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Research Progress on the Relationship Between Mitochondrial Dysfunction and Premature Ovarian Failure from the Perspective of TCM Treatment

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Abstract: Premature ovarian failure (POF) is a prevalent yet challenging condition in gynecology. Its incidence rate has been steadily rising in recent years and is trending among younger age groups. The premature failure of ovarian function, which poses a serious threat to women's physical and mental health, has emerged as a topic of concern in current research. At present, it is believed that the causes of premature ovarian failure are multifaceted, and its pathogenesis is complex, some of which are still not well-understood. Therefore, this article discusses the research progress of the pathogenesis of premature ovarian failure caused by mitochondrial dysfunction and serves as a reference for the prevention and further research of this condition from the perspective of traditional Chinese medicine treatment.

Keywords: Premature ovarian failure; Mitochondrion; Granulosa cells; Oocyte; Traditional Chinese medicine

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1. Introduction

Premature ovarian failure (POF) refers to amenorrhea before the age of 40 as a result of ovarian failure, accompanied by perimenopausal symptoms, which seriously affect women's physical and mental health. The incidence of POF in the general population is 1% to 3%, and premature ovarian failure affects 2% to 10% of amenorrhea patients [1]. The prevalence of premature ovarian failure has increased year by year, especially in recent years, and individuals with the condition often experience various health issues that require medical attention, including infertility and menopausal syndrome. The etiology of premature ovarian failure is very complex; it includes genetic factors, immune factors, hormone abnormalities, enzyme deficiencies, mitochondrial defects, iatrogenic factors, and environmental factors [2]. Most cases of premature ovarian failure are irreversible. In western medicine, hormone replacement therapy is often used, although it requires long-term prescription and increases the risk of cancer and thrombosis. This article mainly discusses the etiology and mechanisms of premature ovarian failure brought on by mitochondrial dysfunction as well as the therapeutic intervention of traditional Chinese medicine on premature ovarian failure, hoping to improve the quality of life of individuals with POF.

2. Premature ovarian failure

Premature ovarian failure (POF) is the final stage of ovarian insufficiency. Clinically, POF includes early-onset ovarian insufficiency and diminished ovarian reserve. Individuals with POF usually present with amenorrhea before the age of 40, with high gonadotropin levels (FSH > 40 IU/L) and low estrogen levels, accompanied by perimenopausal symptoms to varying degrees. The latest guidelines put forward the concept of premature ovarian insufficiency (POI) [3], in order to initiate early intervention. POI refers to a disease in which women have ovarian dysfunction before the age of 40, which is mainly manifested by abnormal menstruation (amenorrhea, rare, or frequent menstruation), elevated gonadotropin levels (FSH > 25 IU/L), and lowered estrogen levels. Diminished ovarian reserve (DOR) refers to the decrease in number and/or quality of oocytes in the ovary, accompanied by a decrease in anti-mullerian hormone (AMH) level and antral follicle count (AFC) but an increase in FSH level. There is a decline in the fertility of these patients, but there is little emphasis on age, etiology, and menstrual status.

3. Mitochondria

Mitochondria are energy factories that participate in the body's energy metabolism, Studies have shown that mitochondria play an important role in follicular development, in which a large amount of energy is required in this process.

At present, follicular atresia is considered the main factor in the pathogenesis of POF [4,5]. Follicular atresia is caused by the apoptosis of ovarian granulosa cells and oocytes, which occurs in a variety of ways. Studies have found that mitochondrial dysfunction may cause granulosa cell apoptosis, thus affecting the growth and development of oocytes, leading to atresia or apoptosis of follicles, and in turn, resulting in diminished ovarian reserve (DOR) or even POF [6,7]. The three possible mechanisms of premature ovarian failure are as follows [8]: (1) abnormal activation of primordial follicles; (2) increased apoptosis rate of follicular cells; (3) follicular maturation disorder. It can be inferred that mitochondria may play an important role in the pathogenesis of premature ovarian failure.

4. Relationship between mitochondria and premature ovarian failure

From the embryonic stage itself, follicles undergo autonomous development and atresia. In the embryonic stage, the primordial follicle, the basic reproductive unit of women, is formed, and it is also the only form of egg reserve. With continuous atresia, there are about 300,000 eggs left. From puberty to premenopausal, follicles undergo periodic changes. In a woman's lifetime, only 400 to 500 follicles generally mature and ovulate, accounting for only about 0.1% of the total. In premature ovarian failure (POF), there are fewer eggs that can mature and ovulate, and the quality of eggs declines.

4.1. Relationship between mitochondrial structural changes and premature ovarian failure

Mitochondria have complex structures and comprehensive functions. They are made up of inner and outer parallel unit membranes, resembling a sac-like structure. The membranes contain different types of proteins and enzymes that participate in basic life activities after binding at corresponding sites [9]. The endogenous pathway of apoptosis is activated by mitochondria. Mitochondrial structural destruction and stress caused by external stimulation are the key steps that initiate the process of apoptosis, which includes changes in mitochondrial permeability, nuclear DNA damage, mitochondrial depolarization, enzyme inactivation, and the unfolding of endoplasmic reticulum proteins, all of which can lead to premature ovarian failure [10].

4.2. Relationship between mitochondrial DNA copy number (mtDNA-CN) and premature ovarian failure

Mitochondrial DNA copy number (mtDNA-CN) refers to the number of mitochondrial genomes. It has

intercellular specificity and is an important indicator to measure mitochondrial function. Mitochondrial DNA is involved in cellular oxidative phosphorylation and ATP synthesis by encoding various components of the respiratory chain, thus regulating cellular metabolism and function. Granulosa cells play an important role in maintaining sufficient mtDNA during oocyte development by expressing information factors related to mtDNA replication. Research has shown that the mtDNA copy number in granulosa cells is positively correlated with that in corresponding oocytes [11]; the apoptosis rate of granulosa cells is higher in patients with decreased ovarian reserve function [12], and the mtDNA copy number in granulosa cells is significantly lower than that in patients with normal ovarian reserve function. In addition, the mtDNA copy number in cumulus granulosa cells was found to be closely related to embryo quality; the mtDNA-CN in cumulus granulosa cells of high-quality embryos is significantly higher than that in cumulus granulosa cells of low-quality embryos [13]. During in vitro fertilization, the mtDNA-CN in cumulus granulosa cells allows for a better prediction of embryo quality, with a positive predictive value of 84.4% and a negative predictive value of 82.1% [14].

4.3. Relationship between oxidative stress and premature ovarian failure

Follicular development requires a large amount of energy supply, but in the process, reactive oxygen species (ROS) are produced. Under normal conditions, there are endogenous antioxidant systems in the cells that can remove the majority of ROS, thus maintaining dynamic equilibrium. However, when the equilibrium is upset by variables, such as old age, emotions, and iatrogenic factors, it leads to excessive buildup of ROS in the body, resulting in harmful oxidative stress (OS).

According to a study [15], the effects of oxidative stress on ovarian function are as follows: (1) oxidative stress damages cells and leads to oocyte apoptosis; granulosa cells are sensitive to oxidative stress damage, and oocytes, in the active state of meiosis, are more susceptible to oxidative stress damage; (2) oxidative stress leads to the destruction of mitochondrial structure, resulting in the destruction of mitochondrial DNA; (3) oxidative stress leads to the dysfunction of mitochondria in the regulation of calcium ions and inhibits the synthesis of ATP by mitochondria, leading to cell apoptosis; (4) oxidative stress-induced apoptosis is mediated by mitochondrial cytochrome C release and caspase-3 activation [16].

4.4. Relationship between Mitofusin 2 (Mfn2) and premature ovarian failure

The mitochondrial fusion protein gene was first discovered by Chen Guanghui and other researchers, and it was named as hypertension related gene-1. In 2001, Santal and several other researchers found that the protein encoded by this gene promotes mitochondrial fusion, so it was renamed as Mitofusin 2 (Mfn2) gene. In addition to being a key molecule involved in mitochondrial fusion and maintaining mitochondrial structure and function, Mfn2 also plays an irreplaceable role as a signal molecule in cell energy metabolism, signal transduction processes, such as Ras, calcium, and oxidative stress, cell proliferation and differentiation, cell apoptosis, as well as other basic life activities. Studies have found that high or low expression of Mfn2 can significantly affect mitochondrial morphology and mobility, resulting in reduced mitochondrial fusion efficiency [17]. Mitochondria, as an important organelle of eukaryotic cells, play a key role in the completion of various biological cell functions, such as energy metabolism, signal transduction, ion balance, regulation of apoptosis, and so on [18].

In a study, the expression level of Mfn2 in granulosa cells and the apoptosis of granulosa cells in patients with normal ovarian function were compared with those in patients with ovarian insufficiency [19]; the findings demonstrated a reduction in the expression level of Mfn2 mRNA and Mfn2 protein and an increase in the apoptosis rate of granulosa cells in the POI group; thus, it was concluded that a low expression of Mfn2 may lead to a change in mitochondrial function and the apoptosis of granulosa cells via the mitochondrial pathway of apoptosis, which may further affect follicular development and ovarian

function, thus contributing to the onset and development of POI.

5. TCM treatment

Traditional Chinese medicine does not have a name for this condition. However, this condition can be attributed to "amenorrhea," "infertility," and "early termination of menstrual flow." Its main pathogenesis is kidney deficiency and imbalance of blunt. Blood stasis, liver depression, phlegm dampness, and spleen deficiency are often seen in this condition. Its primary symptoms include irregular menstruation, amenorrhea, along with hot flashes, night sweats, knee and waist soreness, as well as other menopause-related symptoms.

The influence of mitochondrial dysfunction on ovary involves the whole process of follicular development, which is similar to the TCM theory of how the kidneys play a role in this. Kidney deficiency is the fundamental pathogenesis. With sufficient kidney qi and menstrual blood, there is normal menstruation, and pregnancy can occur. On the contrary, kidney deficiency caused by congenital or acquired factors leads to a disorder in the "kidney-Tiangui-Chongren-uterus" axis, resulting in various gynecological diseases. According to Professor Xia Guicheng, a master of Chinese medicine, the primary strategy for treating a decline in ovarian function is tonifying the kidney while taking into account of both the liver and spleen, with certain emphasis on calming the nerves and strengthening their essence [20].

5.1. Kidney-tonifying method

Zhao Xinyong and several researchers demonstrated the use of Zuogui Pill in improving the mitochondrial function of oocytes in naturally aging mice through mouse experiments; PGC-1α, OPA1, and PINK1 were detected to have some associations with mitochondrial proliferation, mitochondrial fusion, and autophagy, respectively; compared with the control group with young mice, these three proteins in the aging group were found to be significantly downregulated; however, all three proteins were significantly upregulated with the use of Zuogui Pill; they concluded that Zuogui Pill can improve the function of mitochondria but further exploration is still required to understand its specific mechanism [21]. In another study [22], Erxian Decoction has also been proven to have certain effects on improving the ovarian granulosa cells of naturally aging mice.

5.2. Kidney-tonifying and blood-activating method

Through clinical and experimental studies, several researchers investigated the effect of Bushen Huoxue Recipe on ovarian mitochondrial SIRT3 [23]. The results revealed that the expression of ovarian mitochondrial SIRT3 in the Bushen Huoxue Recipe group was significantly higher than that in the model group, and with the increase of equivalent dose, the expression of mitochondrial SIRT3 in the high-dose Bushen Huoxue Recipe group had no significant difference from that in the coenzyme Q10 group, indicating that Bushen Huoxue Recipe can upregulate mitochondrial SIRT3, maintain the inner and outer mitochondrial membrane stability, inhibit granulosa cell apoptosis, and improve ovarian function.

At present, there is little research on the treatment of premature ovarian failure caused by abnormal mitochondrial function in traditional Chinese medicine. However, the research on the relationship between mitochondrial dysfunction and ovarian function has gained widespread attention. In western medicine, hormone replacement therapy is usually prescribed to treat POF. With deepening research, traditional Chinese medicine or a combination of traditional Chinese and western medicine has shown significant effect on premature ovarian failure. In particular, traditional Chinese medicine is beneficial for the improvement of perimenopausal symptoms caused by premature ovarian failure, but further exploration is still required to understand its specific mechanism, so as to have more accurate reference basis for the treatment of premature ovarian failure.

6. Discussion

In conclusion, although little is known about the relationship between mitochondrial dysfunction and premature ovarian failure, more and more studies are now revealing its complexity. The ovaries of patients with POF are equivalent to aging ovaries. Aging tissues show lower mitochondrial protein synthesis rate, decreased mitochondrial DNA copy number, abnormal mitochondrial enzyme activity, as well as lower oxidation capacity and ATP synthesis [24]. The structure and function of mitochondria also show a gradual decline, with the appearance of mitochondrial dysfunction, which is closely related to the increase of ROS production causing oxidative stress. Mitofusin 2 (Mfn2) may cause premature ovarian failure by affecting the permeability of mitochondrial cell membrane in granulosa cells. In conclusion, mitochondrial dysfunction is one of the main causes of premature ovarian failure, but its specific mechanism has not been fully explored. Nowadays, patients with premature ovarian failure are found to be among younger groups, with a rising prevalence. Its causes have also been widely studied. However, there are still much room for exploration in terms of therapeutic options, in order to improve the clinical symptoms of patients with premature ovarian failure, especially in traditional Chinese medicine.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Jiao Z, Shi H, 2014, Advances in Diagnosis and Treatment of Premature Ovarian Failure. International Journal of Obstetrics and Gynecology, 2014(02): 108–111.

[2] Li J, Xu L, Gao Y, 2021, Research Progress and Status Quo of the Etiology, Mechanism and Treatment of Premature Ovarian Failure. China Medical Science, 11(02): 58–61.

[3] Huang X, Cao X, Lin N, et al., 2019, Evaluation and Revision of Chinese Medicine Diagnosis and Treatment Guidelines for Premature Ovarian Failure. Henan Traditional Chinese Medicine, 39(01): 82–86.

[4] Sullivan SD, Castrillon DH, 2011, Insights into Primary Ovarian Insufficiency Through Genetically Engineered Mouse Models. Semin Reprod Med, 29(4): 283.

[5] Jin M, Yu Y, Huang H, 2012, An Update on Primary Ovarian Insufficiency. Sci Chin Life Sci, 55(8): 677.

[6] Wang LY, Wang DH, Zou XY, et al., 2009, Mitochondrial Functions on Oocytes and Preimplantation Embryos. Journal of Zhejiang University Science B, 10(7): 483–492.

[7] Van Blerkom J, 2011, Mitochondrial Function in the Human Oocyte and Embryo and Their Role in Developmental Competence. Mitochondrion, 11(5): 797–813.

[8] Jin M, Yu Y, Huang H, 2012, An Update on Primary Ovarian Insufficiency. Science China Life Sciences, 55(8): 677–686.

[9] Tong C, 2018, Mitochondrial Abnormalities and Premature Ovarian Failure. Journal of Shandong University (Medical Edition), 56(04): 23–27.

[10] Hu K, Liu H, Wan T, et al., 2010, The Relationship Between Mitochondria and Apoptosis. China Animal Husbandry and Veterinary Medicine, 377(12): 86–88.

[11] Otten AB, Theunissen TE, Derhaag JG, et al., 2016, Differences in Strength and Timing of the mtDNA Bottleneck Between Zebrafish Germline and Non-Germline Cells. Cell reports, 16(3): 622–630.

[12] Gorman GS, Chinnery PF, DiMauro S, et al., 2016, Mitochondrial Diseases. Nature Reviews Disease

Primers, 2(1): 1–22.

[13] Ropp PA, Copeland WC, 1996, Cloning and Characterization of the Human Mitochondrial DNA Polymerase, DNA Polymerase γ. Genomics, 36(3): 449–458.

[14] Rahman S, Copeland WC, 2019, POLG-related Disorders and Their Urological Manifestations. Nat Rev Neurol, 15(1): 40–52.

[15] Li H, Zhang Y, Lu L, et al., 2020, Reporting Quality of Polycystic Ovary Syndrome Practice Guidelines Based on the RIGHT Checklist. Medicine (Baltimore), 99(42): e22624. https://doi.org/10.1097/MD.0000000000022624

[16] Qin Y, 2021, Research Progress of Antioxidants to Improve Ovarian Function. Chinese Journal of Reproductive Health, 32(01): 91–94.

[17] Guo Y, 2017, Based on Mfn2 and Mitochondrial Membrane Potential to Explore the Effect of Kidney-Tonifying Traditional Chinese Medicine on the Outcome of IVF Patients with Kidney-Qi-Yin Deficiency. Shandong University of Traditional Chinese Medicine.

[18] Kong D, Yao G, Sun Y, 2020, Research Progress of Mitochondrial Fusion Proteins Involved in Regulating Female Reproductive Function. Journal of Reproductive Medicine, 29(03): 402–406.

[19] Bai G, 2016, The Expression of Mitochondrial Fusion Protein 2 in Ovarian Insufficiency and Its Correlation with the Pathogenesis. Huazhong University of Science and Technology.

[20] Wang J, 2018, Xia Guicheng's Experience in Treating Premature Ovarian Insufficiency from the Theory of "Heart-Kidney-Uterine Axis". Journal of Traditional Chinese Medicine, 59(7): 554–557 + 576. https://doi.org/10.13288/j.11-2166/r.2018.07.004

[21] Zhao X, Sun Y, Zhao H, et al., 2020, Improvement Effect of Zuogui Pill on Mitochondrial Function of Naturally Aging Mouse Oocytes. New Chinese Medicine and Clinical Pharmacology, 31(08): 924–929.

[22] Zhao X, Wang L, Zhou F, 2019, Improvement Effect of Erxian Decoction on Mitochondria of Ovarian Granulosa Cells in Naturally Aging Mice. Chinese Materia Medica and Clinical, 35(04): 10–14.

[23] Zhang Y, 2020, The Clinical Efficacy of Bushen Huoxue Recipe in Improving Ovarian Reserve and the Mechanism of Regulating Mitochondrial SIRT3. Nanjing University of Traditional Chinese Medicine.

[24] Wang B, Gong Z, Song J, et al., 2020, Research Progress of SIRT1 Improving Ovarian Reserve by Inhibiting Oocyte Aging. International Journal of Reproductive Health/Family Planning, 39(01): 45–48 + 58.