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Etiological Mechanism of Decreased Ovarian Reserve Function: An Integrated Perspective of Traditional Chinese and Western Medicine Theories

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Abstract: ***Diminished ovarian reserve (DOR), as an early pathological stage of premature ovarian failure, is characterized by a synergistic effect of physiological aging factors and pathological multifactors in modern medicine. The latter includes core elements such as genetic susceptibility, iatrogenic injury, immune regulation abnormalities, environmental exposure, and psychological stress. The theory of traditional Chinese medicine explains that the essence of its pathogenesis is "deficiency of kidney essence and deficiency of heaven and earth" - these two constitute the fundamental pathological basis for the occurrence and development of diseases, and run through the entire course of the disease; Among them, liver depression and qi stagnation are the key triggering factors, leading to the obstruction of qi and blood circulation and the formation of qi stagnation and blood stasis; The deficiency of qi and blood biochemistry caused by spleen deficiency and loss of luck further exacerbates the deficiency of the source; And blood stasis obstructing collaterals is not only a core pathological product, but also a key link in the deterioration of the disease. The four types of pathological elements mentioned above together constitute a dynamic pathological circulation system of "deficiency of the essence and excess of the substance", ultimately disrupting the functional homeostasis of the "kidney-Tiangui-Chongren-uterus". This multidimensional etiology and pathogenesis analysis provides a systematic theoretical basis for the integrated clinical diagnosis and treatment of DOR with traditional Chinese and Western medicine.***

Keywords: Decreased ovarian reserve, Etiology and pathogenesis, Kidney deficiency, Liver depression, Spleen deficiency, Stasis of blood, Integrated Traditional Chinese and Western Medicine.

1. Introduction

Diminished ovarian reserve (DOR) refers to the impaired ability of ovarian cortical follicles to grow, develop, and form fertile follicles, characterized by a decrease in the number and quality of follicles remaining in the ovary [1]. This pathological state can cause reproductive endocrine dysfunction and progressive decline in fertility. Research has confirmed [2] that the clinical features of DOR are early manifestations of prolonged menstrual cycle and reduced menstrual flow; As the disease progresses, it can progress to frequent or infrequent menstruation, amenorrhea, and ultimately to premature ovarian insufficiency (POI) or premature ovarian failure (POF). From the perspective of disease progression spectrum, DOR, POI, and POF together constitute three consecutive pathological stages of progressive decline in ovarian function.

It is worth noting that in recent years, the incidence rate of DOR has shown a significant upward trend and the age of onset tends to be younger. Without timely intervention, DOR can transform into POI and POF, thus increasing the risk of patients suffering from cardiovascular diseases (such as atherosclerosis), metabolic disorders (such as insulin resistance) and other long-term complications, and having multiple negative effects on women's reproductive health, quality of life and social function. This article provides a systematic review of the research progress on the pathogenesis of DOR in both traditional Chinese and Western medicine, aiming to provide multidimensional theoretical basis for optimizing clinical diagnosis and treatment strategies.

2. Clinical Symptoms

The core pathological manifestation of DOR is a decrease in the number and/or quality of oocytes, leading to impaired ovarian endocrine and reproductive function. Specific features include progressive decline in fertility, significant decrease in serum anti Mullerian hormone (AMH) levels, decrease in antral follicle count (AFC), and increase in basal follicle stimulating hormone (FSH) levels [3].

3. Diagnostic Criteria

At present, there is no internationally unified diagnostic standard for DOR. In clinical practice, a multi index joint evaluation model is commonly used, including but not limited to imaging parameters such as basal FSH and estradiol (E_2), inhibin B, AMH, AFC, ovarian volume, and average ovarian diameter [4]. The current mainstream standard is based on: (1) Poseidon criteria, which states that serum AMH < 1.2 ng/mL or AFC < 5 can be used as the diagnostic threshold for DOR [5]. (2) In 2022, if any of the following indicators are met, it indicates DOR: AMH < 1.1 ng/mL, bilateral ovarian AFC < 5-7, and basal FSH ≥ 10 IU/L for two consecutive menstrual cycles.

4. Etiology and Pathology

Modern medicine believes that DOR is characterized by insidious onset and gradual development, and its pathogenesis has not been fully elucidated. The etiology of this disease can be divided into two categories: physiological and pathological. Physiological factors mainly refer to age-related ovarian

dysfunction, manifested as a decrease in the number of primordial follicles, a decrease in the quality of eggs and embryos, menstrual cycle disorders, and reduced menstrual flow that occur with age; Pathological factors include genetic factors (such as a family history of fragile X syndrome), iatrogenic injuries (history of reproductive system surgery or radiation and chemotherapy), autoimmune abnormalities, infections, environmental exposure, and social psychological factors [4]. Although traditional Chinese medicine does not have the disease name of "ovarian reserve dysfunction", the classic discourse of "premature menstruation with water interruption" is highly consistent with its clinical manifestations and can be classified as "insufficient menstruation", "irregular menstrual flow", "amenorrhea", "infertility", etc. Currently, there is no unified disease name and standardized principles for syndrome differentiation and treatment. Modern research in traditional Chinese medicine has pointed out that its etiology is closely related to external factors such as six lewdness, emotional disorders, loss of control in daily life, and physical endowment [6]. The core pathogenesis always belongs to "deficiency of the essence and excess of the body": the deficiency of kidney essence and deficiency of heaven and earth are the root causes of the disease, while liver depression and qi stagnation, spleen deficiency and lack of movement, and blood stasis and internal resistance are the main symptoms or factors affecting the progression of the disease [7]. Kidney deficiency, liver depression, spleen deficiency, and blood stasis interact with each other, jointly leading to dysfunction of the reproductive axis of the "kidney-Tiangui-Chongren-uterus", resulting in deficiency of ovarian essence and qi, follicular development disorders, and decreased reserve function.

4.1 Kidney Deficiency is the Root Cause of the Disease, and the Core is the Deficiency of Essence and the Exhaustion of Heaven and Earth

The kidneys store essence and are responsible for reproduction. The "Annals of Medicine" states: "Menstruation is entirely carried out by the kidneys, and if the kidneys lack water, the menstrual blood will dry up day by day." The "Fu Qingzhu Women's Health" also emphasizes the core theory of "meridian water originates from the kidneys" and "meridian water originates from the kidneys. Kidney essence serves as the material basis for the transformation of Tiangui, which is a micro substance that promotes the maturation of reproductive function. The book "Su Wen: Ancient Innocence Theory" systematically explains the physiological laws of female reproduction [8]: "At the age of seven, a woman's kidney qi is abundant and her teeth become longer. On the second day of the seventh lunar month, the Ren meridian is unobstructed and the Tai Chong meridian is abundant. When the lunar cycle is at its current time, there is a child... On the seventh day of the seventh lunar month, the Ren meridian is weak, the Tai Chong meridian is weak, the Tiangui meridian is exhausted, and the underground passage is not unobstructed, resulting in a bad shape and no child." This establishes the core position of the "kidney-Tiangui-Chongren-uterus" in the female reproductive system. Kidney deficiency can lead to insufficient Tiangui Hua Yuan, clinically manifested as reduced menstrual flow and delayed menstruation; If the kidney essence is deficient, the heavenly body will not be able to descend, the Chongren will not be prosperous, the blood sea will be empty, and the uterus will be deprived of nourishment, ultimately leading to infertility [9]. Under modern medicine, the hypothalamic pituitary ovarian (HPO) axis precisely regulates female hormone levels through neuroendocrine mechanisms, and its functional abnormalities can lead to hormone disorders and follicular development disorders. It can be seen that the "kidney-Tiangui-Chongren-uterus" axis in traditional Chinese medicine and the modern medical HPO axis have a high degree of consistency in the theory of reproductive function regulation, and the two show significant theoretical homology in regulating human reproductive function [10].

Kidney essence deficiency and Tiangui deficiency constitute the core pathogenesis and fundamental cause of DOR. This mechanism directly dominates the basic state of the quantity and quality of follicles in the ovary, and runs through the entire course of the disease. The essential attribute of follicular reserve is determined by innate kidney essence endowment and relies on the continuous nourishment of acquired kidney qi. As the organ where water and fire coexist, the kidneys contain Yuan Yin and Yuan Yang: Kidney Yin nurtures the development of follicles and the homeostasis of the endometrium, while Kidney Yang warms and promotes follicle maturation, discharge, and menstrual blood biochemistry.

Modern medical research has confirmed that there is a significant correlation between congenital deficiency (corresponding to kidney essence deficiency) and genetic defects (such as FMR1 gene pre mutation, chromosomal aberration, etc.) leading to a reduction in the size or quality of the primordial follicular pool [11], which is an essential intrinsic factor in the occurrence of DOR. Age growth conforms to the physiological law of "seven day exhaustion" and is the main cause of DOR. Its modern biological basis is reflected in the decline of the number and quality of residual ovarian follicles with age. Frequent sexual activity, multiple pregnancies, and surgical procedures can directly deplete the essence and qi in the kidneys, and damage the uterine system. Research has shown that specific pelvic and abdominal surgeries, such as laparoscopic myomectomy and ovarian cystectomy, can significantly reduce levels of AMH, with postoperative DOR status lasting up to six months for ovarian cysts [12].

Chronic wasting diseases and tumor radiotherapy and chemotherapy can severely deplete qi, blood, yin, and yang, ultimately leading to kidney essence depletion. Clinical observations have shown [13] that chemotherapy drugs for malignant tumors can deplete existing follicles and trigger DOR, and the degree of damage depends on the type of drug, cumulative dose, and age of initial treatment. Traditional Chinese medicine belongs to the category of "drug toxicity can harm the kidneys". Radiation therapy is also a risk factor for DOR. Exposure to gonadal radiation can cause premature ovarian failure, and the degree of damage is related to the patient's age, radiation dose, and radiation type [14]. Ionizing radiation has special toxicity to oocytes and can cause irreversible damage (such as accelerated follicular atresia and rapid decline in reserve), clinically manifested as menstrual disorders and ovarian failure. Long term sleep deprivation and

excessive fatigue are in line with the theories of "exhaustion leads to qi depletion" and "annoyance harms yang", and can gradually deplete kidney yin and kidney yang. Modern research has shown that chronic stress and circadian rhythm disorders can disrupt the regulatory function of the HPO axis, ultimately leading to ovarian physiological dysfunction.

4.2 Liver Depression is an Important Trigger, with qi Stagnation, Blood Stasis, and Obstruction of Cellular Networks

Liver qi stagnation is a key pathological link and triggering factor in the progression of DOR. The pathogenesis of this disease exacerbates the deficiency of kidney essence by blocking the operation of qi, inducing blood stasis formation, transforming qi into fire and consuming yin, and interfering with the ovulation process, which hinders the smooth flow of the Chong Ren - Xiong Gong meridian and accelerates the depletion of ovarian reserve.

The liver is responsible for regulating qi circulation and regulating qi flow, while also having the functions of storing blood and regulating emotions. The physiological characteristics of women determine the 'innate nature of the liver system'. The liver's drainage function directly affects the distribution of qi and blood and the connectivity of the Chong Ren meridians. When the liver qi is unobstructed, the qi and blood are regulated, the flow of qi and blood is smooth, the menstrual cycle is regular, and the development of follicles and ovulation process are normal. Emotional disorders can cause liver dysfunction and stagnation of qi [15]. The "Wan Shi Women's Health" states: "Worry and anger, qi stagnation and blood stasis lead to menstrual closure [16]. Contemporary women of childbearing age are subjected to multiple social pressures, and long-term psychological stress such as anxiety, depression, or emotional agitation first affects the liver meridian, resulting in liver depression syndrome. This is the core cause and progression factor of DOR, particularly evident in young populations. Research has confirmed that persistent anxiety and depression can lead to abnormal decline in ovarian reserve indicators [17].

Qi is the commander of blood, and when Qi is stagnant, blood flow is obstructed, blood stasis stops and the Chong Ren cellular network is blocked. Modern medical research has shown that chronic negative emotions can interfere with the neuroendocrine regulation of the HPO axis [18]. Dysfunction of the HPO axis can lead to abnormal secretion of sex hormones, directly damaging ovarian physiological function [19], and forming a pathological microenvironment of "blood stasis" locally, disrupting follicular blood flow perfusion and nutritional support.

Over time, liver depression can transform into fire evil, burn and burn kidney yin and liver blood, deplete body fluids and essence, and worsen kidney essence deficiency. The academic community has proposed [20][21] that there is an inherent correlation between the phenomenon of "phase fire hyperactivity" and oxidative stress and inflammatory activation, which can damage the function of oocytes and granulosa cells. The sustained increase of reactive oxygen species (ROS) is a core marker of cellular oxidative damage and a key factor in inducing programmed cell death in oocytes [22]. ROS imbalance can cause mitochondrial DNA mutations and lipid peroxidation reactions, severely damaging the spindle structure and chromosome configuration of oocytes, and reducing gamete mass; Simultaneously inducing apoptosis of granulosa cells, accelerating the process of follicular atresia, and hindering the final maturation of oocytes [23].

4.3 Spleen Deficiency is the Source of Biochemical Deficiency, and Insufficient qi and Blood Nourish the Uterus

The spleen is the foundation of postnatal life, responsible for regulating the source of Qi and blood transformation. The Chong meridian belongs to the Yangming Stomach Meridian, and the spleen and stomach transport water and grain essence to generate qi and blood, continuously nourishing the congenital kidney essence, and infusing it into the Chong and Ren meridians to nourish the physiological functions of the uterus and ovaries. The essence of water and grain produced by the spleen and the essence sealed by the kidneys together form the material basis for blood production. The two work together to regulate water metabolism, thereby optimizing ovarian blood flow perfusion and functional status [10].

Deficiency of temperament can lead to deficiency of kidney qi and a lack of sources of Qi and blood transformation; Insufficient spleen yang can trigger a slight fire in the gate of life. Factors such as improper diet, excessive thinking, or chronic fatigue can lead to spleen dysfunction, qi and blood biochemical disorders, which are the basic pathological elements of DOR. The pathogenesis is mainly reflected in three pathological processes: congenital loss of kidney essence due to insufficient nourishment, deficiency of qi and blood, and accumulation of pathological products of phlegm and dampness. The three factors jointly weaken the ovarian nourishing mechanism, accelerate reserve depletion, and often interact and coexist with pathological mechanisms such as kidney essence deficiency, liver qi stagnation, and blood stasis.

4.4 Blood Stasis as a Pathological Product and Secondary Cause, Obstructing Collaterals and Damaging Eggs

Blood stasis is defined as a pathological product formed by the obstruction of blood circulation or the retention of blood outside the meridians in the body. It has special significance in gynecological diseases, and "uterine stasis" is a common pathogenesis of menstrual disorders and infertility. Zhang Zhongjing's "Synopsis of the Golden Chamber" explains: "Women's various diseases are caused by deficiency, cold stagnation, and qi stagnation, resulting in menstrual flow closure for many years, cold coagulation, and stagnation of the cell door." It reveals that this disease is often caused by the interaction of body deficiency, cold coagulation, and qi stagnation.

Modern women have a preference for raw and cold food or thin clothing, which makes them susceptible to invasion by cold pathogens. Cold belongs to the Yin evil, which often invades the Jiao and targets the Chong Ren cellular network. When the blood is warm, it flows smoothly; when it encounters cold, it coagulates; when cold pathogenic factors

accumulate for a long time, they damage the Yuan Yang; when the warmth is lost, it leads to the stagnation of qi and blood; when the menstrual water is abnormal, there may be insufficient or absent menstruation. In addition, social pressure can lead to emotional imbalances such as anxiety and depression, liver dysfunction can cause qi stagnation, and obstruction of the Chong Ren pathway can make menstrual blood flow difficult. Kidney deficiency and blood stasis are mutually causal [24]: the root of qi is in the kidneys, and when the kidney qi weakens, it promotes weakness and causes blood stasis due to poor blood circulation; Stagnation of the meridians and obstruction of the distribution of qi and blood, resulting in obstruction of the flow of qi and blood, ultimately leading to "blocked passage", ovarian function decline, and ovulation disorders [25]. In the process of DOR, blood stasis is both a core pathological product and a secondary pathogenic factor, continuously hindering the circulation of qi and blood and material metabolism. Pelvic surgical procedures, such as ovarian cystectomy and removal of endometriosis, can directly damage the microvascular network and form pathological stasis [26].

Blood stasis blocks the meridians, making it difficult for qi and blood to reach the ovarian tissue. Like a barren land lost to irrigation, the follicular microenvironment deteriorates, hindering its development and maturation, and reducing gamete quality, ultimately resulting in reduced follicular reserve and functional decline. The state of blood stasis can easily lead to the accumulation of local metabolic waste, forming complex pathological products such as "blood stasis and toxin accumulation" or "phlegm blood stasis". This type of product can damage the ovarian parenchymal structure, microvascular system, and internal environment homeostasis, induce tissue fibrosis, microcirculation disorders, and chronic inflammatory reactions, directly disrupting the integrity of the follicular pool or damaging the developmental potential of oocytes. Therefore, the essence of blood stasis is the pathological manifestation of kidney liver spleen dysfunction in the local ovary, which constitutes a key mechanism that hinders the normal development of follicles and accelerates the progression of DOR.

5. Summary

The pathological mechanism of ovarian reserve dysfunction in traditional Chinese medicine presents multidimensional dynamic evolution characteristics, and its core pathogenesis is located on the basis of "deficiency of kidney essence and deficiency of Tiangui". Under this framework, liver qi stagnation constitutes a key initiating and progressing factor, spleen dysfunction is a fundamental supporting link disorder, and blood stasis obstructing collaterals is the core pathological product and worsening factor. The four are interrelated during the course of the disease, forming a closed loop of pathogenesis, ultimately leading to a deep disorder of the reproductive axis of "kidney-Tiangui-Chongren-uterus", resulting in irreversible depletion of ovarian reserve.

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