counter age-related fertility decline, preserve oocyte quality and improve reproductive outcomes. Below are the potential benefits of targeting SIRT1 for improving oocyte quality and fertility[21].

Oocytes are particularly sensitive to oxidative stress, which increases with age and contributes to the deterioration of oocyte quality. Reactive oxygen species (ROS) accumulate in oocytes and can lead to DNA damage, mitochondrial dysfunction and apoptotic cell death. By reducing oxidative stress in oocytes, targeting SIRT1 could preserve the structural integrity of oocytes, improve their developmental competence and reduce age-related oocyte loss. This could lead to higher oocyte quality, improved fertilization rates and better outcomes in assisted reproductive technologies (ART), such as *in vitro* fertilization (IVF)[12].

Aging oocytes accumulate DNA damage due to environmental stressors and oxidative insults. Reduced capacity for DNA repair in aging oocytes is a major contributor to reduced fertility and higher rates of chromosomal abnormalities, such as aneuploidy. SIRT1 plays a role in regulating DNA damage response and repair pathways. It deacetylates proteins like p53 and KU70, enhancing their roles in DNA repair, particularly in the non-homologous end joining (NHEJ) and homologous recombination (HR) pathways. SIRT1 also interacts with PARP1, a key enzyme in the detection and repair of single-strand DNA breaks. By boosting DNA repair efficiency in oocytes, SIRT1 activation could decrease the incidence of genetic abnormalities in eggs and embryos. This may improve the overall success rates of fertility treatments by reducing the likelihood of miscarriages and congenital defects[19].

Mitochondrial dysfunction is a hallmark of oocyte aging and a major cause of reduced energy production and increased oxidative stress. Mitochondria play an essential role in providing the energy required for oocyte maturation, fertilization and early embryonic development. By improving mitochondrial function, targeting SIRT1 could increase the energy available for oocyte maturation, enhance developmental competence and reduce mitochondrial DNA mutations. This could lead to better outcomes in ART and may help delay age-related fertility decline[19].

Apoptosis, or programmed cell death, increases in oocytes as women age, contributing to a decrease in the ovarian reserve (the number of viable oocytes). SIRT1 is involved in regulating apoptosis by interacting with proteins such as p53 and FOXO3a, both of which are involved in promoting cell survival. By preventing excessive oocyte apoptosis, SIRT1 activation could help maintain a healthier ovarian reserve, preserving fertility for a longer period. This is particularly important for women who wish to delay childbirth and may benefit from strategies that protect their ovarian reserve[12].

Ovarian aging is characterized by a decline in oocyte quality and quantity, ultimately leading to menopause. SIRT1 is involved in processes that delay cellular aging, including regulating inflammation, metabolism and stress responses. Targeting SIRT1 could provide a strategy to delay ovarian aging, allowing women to maintain fertility for a longer period. This could be particularly beneficial for women who are at risk of early ovarian aging due to genetic factors or environmental exposures[21].

Table 2: SIRT1 Activators and nutrient supplementation: Potential interventions for oocyte ageing

Intervention	Proposed mechanism of action on SIRT1/aging pathway	Experimental model	Key outcomes related to oocyte health
SRT1720	Direct SIRT1 activator	*Drosophila* oocytes	Preserved SIRT1 activity (low H4K16ac) during aging; significantly reduced age-dependent chromosome segregation errors[33]
Echinacoside (ECH)	Targets GJA1/SIRT1 pathway; restores mitochondrial function	Mouse oocytes	Improved spindle and cytoskeletal stability; restored mitochondrial membrane potential; reduced ROS and DNA damage (γ-H2AX)[35]
Coenzyme Q10 (CoQ10)	Mitochondrial nutrient; may enhance SIRT1 activity by improving NAD+/NADH balance	Human & Mouse oocytes	Improved ovarian response, embryo quality and mitochondrial function in aged models; counteracts oxidative stress[34]
Resveratrol	Indirect SIRT1 activator (allosteric modulator/ increases NAD+)	Multiple models (e.g., keratinocytes)	Activates AMPK-FOXO3 cascade; linked to anti-aging and stress resistance in various cell types; protective effects in ovarian models suggested[32]
Metformin	Activates AMPK, leading to increased NAD+ and subsequent SIRT1 activation	Granulosa cells	Reduces follicular atresia and oxidative stress via PI3K/AKT/mTOR pathway; improves insulin sensitivity, indirectly benefiting ovarian health[34]

AMPK (AMP-activated protein kinase, PI3K/AKT/mTOR (Phosphatidylinositol 3-kinase (PI3K) / Protein Kinase B (AKT) / Mammalian Target of Rapamycin (mTOR) and (γ-H2AX (phosphorylated form of the histone variant H2AX)

Pharmacological activation of SIRT1: Several natural and synthetic compounds have been identified as activators of SIRT1, offering the potential for therapeutic interventions aimed at improving fertility. Resveratrol is a polyphenolic compound found in grapes and red wine and is a well-known activator of SIRT1. Studies in animal models have shown that resveratrol supplementation can improve oocyte quality, delay ovarian aging and enhance fertility by activating SIRT1[21,22]. Synthetic SIRT1 Activators, such as SRT1720, have been developed to selectively activate SIRT1. These compounds have shown promise in preclinical studies, improving mitochondrial function and reducing oxidative stress in various tissues, including oocytes[22]. Potential Benefits of SIRT1 Activators include increased Oocyte quality. Through their effects on oxidative stress, DNA repair and mitochondrial function, SIRT1 activators could enhance the quality of oocytes, leading to improved fertilization rates and higher success rates in ART. It can help to improve Ovarian Reserve by preventing apoptosis and oxidative damage, particularly in women with premature ovarian aging or polycystic ovary syndrome (PCOS). Also, It can help to delay reproductive aging. By delaying ovarian aging, SIRT1 activators could offer a way to extend the reproductive lifespan, allowing women to conceive later in life with higher success rates[3,22,23].

Targeting SIRT1 offers a promising therapeutic approach to improve oocyte quality and fertility. By enhancing antioxidant defenses, promoting DNA repair, preserving mitochondrial function and preventing apoptosis, SIRT1 activation could counter the effects of oocyte aging and improve reproductive outcomes. Both natural compounds, like resveratrol and synthetic SIRT1 activators, hold potential for clinical applications in fertility preservation and treatment.

Table 2 translates mechanistic insights into potential clinical applications, summarizing interventions that target SIRT1 to improve oocyte quality.

FUTURE DIRECTIONS AND CHALLENGES

While SIRT1-targeted therapies show significant promise in improving oocyte quality and fertility, several challenges remain. These include Long-term Safety and Personalized Approaches. Prolonged activation or overexpression of SIRT1 could have unintended side effects, such as increased cancer risk or metabolic dysregulation. Thus, long-term studies are needed to assess the safety of SIRT1-targeted therapies. Women with different causes of infertility (e.g., age-related decline vs. polycystic ovary syndrome) may respond differently to SIRT1-based therapies. Personalized approaches that consider an individual's genetic and reproductive background may be necessary to optimize treatment outcomes[18,19].

Targeting SIRT1 offers a novel and promising approach for improving oocyte quality and fertility. Both natural and synthetic SIRT1 activators, as well as gene therapy techniques, have the potential to delay reproductive aging, reduce oxidative stress, enhance DNA repair and improve mitochondrial function in oocytes. While challenges remain, especially in terms of delivery, specificity and safety, ongoing research may pave the way for new fertility treatments that harness the power of SIRT1[26].

Targeting Sirtuin 1 (SIRT1) for clinical use holds significant potential, especially in areas like fertility preservation, metabolic diseases, neurodegeneration and aging. However, despite the promise of SIRT1-based therapies, several challenges and limitations must be considered before they can be widely adopted in clinical settings. One of the primary

challenges in targeting SIRT1 is the poor bioavailability and pharmacokinetic properties of many natural SIRT1 activators, particularly resveratrol. Resveratrol, a well-known SIRT1 activator, has been studied extensively, but its clinical utility is limited by its rapid metabolism, low systemic concentrations and poor tissue penetration[27].

Another challenge in targeting SIRT1 is the risk of off-target effects. SIRT1 activators, especially synthetic molecules like SRT1720, may interact with other proteins or enzymes beyond SIRT1, leading to unintended side effects. This lack of specificity can result in undesired outcomes, such as metabolic imbalances or increased susceptibility to certain diseases. Synthetic activators like SRT1720 were initially developed to selectively target SIRT1, but studies have shown that they can also activate other sirtuin family members (e.g., SIRT2 and SIRT3) or unrelated pathways. This broad activation can lead to side effects such as insulin resistance and impaired glucose metabolism in animal models[27].

FUTURE DIRECTIONS

The need for further research to elucidate the precise role of SIRT1 in oocyte aging is emphasized. Although significant progress has been made in understanding the role of Sirtuin 1 (SIRT1) in cellular aging, metabolism and DNA repair, its precise role in oocyte aging remains only partially elucidated. Oocyte aging is a critical factor in age-related fertility decline and given the emerging evidence linking SIRT1 to improved oocyte quality, there is a growing need for further research in several key areas. This research could open new therapeutic avenues to counteract reproductive aging.

Clarifying the mechanisms of SIRT1 in Oocyte Aging is still not fully understood. It is known to be involved in several cellular processes, including DNA repair, mitochondrial function and oxidative stress reduction, all of which play critical roles in maintaining oocyte quality. However, the specific mechanisms through which SIRT1 influences these pathways in the context of oocyte aging need further exploration[9,22].

SIRT1 represents a promising target for delaying oocyte aging and improving fertility, but significant gaps in our understanding of its precise role remain. Further research is needed to elucidate the detailed molecular mechanisms by which SIRT1 regulates oocyte health, including its involvement in DNA repair, mitochondrial function and oxidative stress responses. Additionally, the interplay between SIRT1 and other sirtuins, the influence of lifestyle factors and the long-term safety and efficacy of SIRT1-targeted therapies need to be rigorously investigated before clinical application. Addressing these research gaps could ultimately lead to new therapeutic strategies for combating reproductive aging and extending fertility[1,21]. Future research on Sirtuin 1 (SIRT1) has the potential to uncover novel therapeutic strategies that could address a variety of age-related conditions, including oocyte aging, infertility and overall reproductive health. While significant progress has been made in understanding the biological role of SIRT1, several areas still need exploration to advance the development of SIRT1-based therapies.

CONCLUSION

SIRT1 plays a crucial role in maintaining oocyte quality and combating oocyte aging. The key findings regarding SIRT1's role in oocyte aging are reduction of Oxidative Stress, maintenance of mitochondrial function, enhancement of DNA repair, regulation of apoptosis and regulation of metabolic processes. The potential therapeutic implications of targeting SIRT1 have garnered significant interest due to its potential therapeutic applications across various medical fields. Small molecules like resveratrol have shown promise in activating SIRT1. Further research is needed to identify more points and specific SIRT1 activators. Ensuring the safety and effectiveness of SIRT1-based therapies is critical for their approval and use in clinical settings. A deeper understanding can lead to the development of targeted therapies to maintain oocyte quality and fertility in aging women.

SIGNIFICANCE STATEMENT

This review highlights the important role of SIRT1 in maintaining oocyte quality and mitigating age-related reproductive decline through the regulation of oxidative stress, mitochondrial function, DNA repair, apoptosis and metabolic processes. Understanding these mechanisms may support the development of SIRT1-targeted strategies for preserving oocyte quality and improving fertility outcomes. However, further research is needed to establish the safety, efficacy and clinical applicability of SIRT1-based interventions.

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