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Review Article

The Sirtuin & Nrf2 Connection: Understanding their Impact on Diminished ovarian Reserve and Female Fertility

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ABSTRACT

Diminished ovarian reserve (DOR) is a condition characterized by a decrease in the number and quality of oocytes, leading to reproductive decline & aneuploidies by >71%. Sirtuin a family of NAD+ dependent deacetylases have emerged as critical regulators of ovarian function and aging. This review summarizes the current understanding of Sirtuin and Nrf2 in diminished ovarian reserve, exploring their role in ovarian senescence, follicular depletion,

meiotic and mitotic errors in reproductive decline. This review explores the intricate interplay between Sirtuin and nuclear factor erythroid 2-related factor 2 (Nrf2) in the context of DOR and its impact on female fertility. Sirtuin, a family of NAD+-dependent deacetylases, and Nrf2, a transcription factor involved in antioxidant response anti-inflammatory, play pivotal roles in regulating ovarian function, aging, and oxidative stress. We delve into their molecular mechanisms, including their involvement in ovarian senescence, follicular depletion, meiotic errors, and oxidative stress regulation. Furthermore, we discuss the therapeutic potential of targeting Sirtuin and Nrf2 pathways for improving reproductive outcomes in women with DOR. Understanding the Sirtuin & Nrf2 connection provides valuable insights into the pathophysiology of DOR and offers promising avenues for developing novel therapeutic interventions to enhance female fertility.

Keywords: Diminished ovarian reserve; Female infertility; L-Ergothioneine; Nrf2; Nicotinamide mononucleotide; Sirtuin

INTRODUCTION

The terms ovarian reserve and ovarian aging or senescence, are often linked with diminished or premature oocytes. From a clinical perspective, ‘‘ovarian reserve’’ is often used to describe that pool of follicles that can be either stimulated to produce eggs in assisted reproduction, or to be of sufficient number to allow normal ovulation.[1] The term ‘ovarian reserve’ refers to the functional potential of the ovary and reflects the number and quality of oocytes within it.[2] Diminished ovarian reserve is a condition characterized by a decrease in the number and quality of oocytes, leading to reproductive decline & aneuploidies by >71%.

Usually healthy female possesses ~400,000 primordial follicles at the beginning of puberty, each of which contains an immature ovum. About 300 to 400 follicles reach maturity during the reproductive life span of an adult female. The rest of the follicles are lost with apoptosis, which continues approximately for seven months during periods when there is no ovulation, such as pregnancy, breastfeeding, or use of oral contraceptives. The most of oocytes are lost via apoptosis which is a more accelerated process in the last 10-15 years before menopause.[3] As per *Amanvermez R. et al,* during the aging process, both the number and quality of the oocytes in the ovaries decrease and reach to a point beyond which no more viable offspring may be produced and the associated cyclic endocrinological activities cease, entering menopause in females at an average age of 50 years. Females who delayed childbearing with

or without their willing until their 30 years or 40 years constitute the largest portion of the total infertility population.[4]

The age-related decline of female fertility is frequently associated with the reduced monthly likelihood of conception and the increased probability that a pregnancy will terminate (e.g. the loss of embryo, pregnancy, fetal, and spontaneous abortion) eventually after conception or implantation between the ages of 35-45. In addition to these, scientific reports confirmed that the probability of achieving a pregnancy within one year was significantly higher in women <30 years than in women >35 years.[5,6]

Female age is negatively associated with ovarian reserve and positively related to chromosomal abnormalities in oocytes and subsequently embryos. Furthermore, some medical conditions are linked to and develop with age progression and can potentially affect fertility. Another crucial factor for the aging-related decline of oocytes is the meiotic spindle apparatus. As demonstrated by *Wasielak, et al,* during mammalian oocyte maturation, proper spindle assembly ensures even distribution and segregation of chromosomes during meiosis. Herewith, there are fundamental differences in meiotic divisions; in meiosis I, homologous chromosomes are segregated, while in meiosis II, sister chromatids are segregated. Interestingly, aging also affects chromatin remodelling, and there are known mitotic errors that might occur during the cell cleavage of the early embryo. It happens that embryos contain both euploid and aneuploid blastomeres, and notably, mosaicism is detected in embryos with correct morphology.[7]

Role of Sirtuin in Ovarian function and ovarian aging:

The Sirtuin-Silent information regulator protein family, which are conserved proteins belonging to class III histone deacetylases. Notably, Sirtuin share a nicotine adenine dinucleotide (NAD+) binding catalytic domain and acts specifically on different substrates depending on the biological processes in which they are involved.[8] In recent years emerging research has highlighted the role of cellular signalling and genes involving Sirtuin and nuclear erythroid 2-related factor 2 (Nrf2) genes in the pathogenesis of female infertility.[9]

Sirtuin, has a major role in female reproductive longevity, the expression of Sirtuin has been identified in oocytes across various mammalian species, including humans. Sirtuin is present in the whole ovarian follicle, ovarian epithelium, stroma, and luteinized granulosa cells. Sirtuin are major determinant influencing ovarian aging and the quality of gametes. Sirtuin also regulate important physiological functions, including aging and cell metabolism, mainly by protecting cells and tissues from oxidative damage.[10]

Sirtuin participates in several cellular processes including regulation of heterochromatin and gene silencing[11], telomere maintenance, and repair of DNA damage.[12] Sirtuin is predominantly nuclear in prophase 1- arrested oocytes but then localizes to the spindle at metaphase II. The localization of Sirtuin to spindle microtubules in Metaphase II arrested eggs suggests a role of Sirtuin in spindle regulation.[13] Sirtuin senses the DNA damage with the scope to preserve telomere integrity from oxidative stress and may also modulate genome stability and telomere length.[14]

Role of Sirtuin in Diminished ovarian reserve (DOR):

The amount of Sirtuin in ovarian cells is associated with the state and health of the female reproductive system. The age-dependent reduction in ovarian reserve was associated with decreased Sirtuin expression, while the age-dependent decline in women's ovarian reserve was associated with reduced expression of specific Sirtuin. These observations indicate that Sirtuin are biomarkers of ovarian reserve and ovarian aging.

One of the main factors associated with conception failure is the reduced quality of oocytes in older women, often correlated with an alteration in nuclear and mitochondrial DNA.[15] With advancing age, the integrity of the genome is gradually lost, resulting in changes in chromatin accessibility. The chemical perturbations that can result in DNA lesions, genomic mutations, and transcriptional changes increase with age. Epigenetic modifications affect gene transcriptional regulation and very often involve histone phosphorylation, acetylation, and methylation. Histone acetylation and deacetylation are catalyzed by enzymes known as histone acetyltransferases (HATs) and histone deacetylases (HDACs), which can transfer or remove one of the acetyl groups from or to lysine residues at histone H3 and H4.[16] HATs are classified into type A and type B superfamilies' while HDACs are divided into classes I, II, III, and IV. Class I includes HDAC1, 2, 3, 8, and while class II, the only class of enzymes that can shuttle between nucleus and cytoplasm, includes HDAC4, 5, 6, 7, 9, and 10. Class III HDACs, also called Sirtuin, require NAD+ for the deacetylation reaction. Class IV includes only HDAC11.[17]

The main class of epigenetic enzymes involved in oocyte aging are Sirtuin. A recent study also describes Sirtuin as protectors of germ cells against oxidative stress.[18] Some Sirtuin are involved in chromatin regulation via acetylation of histone H4 and H3, respectively.[19] The Sirtuin family member most involved in fertility processes is Sirtuin, which is mainly nuclear and participates in heterochromatin formation.[20] Sirtuin plays a vital role in sustaining

genomic integrity by maintaining the normal chromatin state of cells, thus protecting cells from oxidative stress, promoting DNA stability, and decreasing various female fertility errors. (As mentioned in Figure no 1)

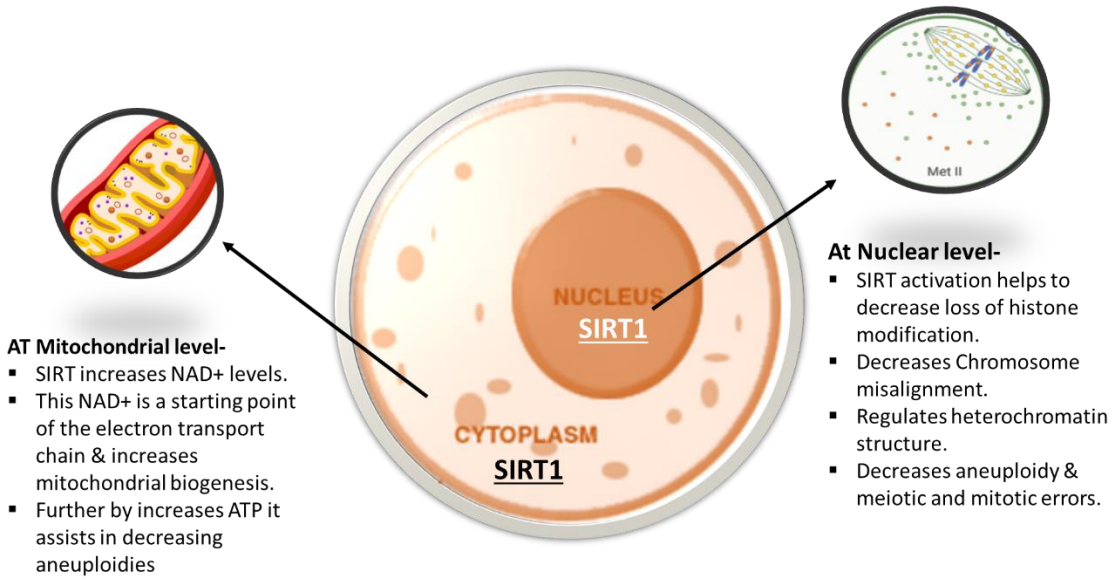

Figure no 1: Overview of the Sirtuin and its roles at nuclear and cytoplasmic levels in oocyte. Sirtuin at the mitochondrial level increases NAD levels. This NAD acts as a precursor of the electron transport chain & increases mitochondrial biogenesis. Further increasing ATP it assists in decreasing aneuploidies. At Nuclear level Sirtuin activation helps to decrease loss of histone modification and decreases chromosome misalignment, regulates heterochromatin structure, and decreases aneuploidies and meiotic & mitotic errors.

Role of Nrf2 in ovarian function and ovarian aging:

Nrf2 is the member of cap and collar (CNC) and functions as a basic leucine zipper (bZIP) transcription factor[21], overseeing the expression of a diverse spectrum of genes implicated in antioxidant defense, detoxification, and cellular safeguarding. Normally, Nrf2 is confined within the cytoplasm through its interaction with Kelch-like ECH-associated protein 1 (Keap1). Upon encountering oxidative stress, Nrf2 disengages from Keap1, relocates to the nucleus, and associates with the antioxidant response element (ARE) situated in the promoter regions of specific genes. This interaction stimulates the transcriptional activation of these target genes, thereby initiating cellular responses aimed at combating oxidative damage and maintaining cellular homeostasis.[22]

Nrf2 emerges as a pivotal regulatory molecule in the context of oxidative stress, exerting a substantial influence on ovarian aging processes.[23] Recent investigations underscore Nrf2's role as a protective agent against both physiological and pathological ovarian aging, serving as a crucial cellular defense mechanism against the deleterious effects of aging. With advancing age, women experience a notable elevation in oxidative stress levels coupled with a concomitant decline in ovarian antioxidant capacity. This imbalance in intracellular redox status profoundly affects both oocytes and granulosa cells.[24,25,26] Moreover, there is a discernible reduction in Nrf2 expression levels within ovarian tissue with increasing age, indicative of a diminishing antioxidant capacity within the ovary over time.[27]

Role of Nrf2 in Diminished ovarian reserve:

Nrf2 exhibits predominant cytosolic expression within granulosa cells.[28] In the context of ovarian biology, the process of inflammatory aging, characterized by a persistent and mild inflammatory state, emerges as a significant contributor to diminished ovarian reserve (DOR). The age-related decline in both oocyte quantity and quality leads to progressive fertility decline and eventual natural infertility. Notably, the expression of Nrf2 in oocytes diminishes with age, and the depletion of Nrf2 exerts detrimental effects on oocyte maturation and DOR progression. In 2018, *Rujun, et.al* demonstrated that Nrf2 depletion affects meiotic apparatus in oocyte, with a high percentage of spindle/chromosome defects, including loose spindles and chromosomal misalignment.[27] Activation of Nrf2 serves as a pivotal regulator of the antioxidant and anti-inflammatory response, orchestrating the expression of numerous antioxidant proteins aimed at shielding cells from oxidative damage & decreasing chromosomal abnormalities—a prevalent challenge in reproductive processes. In the female reproductive system, Nrf2 activation bolsters defense mechanisms against oxidative stress within ovarian cells, thereby fostering improved follicular development and enhanced oocyte quality in individuals with diminished ovarian reserve. Studies have elucidated that activating Nrf2 pathways can ameliorate the adverse effects of diverse environmental and biological stressors on ovarian function and decrease chromosomal abnormalities by increasing Cyclin B1, thereby facilitating healthier ovulation cycles.[29] (As shown in Figure no 2)

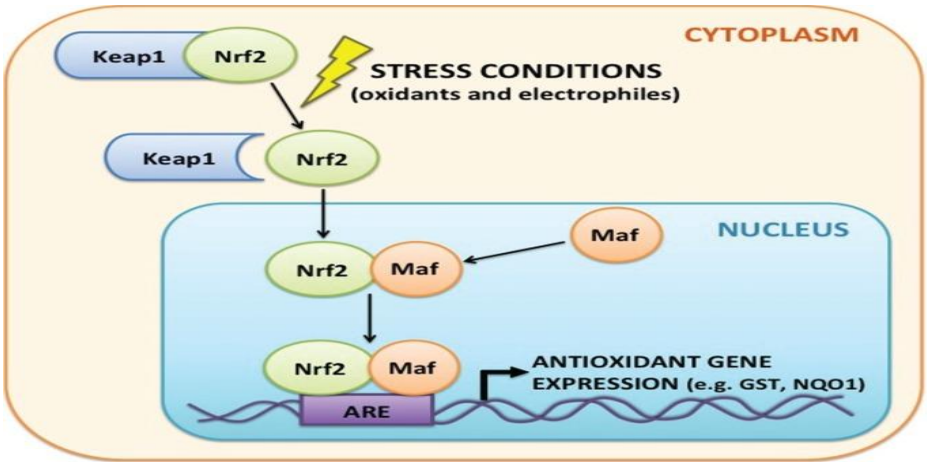

Figure 2: Overview of the Nrf2/Are axis. Under basal conditions, Nrf2 binds to its repressor keap 1 which leads to ubiquination followed by proteasome degradation. During oxidative stress, free Nrf2 translocates to the nucleus, where it dimerizes with members of the small Maf family and binds to ARE genes. The activation of ARE genes activates antioxidant gene expression and reduces inflammation and oxidative stress in oocytes.[30]

Mechanism and interplay of Sirtuin and Nrf2 action in DOR:

Sirtuin and Nrf2 have garnered attention in the context of diminished ovarian reserve (DOR), with evidence pointing to reduced expression observed in ovarian tissue from individuals affected by DOR. Sirtuin is instrumental in preserving ovarian function and retarding ovarian aging, processes intricately linked with DOR. With advancing age and the presence of comorbid conditions, there is a concomitant down-regulation of Sirtuin genes, alongside a parallel reduction in Nrf2 gene expression. Up-regulating these genes represents a promising therapeutic strategy to address fertility complications associated with aging and diminished ovarian reserve.

The interplay between Sirtuin and Nrf2 is a subject of considerable interest. Specifically, Sirtuin1 has been identified as capable of indirectly modulating Nrf2 activity by deacetylating specific proteins that interact with Nrf2.[31] This process enhances Nrf2 stability and activity, leading to a synergistic effect that strengthens cellular defense mechanisms against meiotic and mitotic errors, chromosomal abnormalities, apoptosis, oxidative stress and inflammatory response. Such coordinated action is vital for preserving cellular health in reproductive tissues and mitigating the effects of diminished ovarian reserve.

1. Regulation of meiotic errors: Regulation of meiotic errors in oocytes involves the intricate functions of Sirtuin and Nrf2. Sirtuin play a pivotal role in regulating mitosis and meiosis across various stages of follicular development. Specifically, they facilitate chromatin condensation by directly deacetylating histone H4 at lysine 16 (H4K16ac) during the G2/M transition. Depletion of Sirtuin can lead to meiotic arrest at metaphase I or the production of aneuploid metaphase II eggs, characterized by altered spindle morphologies and chromosome misalignment. At a molecular level, Sirtuin regulates pathways essential for oocyte maturation, including chromatin structure and spindle function. Their epigenetic regulation through histone deacetylation occurs early after the meiotic resumption, followed by deacetylase activity targeting spindle microtubules.[32]
Activation of Nrf2 enhances antioxidant defenses, potentially shielding oocytes from meiotic errors induced by oxidative damage. Conversely, dysregulation of the Sirtuin-NRF2 interplay may exacerbate oxidative stress, compromising oocyte quality and increasing susceptibility to meiotic errors. Although further investigation is warranted to comprehend the intricate crosstalk between Sirtuin and Nrf2 in the context of meiotic errors, their roles in oxidative stress response and cellular homeostasis underscore their significance as critical regulators in maintaining oocyte quality and fertility.

2. Regulation of follicular development and survival: Sirtuin plays a pivotal role in regulating the development, growth, and survival of ovarian follicles, which are indispensable for reproductive success. They contribute to maintaining cell membrane stability, modulating autophagy (through regulation of mTOR), and reducing DNA damage, ultimately promoting the maturation of follicles and enhancing the likelihood of ovulation.
Sirtuin1 can influence Nrf2 activity by deacetylating its regulatory proteins, such as p53 and KEAP1[33] this process facilitates Nrf2 nuclear translocation and subsequent activation of anti-inflammatory & antioxidant gene expression. Conversely, activation of Nrf2 can augment Sirtuin1 expression and activity, thereby bolstering antioxidant defenses and promoting follicular survival. Dysregulation of the interplay between Sirtuins and Nrf2 may lead to follicular atresia, ultimately resulting in impaired oocyte quality and infertility.

3. Regulation and maintenance of mitochondrial function: Sirtuin play a crucial role in regulating mitochondrial biogenesis, dynamics, and function, thereby ensuring optimal energy production. They promote mitochondrial biogenesis by activating key transcription factors such as PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) in ovarian cells. Activation of these factors induces the expression of genes involved in mitochondrial replication, transcription, and translation, ultimately resulting in increased mitochondrial mass and function. Augmented mitochondrial function and biogenesis facilitate oocyte-sperm fusion, thereby enhancing the likelihood of successful fertilization.[34]

Activation of Nrf2 leads to its translocation into the nucleus, where it stimulates the expression of genes involved in mitochondrial biogenesis. Conversely, Nrf2 activation can enhance Sirtuin1 expression and activity, establishing a positive feedback loop that promotes mitochondrial biogenesis and anti-inflammatory defenses. Dysregulation of the interplay between Sirtuin and Nrf2 may lead to mitochondrial dysfunction, oxidative stress, and impaired oocyte quality, thereby contributing to infertility and reproductive aging.

4. Regulation of Oxidative stress response: Sirtuin play a pivotal role in mitigating oxidative stress by modulating antioxidant defense mechanisms within mitochondria. They activate enzymes such as superoxide dismutase 2 (SOD2) and catalase, which scavenge reactive oxygen species (ROS) generated during mitochondrial respiration. Additionally, Sirtuin inhibits the expression of FOXO1 gene, thereby reducing oxidative stress levels. By diminishing ROS levels, Sirtuin safeguards ovarian cells from oxidative damage and uphold mitochondrial integrity.[9]

Nrf 2, a transcription factor, governs the cellular antioxidant response by regulating the expression of genes encoding antioxidant enzymes, detoxification enzymes, and stress response proteins. Under normal conditions, NRF2 is sequestered in the cytoplasm by its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1).[23] However, exposure to oxidative stress prompts the dissociation of NRF2 from KEAP1, enabling its translocation into the nucleus. Once in the nucleus, NRF2 binds to antioxidant response elements (AREs) in the promoters of target genes, promoting their transcription.

Activation of Nrf2 results in the up regulation of genes encoding antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1), which scavenge ROS and alleviate oxidative damage. Furthermore, NRF2 modulates the expression of genes involved in redox balance, metabolism, and inflammation, thereby facilitating cellular adaptation and survival under conditions of oxidative stress.

The interplay between Sirtuins and Nrf2 is intricate, involving mutual regulation and crosstalk between their signalling pathways. Sirtuin1, for instance, can directly deacetylate Nrf2, promoting its nuclear translocation and transcriptional activity, thereby augmenting antioxidant gene expression and cellular antioxidant defences. Conversely, activation of Nrf2 can enhance Sirtuin1 expression and activity, establishing a positive feedback loop that reinforces antioxidant responses and cellular resilience to oxidative stress. Dysregulation of the Sirtuin-NRF2 axis has been implicated in various pathological conditions associated with oxidative stress, including aging, neurodegenerative diseases, cancer, and metabolic disorders.

5. Regulation of Apoptosis: Sirtuin participate in the regulation of apoptosis (programmed cell death) in ovarian cells by influencing mitochondrial function. Specifically, Sirtuin1 and Sirtuin3 modulate the activity of pro-apoptotic and anti-apoptotic proteins, such as members of the Bcl-2 family, thereby impacting the mitochondrial apoptotic pathway. By promoting the survival of healthy ovarian cells and restraining excessive cell death, Sirtuin contribute to the maintenance of tissue homeostasis and functionality.

Activation of the Nrf2 signalling pathway induces the expression of HO1 and cytoprotective genes, which bolster cell survival. NRF2 also regulates apoptosis by modulating the expression of genes associated with apoptosis, including members of the BCL-2 family, caspases, and apoptotic regulators. NRF2 activation can suppress

apoptosis by up regulating anti-apoptotic genes and dampening pro-apoptotic signalling pathways, thereby shielding ovarian cells from apoptosis-induced depletion and fostering follicular survival.[30]

Sirtuins and Nrf2 engage in a multifaceted interplay in the regulation of apoptosis within the context of diminished ovarian reserve (DOR). Sirtuin1 can interact with Nrf2 and modulate its activity by deacetylating its negative regulator KEAP1, thereby stabilizing Nrf2. Conversely, activation of Nrf2 can enhance Sirtuin expression and activity, establishing a positive feedback loop that strengthens antioxidant & antinflammatory defences and enhances cell survival in ovarian cells. Dysregulation of the Sirtuin-Nrf2 axis may contribute to heightened apoptosis, o and follicular depletion in DOR, culminating in impaired ovarian function and a decline in fertility.

Therapeutic potential of up-regulating Sirtuin and Nrf2 in DOR:

While research on the therapeutic potential of Sirtuin in DOR is still in its early stages, preclinical studies and emerging evidence from other related fields suggest promising avenues for further exploration. Targeting Sirtuin offers a promising therapeutic strategy for DOR. Sirtuin up-regulators such as Nicotinamide mononucleotide (NMN) has shown potential in improving ovarian function and fertility in animal models and human studies.

NMN is a naturally occurring nucleotide nucleotide precursor of NAD+, which is produced by NAD rescue pathway.[32] NMN a product of nicotinamide phosphoribosyl transferase (NAMPT) reaction and a key NAD+ intermediate, can reverse defects in mitochondrial homeostasis , DNA repair as well as cell survival caused by insufficient NAD+.[33] An Increase in NAD+ through NMN is expected to improve aging-related DNA damage through Sirtuin activation.[34] Another important factor is, that telomere length is a molecular gauge of aging, and supplementation with NMN elongates telomere length in human oocytes.[35] Supplementation of NMN restores the NAD+ levels in oocytes and enhances their maturation rate, fertilization ability, and subsequent embryonic development potential this further improves the quality of age's oocytes by recovering mitochondrial function.[36] NMN supplementation increases blood NAD concentrations and is safe and well tolerated with oral dosing up to 900 mg NMN daily for minimum 2 months.[37] Activation of Sirtuin through NMN leads to deacetylation of histones and helps to decrease spindle formation errors, as a result up upregulation of Sirtuin will help to achieve more mature follicles, improved DNA quality, improved embryo quality, and better embryo grades.

L-Ergothioneine (L-Erg) is a naturally occurring amino acid and is a thiourea derivative of histidine containing a sulphur atom on the imidazole ring. Carnitine /organic cation transporter 1(OCTN1) is the only Known uptake transporter for ergothioneine with is a food-derived (Schitake mushroom) strong antioxidant L-Erg then activates Nrf2 and heterodomerizes small maf proteins and avitivates the antioxidant response element (ARE). The ARE is the central cellular mechanism for alleviating oxidative stress, it further activates the HO1 axis and regulates inflammatory genes. Further L-Erg helps increase Cyclin B1 and decreases spindle defects, chromosomal abnormalities & meiotic, and mitotic errors.

Additionally in synergy, both NMN and L-Erg promote successful fertilization, embryo development, successful implantation, decreased spindle formation errors and further risks of miscarriage. Additionally, it mitigates the effect of apoptosis, inflammation, oxidative stress and tropoblast invasion leading to higher embryo quality, increased live birth rates, and decreased rate of genetic defects. Overall the synergistic effect of NMN & L-Erg improves various aspects of female fertility due to diminished ovarian reserve. (As shown in Figure no 3)

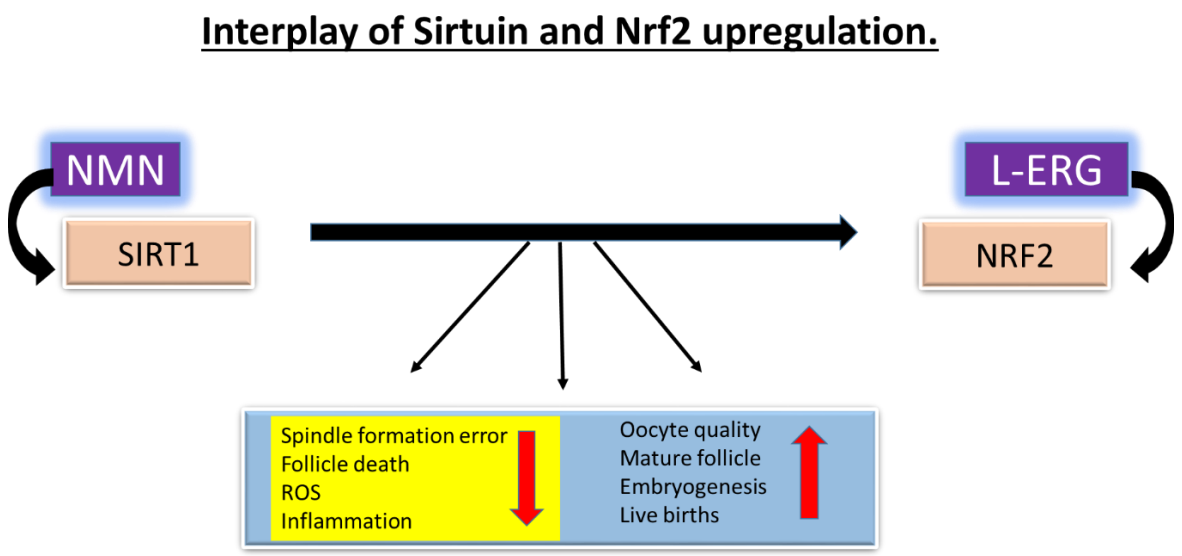

Figure 3: Summary of interplay of up regulation Sirtuin and Nrf2.NMN (Nicotinamide mononucleotide) and L-Erg (L-Ergothionene) act as potent Sirtuin and Nrf2 up regulators and its implication to reduce female fertility errors.

CONCLUSION

As an overall conclusion of this review, the upregulation of Sirtuin and Nrf2 has emerged as a promising therapeutic strategy for females having Diminished ovarian reserve (DOR). By up-regulating these genes, it is possible to improve ovarian function, enhance egg quality, and increase fertility outcomes. Upregulating Sirtuin and Nrf2 using NMN (Nicotinamide mononucleotide) & L-Erg (L-Ergothioneine) plays a critical role in maintaining genomic stability, decreasing meiotic and mitotic errors and regulating cellular metabolism, all of which are essential for optimal ovarian function.

Further research is needed to fully understand the mechanisms by which Sirtuin and Nrf2 exert their beneficial effects in DOR and to explore their potential as therapeutic targets for the treatment of female infertility. However existing evidence suggests that up regulation of these pathways using NMN & L-Erg hold a great promise for improving reproductive health and empowering women with DOR to build their families.

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