

The current situation and thinking of acupuncture and moxibustion in the prevention and treatment of premature ovarian insufficiency

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Abstract: With the adjustment of my country's fertility policy, improving the low fertility level and improving the fertility of women of childbearing age have become the focus of current clinical research, and premature ovarian insufficiency is the main cause of infertility in women of childbearing age. In recent years, researchers have made some progress in the clinical efficacy and mechanism research of acupuncture and moxibustion in the prevention and treatment of premature ovarian insufficiency. At the same time, the article combs and thinks about the problems and problems existing in the research on the prevention and treatment of premature ovarian insufficiency with acupuncture and moxibustion.

1. Introduction

According to the Regulations on the National Population Census and the State Council 's Notice on Conducting the Seventh National Population Census, the national population in the seventh national population census was 1.412 billion people, with an average annual growth rate of 0.53%, a decrease of 0.04 percentage points from the average annual growth rate of 0.57% from 2000 to 2010 [1]. Ages 60 and over make up 264.02 million people, or 18.70% of the population, a rise of 5.44 percentage points. Those between the ages of 15 and 59 make up 894.38 million people, or 63.35%, a reduction of 6.79 percentage points [2]. The State Council of China has successively issued "Decision on Optimizing Fertility Policies to Promote Long Term Balanced Population Development", "Decision of the Communist Party of China Central Committee and the State Council on Optimizing Fertility Policies to Promote Long Term Balanced Population Development" on July 20, 2021, and "Decision of the Communist Party of China Central Committee and the State Council on Optimizing Fertility Policies to Promote Long Term Balanced Population Development" on July 21, 2021. In addition, at a meeting on May 31, 2021, the Political Bureau of the CPC reviewed the above documents. Thus it can be seen that the State Council of China attaches great importance to China's population growth model, and the prospect of fertility is being thoroughly investigated in the

nation. Clinical research is now focused on improving China's low fertility rate, increasing the fertility of women of childbearing age, and promoting long-term balanced population development policies. These issues can be seen in the implementation of major decisions such as having two children alone, having two children comprehensively, and supporting three children [3].

Among women who experience ovarian dysfunction before the age of 40, a frequent reproductive ailment is called primary ovarian insufficiency (POI), as shown in Figure 1. This condition is marked by menstruation irregularities, along with high levels of gonadotropins and low levels of estrogen. Women who experience sparse menstruation or amenorrhea for more than 4 months prior to the age of 40 and have follicle stimulating hormone (FSH) levels >25 U/L measured twice at intervals of more than 4 weeks meet the diagnostic criteria for POI, according to the 2016 European Society of Human Reproduction and Embryology (ESHRE) guidelines, as shown in Figure 2. According to the survey, Chinese women experience POI at an incidence rate of 1%, with age groups experiencing varied incidence rates. Before the age of 20, before the age of 30, before the age of 35, and before the age of 40, it is 1/10000, 1/1000, 1/250, and 1/100. Women's physical and emotional health are adversely impacted by POI because of its complex etiology, fast progression, and lack of effective treatment options. Additionally, with the rise in reproductive age, attention is now being paid to the harm that POI does on fertility. Acupuncture and moxibustion, which are examples of non-drug therapy, have little side effects and have increasingly come to be favored therapeutic options for women, making them a current research hotspot.

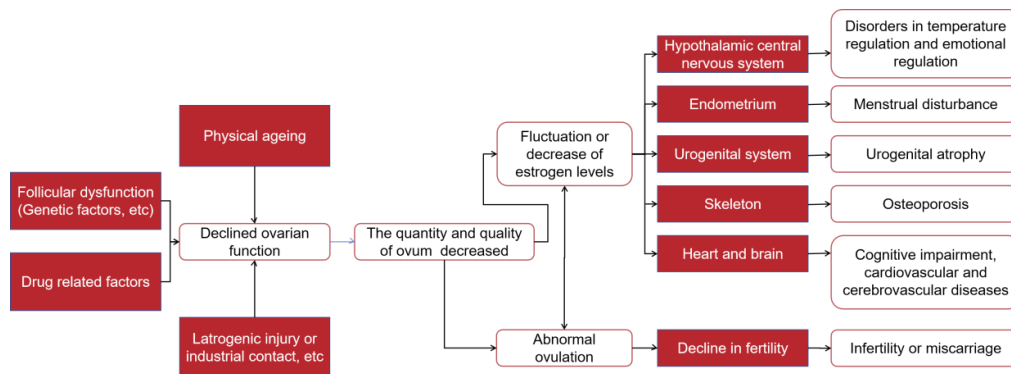


Figure 1: Pathogenesis of POI

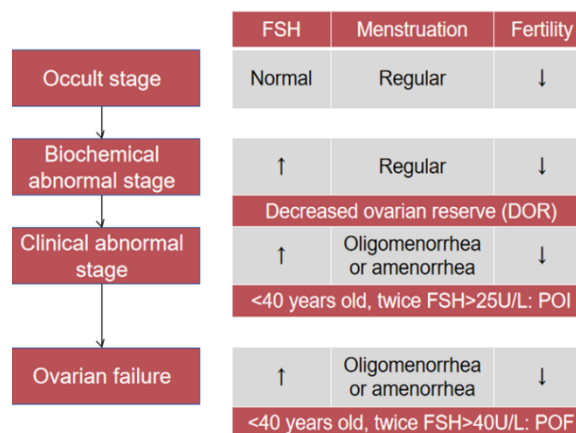


Figure 2: Disease progression and diagnostic criteria of POI

2. Modern Medical Understanding and Research Status of POI

The ovarian cortex's non-growing or stationary primordial follicles are referred to as having a reserve function. Their growth, development, and the amount and quality of fertilized eggs are all intimately related to this reserve function. A decrease in ovarian reserve function and even the emergence of premature ovarian insufficiency (POI) in many women of childbearing age are results of changes in women's living conditions, lifestyles, and pace in modern society. These changes include frequent or ongoing mental stress, overwork, and poor lifestyle choices. The causes of POI are currently thought to include a variety of factors, including heredity, immunity and environment, and causes are connected to things like long-term mental stress, extreme weight loss, indiscriminate drug use, smoking, and alcohol intake [4,5]. The relevant cellular signaling pathways include Transforming Growth Factor Signaling Pathway (TGF- β), Wnt/-Catenin Signaling Pathway, Vascular Endothelial Growth Factor (VEGF), Phosphatase and Tensin Homologous Genes/Phosphatidylinositol 3 Kinase/Serine-Threonine Protein Kinase (PTEN/PI3K AKT mTOR) Signaling Pathway, etc [6]. As the primary causes of infertility in women of reproductive age, POI's effects on estrogen levels and gonadotropin levels—which, in turn, produce decreased menstrual flow, amenorrhea, and ovulation dysfunction—have emerged as major contributors to the aging process. Additionally, low estrogen levels brought on by POI in women may result in long-term health issues like cardiovascular diseases, osteoporosis, Alzheimer's disease. And it can cause other conditions that have a significant impact on women's quality of life, such as hot flashes, sweating, lack of libido, low vaginal discharge, palpitations, chest tightness, and sleep issues. It can be seen that low estrogen levels brought on by POI will seriously affect the living conditions and quality of life of women [7-11]. Currently, the primary objectives of POI treatment are to improve fertility and lessen the symptoms of low estrogen. Hormone replacement therapy (HRT) and assisted reproductive technology are the primary therapeutic modalities. Iatrogenic variables are also a contributing component in the development of POI. Female ovarian function may be harmed by pelvic surgery, particularly ovarian surgery, pelvic radiation therapy, tumor chemotherapy, and specific medicines. When comparable surgeries are performed (complete hysterectomy, uterine artery embolization, etc.), the main effects on ovarian function are the direct tissue injury to the ovaries and the disruption of the ovarian blood supply. Environmental elements that are chemical and physical in nature may also have an impact on female ovarian function, resulting in a decline in ovarian function. In many contemporary urban contexts, endocrine disruptors, volatile organic compounds, persistent organic pollutants, heavy metals, and agricultural pesticides not only cause cancer, mutation, and teratogenicity, but also negatively impact ovarian health. The development of POI treatment research is, however, constrained by the absence of a definite pathology and etiology. Sequential treatment with estrogen and progesterone has significant short-term effects, but prolonged use has significant negative side effects and cannot effectively promote the regeneration and repair of damaged ovarian tissue [12,13].

3. Traditional Chinese Medicine Understanding of POI

In traditional Chinese medicine, POI is classified under the headings of "infertility," "blood depletion," and "early cessation of menstruation." According to traditional Chinese medicine, POI is primarily caused by kidney deficiencies. The "Su Wen Ancient Innocence Theory" explains that a woman's kidney qi is abundant and her teeth are longer when she is seven years old. On the 27th day, when the Heavenly Gui arrives, the Ren pulse is open, the Tai Chong pulse is mighty, and the menstruation continues, thus she bears children. When the Heavenly Gui is depleted on the seventh day, the Ren pulse is weak, the Tai Chong pulse is weak, the Ren pulse is weak, and the tunnel is blocked, thus her shape is poor, and she is childless [14]. According to the "Classic of Women's

Medicine", kidney water is the only substance used in moon water. The kidney serves as the body's natural basis by managing reproduction and storing essence. The Heavenly Gui will arrive on time when the kidney is full of qi, and the menstruation will occur when the energy flow is full. There is a lot of kidney essence, and blood is converted into kinetic energy. Blood serves as the basis for both pregnancy and women's monthly errands. According to "The Book of Jing Yue", Those who have died of blood, due to the loss of Chong Ren, the source is cut off from their flow; Deficiency of kidney yang leads to the inability to renew the essence of the kidney and generate qi, which results in the loss of energy storage and secretion due to the inability to warm and nourish the uterus. Additionally, it causes insufficient yang qi, qi and blood, as well as weak agitation. When partially opened, it can prevent moon water from draining; if the kidney yin is depleted, there won't be enough essence and blood, which causes a shortage of Chong and Ren blood. The menstrual fluids will gradually break as a result of the Ren meridian's Qi failing, which results in the loss of nutrients in the uterine and cellular channels. This disease may develop if menstruation is not maintained [15]. Liver depression is one of the important pathological characteristics of POI. According to "Su Wen Da Qi Pian, " one of the significant pathological features of POI is liver depression: "The liver also regulates the female Tiangui. The body uses yang instead of yin, which plays a significant role in controlling menstruation flow, while the liver retains blood. Blood is present at birth in women, and the Chongmai connects the cell to the liver. Blood is present in the Chongmai, which is a crucial assurance of regular menstruation. The primary component of menstruation, blood, is produced by the middle energizer and is kept in the liver. The liver is in charge of reducing stress, enhancing blood flow, and preventing depression. It controls blood circulation in addition to controlling blood storage. The Foot Jueyin Liver Meridian is linked to both the Chong and Ren meridians. The Foot Jueyin Liver Meridian's Qi mechanism achieves its peak, which benefits the Chong and Ren meridians as well. The Ren meridians are full, the Qi mechanism is unhindered, and the meridian blood will appear when it is appropriate, according to the manifestation. The dysfunction of blood storage and relaxation, loss of blood circulation, injury to ovarian function, and low ovarian reserve function affect the function of the seven emotions, which in turn affects the function of the liver relaxation, causing liver qi to stagnate, oligomenorrhea, amenorrhea, and infertility. The primary factor leading to POI is the imbalance between Chong and Ren. It is noted in "Lingshu Five Tones and Five Flavors" that "Chong and Ren meridians originate from the cell". All twelve meridian's qi and blood fulfill in the Chongmai, creating a sea of blood. Additionally compatible with the Foot Yangming Stomach meridian is the Shaoyin meridian. It has natural qi to support it and acquired water grains to provide it with subtle sustenance. The Ren Meridian is part of the Sea of Yin Meridians, which is in charge of the human body's essence, blood, and bodily fluids. As the primary embryo, it serves to nourish and nurture the embryo. Menstruation is a physiological occurrence that is controlled by the kidney, Tiangui, Chongren, and uterine axis. The uterus secretes and purses menstrual blood on a regular basis under the combined influence of numerous organs and meridians. According to The Book of Jingyue, "Those who have died of blood, their flow is cut off due to the loss of Chong and Ren. " No woman remains healthy after ten and a half months of disease and harm. Amenorrhea and infertility are pathological indications that occur when the Chong and Ren meridians are blocked, preventing the essence of the water and grain from overflowing the uterus.

4. Research Status and Advantages of acupuncture and moxibustion on Prevention and Treatment of POI

Acupuncture and moxibustion, as an important part of traditional Chinese medicine, according to the strategic deployment of the Opinions of the CPC Central Committee and the State Council on Promoting the Inheritance, Innovation and Development of Traditional Chinese Medicine, Several

Policies and Measures on Accelerating the Characteristic Development of Traditional Chinese Medicine, the Outline of the "Healthy China 2030" Plan, and the Outline of the Strategic Plan for the Development of Traditional Chinese Medicine (2016-2030), the development of traditional Chinese medicine acupuncture and moxibustion must meet the major needs of the country and the people's life and health, Strive to make outstanding contributions to building a healthy China and a community of human health. Our project team's preliminary clinical research revealed that acupuncture can considerably raise E2 levels in POI patients, lower FSH and LH levels, and regulate the female reproductive system in both directions. In patients with early-onset ovarian insufficiency, acupuncture combined with hormone medications has a certain therapeutic effect on enhancing serum levels of follicle stimulating hormone (FSH), anti-Mullerian hormone (AMH), antral follicle count (AFC), and traditional Chinese medicine symptoms [16-18].

Table 1: “Thirteen Acupuncture and Moxibustion” for regulating menstruation and promoting pregnancy created by Professor Fang Yigong

Effect	Acupoints
Adjusting Chongren	Guanyuan(CV4), Zhongwan(CV12), Tianshu(ST25), Dahe(KI12), Zigong(EX-CA1), Ciliao(BL32)
Tranquilizing and sedating the mind	Baihui(GV20), Shenting(GV24), Benshen(GB13)
Tonifying the liver and kidney	Shenshu(BL23), Taixi(KI3), Taichong(LR3)
Auxiliary acupoints	Sanyinjiao(SP6)

Combined with the team's examination of acupuncture, moxibustion, and similar therapies' advancements in basic and clinical research in the prevention and treatment of premature ovarian failure, as well as their use in the last five years in the treatment of POI. In conclusion, the mechanism of acupuncture and moxibustion in the treatment of POI is generally related to six aspects: regulating the immune balance, increasing ovarian blood supply, inhibiting the expression of proteins and genes, regulating the expression of hormone receptors, and inhibiting the phosphorylation of signal pathways. These aspects are also known as the HPOA, immune balance, increasing ovarian blood supply, and inhibiting protein and gene expression. Acupuncture, moxibustion, and related therapies are primarily grouped into three groups for the prevention and treatment of premature ovarian failure: conventional acupuncture and moxibustion, acupuncture and moxibustion combination therapy, and acupuncture and moxibustion combined medication therapy. The majority of the acupoint selection strategies used for POI acupuncture treatment are based on notions from traditional Chinese medicine, such as choosing acupoints based on their primary therapeutic functions and dialectical compatibility [19-21]. "Why is acupuncture and moxibustion entering mainstream medicine?" was the title of an article in the American magazine Time on April 29, 2022. The report made note of the fact that acupuncture and moxibustion research in the areas of gynecology and reproduction will be the primary research direction in the future, and that this research should also examine how acupuncture and moxibustion affects female hormone levels, such as by reducing menopausal hot flashes or resolving irregular menstruation. The use of acupuncture and moxibustion for the treatment of gynecological issues is growing in popularity due to research indicating that these practices can enhance levels of estrogen and other hormones. Some scientists also study how acupuncture and moxibustion affect fertility. According to several tiny preliminary studies, its use may be associated with quicker pregnancies and better outcomes from in vitro fertilization. Numerous scientific and clinical research have demonstrated the efficacy of acupuncture and moxibustion in the management of POI. It offers promising clinical possibilities for reestablishing the menstrual cycle, treating low estrogen symptoms, lowering stress levels, enhancing pregnancy outcomes, and enhancing quality of life. The Chinese Expert Consensus on Clinical Diagnosis and Treatment of Early Ovarian Insufficiency and the

European Guidelines of the Society of Human Reproduction and Embryology both recommend acupuncture and moxibustion treatment for POI [22]. Currently, there are many different types of acupuncture and moxibustion therapy for POI, including traditional acupuncture, electroacupuncture, warm needle, catgut embedding, ear points, and numerous distinctive acupuncture techniques. For example, a well-known method created by Professor Fang Yigong from China Academy of Chinese Medical Sciences is shown in Table 1. It has a wide range of applications, simple and effective processes, strong safety standards, etc. Traditional Chinese medicine's concept of "treating the disease before it happens" is fully reflected in how acupuncture and moxibustion can help POI patients' hormone levels, menstrual cycle recovery, reproductive function, and clinical symptoms. This results in a delay in the progression of POI.

5. Deficiencies and thoughts on prevention and treatment of POI by acupuncture and moxibustion

Combining the project team's research foundation with the state of domestic research today, the author is of the opinion that acupuncture and moxibustion fall short in the following three areas when it comes to preventing and treating POI.

There is currently little large sample, multicenter clinical randomized controlled study, and evidence-based medical evidence supporting the use of acupuncture and moxibustion to increase FSH levels and restore fertility. The employment of acupuncture and moxibustion therapy has several advantages over hormone therapy, including a standardized and uniform operation, high clinical repeatability, a quick procedure, a long-lasting curative impact, and the possibility to prevent hormone drug side effects including unpleasant taste and psychological pressure. It has a low financial cost and is simple for patients to accept. In the clinical practice and study of enhancing fertility, assisted reproduction, and in vitro fertilization embryo transfer technology, acupuncture and moxibustion can successfully cure and prevent infertility caused by impaired ovarian reserve function. Establishing a consistent, large sample, multicenter clinical randomized controlled research is thus especially important.

Animal POI models are still in the early exploratory stages of study. At the moment, ovarian toxic chemical models, autoimmune models, and chemotherapeutic medication models are the main animal models developed for POI. Cyclophosphamide and Tripterygium wilfordii glycosides are the two main medications utilized in chemotherapy drug models. The pituitary ovarian axis autoimmune targeted destruction, crude ovarian antigen immunized animals, animal thymectomy, and mouse zona pellucida peptide fragments are the different categories of the autoimmune model. The deoxyethylcyclohexene and galactose models of ovarian hazardous substances are the most prevalent. These three modeling techniques are now acknowledged as POI techniques because of how easy they are to use, how successful they are, and how well they simulate. Gene knockout models are difficult to promote and employ due to their high cost and can only fully describe the function of one or a small number of genes. They also cannot fully explain the cause of POI. New modeling techniques like stress models, superovulation models, and ionizing radiation models are currently the subject of little investigation. Exploring the pathogenic mechanism of POI requires establishing a uniform modeling methodology and evaluation standards.

The basic science of acupuncture and moxibustion is currently making strides in the study of the specificity of acupoints and acupoint sensitization, further elucidating the regulation and mechanism of acupuncture systemic regulation, exposing the segmental and extensive regulation and mechanism of acupoint target organ connection, and highlighting the mechanism and significance of acupoint sensitization in disease diagnosis and treatment. When examining the characteristics of POI acupoint sensitization phenomena, it is a good idea to use POI as a carrier for the phenomenon and patterns of

acupoint sensitization. It is also crucial to explore acceptable data analysis methodologies. The majority of data analysis techniques used in observational trials today solely involve descriptive analysis, primarily characterizing the surface distribution pattern of palpationally sensitive locations. There haven't been any publications on the meridians' sensitization phenomena or other aspects of them, such their diagnostic threshold, sensitization rate, pattern of sensitization's geographic distribution, or its affecting elements. The quality control of studies is currently only sometimes discussed in research on POI acupoint sensitization, which leads to low trustworthiness of experimental data. As a result, the beneficial acupoints for POI acupuncture treatment are chosen to prevent and treat a variety of symptoms, including infertility brought on by POI, menstrual cycle issues, persistent amenorrhea, premature aging of the appearance, body changes, tumor susceptibility, irritability, insomnia and depression, palpitations, chest tightness, and general fatigue. The long-term management of health and clinical research of assisted reproduction, in vitro fertilization, and embryo transfer technology, as well as the prevention of cardiovascular illnesses, osteoporosis, Alzheimer's disease, and other disorders associated with low estrogen levels, are of major significance.

6. Conclusion

In conclusion, POI is a challenging and intricate condition that has an impact on the physical and emotional health of women. The pathophysiology of it is complicated, and the therapeutic outcomes of existing treatments are insufficient. In modern medicine, the pathophysiology of POI is frequently investigated from angles including genetic, autoimmune, iatrogenic, environmental, etc. Hormone replacement therapy is the major emphasis of the therapy. However, it is challenging to accomplish specific therapeutic benefits in clinical practice because of its rigorous indications and contraindications as well as adverse reactions brought on by hormones. According to traditional Chinese medicine, kidney deficiency—which is closely related to liver depression and spleen deficiency—is the primary cause of this disease's onset. On the basis of precise dialectics, the kidney, liver, and spleen are tonified, soothed, and strengthened using acupuncture, moxibustion therapy, acupoint catgut implantation, and other exterior treatment techniques. A protracted treatment cycle and some patients' acupuncture phobia hinder patient compliance, which makes it challenging to establish a long-term systematic treatment, even if acupuncture and moxibustion have produced some positive outcomes in the treatment of POI. In the future, it should, on the one hand, be based on the theoretical underpinnings of traditional Chinese medicine's "prevention before disease," advocating for patients to achieve "prevention before disease, prevention after disease", early screening of high-risk factors for POI, minimizing unnecessary pelvic surgeries, and reducing exposure to pollutants in the environment. However, combining traditional Chinese medicine research with contemporary medical research, utilizing each field's strengths, advancing animal models, developing new research techniques, and completing large sample, multicenter clinical randomized controlled studies will ultimately result in a higher level of evidence for evidence-based medicine.

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