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Review Article

Role Of Sirtuins, Nrf2 Genes and Their Interplay in Female Fertility Outcomes with Co Morbid Conditions Such as Obesity, Hypothyroidism, Diabetes, and PCOS: A Comprehensive Review

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ABSTRACT

Female infertility is a widespread concern affecting millions globally, with a significant portion concentrated in India alone, comprising approximately 25% of the affected population. Despite advancements in assisted reproductive technologies (ART) offering solutions to certain infertility challenges, the underlying molecular mechanisms contributing to fertility impairments remain complex and often poorly understood. Female fertility is a complex process influenced by various genetic and environmental factors. Sirtuins and Nrf2 genes have emerged as key players in maintaining reproductive health, particularly in the context of comorbid conditions such as obesity, hypothyroidism, diabetes, and polycystic ovary syndrome (PCOS). Sirtuins, a family of NAD+-dependent class 3 histone deacetylases (HDACs), were initially identified as longevity genes. However, subsequent studies have revealed their involvement in various physiological processes, including cell proliferation, apoptosis, cell cycle progression, and insulin signaling, which are crucial for female fertility. Sirtuins have been shown to activate the Nrf2 pathway, a transcription factor involved in the antioxidant response and cellular defense against oxidative stress. The interplay between these two genes has been implicated in modulating female fertility outcomes. This review aims to summarize the current understanding of the role of sirtuins and Nrf2 genes in female fertility, focusing on their individual and combined effects in the presence of comorbid

conditions. We will discuss the molecular mechanisms by which these genes influence reproductive health, including the regulation of oocyte quality, embryo development, implantation, and endometrial receptivity, this review aims to provide a comprehensive understanding of their role in female fertility outcomes.

Keywords: Sirtuins; Nrf2; Interplay; Diabetes; Obesity; PCOS; Hypothyroidism; Female fertility

INTRODUCTION

Sirtuins, a family of evolutionarily conserved NAD+-dependent protein deacetylases, exhibit diverse biological functions. They primarily regulate post-transcriptional modifications and belong to a group of histone deacetylases. Across bacteria, yeast, and mammals, sirtuins share highly conserved catalytic core regions. In mammals, seven sirtuin isoforms (SIRT1-7) have been identified, each with distinct subcellular localization and enzymatic activities.[1] Initially identified as longevity genes, sirtuins were found to extend yeast lifespan significantly. Sirtuins play pivotal roles in various cellular processes, including metabolism, DNA repair, stress response, and aging.[2] Sirtuins are extensively distributed throughout the female reproductive system, including the entire ovarian follicle. Within the ovarian follicle, sirtuins are present in various components such as the ovarian epithelium, stroma, and luteinized granulosa cells. Their presence in these different cellular compartments underscores their diverse roles in regulating ovarian function and folliculogenesis.[3] Sirtuins likely contribute to essential processes within the ovarian follicle, including oocyte development, follicular growth, hormone production, and maintenance of ovarian tissue homeostasis. Sirtuins regulate reproductive function at multiple levels, influencing ovarian physiology, oocyte quality, embryo development, and implantation. Through their deacetylase activity, sirtuins modulate the activity of key transcription factors, co-regulators, and enzymes involved in reproductive processes. In addition, different members of the sirtuin family have been shown to regulate different biological activities.[4] Previous studies demonstrated that Sirtuins have emerged as a central player in female reproductive health. Sirtuins primarily regulate transcriptional silencing, mitochondrial function, insulin signaling, apoptosis, cell proliferation and survival, tissue regeneration, differentiation, stress response, meiosis, and mitotic, genome stability telomere silencing, and ribosomal DNA (rDNA) transcription.[3,5,6] Sirtuins are major determinants influencing ovarian aging and the quality of gametes. As age advances and with co-morbid conditions such as obesity, hypothyroidism, PCOS, and diabetes, sirtuin genes are downregulated. It has also been reported that Sirtuins is associated with the activation of nuclear factor-E2-related factor 2 (Nrf2), thereby regulating ovarian follicle development, oocyte maturation, and embryo implantation.[7] In a recent study by Ma et al., the intricate relationship between Sirtuins and Nuclear factor erythroid 2-related factor 2 (Nrf2) was investigated, particularly in the context of oocytes. Their findings unveiled that depletion of Sirt1 resulted in a reduction of Nrf2 expression, suggesting the presence of a signaling pathway involving Sirt1-Nrf2-Cyclin B1 in oocytes. Furthermore, immunoblotting analyses demonstrated lower levels of Nrf2 protein in oocytes obtained from aged mice indicating a potential association between Nrf2 depletion and age-related meiotic defects. Notably, the study provided compelling evidence that overexpression of Nrf2 could ameliorate maternal age-associated meiotic defects, underscoring the significance of Nrf2 in mitigating age-dependent deficits in oocyte quality. Additionally, the researchers observed a correlation between Nrf2 expression levels and human female age in ovarian granular cells, implying a potential link between decreased Nrf2 expression and the decline in reproductive capacity observed in older women. These findings offer valuable insights into the molecular mechanisms underlying age-related changes in oocyte quality and reproductive aging, suggesting Nrf2 as a

potential therapeutic target for preserving fertility in aging women.[8] Nrf2 is a transcription factor that acts as a master regulator of the antioxidant response and cellular defense mechanisms. Under conditions of oxidative stress or cellular injury, Nrf2 controls the expression of genes encoding antioxidant enzymes, detoxification enzymes, and stress response proteins to mitigate cellular damage and promote cell survival. In the context of reproductive health, Nrf2 plays a critical role in protecting ovarian and uterine tissues from oxidative stress-induced damage. By upregulating antioxidant and detoxification pathways, the Nrf2 gene helps maintain the redox balance necessary for optimal ovarian function, oocyte quality, implantation and endometrial receptivity. Dysregulation of Nrf2 signaling has been implicated in various reproductive disorders, including infertility, miscarriage, and pregnancy complications.[9] A previous study revealed that comorbid conditions associated with infertility, such as type 2 diabetes (T2D), type 1 diabetes (T1D), and hypothyroidism (HT), are linked to significantly lower levels of sirtuin mRNA expression, resulting in fertility failure in female.[10] This review aims to understand the interplay between sirtuins and Nrf2 in the context of female fertility outcomes, with a focus on metabolic disorders such as obesity, hypothyroidism, diabetes and polycystic ovary syndrome (PCOS).

IMPACT OF OBESITY ON FEMALE FERTILITY:

Obesity presents a multifaceted challenge to female fertility, affecting various aspects of reproductive health. One of the primary ways obesity impacts fertility is through menstrual irregularities, disrupting the normal ovulatory process and making conception difficult. Additionally, obesity is strongly linked to conditions such as polycystic ovary syndrome (PCOS), characterized by hormonal imbalances and irregular ovulation, further complicating fertility. Poor oocyte quality is another consequence of obesity, reducing the likelihood of successful fertilization and embryo development. Furthermore, obesity can alter the endometrial lining of the uterus, diminishing its receptivity to embryo implantation and increasing the risk of pregnancy complications. In assisted reproductive technologies (ART), obesity may lower success rates due to reduced response to fertility treatments and higher rates of complications.[11,12,13]

INTERPLAY BETWEEN SIRTUINS AND Nrf2 IN MITIGATING THE EFFECTS OF OBESITY ON FERTILITY:

In obesity-related reproductive dysfunction, sirtuins, are emerging as key regulators of metabolic homeostasis and ovarian function. Dysregulation of sirtuin activity may disrupt metabolic processes, leading to ovulatory dysfunction and impaired fertility. Additionally, sirtuins possess anti-inflammatory and antioxidant properties crucial for mitigating chronic low-grade inflammation and oxidative stress characteristic of obesity (Figure no 1) However, alterations in sirtuin activity due to obesity could exacerbate harmful effects on the reproductive system.[7] Furthermore, sirtuins play roles in epigenetic regulation and mitochondrial function, essential for oocyte quality and embryo development. Jukarainen et al. demonstrated a relationship between low sirtuin levels in obesity and female fertility. Specifically, studies indicate that obesity is associated with reduced expression of sirtuin isoforms in adipose tissue. This down-regulation of the NAD+/sirtuin pathway is linked to adipose tissue dysfunction observed in obesity and overnutrition. Additionally, the negative correlation between sirtuin expression and measures of adiposity suggests that decreased sirtuin levels may contribute to inflammation, insulin resistance, and other metabolic disturbances in obesity.[14] Another study by Kurylowicz concluded in obesity, the downregulation of sirtuins can lead to impaired glucose and lipid metabolism, increased inflammation,

and altered adipose tissue function, ultimately exacerbating the metabolic disorders associated with obesity.[15] In obesity-related reproductive dysfunction, Nrf2 serves as a critical guardian of cellular defense mechanisms against oxidative stress. Obesity instigates increased production of reactive oxygen species (ROS) and oxidative stress in reproductive tissues, yet paradoxically, Nrf2 gene downregulation exacerbates oxidative stress and impairs antioxidant defenses. Nrf2 activation mobilizes antioxidant enzymes and detoxification proteins to neutralize ROS and maintain redox balance, crucial for ovarian function, oocyte quality, endometrial receptivity, implantation, and inflammation regulation. By mitigating oxidative damage and inflammation, Nrf2 activation supports optimal conditions for fertility and pregnancy establishment in obesity-related challenges.[16] The interplay between sirtuins and Nrf2 plays a crucial role in mitigating the adverse effects of obesity on fertility. Both sirtuins and Nrf2 are downregulated in obesity-related reproductive dysfunction, leading to increased oxidative stress, inflammation, and metabolic disturbances. Activation of Nrf2 induces the expression of antioxidant enzymes and detoxification proteins, along with sirtuin activity, counteracting oxidative damage and restoring redox balance. Sirtuins can enhance Nrf2 activity through mechanisms such as deacetylation and transcriptional regulation, amplifying the antioxidant and anti-inflammatory response. This collaborative effort protects reproductive tissues from obesity's detrimental effects, preserving ovarian function, oocyte quality, embryo development, implantation and endometrial receptivity.[6,16,17]

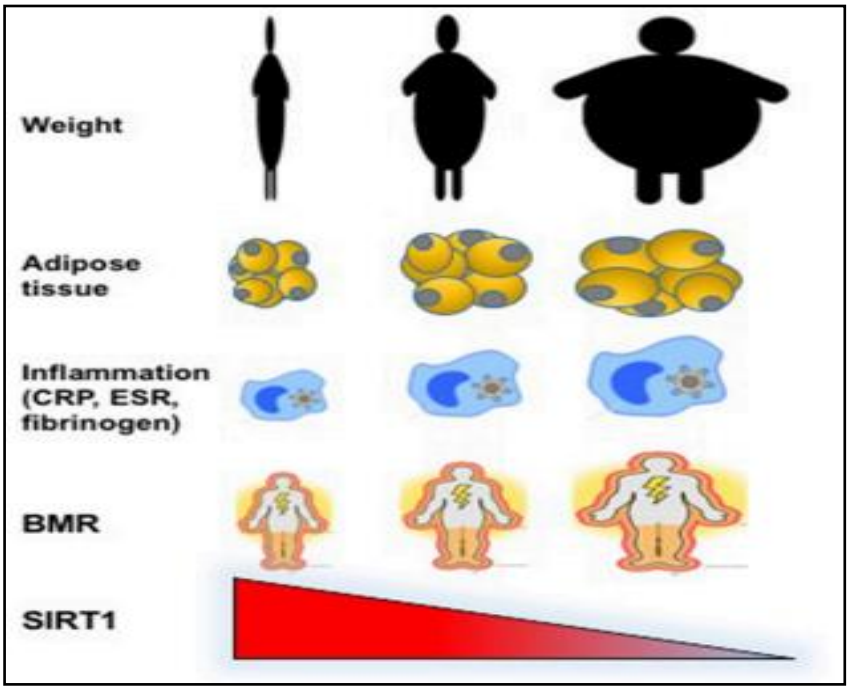

Figure 1: Graphical representation of the inverse relationship between circulating levels of SIRT1 and various factors including weight, fat abundance and distribution, as well as inflammatory and metabolic parameters in underweight, normal weight, and obese individuals[18]

IMPACT OF HYPOTHYROIDISM ON FEMALE FERTILITY

Hypothyroidism, marked by insufficient thyroid hormone production, exerts profound implications for female reproductive health. Thyroid hormones intricately regulate menstrual cycle dynamics, ovulation, and fertility, making thyroid dysfunction a significant contributor to reproductive disorders. Manifesting as menstrual

irregularities, hypothyroidism disrupts the delicate hormonal balance essential for normal menstruation, potentially leading to heavy or irregular periods, shortened cycles, or even amenorrhea. Furthermore, the condition often results in anovulatory cycles, impairing follicle development and oocyte maturation, thereby reducing fertility. Untreated hypothyroidism during pregnancy escalates the risk of adverse outcomes, including miscarriage, preterm birth, and gestational hypertension, emphasizing the critical role of thyroid hormones in fetal neurodevelopment and growth. Notably, women with hypothyroidism may exhibit diminished responsiveness to fertility treatments like ovulation induction and IVF.[19,20,21]

INTERPLAY BETWEEN SIRTUINS AND Nrf2 IN HYPOTHYROIDISM IN FEMALES:

In hypothyroidism-related reproductive dysfunction, Sirtuins and Nrf2 play critical roles in safeguarding reproductive health through intricate mechanisms involving metabolic regulation, antioxidant defense, inflammation modulation, and cellular protection. Sirtuins, regulate metabolic homeostasis by promoting mitochondrial biogenesis, enhancing fatty acid oxidation, and improving insulin sensitivity in reproductive tissues, countering the metabolic disturbances caused by thyroid hormone deficiency. Studies have shown that patients with hypothyroidism exhibit lower levels of sirtuins.[3,6] Additionally, Wei et al revealed that the expression of sirtuins genes is downregulated in the hypothyroidism group compared to the control group. Moreover, they possess antioxidant properties and activate antioxidant response pathways, such as the Nrf2 gene, to mitigate oxidative stress and protect reproductive tissues from damage.[22] Similarly, another study by Sultan et al concluded sirtuin level is reduced in hypothyroidism mentioned in Figure 2. Additionally, Sirtuins exhibit anti-inflammatory effects by suppressing NF-κB-mediated pro-inflammatory gene expression, reducing inflammation in reproductive tissues associated with hypothyroidism.[10] Furthermore, Sirtuins promote cellular protection and resilience by activating stress response pathways, such as the SIRT1/AMPK and SIRT1/FOXO pathways, thereby protecting reproductive tissues from cellular damage and dysfunction.[3,4]

The role of Nrf2 in hypothyroidism-related reproductive dysfunction is pivotal, as it orchestrates cellular defense mechanisms against oxidative stress, inflammation, and DNA damage. However, in hypothyroidism, there is often a reduction in Nrf2 activity, leading to increased susceptibility to oxidative stress, inflammation, and cellular damage in reproductive tissues. Reduced Nrf2 activity compromises antioxidant defenses, exacerbating oxidative damage and impairing fertility. Additionally, decreased Nrf2 activity fails to adequately suppress inflammatory signaling pathways, resulting in increased inflammation in reproductive tissues, further disrupting ovarian function and endometrial receptivity. Moreover, diminished Nrf2-mediated DNA repair mechanisms increase susceptibility to DNA damage, leading to genomic instability and cellular dysfunction, contributing to infertility in hypothyroidism-related reproductive dysfunction.[23]

The interplay between Sirtuins and Nrf2 in hypothyroidism-related female infertility represents a complex relationship where these two regulatory systems interact synergistically to mitigate the adverse effects of thyroid hormone deficiency on reproductive health. Sirtuins modulate metabolic processes and cellular responses to stress, while Nrf2 serves as a master regulator of cellular defense mechanisms against oxidative stress. Together, they combat oxidative stress, maintain cellular homeostasis, and promote reproductive function in hypothyroidism. Sirtuins can directly activate Nrf2, enhancing its antioxidant response, while Nrf2 activation can promote Sirtuin expression and activity, forming a positive feedback loop that amplifies cellular antioxidant defenses and promotes cellular resilience to oxidative stress.

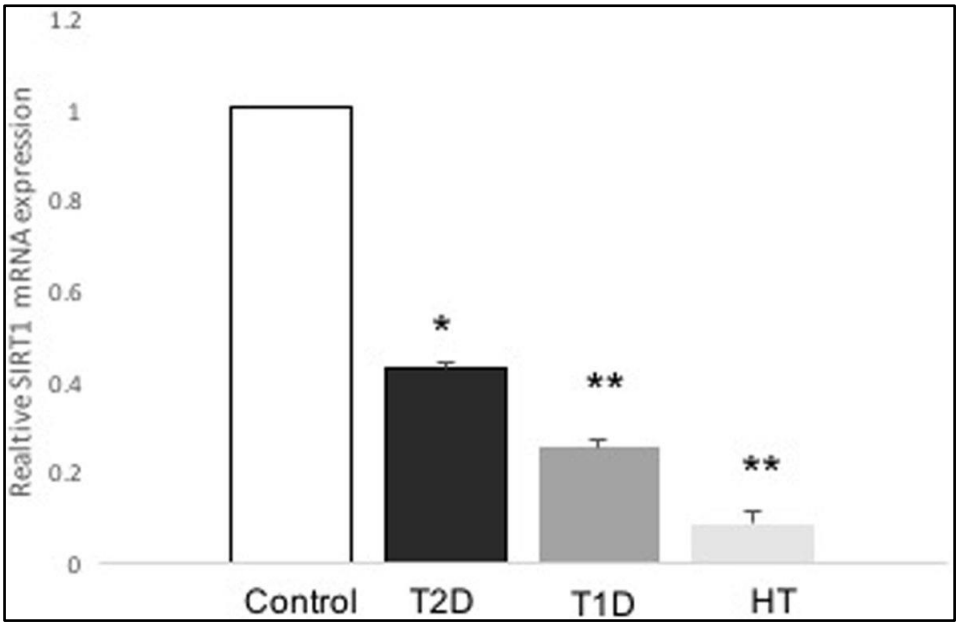

Figure no 2: Expression levels of SIRT1 in patients with T2D, T1D, HT, and control individuals.[10]

THE IMPACT OF DIABETES ON FEMALE FERTILITY

Diabetes, a chronic metabolic disorder, can have a significant impact on female reproductive health and fertility. The complex interplay between diabetes and female infertility has been the subject of growing research and clinical attention. One of the primary mechanisms by which diabetes can compromise female fertility is through the development of polycystic ovary syndrome (PCOS). Diabetes, particularly type 2 diabetes, is closely associated with PCOS, as both conditions share underlying insulin resistance as a key pathogenic factor.[24] The presence of PCOS in women with diabetes can further exacerbate fertility challenges, leading to difficulties in achieving and maintaining pregnancy. In addition to PCOS, diabetes can also directly affect ovarian function and the menstrual cycle. Hyperglycemia, a hallmark of diabetes, has been shown to disrupt the normal hormonal regulation of the ovaries, leading to menstrual irregularities, delayed puberty, and even amenorrhea.[25] Furthermore, diabetes-related complications, such as neuropathy and vascular dysfunction, can impair uterine and ovarian blood flow, further compromising reproductive function. Interestingly, the impact of diabetes on female fertility may vary depending on the type and stage of the disease. While historically, women with type 1 diabetes have experienced higher rates of amenorrhea and infertility due to central hypogonadism, the intensification of insulin therapy and improved metabolic control have helped mitigate these issues. However, the sharp rise in the incidence of type 2 diabetes, even among younger populations, suggests that more women of reproductive age will encounter diabetes-related reproductive problems in the future. Diabetes can adversely affect the outcomes of fertility treatments such as in vitro fertilization (IVF) and intrauterine insemination (IUI). Women with diabetes may have lower success rates with assisted reproductive technologies due to the adverse effects of diabetes on ovarian function, egg quality, and endometrial receptivity.[26]

THE INTERPLAY BETWEEN SIRTUINS AND Nrf2 IN DIABETES AND FEMALE FERTILITY:

Sirtuins are implicated in the complex relationship between diabetes and female reproductive health. Diabetes disrupts sirtuin function, leading to adverse effects on ovarian function, oocyte quality, and endometrial receptivity. For instance, reduced levels of sirtuins have been associated with conditions like polycystic ovary syndrome (PCOS), endometriosis, Diminished Ovarian Reserve (DOR) and age-related infertility. Additionally, studies have shown that patients with type 1 or type 2 diabetes and hypothyroidism exhibit lower levels of sirtuins essential in counteracting oxidative stress. Sirtuins regulate metabolic pathways, oxidative stress responses, and mitochondrial function, crucial for maintaining female reproductive health, thereby mitigating the detrimental effects of diabetes. Nrf2 emerges as a critical regulator in the interplay between diabetes and female fertility. Reduced Nrf2 levels in diabetes correlate with decreased expression of antioxidant genes, contributing to oxidative stress and inflammation. Conversely, Nrf2 activation has anti-diabetic effects by attenuating oxidative stress and inflammation. Nrf2 also plays a role in maintaining cellular homeostasis during pregnancy, influencing trophoblast cell survival and placental function. Dysregulation of Nrf2 has been associated with adverse pregnancy outcomes, including gestational diabetes mellitus, impacting female fertility.[6,27]

The interplay between sirtuins and Nrf2 is crucial in regulating female fertility, especially in diabetes-related infertility. This interplay is relevant in diabetes, where dysregulated glucose and lipid metabolism and increased oxidative stress affect ovarian function, embryo development, oocyte quality, and endometrial receptivity. Dysregulation of PI3K/PTEN/Akt and TSC/mTOR signaling pathways, influenced by sirtuins, can lead to impaired follicular development and ovulation. Furthermore, Nrf2's role in maintaining placental function is crucial for successful pregnancies, with dysregulated Nrf2 contributing to adverse pregnancy outcomes.[28,29]

THE IMPACT OF PCOS ON FEMALE FERTILITY:

The impact of polycystic ovary syndrome (PCOS) on female infertility is significant, with PCOS being one of the most common causes of anovulatory infertility. Approximately 90-95% of anovulatory women seeking treatment for infertility have PCOS. Women with PCOS may experience irregular menstrual cycles, oligomenorrhea, or amenorrhea due to hormonal imbalances characterized by elevated luteinizing hormone, reduced follicle-stimulating hormone, and increased levels of androgens and insulin.[30] These hormonal imbalances can lead to ovulation problems caused by unbalanced hormones, irregular menstrual cycles, inadequate uterine lining preventing egg implantation, and thickened ovaries preventing spontaneous ovulation. Despite these challenges, PCOS is considered one of the most common and treatable causes of infertility in women. Treatment options for PCOS-related infertility may include medication to induce ovulation or more advanced interventions like in vitro fertilization (IVF) to support achieving a healthy pregnancy. Overall, the impact of PCOS on female infertility underscores the importance of timely diagnosis, appropriate management, and personalized treatment strategies to address the reproductive challenges faced by women with this condition.[31]

THE INTERPLAY BETWEEN SIRTUINS AND Nrf2 IN POLYCYSTIC OVARY SYNDROME (PCOS)

The role of sirtuins in polycystic ovary syndrome (PCOS) is significant, as these NAD+-dependent deacetylases play a crucial role in the disorder's pathogenesis and progression. Sirtuins have been extensively studied in the

context of PCOS. Decreased sirtuin activity or inhibition of its related pathways is a common pathological process observed in PCOS. This downregulation of sirtuins is associated with increased oxidative stress markers, methylglyoxal levels, and impaired ovulation. Sirtuins positively regulate ovulation and improve oocyte quality by modulating signaling pathways crucial for follicular development and maturation. Additionally, sirtuins help ameliorate metabolic disturbances associated with PCOS by enhancing insulin sensitivity and glucose metabolism.[32] Furthermore, sirtuins enhance the antioxidant response by activating Nrf2, mitigating oxidative stress-induced damage in PCOS. Oxidative stress, implicated in female infertility, including PCOS, is counteracted by Nrf2, a master regulator of cellular defense mechanisms. Excessive ROS production in granulosa cells contributes to PCOS development. Activation of the Nrf2 pathway has shown beneficial effects in PCOS models.[33]

The interplay between sirtuins and Nrf2 in PCOS is crucial for maintaining cellular homeostasis and protecting against oxidative stress, which are key factors in reproductive dysfunction. Sirtuins, act as redox state sensors in oocytes, granulosa cells, and embryos. Nrf2 enhances antioxidant defenses and alleviates PCOS symptoms. The reciprocal relationship between sirtuins and Nrf2 is essential. Decreased sirtuin expression in PCOS correlates with increased oxidative stress, impaired ovulation, and metabolic disturbances, highlighting the importance of maintaining sirtuin-Nrf2 balance for optimal reproductive health in PCOS.[33,34]

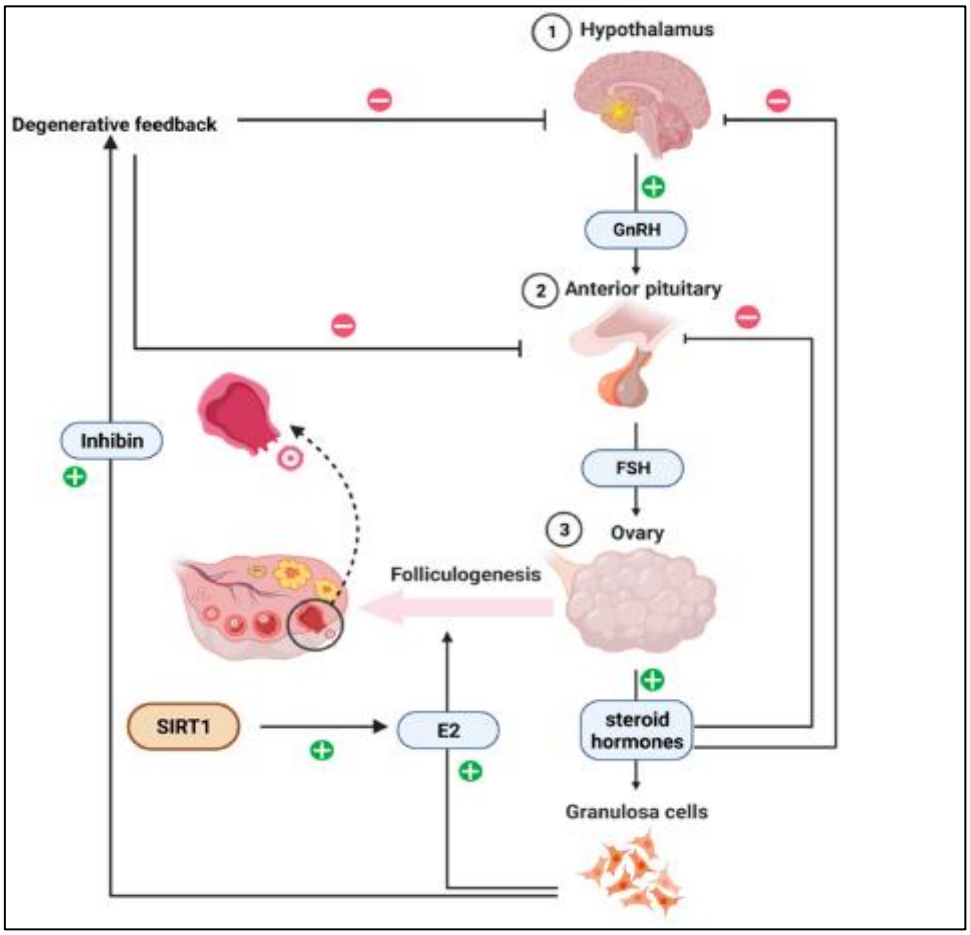

Figure 3: Regulation of steroid hormone synthesis by the hypothalamic-pituitary[31]

CONCLUSION

The intricate interplay between Sirtuins and Nrf2 in female fertility outcomes, especially in age-related infertility the presence of comorbid conditions such as obesity, hypothyroidism, diabetes, and PCOS underscores their critical roles in reproductive health. Decreased expressions of Sirtuins and Nrf2 have been linked to a cascade of detrimental effects on fertility, including spindle formation errors, meiotic and mitotic errors leading to aneuploidies, and a surprisingly 80% rate of early embryo mortality. These molecular dysregulations contribute significantly to compromised embryogenesis, reduced embryo quality, and an increased incidence of embryo malformations, ultimately resulting in reduced pregnancy rates. Understanding the molecular mechanisms underlying the Sirtuins -Nrf2 gene and its implications on female fertility outcomes is crucial for developing targeted interventions to mitigate the adverse effects of comorbid conditions on reproductive health. Future research and therapeutic strategies aimed at restoring Sirtuins and Nrf2 levels and addressing the associated molecular alterations hold promise for improving fertility outcomes in women facing these challenges.

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