

Review of Current Chinese and Western Medical Treatment Modalities for Premature Ovarian Insufficiency

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Abstract: *Premature ovarian insufficiency (POI) is an increasingly prevalent reproductive endocrine disorder characterized by fluctuating decline of ovarian function during its course. The pathogenesis and treatment of POI involve multiple factors, mechanisms, and signaling pathways. In recent years, Western medical treatment has witnessed numerous emerging modalities, including stem cell therapy, extracellular vesicle therapy, human growth hormone therapy, and melatonin. These novel therapeutic approaches not only retain the advantages of conventional treatments but also activate follicular development to effectively restore ovarian function; some modalities even enhance embryo quality and achieve pregnancy. Traditional Chinese medicine (TCM) offers diverse therapeutic modalities that regulate disrupted sex hormone levels, alleviate hypoestrogenic symptoms, and simultaneously address patients' reproductive needs. Treatment modalities are flexible and convenient, encompassing oral administration, external application, and combined internal-external therapies, demonstrating significant clinical efficacy with the added benefits of being non-invasive and relatively cost-effective compared to certain Western medical treatments. Integrated Chinese and Western medicine therapy enhances the therapeutic effects of both medical systems, rapidly ameliorating the long-term impact of elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, as well as reduced estradiol (E₂) levels, on female patients. This review elaborates on six aspects: pathogenesis of POI, Western medical therapies, TCM internal treatment modalities, TCM external treatment modalities, combined TCM internal-external therapies, and integrated Chinese-Western medicine therapy, aiming to provide clinicians with diverse perspectives for the diagnosis and treatment of POI.*

Keywords: Stem cell therapy, Traditional Chinese medicine, Hormone replacement therapy, Integrated medicine.

1. Introduction

Premature ovarian insufficiency (POI), formerly termed premature ovarian failure or premature menopause [1], is characterized by menstrual disturbances in women under 40 years of age accompanied by elevated follicle-stimulating hormone (FSH) levels (>25 IU/L on two occasions at least 28 days apart). Beyond infertility, POI is associated with multiple health risks, including menopausal symptoms, decreased bone density and increased fracture risk, early progression of cardiovascular disease, psychological effects (potentially including depression and anxiety), early cognitive decline, and dry eye syndrome [2], thereby exerting adverse effects on the physical and mental health, as well as occupational and daily functioning, of numerous women.

2. Current Research Status of POI

The etiology of POI encompasses genetic, autoimmune, infectious, environmental, and iatrogenic factors [3]. While the cause remains unidentified in the majority of cases, 4% to 30% of cases are attributed to autoimmunity. The ovary is a frequent target of autoimmune attack; autoimmune etiology is considered the primary mechanism in POI, which may also occur as an isolated condition [4]. Aberrant granulosa cell apoptosis represents a critical link in POI pathogenesis, primarily involving PI3K/Akt and Wnt/ β -catenin signaling pathways, which are intimately associated with suppression of oocyte growth. This not only accelerates follicular atresia and diminishes ovarian function but ultimately leads to decline in female reproductive capacity [5].

3. Western Medical Treatment Modalities

3.1 Oral Pharmacotherapy

Hormone replacement therapy (HRT) with estrogen and progestin constitutes the principal therapeutic measure for POI [6]. HRT formulations approximating normal ovarian hormone production are recommended, with continuation until the natural menopausal age of approximately 50 years [7]. Scientifically designed HRT regimens effectively alleviate POI-related symptoms and prevent the development of osteoporosis, cardiovascular disease, and cognitive decline [8].

3.2 Stem Cell Therapy

Stem cells are diverse in type, with significant variations in therapeutic potential among different sources. Igboeli P reported two Caucasian women who received intraovarian injection of autologous bone marrow-derived mesenchymal stem cells (BMSCs), with serum estrogen levels increasing by approximately 150% compared to preoperative levels at 7 months post-treatment [9]. Bone marrow mesenchymal stem cells (BMSCs) offer numerous advantages including abundant source availability, rapid self-renewal, robust differentiation capacity, low immunogenicity, and minimal ethical concerns. Huang Y posited that BMSCs facilitate restoration of ovarian function and fertility [10]. Sun L administered human umbilical cord mesenchymal stem cell (hucMSC) therapy for cisplatin chemotherapy-induced ovarian granulosa cell apoptosis, demonstrating that stem cell therapy exerts preventive and therapeutic effects on POI to a

certain extent [11]. Cheng Zixin systematically compared stem cells from various sources, concluding that stem cell transplantation not only ameliorates POI but even restores menstruation and pregnancy in some patients, although some embryos exhibit poor quality with increased miscarriage risk [12].

3.3 Extracellular Vesicles (EVs)

EVs are a class of membrane-bound vesicles secreted by cells, including exosomes, microvesicles, and apoptotic bodies, which play crucial roles in intercellular communication, transport, and signal transduction. Reproductive system-related EVs actively participate in regulating various physiological events, including gamete maturation, fertilization, and embryonic and fetal development [13]. Studies have demonstrated that extracellular vesicles (EVs) exhibit therapeutic potential in restoring ovarian tissue damage, promoting ovarian granulosa cell proliferation, and inhibiting granulosa cell apoptosis [14]. Almiñana C et al. identified differences in oviductal EV secretion and content in vivo and in vitro, with experimental results indicating that in vivo EVs effectively prolong embryo survival and enhance embryo quality [15]. Leng Yawen suggested that human umbilical cord mesenchymal stem cell (hucMSC)-derived extracellular vesicles share similar regenerative, reparative, and immunomodulatory advantages with hucMSCs while partially circumventing the risks associated with stem cell transplantation [16].

3.4 Human Growth Hormone (GH) Injection

Growth hormone is a peptide hormone under dual control by growth hormone-releasing hormone and somatostatin produced by the hypothalamus. GH primarily promotes various physiological functions including somatic growth and development, substance metabolism, and reproduction [17]. Since the 1990s, GH has been applied as an adjunctive agent in reproductive medicine. Research has demonstrated that GH not only regulates ovarian steroidogenesis and angiogenesis but also acts on endometrial cell metabolism and proliferation, and can improve female sexual function [18]. As an adjuvant ovarian stimulation therapy, experimental evidence has shown that GH effectively improves oocyte quality and enhances clinical outcomes [19]. Luo Weiwei et al., through clinical comparative studies, demonstrated that recombinant human growth hormone injection effectively improves pregnancy outcomes in infertile patients with premature ovarian insufficiency (POI) [20]. Most studies suggest that GH supplementation reduces artificial insemination embryo miscarriage rates and effectively increases artificial insemination live birth rates [21]. Currently, reports on GH application in POI patients remain scarce, necessitating extensive prospective studies to validate its efficacy.

3.5 Melatonin (MT)

Melatonin is a potent endogenous antioxidant and free radical scavenger that protects ovarian function through multiple pathways including antioxidant defense, mitochondrial protection, and hormonal regulation [22]. Studies have found that melatonin promotes expression of antioxidant proteins SLC7A11, Nrf2, and GPX4, suggesting therapeutic value of

MT in POI intervention [23]. In a randomized controlled clinical trial employing combined HRT and melatonin therapy, the combination not only improved serum sex hormone levels in POI patients but also demonstrated that melatonin therapy enhances antioxidant capacity in POI patients [24]. Zou H suggested that immature human oocytes can develop into healthy offspring through melatonin-mediated protection of mitochondrial function, thereby increasing high-quality blastocyst formation rates [25].

3.6 Gut Microbiota Modulation

Ju Shan found that gut microbiota dysbiosis is closely correlated with POI severity [26]. Shin SY et al., through guinea pig laparotomy-induced POI experiments, demonstrated that POI leads to intestinal bacterial dysbiosis, suggesting that modulation of gut microbiota may contribute to POI treatment and prevention [27]. Zheng found that *Lycium barbarum* polysaccharides exert certain protective effects against POI development [28]. Lin demonstrated that quercetin ameliorates ovarian damage and increases normal follicle numbers by modulating *Akkermansia* and *Lactobacillus* populations in POI mice, reducing CCR9⁺/CXCR3⁺/CD4⁺ T-lymphocyte counts and IL-12 secretion [29].

3.7 Ovarian Tissue Cryopreservation and Transplantation

Prior to chemoradiotherapy, healthy ovarian tissue is surgically removed via laparoscopy, subjected to programmed cryopreservation, and stored in liquid nitrogen at -196°C. To enhance transplantation success rates, autologous ovarian tissue may undergo pretreatment prior to transplantation. Upon patient request for fertility restoration, comprehensive multidisciplinary review precedes thawing and transplantation of the cryopreserved ovarian tissue. This approach not only effectively restores ovarian function but also enhances fertility to a certain extent [30]. The primary risk of post-cryopreservation ovarian tissue transplantation is reintroduction of tumor cells into the autologous host, particularly in leukemia patients. Studies have shown that dexamethasone culture of leukemia cells prior to ovarian tissue retransplantation cannot prevent reintroduction of leukemia cells into the host [31]. A research team performed ovarian tissue cryopreservation (OTC) and retransplantation (OTCT) in 10 Chinese women with various diseases; all patients maintained normal ovarian function one year postoperatively [32]. This modality demands exceptionally high physician expertise and equipment, and is currently available only at several hospitals in Beijing and Shanghai.

4. Traditional Chinese Medicine Treatment Modalities

POI is associated with kidney essence (Jing) deficiency; harmonizing Yin-Yang and regulating the Conception, Governing, Thoroughfare, and Belt vessels (Ren, Du, Chong, Dai) are particularly important [33]. Under the guidance of TCM syndrome differentiation and treatment principles, integrating the academic experience and perspectives of numerous renowned TCM practitioners, treatment is approached from the five-organs (Wu Zang) perspective with

kidney deficiency as the core pathogenesis. The principal syndrome patterns are summarized as kidney essence deficiency, liver depression with kidney deficiency, and spleen-kidney dual deficiency. Treatment focuses primarily on kidney tonification, with concurrent consideration of spleen fortification and liver nourishment.

4.1 Oral Herbal Administration

This primarily involves oral administration of herbal decoctions, with formulation approaches broadly divided into two schools: classical TCM prescriptions and empirically derived formulas. Zhou Mianli et al., through murine experiments, found that Erxian Decoction (Er Xian Tang) can improve ovarian function in POI mice via the mTOR/4E-BP1 signaling pathway [34]. Studies suggest that Zhuluan Decoction (Zhu Luan Tang) improves ovarian reserve function by activating the PI3K/Akt/mTOR signaling pathway, reducing autophagy-related protein expression of Beclin1, ATG5, and LC3, and inhibiting KGN cell hyperautophagy [35]. Huang Feng posited that Wubie Huigui Decoction (Wu Bie Hui Gui Tang) effectively improves patients' sex hormone levels by regulating hypothalamic-pituitary-ovarian axis function, thereby promoting ovarian function recovery and follicular growth and development [36]. Some scholars suggest that Danggui Shaoyao San (Danggui Shaoyao Powder) can inhibit aberrantly activated TGF β 1-Smad signaling pathway, reducing excessive follicular atresia, promoting granulosa cell proliferation and differentiation, and improving ovarian reserve function [37]. Yang Yongqin et al., through rat experiments, concluded that Butian Dazao Pill (Bu Tian Da Zao Wan) can regulate serum reproductive hormones and cytokine levels in autoimmune premature ovarian failure mice, alleviate ovarian inflammatory responses, and modulate immune dysfunction, thereby improving ovarian reserve function [38].

4.2 External TCM Therapies

These are primarily acupuncture-based therapies including filiform needle acupuncture, electroacupuncture, acupoint catgut embedding, abdominal acupuncture, and auricular acupuncture, supplemented by moxibustion, cupping therapy, five-element music therapy, tuina massage, and TCM exercise (Qigong) [39]. Acupuncture treatment for POI is primarily based on TCM zang-fu (visceral manifestation) and meridian theories, with treatment focusing on the liver, spleen, and kidney meridians. Clinical practice frequently employs menstrual regulation and fertility promotion methods and the method of regulating the Conception and Governing vessels to tonify the kidney, with emphasis on acupoints of the Conception (Ren) and Governing (Du) vessels.

Studies have found that the thirteen-needle menstrual regulation and fertility promotion method combined with Conception vessel moxibustion can ameliorate discomfort symptoms and sex hormone levels in POI patients, effectively enhancing therapeutic efficacy [40]. Shi Jufang discovered through clinical experiments that acupuncture combined with five-element music therapy effectively alleviates clinical symptoms in spleen-kidney Yang deficiency-type POI patients while relieving anxiety, depression, and insomnia induced by POI [41].

Wan Xiaoman selected kidney deficiency and blood stasis-type POI patients and, following three consecutive menstrual cycles of treatment, found that "dual fixation and single unblocking" acupuncture combined with fire dragon cupping therapy effectively regulates serum reproductive hormone levels, improves local ovarian blood flow, and promotes dominant follicle growth [42]. Studies have found that electroacupuncture at the "Gongsun" (SP4) acupoint restores ovarian reserve function in POI rats, exhibiting anti-aging effects [43].

4.3 Combined Internal-External Therapy

This is the most widely applied and prevalent therapeutic modality in clinical practice, offering diverse forms and flexible combination patterns with enhanced therapeutic effects. In a comparison of Zishui Qinggan Yin (Zishui Qinggan Decoction) combined with acupoint embedding versus Femoston (a sequential HRT regimen), the decoction combined with acupoint embedding was found to improve kidney deficiency and liver depression-type clinical symptoms, reduce serum FSH and LH levels, elevate E₂ levels, and improve mood and insomnia [44]. Huang Yanhui et al. posited that Yangchao Tiaochong Decoction (Yangchao Tiaochong Tang) combined with acupuncture benefits the sex hormone levels and restoration of uterine blood supply in POI patients, promoting ovarian function recovery [45]. Xu Qianni et al. found that Yishen Huoxue Decoction (Yishen Huoxue Tang) combined with acupuncture may activate the PI3K/AKT signaling pathway to improve patients' clinical symptoms and effectively enhance ovarian function [46]. Cheng Shu suggested that modified Zuogui Pill (Zuo Gui Wan) combined with press-needle therapy improves liver-kidney Yin deficiency-type TCM syndromes, with significant effects on various aspects of ovarian function [47].

5. Integrated Chinese and Western Medicine Therapy

Studies suggest that combined TCM and HRT therapy effectively improves hypoestrogenic manifestations in POI patients [48]. Miao Jing et al., through network Meta-analysis, screened 14 Chinese patent medicines; 14 Chinese patent medicines combined with HRT demonstrated significant efficacy in improving POI. Concurrently, they summarized and compared Chinese patent medicine efficacy: for correcting sex hormone disorders and increasing follicular reserve, Fuke Yangrong Capsules or Liuwei Dihuang Pill (Liuwei Dihuang Wan) combined with HRT should be prioritized; for perimenopausal transition, KunTai Capsule (KunTai Capsule) combined with HRT is indicated for symptom relief; for overall improvement of ovarian function, Compound Ejiao Syrup, Guishen Pill (Guishen Wan), or Zishen Yutai Pill (Zishen Yutai Wan) combined with HRT are appropriate [49]. With conventional Western medicine combined with Qingxin Wenshen Decoction (Qingxin Wenshen Tang), Ma Weirong posited that this therapy improves discomfort symptoms in spleen-kidney Yang deficiency-type POI, effectively restores ovarian blood flow, and enhances ovarian function [50]. Sun Jinfeng selected 86 POI patients as study subjects; the control group received Western medicine treatment, while the observation group received additional Bugan Yishen Tiaochong Decoction

(Bugan Yishen Tiaochong Tang) on the basis of the control group, with both groups receiving three consecutive months of treatment. The results demonstrated that Bugan Yishen Tiaochong Tang combined with Western medicine exhibits favorable efficacy in treating POI [51]. Zhou Mengdan administered different treatment regimens: Femoston alone versus electroacupuncture combined with Femoston. Comparative analysis of treatment outcomes revealed that the combined therapy group enhanced POI treatment efficacy [52].

6. Conclusion

POI is a branch of ovarian dysfunction with the disease site located in the ovary. Unknown causes lead to premature depletion of primordial follicles [53]. Simple Western pharmacotherapy (HRT) improves the hypoestrogenic state induced by POI but exerts no reversing effect on ovarian function and cannot fulfill the reproductive requirements of POI patients. Current key points in Western medical treatment include not only regulating disrupted hormones to alleviate hypoestrogenic clinical symptoms in POI patients but also restoring ovarian function, increasing pregnancy rates, and reducing the probability of adverse events such as miscarriage. Some treatment modalities are currently in clinical trial stages domestically, requiring large-sample clinical studies to improve success rates and safety. TCM treatment focuses on kidney deficiency as the core pathogenesis, emphasizing kidney tonification and menstrual regulation, assisting follicular development, restoring ovarian function, and increasing pregnancy probability. TCM treatment modalities are diverse and non-invasive. Integrated Chinese and Western medicine therapy enhances therapeutic effects and represents a prevalent clinical treatment regimen. To date, both simple and combination therapies possess limitations, warranting further follow-up research. This study aims to provide diverse perspectives for clinical diagnosis and treatment of POI, facilitating healthcare practitioners in selecting appropriate treatment regimens for individual patients, with continued research on POI expected to improve cure rates.

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