

# Advances in Traditional Chinese Medicine for Managing Diminished Ovarian Reserve: Mechanisms and Clinical Insights

Yonghui Liu<sup>1</sup>, Mingchan Wei<sup>2</sup>, Yasheng Deng<sup>1</sup>, Yanping Fan<sup>1</sup>, Yiqing Zheng<sup>1</sup>, Zhaobing Ni<sup>1</sup>, Jiang Lin<sup>1</sup>

<sup>1</sup>College of Basic Medicine, Guangxi University of Chinese Medicine, Nanning, 530200, People's Republic of China; <sup>2</sup>Guangxi International Zhuang Medicine Hospital, Nanning, Nanning, 530200, People's Republic of China

Correspondence: Jiang Lin, Email 1713552545@qq.com

**Abstract:** Diminished Ovarian Reserve (DOR) is characterised by a decrease in the number and quality of oocytes, accompanied by biological markers such as a decrease in anti-Müllerian hormone (AMH), a decrease in the sinus follicle count (AFC), and an increase in follicle stimulating hormone (FSH). In response to the limitations of modern medical treatments, traditional Chinese medicine (TCM) has demonstrated unique advantages in the treatment of DOR. In this paper, we systematically reviewed the literature in the past decade to analyse the scientific content of TCM intervention in DOR from the dimensions of molecular mechanism and clinical application. It was found that single components (paeoniflorin, *Epimedium* glycosides, etc.), TCM pairs (*Cuscuta chinensis*–*Sambucus nigra* and *Semencuspidatae*–*Epimedium*), TCM combinations (Liuweidihuangwan, Haifuyuyuyitang, *Angelica sinensis*–*Paeonia lactiflora*, etc.), and a variety of acupuncture therapies can improve the ovarian function through a multi-targeted modulation mechanism: ① regulating the signalling pathways, such as PI3K/AKT, to promote the development of the follicle; ② regulating the hypothalamic-pituitary-ovarian axis balance hormone levels; ③ enhance anti-oxidative stress through Nrf2/HO-1/NLRP3 signalling; ④ inhibit the expression of granulosa cell apoptosis-related factors (Bax/Caspase-3). Clinical data showed that TCM interventions significantly increased AMH levels, increased AFC and decreased FSH levels in patients. The study confirms that TCM exerts therapeutic advantages through multi-component synergistic effects, from improving the ovarian microenvironment, regulating reproductive endocrinology, delaying follicular atresia, etc. which provides a theoretical basis and practical reference for the integrated treatment of DOR. It is suggested that standardised clinical studies should be carried out to establish an evaluation system for the efficacy of TCM and to promote the development of precise treatment options.

**Keywords:** diminished ovarian reserve, traditional Chinese medicine, molecular mechanisms, ovarian function

## Foreword

Diminished Ovarian Reserve (DOR) is a clinical syndrome characterised by a decrease in the number and quality of ovarian follicles, with pathological features such as reduced levels of anti-Müllerian hormone (AMH), reduced sinusoidal follicle counts (AFC), and elevated levels of follicle-stimulating hormone (FSH), among other biomarker abnormalities.<sup>1</sup> Epidemiological survey data show that the prevalence of DOR has increased significantly from 19% in 2004 to 26% in 2014, and now accounts for approximately 20% of ovarian-related diseases in women, with a significant trend towards younger age.<sup>2–4</sup> This disease not only directly leads to decreased fertility but also may progress to Premature Ovarian Failure (POF) within 1–6 years if not intervened in a timely manner, posing a dual threat to women's reproductive and psychological health.<sup>4</sup>

Modern medicine mainly uses hormone replacement therapy (HRT), dehydroepiandrosterone (DHEA) and growth hormone as therapies.<sup>5</sup> Although these therapies temporarily improve hormone levels and ovarian responsiveness, long-term application may induce serious complications such as increased risk of breast cancer and endometrial hyperplasia.<sup>6</sup> Although emerging coenzyme Q10 interventions have shown potential in improving embryo quality and clinical

pregnancy rates, their long-term efficacy and safety still need to be validated in large-scale cohort studies.<sup>7,8</sup> Two key limitations of existing treatment protocols prevail: first, there is an efficacy discrepancy between symptomatic relief and improvement in ovarian function; and second, the system for monitoring the safety of long-term drug use has not yet been developed.

Against this background, the advantages of Chinese medicine's overall regulation have gradually come to the fore. Based on the theory of "the kidney is the master of reproduction", TCM interventions have shown unique efficacy in improving AMH levels and increasing the natural pregnancy rate through multi-targeted regulation (eg, hypothalamus-pituitary-ovary axis, mitochondrial function, and oxidative stress pathway, etc.).<sup>9</sup> However, it should be noted that the safety of TCM treatment still needs to be systematically evaluated: for example, some heavy metal-containing minerals may cause accumulation toxicity (eg, the free mercury content of cinnabar can reach 27–354 µg/g, and the soluble mercury content can reach 8–17 µg/g),<sup>10</sup> and the phytopharmaceutical-chemical interactions may affect the hepatic enzyme activities (CYP3A4 inhibition rate can reach 41%).<sup>11</sup> In this study, we systematically reviewed the mechanism studies (involving 12 signalling pathways, including PI3K/AKT) and clinical evidence on the treatment of DOR by TCM in the past ten years, focusing on the strategy of efficacy–safety balance, with a view to providing theoretical basis for the establishment of a risk prevention and control system combining traditional Chinese and Western medicines and the development of new Chinese medicinal preparations. The specific mechanism of action is shown in Figure 1.

## Traditional Chinese Medicine for DOR

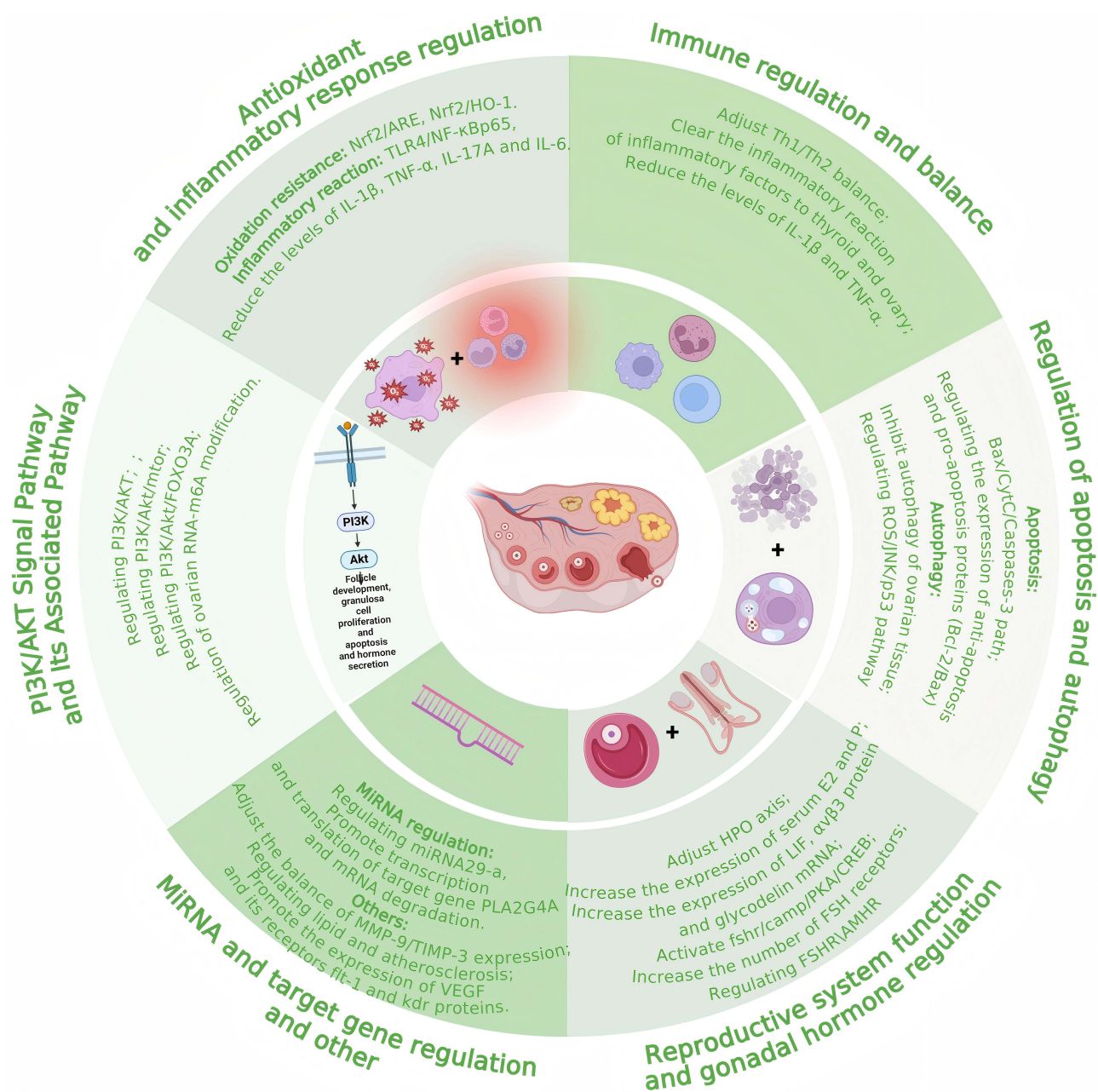
### Traditional Chinese Medicines and Their Monomer Components

In the study of treating DOR, red ginseng and *Epimedium* and their monomer active components have demonstrated unique pharmacological activities and therapeutic potentials. Red ginseng significantly inhibits the phosphorylation expression of PI3K/AKT signalling pathway, promotes follicular development and improves serum hormone profiles through the mechanism of benefiting qi and tonifying the kidney and filling in the essence, and its property of elevating the levels of AMH and GnRH has a dual improvement effect on the function of ovarian reserve.<sup>12</sup> *Epimedium*, on the other hand, effectively relieves clinical symptoms of DOR patients through the biological effects of spleen and kidney dual tonic, and excels in increasing the proportion of high-quality embryos and normal fertilisation rate, ultimately achieving systematic optimisation of the effects of fertility support.<sup>13</sup>

Modern pharmacological studies have revealed that the active ingredients of many Chinese medicines have multi-target regulatory properties: paeoniflorin restores the function of estradiol synthesis in ovarian granulosa cells through the activation mechanism of FSHR/cAMP/PKA/CREB signaling pathway, increasing the number of sinus follicles by 42% and luteal formation rate by 29% in a mouse model;<sup>14</sup> *Epimedium* glycoside has a bidirectional regulation of granulosa cells, significantly elevating estradiol secretion and cell proliferation rate at a concentration of 5 µg/L concentration significantly elevated estradiol secretion and cell proliferation rate;<sup>15</sup> total flavonoids of *Cuscuta sinensis* elevated ovarian index through FSH-cAMP/PKA pathway activation;<sup>16</sup> serpentin reduced the levels of inflammatory factors IL-1β and TNF-α while increasing SOD activity through Nrf2/HO-1/NLRP3 pathway regulation;<sup>17</sup> dandelion extract, on the other hand, significantly increased the number of mature oocytes and the rate of high-quality embryos.<sup>18</sup> These studies provide a scientific basis for the synergistic treatment of DOR with multiple components of traditional Chinese medicine.

### Chinese Medicine Pairs

Chinese medicine pairs in the prevention and treatment of DOR have focused on two groups of typical pairings: *Cuscuta chinensis*–*Sambucus* spp. and Xianmao–*Epimedium*. He Yan's team demonstrated that the *Cuscuta chinensis*–Mulberry parasitic vine pair has the dual effects of nourishing the liver and kidney and protecting the foetal element. Its mechanism of action involves regulating the balance of endometrial matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-3 (TIMP-3) expression, effectively improving the endometrial tolerance of the model mice, and the experiments observed that the animals' physical signs improved significantly (moist fur, increased vitality, body weight gain), and uterine tissues showed a healthy, reddish state and increased elasticity, and the pairing can significantly enhance anti-müllerian hormone (AMH) and improve the quality of the fetus. This formula can significantly increase the level of anti-Müllerian hormone (AMH) and the



**Figure 1** Shows the mechanism of traditional Chinese medicine in the treatment of diminished ovarian reserve (DOR) through multiple pathways such as anti-oxidation, immune regulation, PI3K / AKT signaling pathway, apoptosis autophagy, miRNA regulation and reproductive hormone balance.

balance of sex hormones, thus enhancing the ovarian reserve function.<sup>19</sup> Xie Ying et al further found that *Cuscuta sinensis* alone could achieve bidirectional regulation of hormone levels by modulating lipid metabolism-related signalling pathways and atherosclerotic pathways, providing a new molecular mechanism explanation for the improvement of ovarian reserve.<sup>20</sup>

In the study of the *Xianmao–Epimedium* pair, Hu Changrong's team used network pharmacology technology to analyse its action network, and found that its main active ingredients may cover quercetin, lignans, kaempferol and  $\beta$ -sitosterol, etc., and the target network involves key molecules such as AKT1, IL-6, TP53, VEGFA and CASP3. In-depth analyses showed that these components may exert therapeutic effects by modulating complex biological processes such as cancer-related pathways, AGE-RAGE signalling, IL-17 inflammatory pathway, PI3K-AKT survival pathway, apoptotic program, HIF-1 hypoxia-responsive pathway and NF- $\kappa$ B inflammatory network.<sup>21</sup>

Comprehensively, existing studies have shown that TCM treatment of DOR exhibits multidimensional regulatory advantages: on the one hand, it improves ovarian function through specific signalling pathway activation, hormone secretion regulation and cellular damage repair; on the other hand, single herbs (eg, red ginseng, *Epimedium*) and classical pairs of herbs significantly enhance ovarian reserve capacity through multi-targeted synergistic effects. These research results not only systematically explain the mechanism of DOR treatment by TCM but also provide a scientific basis for clinical practice and a direction for innovative drug research and development, fully demonstrating the unique value of TCM in reproductive health (Table 1).

## Traditional Chinese Medicine Prescriptions for the Treatment of DOR

At present, there are 14 traditional Chinese medicine prescriptions for the treatment of DOR, most of which are derived from ancient books such as “The Essentials of the Golden Quarter”, “The Encyclopaedia of Jingyue”, and “Fu Qingzhu’s Women’s Science”, etc., which have been clinically tested for thousands of years, with remarkable therapeutic efficacy, and have been followed by successive generations of medical doctors to the present day. Through the TCM dialectic

**Table 1** Summary of Traditional Chinese Medicine Treatment Strategies for DOR

Typology	Herbs Name/Latin Name	Efficacy	Indicator Efficacy	Mechanism of Action
Effective components of Chinese herbal medicine	Paoniflorin	—	Improve ovarian index and serum hormone level. Increase the number of antral follicles and corpus luteum.	Regulating FSHR/cAMP/PKA/CREB signal pathway.
	Icariin	—	Improve the secretion of estradiol in granulosa cells. Increase the proliferation level of granulosa cells.	Molecular pathway for regulating aromatase gene transcription in granular cells.
	Total flavonoids of <i>Cuscuta chinensis</i>	—	Improve ovarian quality, the number of follicles and corpus luteum. Improve the wet mass of left and right ovaries. FSH↓, FSH/LH↓	Activate FSH-cAMP/PKA signal transduction pathway.
	Osthol	—	Increase the number of follicles and corpus luteum in ovarian tissue. AMH↑, E2↑	Improve the activities of SOD and CAT and the expression levels of Nrf2 and HO-1 protein, decrease the levels of LH, FSH, IFN-γ, TNF-α and MDA and the expression levels of NLRP3 protein, and alleviate the inflammatory reaction and oxidative stress injury in rats.
	<i>Taraxacum officinale</i> Wigg	—	Increase the number of mature eggs, high-quality embryos and available embryos.	—
Single Chinese herbal medicine	Ginseng Rubra Radix	Tonifying qi and reinforcing healthy qi, tonifying the kidney and replenishing essence	Increase the number of follicular cells and corpus luteum, FSH↓, LH↓, AMH↑, E2↑	Down-regulate the phosphorylation expression of PI3K/Akt signaling pathway.
	Epimedium Folium	Tonifying and replenishing the spleen and kidney	Increase the number of high-quality embryos and improve the normal fertilization rate.	—
Chinese herbal medicine pair	Ginseng Radix et Rhizoma Rubra: Enriching and tonifying the liver and kidney, constraining seminal emission and calming fetus. Taxilli Herba: Enriching and tonifying the liver and kidney, strengthening sinews and invigorating bones, dispelling wind and drying dampness, calming fetus	Ginseng Radix et Rhizoma Rubra: Enriching and tonifying the liver and kidney, constraining seminal emission and calming fetus. Taxilli Herba: Enriching and tonifying the liver and kidney, strengthening sinews and invigorating bones, dispelling wind and drying dampness, calming fetus	Improve uterine coefficient and ovarian coefficient, LH↓, FSH↓, AMH↑, E2↑	Adjust the balance of MMP-9/TIMP-3 expression.
	Curculiginis Rhizoma- Ginseng Radix et Rhizoma Rubra	Tonifying kidney yang	—	Target: AKT1, IL-6, TP53, VEGFA, CASP3. Pathway: cancer pathway, AGE-RAGE signaling pathway, IL-17 signaling pathway, PI3K-AKT signaling pathway, apoptosis, HIF-1 signaling pathway, NF-κB signaling pathway, etc.



typing of DOR, traditional Chinese medicine prescriptions for DOR can be classified into the category of nourishing the liver and kidneys, invigorating blood circulation and removing blood stasis, and other categories.

## Nourishing the Liver and Kidneys

Traditional Chinese medicine compound formulas used for the treatment of DOR that nourish the liver and kidneys include: Six-flavoured Dihuang Pill, Zuo Gui Wan, Yulin Zhu, Yu Gui Wan, Ding Jing Tang, Nourishing Essence and Planting Jade Tang, and Gui Kidney Pill. Gao Ting et al showed that Liu Wei Di Huang Wan<sup>22</sup> could effectively regulate the estrous cycle in mice, significantly elevate serum hormone levels and promote follicular development through the triple mechanism of anti-oxidative stress, inhibition of inflammatory response and immunomodulation, which was ultimately manifested as a dual improvement in the number of litters and survival rate of pups. Clinical data of Zuo Gui Wan<sup>23–25</sup> showed that it could increase the acquisition rate of IVF-ET effective embryonic cycles to 57.6%, and its mechanism of action involves: ①regulating the TLR4/NF- $\kappa$ Bp65 signalling pathway, and down-regulating the inflammatory factors, such as IL-1 $\beta$ , TNF- $\alpha$ , etc.; ② decreasing the expression of key proteins, such as TLR4, NF- $\kappa$ Bp65, MyD88, and p-I  $\kappa$ B- $\alpha$ , etc.; ③significantly improving ovarian/uterine indices. Significantly improved ovarian/uterine index, elevated mean sinus follicle count (AFC) and reduced follicular atresia. Yulin Zhu,<sup>26,27</sup> through the regulation of PI3K/AKT apoptosis signalling pathway, achieved: ① reversal of the abnormally high expression of apoptosis markers such as Caspase-3/9, BAX and cytochrome C; ② reduction of TUNEL positivity and apoptosis of granulosa cells in ovarian tissues; and ③simultaneous improvement of the abnormal mitochondrial function, which was clinically manifested by the restoration of the menstrual cycle and the normalisation of hormone levels. Right Angelica Pill<sup>28,29</sup> significantly optimised the diameter of sinus follicle development and ovarian volume while elevating serum E2 levels. Clinical observations of Dingjing Tang<sup>30,31</sup> showed that it could effectively regulate the regularity of the menstrual cycle and significantly increase the AFC value. Nourishing Essence and Planting Jade Soup<sup>32,33</sup> achieves ovarian cortical structural repair through dual regulatory mechanisms: ①epigenetic modification of ovarian RNA-m6A; ②activation of the PI3K/AKT signalling pathway, as evidenced by an increase in the number of growing follicles and elevation of uterine/ovarian wet weight. By inhibiting autophagy in ovarian tissue, Gui Ren Wan<sup>34</sup> can improve ovarian morphology and serum hormone levels, increase primordial follicles and growing follicles, reduce atretic follicles, and then improve ovarian reserve function.

Modern pharmacological studies reveal that the above formulae act on the hypothalamic-pituitary-ovarian axis through a multidimensional mechanism of action – including antioxidant damage, inhibition of inflammatory factors, modulation of key signalling pathways and maintenance of ovarian microenvironmental homeostasis - to ultimately achieve an overall improvement in ovarian reserve function.

## Promoting Blood Circulation and Eliminating Blood Stasis

Clinical studies have confirmed the significant efficacy of blood circulation and elimination of blood stasis Chinese herbal compounds in DOR, which mainly include the three classic formulas, namely, Haifuyuyuyuyu Tang, Guizhi Poria Pill, and Wenjing Tang. Cai Caolei's team showed<sup>35</sup> that Haifu yuyu tang could effectively improve clinical symptoms such as abnormal menstrual flow and significantly increase endometrial thickness in patients with DOR. Several evidence-based studies<sup>36–38</sup> indicated that Wenjing Tang, through a multi-targeted mechanism of action, not only increased ovarian volume and sinus follicle count (AFC) but also optimised endometrial tolerance indexes and improved endometrial and subendometrial blood perfusion parameters. In addition, the formula demonstrated significant advantages in improving ovulation success, embryo implantation rate and clinical pregnancy rate.

Modern pharmacological studies have revealed that this formula can effectively enhance the ovarian reserve function of DOR patients by regulating the function of hypothalamic-pituitary-ovarian axis, improving ovarian microcirculation, and inhibiting follicular closure. The synergistic mechanism of its multi-components not only improves reproductive endocrine indexes but also enhances the physiological functions of the female reproductive system as a whole, providing DOR patients with a therapeutic solution with both efficacy and safety.

## Others

In addition to the prescriptions described in the previous section, traditional Chinese medicine prescriptions commonly used in the treatment of DOR include *Angelica sinensis* and *Paeonia lactiflora* powder, Zhi Bai Di Huang Wan, Ding Kun Dan, and Kun Tai capsule (derived from Huanglian and *Agaricus* soup). Several studies have shown that these compound formulas have significant efficacy in improving clinical symptoms and reproductive outcomes in patients with DOR through a multi-targeted mechanism of action.

As a classic gynecological formula, the efficacy of *Angelica sinensis* and *Paeonia lactiflora* powder<sup>39–43</sup> is reflected in the following: (1) morphological improvement of reproductive organs: significantly increase ovarian volume, improve ovarian index, promote the number of growing follicles and mature follicles, synchronously reduce the number of atretic follicles, optimize the structure of the ovarian stroma, and reduce the degree of fibrosis of the mesenchyme; (2) endometrial remodeling: induce endometrial lining to form a wave-like structure, and regulate the arrangement of uterine glandular epithelial cells and myometrial fibroblasts by regulating the endometrial gland. Endometrial remodelling: induces the endometrium to form a wave-like structure, and increases the density of glands and the distribution of blood vessels by regulating the arrangement of epithelial cells and the direction of myometrial fibres; (3) Reproductive function enhancement: clinical data have shown that it can increase the pregnancy rate and the average number of embryos implanted; (4) Molecular mechanism: by regulating the function of hypothalamus-pituitary-ovary axis, activating the PI3K/AKT/FOXO3a signaling pathway, modulating the TGF- $\beta$ 1/Smads signaling, upregulating the levels of serum oestradiol (E2), progesterone (P) levels, and promotes uterine tissue leukemia inhibitory factor (LIF), integrin  $\alpha\beta$ 3 protein and endometrial glycoprotein (glycodelin) mRNA expression.

The intervention mechanisms of Zhi Bai Di Huang Wan<sup>44–47</sup> include: (i) immune regulation: correcting the balance of Th1/Th2 cells; (ii) haemodynamic improvement: lowering the uterine arterial resistance index (RI) and pulsatility index (PI); (iii) enhancement of the reproductive system function: increasing the thickness of the uterine endometrium, optimizing the volume of the ovaries and the state of blood supply, and enhancing the rate of menstrual resumption, the rate of spontaneous pregnancy, and the success rate of assisted reproduction techniques; and (iv) endocrine regulation: effectively improving serum leukemia inhibiting factor (LIF) and integrin  $\alpha\beta$ 3 protein and glycodelin. Endocrine regulation: effectively improve serum follicle stimulating hormone (FSH), luteinising hormone (LH) and other hormone levels.

Dingkundan<sup>48–52</sup> works through a dual mechanism: (i) signalling pathway regulation: inhibiting the over-activation of PI3K/AKT/mTOR pathway; (ii) gene expression regulation: down-regulating the expression level of specific mRNA. Clinical data show that it can significantly improve the regularity of menstrual cycle, increase the number of eggs, the rate of quality eggs, the rate of fertilisation and the rate of natural pregnancy.

The effects of Kuntai capsule (Huanglian Ajiao Tang)<sup>53–73</sup> include: (1) neuroendocrine regulation: improve the ovarian reserve function through the homeostatic regulation of H-P-O axis; (2) apoptosis regulation: balance the Bcl-2/Bax protein ratio; (3) improvement of the reproductive outcome: significantly increase the level of E2 of single mature follicle in the day of HCG, increase the number of embryos that can be transplanted, and at the same time effectively alleviate the endocrine disorders related clinical symptoms.

Comprehensive analysis showed that traditional Chinese medicine compound treatment of DOR has multi-dimensional intervention advantages (Table 1), which are mainly reflected in: improvement of clinical symptoms; significant optimisation of reproductive endocrine regulation; enhancement of fertility and clinical pregnancy rate; and remodelling of the uterine microenvironment. The mechanism of action involves multiple biological processes such as signalling pathway regulation, gene expression modification, and apoptosis balance, reflecting the therapeutic characteristics of TCM holistic regulation. See Table 2.

## Self-Drafted Prescriptions for DOR

Self-designed prescription (also known as empirical prescription) is a special formula that is scientifically formulated by a Chinese medicine practitioner based on clinical experience and the theory of identification and treatment of Chinese medicine, selecting local herbs and determining the dosage through the four diagnostic consultations, and following the

**Table 2** Summary of Traditional Chinese Medicine Prescription Strategies for DOR

Typology	Prescription Name	Principles of Treatment	Indicator Efficacy	Mechanism of Action
Enriching and tonifying the liver and kidney	Liawei Dihuang Pills	Enriching and tonifying the liver and kidney	Improve serum hormone level, increase litter size and survival number.	Anti-oxidative stress, reducing inflammatory reaction and immune regulation.
	Zuogui Pills	Enriching and tonifying kidney yin, enriching and tonifying kidney essence	AFC↑, FSH↓, LH↓, FSH/LH↓, AMH↑, E2↓	Regulate TLR4/NF-κBp65 signal pathway.
	Yulin Zhu	Tonifying the kidney and fortifying the spleen, reinforcing yang, tonifying and replenishing marrow and essence, regulating and harmonizing qi and blood	FSH↓, FSH/LH↓, E2↑	Regulate PI3K/AKT related apoptosis signal pathway. Reverse the high expression of Caspase-3, Caspase-9, BAX, cytochrome c, PI3K and P-AKT.
	Yougui Pills	Warming and tonifying kidney yang, enriching and tonifying kidney essence	LH↓, FSH↓, E2↑, AFC↑	—
	Dingjing Decoction	Soothing the liver and tonifying the kidney, nourishing blood and regulating menstruation	AFC↑	—
	Yangjing Zhongyu Decoction	Tonifying the kidney, replenishing essence, replenishing essence	FSH↓, LH↓, E2↑, AMH↑	Regulate ovarian RNA-m6A modification. Regulate PI3K/AKT signal pathway.
	Guishen Pills	Tonifying the kidney and replenishing essence	FSH↓, LH↓, E2↑, AMH↑	Inhibition of autophagy in ovarian tissue: decrease the protein and mRNA levels of LC3 and Beclin I in ovarian tissue, and increase the protein and mRNA levels of p62.
Activating the blood and removing blood stasis	Xuefu Zhuyu Decoction	Activating the blood and resolving stasis, moving qi and unblocking meridians	FSH↓, FSH/LH↓	—
	Wenjing Decoction	Regulating and harmonizing qi and blood, nourishing blood and dispelling stasis	FSH↓, FSH/LH↓, LH↓, E2↑, AMH↑, AFC↑	—
Other	Danggui Shaoyao Powder	Nourishing the liver and harmonizing blood, fortifying the spleen and dispelling dampness	bFSH↓, bLH↓, E2↑, AFC↑	Adjust the HPO axis function. Regulate PI3K/AKT/FOXO3a signal pathway. Regulate TGF-β1/Smads signal pathway. Increase the expression of serum E2 and P and the expression of LIF, αvβ3 protein and glycodeilmRNA in uterine tissue.
	Zhibai Dihuang Pills	Enriching and tonifying the liver and kidney, clearing heat and purging fire	FSH↓, LH↓, E2↑, AMH↑	Adjust Th1/Th2 balance.
	Dingkun Dan	Tonifying the kidney and fortifying the spleen, tonifying and replenishing qi and blood, regulating menstruation, soothing the liver and regulating qi	Improve the number of eggs obtained, egg quality, fertilization rate and natural pregnancy rate. FSH↓, LH↓, AMH↑, E2↑	Regulate PI3K/AKT/mTOR signaling pathway: inhibits the phosphorylation level and mRNA expression of mTOR, AKT and PI3K.
	Kuntai Capsules (Huanglian Ejiao Decoction).	Enriching yin and downbearing fire, tranquilizing the spirit and Relieving vexation, enriching and tonifying the liver and kidney	FSH↓, LH↓, E2↑	Increase the expression of GDF9 and Egr-1; Up-regulating the expression of Bcl-2 protein and down-regulating the expression of Bax protein in ovary; Regulating Smad2/3/7 expression in ovarian tissue.

principle of the combination of the ruler, ministers and auxiliaries,<sup>74</sup> according to the characteristics of the patient's individualised symptoms. In the clinical treatment of early-onset ovarian insufficiency (DOR), the common self-proposed formulas are mainly based on the theory of “the kidney is the master of reproduction” and can be classified into four categories according to the core mechanism of action: tonifying the kidney to fill the essence, tonifying the kidney to nourish yin, tonifying the kidney to activate blood circulation, and tonifying the kidney to regulate menstruation, reflecting the Chinese medicine concept of treating the same disease with the same treatment for the same condition and treating the same disease with different treatment for different conditions.

## Replenishing the Kidney and Filling the Essence

In Chinese medicine theory, the therapy of replenishing the kidney and filling the essence, which is centred on the axis of “kidney essence - tianjie - chongren” as the core treatment for improving reproductive function, is mainly aimed at optimizing reproductive function by targeting and regulating the key signalling pathway of follicular development. Experimental studies have shown that the Rejuvenation Formula<sup>75,76</sup> significantly inhibited apoptosis and primary follicular atresia by activating the AKT signalling pathway, and improved the serum hormone level of the VCD-induced diminished ovarian reserve (DOR) rat model, while the Kidney Replenishing and Ovulation Promoting Formula<sup>77</sup> synergistically acted through the PI3K/AKT/mTOR, Bax/CytC/Caspases-3 and Nrf2/ARE multiple pathways. / ARE multi-pathway synergism, which not only improved the motility cycle disorder but also increased the ovarian/uterine index, increased the number of primordial follicles, sinus follicles and corpus luteum while decreasing the counts of secondary follicles and atretic follicles, and promoted the thickening of endometrial lining and the development of glands; Jikgui Yichong formula, through regulating the PI3K/AKT pathway, significantly regulated follicle number and distribution while improving the weight factor of the ovaries and the morphology of the tissues.<sup>78</sup> Kidney and Blood Formula focuses on activating the PI3K/AKT/mTOR signalling pathway to increase the number of mature follicles and the total number of follicles;<sup>56</sup> and Qi Zi Yi Ren Li Chong Tang effectively reduces granulosa cell apoptosis and protects the primordial follicular reserve while improving ovarian histological morphology and serum hormone levels through the transcriptional regulation of the PLA2G4A gene mediated by miRNA29-a.<sup>79</sup> Although these combinations have different targets, they all focus on regulating the dynamic balance of follicle survival and maturation, and ultimately achieve the overall improvement of ovarian reserve function.

## Kidney Tonifying and Yin Nourishing

In the system of kidney tonifying and essence filling therapy, which is based on nourishing yin and lowering fire in Chinese medicine theory, Purple Sophora formula significantly increased the number of follicles at all levels and luteal counts, and simultaneously reduced the proportion of atretic follicles and the percentage of TUNEL-positive ovarian cells by regulating the secretion of gonadotropins of hypothalamus-pituitary-ovary axis (HPOA) and inhibiting granulocyte apoptosis mediated by the PI3K/AKT pathway.<sup>80</sup> In addition, by regulating the PTEN/PI3K/AKT signalling pathway, Yi Kidney Meridian Regulating Formula can effectively improve the disorders of the estrous cycle, enhance the gonadotropic index, and increase the number of follicles at all levels of growth in the ovary;<sup>81</sup> and by regulating the function of the neuroendocrine system, Zi Gui Nian Zhen Capsules can improve the function of the ovary and the quality of the oocyte, and at the same time, significantly enhance the tolerance of the uterus lining and the proliferation of the activity.<sup>82</sup> Although the above prescriptions have different mechanisms of action, they all reflect the principle of nourishing yin and reducing fire, and achieve the reconstruction of the dynamic balance of hormone levels by regulating the function of the hypothalamic-pituitary-ovarian axis (HPOA), and synergistically improve the ovarian microenvironment and reproductive endocrine status.

## Nourishing the Kidney and Activating Blood

Based on the theory of “kidney deficiency and blood stasis”, Chinese medicine activates blood and removes blood stasis, which is an important means to regulate follicular development by improving ovarian microcirculation and antioxidant capacity. It was found that Baoqing granules significantly improved ovarian wet weight and index, increased the number of dominant follicles and granulosa cell layers, and simultaneously improved serum hormone levels by down-regulating the expression of Bax protein and up-regulating the expression of Bcl-2 and VEGF proteins;<sup>83</sup> He’s Nest Nourishing Formula effectively promoted follicular growth, increased the number of corpus luteum and ovulated eggs through the modulation of the ROS/JNK/p53 signalling pathway and optimized the serum hormone profile.<sup>84</sup> The He’s Nest Nourishing Formula effectively promotes follicular development, increases the number of corpus luteum and ovulatory oocytes, and optimises serum hormone profiles;<sup>84,85</sup> Zigui Wujing Capsules enhance endometrium-specific proliferative capacity through neuroendocrine regulation;<sup>78,82</sup> and Yulin Formula targets the downstream molecules of the wnt4 pathway to significantly enhance the quality and quantity of follicular development.<sup>86</sup> Although the intervention pathways of each formula are different, they all focus on improving ovarian blood flow and perfusion and apoptosis



regulation, restoring the microenvironment of follicular development through multi-target synergism, reflecting the integrative therapeutic feature of Chinese medicine “activating blood circulation and promoting collaterals, nourishing kidneys and nourishing the ovaries”.

## Kidney Tonic and Menstruation Regulator

Under the framework of TCM menstruation regulator and fertility promoter theory, the characteristic therapies aiming at restoring the reproductive endocrine rhythms are mainly embodied in the following: Kidney tonic and fertility promoter formula achieves the prevention and treatment of DOR through a dual regulating mechanism, which regulates the secretion of gonadal hormones of the hypothalamic-pituitary-ovarian-adrenal (HPOA) axis, and exerts a reproduction protective effect by protecting the granulosa cells of the ovary from the damage of the pyroptosis pathway;<sup>87</sup> Qi Yue tea, on the other hand, targeted the ovarian apoptosis regulation mechanism, by specifically reducing the expression level of pro-apoptotic factor Bax in ovarian tissues, significantly elevating the ovarian body mass index and anti-Müllerian hormone (AMH) values, and synchronously improving the balance of serum reproductive hormone profiles;<sup>88</sup> Kidney tonifying and blood-healing formula innovatively acted on the angiogenesis regulation system by promoting the secretion of vascular endothelial growth factor (VEGF) and its receptors, flt-1, kdc, flt-1, flt-1, flt-1, and kdc. By promoting the expression of vascular endothelial growth factor (VEGF) and its receptors, flt-1 and kdr protein, it enhances the ovarian blood supply, and at the same time, by regulating the dynamic balance of the Bcl-2 family of proteins (activation of anti-apoptotic Bcl-2/inhibition of pro-apoptotic Bax), it achieves the enhancement of the ovarian index and optimisation of serum hormone levels.<sup>89</sup> All of the above therapies are adhering to the essence of the theory of “meridian-blood homology”, and through the core intervention strategy of qi and blood harmonisation, they can systematically improve ovarian physiological function indexes and the coordination of endocrine rhythms.

In summary, Chinese medicine has developed the above four types of self-proposed formulas based on the theory of “the kidney is the master of reproduction” in the treatment of early-onset ovarian insufficiency (DOR). Although the target points of each type of formula are different (eg AKT pathway, ROS/JNK/p53 pathway, VEGF expression, etc.), they all embody the therapeutic characteristics of multi-target synergism, and through the regulation of follicular development, inhibition of apoptosis of granulosa cells, and improvement of the microenvironment of the ovary, they ultimately achieve the enhancement of the reserve function of the ovary, optimization of hormone levels, and repair of endometrial lining, which demonstrates the discriminative thinking of Chinese medicine and its advantage of holistic regulation of “treating different diseases together”. This demonstrates the advantages of TCM’s “treating different diseases at the same time” and holistic regulation. See [Table 3](#) for details.

## Acupuncture for DOR

Acupuncture therapy, as one of the common methods of external treatment in Chinese medicine, plays a unique role in regulating endocrine function, promoting ovulation, regulating immunity, improving ovarian reserve function and microenvironment and other gynecological disorders, and there are various dialectical methods of acupuncture treatment for DOR, including internal organs dialectics, meridian dialectics and menstrual cycle dialectics. On the basis of ordinary acupuncture, for the research and treatment of DOR, unique methods such as 13 needles for regulating menstruation and promoting pregnancy and acupuncture sequential therapy have been developed, and electro-acupuncture therapy has been formed by combining with modern science and technology in order to continuously develop the therapeutic means of acupuncture.

## General Acupuncture

Acupuncture has demonstrated significant effects in the treatment of DOR and IVF-ET. It was found that acupuncture on Guanyuan, Sanyinjiao, Sea of Blood, Taixi, and Baihui could improve the hormone levels and clinical symptoms of DOR patients, especially for patients with kidney deficiency and blood stasis type.<sup>90</sup> For patients with kidney deficiency and liver stasis type, acupuncture points such as Guanyuan, Uterus, and Sanyinjiao not only improved the clinical symptoms in TCM but also enhanced the ovarian reserve function indexes, including AMH level, AFC, ovarian size, and blood perfusion parameters.<sup>91</sup> During IVF-ET, acupuncture can increase

**Table 3** Summary of Self-drafted TCM Prescription Strategies for DOR

Typology	Prescription Name	Composition	Principles of treatment	Indicator efficacy	Mechanism of action
Tonifying kidney	Bushen Cuiuan Recipe	Tu-si-zi, Nv-zhen-zi, Gou-qi-zi, Sang-ji-sheng, Xu-duan, Niu-xi, Dang-gui, Chi-shao, Ze-lan	Tonifying the kidney and activating blood	FSH↓, FSH/LH↓, LH↓, AMH↑.	Regulate PI3K/AKT/mTOR, Bax/CytC/Caspases-3 and Nrf2/ARE signal pathway
	Qizi Yishen Lichong Decoction	Nv-zhen-zi, Gou-qi-zi, Tu-si-zi, Sha-yuan-zi, Fu-pen-zi, Sang-shen, Xiang-fu, Sang-ji-sheng, Xu-duan, Ba-ji-tian	Tonifying the kidney and replenishing essence	FSH ↓, AMH ↑, E2 ↑	Regulate miRNA29-a, and promote the transcription and translation of target gene PLA2G4A and mRNA degradation.
	Bushen Huoxue Recipe	Tu-si-zi, Bu-gu-zhi, Shan-zhu-yu, Shu-di-huang, Shan-yao, Dang-gui, Bai-shao, Shu-di-huang, Huang-qi, Yi-mu-cai, Dan-shen, Xiang-fu, Chuan-xiong	Tonifying the kidney and replenishing essence, nourishing blood and activating the blood	Increase the number of mature and total numbers.	Regulate PTEN/PI3K/AKT signal pathway.
	Yishen Tiaojing Recipe	Shu-di-huang, Dang-gui, Gui-jia, Shan-yao, Shan-zhu-yu, Rou-cong-rong, Xiang-fu, Dang-shen, Dan-shen, Huang-qi, Gou-qi-zi, Yin-yang-huo, Tu-si-zi, Ba-yue-zha	Tonifying the kidney and fortifying the spleen, soothing the liver and activating the blood	Increases gonadal index in rats.	Regulate PTEN/PI3K/AKT signal pathway.
	Bushen Cuyun Recipe	Hong-liao, Tu-fu-ling, Fu-ling, Gou-qi-zi, Sang-ye, Xuan-gou-zi, Rou-gui, Hui-xiang, Ding-xiang, Chen-pi	Tonifying and replenishing kidney qi	Improved morphology, indices, cycle, post-last growth and corpus luteum.	Gonadoids that regulate the HPOA axis and protect ovarian granulosa cells from scorching.
	Bushen Yiqi Hexue Recipe	Shu-di-huang, Tu-si-zi, Bu-gu-zhi, Gui-ban-jiao, Lu-jiao-jiao, Shan-zhu-yu, Shan-yao, Gou-qi, Dang-gui, Bai-shao, Chuan-qiong, Yi-mu-cai, Dang-shen, Huang-qi	Tonifying the kidney, replenishing qi, harmonizing blood	FSH↓, FSH/LH↓, E2↑, AMH↑	Promote the expression of VEGF and its receptors flt-1 and kdr proteins.
Other	Gengnanchun Recipe	Chai-hu, Dang-gui, Chuan-xiong	Soothing the liver and regulating qi, activating blood and nourishing blood, releasing depression.	AMH ↑, FSHR ↑	Activate AKT signaling pathway and reduce apoptosis.
	Zigui Yichong Recipe	Di-huang, Ye-xia-zhu, Shan-zhu-yu, Nv-zhen-zi, Gou-qi-zi, Huang-qi, Dang-shen, Bai-zhu, Dang-gui, Shao-yao, Xiang-fu, Gan-cao	Tonifying the kidney and replenishing essence, regulating and harmonizing the liver and spleen, regulating and harmonizing qi and blood	AMH ↑, E2 ↑.	Regulate PI3K/AKT signal pathway.
	Zihuai Recipe	Zi-he-che, Shan-yao, Tu-si-zi, Gou-qi-zi, Huang-qi, Dang-gui, Yin-yang-huo, Huang-qin, Hong-dou-shan, Xu-duan, Di-huang, Xiang-fu, Gan-cao	Tonifying the kidney and replenishing essence, soothing the liver and nourishing blood	Increase the number of growth at all levels and the number of corpus luteum. Number of atresia.	Regulate gonadal hormone of HPOA axis and inhibits apoptosis of granulosa cells mediated by PI3K/AKT.
	He's Yangchao Recipe	Shao-yao, Tu-si-zi, Rou-cong-rong, Dang-gui, Xuan-gou-zi, Ge-gen, Tian-dong, Ce-bai-ye	Tonifying and replenishing kidney qi, tonifying and replenishing blood and essence, emolliating the liver and replenishing the heart	INHB↑, E2↑, P↑.	Regulate ROS/JNK/p53 signal pathway.
	Zigui Nvzhen Capsule	Nv-zhen-zi, Dong-chong-xia-cao, Shu-di-huang, Xi-yang-shen, Dang-gui, Huang-qi, Shan-zhu-yu	Tonifying the kidney and soothing the liver	Improve ovarian function and oocyte quality. Improve endometrial characteristics and proliferation.	Regulate neuroendocrine system.
	Yulin Recipe	Tu-si-zi, Xian-ling-pi, Gou-qi-zi, Fu-pen-zi, Rou-cong-rong, Ba-ji-tian, Dang-gui, Chuan-xiong, Shu-di-huang, She-chuang-zi	Tonifying and replenishing blood and essence	Improve the quality and quantity of follicles.	Regulating the downstream of wnt4 pathway.
	Qiyue Tea	Gou-qi-zi, Yue-ji-hua	Tonifying the kidney and replenishing essence, soothing the liver and regulating qi, activating blood and nourishing blood	AMH ↑, FSH ↓.	Decrease the expression of apoptosis factor Bax in ovarian tissue.
	Baoqing Granules	Shu-di-huang, Shan-yao, Shan-zhu-yu, Tu-si-zi, Gou-qi-zi, Rou-cong-rong, Wu-wei-zi, Long-gu	Tonifying the kidney and replenishing essence, enriching yin and nourishing blood	FSH↓, LH↓, AMH↑, E2↑	Decrease the expression of Bax protein in ovarian tissue and enhance the expression of Bcl-2 and VEGF protein.

embryo implantation rates and improve pregnancy outcomes.<sup>92</sup> Further studies have shown that acupuncture can promote egg development in patients with DOR by affecting the expression of specific factors in follicular fluid, such as ICAM-1 and COX-2, thereby increasing the in vitro fertilisation rate and improving the outcome of IVF-ET.<sup>93</sup>

In addition, acupuncture therapy can effectively improve the symptoms and fertility indicators of patients with diminished ovarian reserve, as well as alleviate related gynaecological problems. Acupuncture on the ovaries, uterus, and tai chong can regulate the blood flow parameters of the ovaries and uterus, increase the number of basal sinus follicles and the volume of the ovaries, alleviate local symptoms, and promote the recovery of ovarian function.<sup>94</sup> Zhang Junxin<sup>95</sup> and others showed that acupuncture treatment given to patients with DOR can effectively improve patients' clinical symptoms in Chinese medicine, improve basal sex hormone levels and ovarian function, and have a high overall clinical effectiveness rate. Moreover, acupuncture can also effectively relieve dysmenorrhoea symptoms and reduce chocolate cyst masses in DOR patients.<sup>96</sup> For patients with infertility, especially due to DOR, acupuncture on both ventral and dorsal sets of acupoints has been shown to decrease FSH levels, increase the number of AFCs, elevate the level of AMH, reduce anxiety symptoms, and increase the number of available embryos in ovulation-promoting cycles with a good safety profile.<sup>97</sup>

As for basic animal research, acupuncture may inhibit NLRP3 mRNA expression through the Nrf2/HO-1 signalling pathway, thereby inhibiting the inflammatory response, which in turn restores the motility cycle in DOR model rats and effectively regulates rat sex hormone levels.<sup>98</sup> Acupuncture can also clear the inflammatory response of inflammatory factors to the thyroid and ovary by lowering the levels of IL-17A and IL-6 in rats in order to increase the levels of FSH, LH, GnRH, and AMH, repair ovarian tissues, and activate the ovarian reserve function.<sup>99</sup> In addition, Dong Wenjia<sup>100</sup> et al showed that acupuncture points such as Vital Gate, Guanyuan, and Ren Yu could increase bilateral ovarian weight, increase ovarian index, significantly reduce the number of atretic follicles, and improve ovarian reserve function in DOR rats.

Acupuncture effectively improves the symptoms and quality of life of patients with diminished ovarian reserve function by regulating the PI3K/AKT/mTOR signalling pathway, increasing the number of FSH receptors and adjusting the expression of anti-apoptotic and pro-apoptotic proteins,<sup>101</sup> and acupuncture treatment at specific acupoints such as Guanyuan and Sanyinjiao points showed good results and safety.

## Electroacupuncture

Electroacupuncture therapy is a kind of acupuncture method based on the needling of millimetre needles to obtain qi, applying electroacupuncture instrument to output pulsed current, and acting on the human body parts through millimetre needles to achieve the treatment of diseases.<sup>102</sup> Through combining, the research and treatment of DOR by electroacupuncture therapy mainly include: ordinary electroacupuncture, electroacupuncture with different timing, electroacupuncture cycle therapy, and electrical stimulation of transcutaneous acupoints.

Through the use of electroacupuncture acupoints of the liver meridian such as Taichong, Ligou, Ququan and Qiuquan and Qiuqin can effectively improve the clinical symptoms of patients with liver-depressed DOR regulate serum hormone levels, increase the AFC, and improve the ovarian blood supply.<sup>103</sup> Further studies also found that electroacupuncture could significantly improve the ovarian reserve function of rats by regulating the expression of FSHR \AMHR and its downstream PI3K/AKT/FOXO3a cell signalling pathway in ovarian tissues, which was mainly manifested as: increasing the number of sinusoidal follicles in the ovary, and improving the level of peripheral blood serum reproductive endocrine hormones and the ovarian mass index, and at the same time, it could also improve the growth retardation in the offspring of DOR rats.<sup>104</sup> Different timing of electroacupuncture can also produce different effects. Yu Shudan et al found that electroacupuncture of Zhongsiao/Tianshu in rats with ovarian damage before modelling may protect ovarian reserve function by inhibiting follicular development and stabilizing AMH gene transcription and protein expression.<sup>105</sup> In addition, electroacupuncture cycle therapy may also improve ovarian function and increase the number of eggs and high-quality embryos in IVF patients, thus increasing the HCG-positive rate, embryo implantation rate, and clinical pregnancy rate.<sup>106</sup> Qin Caifang et al also found that electroacupuncture cycle therapy not only promotes the growth of endometrial thickness but also reduces the resistance to blood flow in the uterine arteries, promotes the

transformation of the patient's endometrium to A-type, and improves the tolerance of the endometrium.<sup>107</sup> Transcutaneous electrical stimulation of acupuncture points can also increase the number of eggs acquired, the number of high-quality embryos, improve serum sex hormone levels, and further improve ovarian reserve function.<sup>108,109</sup>

## Thirteen Needles for Regulating Menstruation and Promoting Pregnancy

Thirteen needles for regulating menstruation and promoting pregnancy is also one of the commonly used needles in clinical practice, which has the effect of tranquilizing the mind, regulating Chong Ren and tonifying the kidney essence. Li et al found that the use of this needle method improved serum hormone levels, increased sinus follicle counts, menstrual conditions and anxiety symptoms of patients with DOR, and had a better safety profile.<sup>110</sup> Other studies have also found that the thirteen injections for regulating menstruation and promoting pregnancy can improve the number and quality of eggs and the number of available embryos, increase the number of AFC, and improve the pregnancy outcome of IVF-ET in patients with DOR.<sup>111–114</sup>

## Acupuncture Sequential Therapy

Acupuncture Sequential Therapy<sup>115</sup> is based on the reproductive physiological characteristics of different times of the menstrual cycle, based on the identification of the disease, combined with the identification of the evidence, and the cycle of using different acupuncture methods corresponding to that time. By treating DOR patients with acupuncture sequential therapy, the HCG day E2 value, AFC, the number of eggs obtained, the number of fertilised eggs, the number of high-quality embryos can be increased, and also the embryo implantation rate can be increased and the cycle cancellation rate can be reduced, so as to effectively improve the ovarian reserve function of DOR patients, and then to improve the clinical pregnancy rate of in vitro fertilization-embryo transfer.<sup>116</sup>

## Other Acupuncture Therapies

In addition, snap-needle and meridian row acupuncture belong to special other acupuncture therapies. Among them, snap-needle therapy is a method of fixing special small needles into the skin or subcutaneously for a longer period of time, and exerts its effect on the target organs by giving persistent and gentle benign stimulation to specific acupoints.<sup>117</sup> Shen Jie et al found that snap-needle therapy can effectively regulate serum sex hormone levels in patients with DOR, reduce AMH levels, and improve their clinical symptoms.<sup>118</sup> Puncture method is a modern medical practitioner in the ancient acupuncture method based on the combination of clinical practice created by the method of acupuncture, puncture method based on meridian identification, puncture along the blood vessels, puncture to the pain point as the centre of puncture or puncture of the compressed nerve pathway for treatment.<sup>119</sup> Tang Wenlong et al found that meridian puncture may improve clinical symptoms and menstrual cycles of DOR patients by regulating the function of the hypothalamic-pituitary-ovarian axis, improving serum hormone levels, and then improving ovarian reserve function.<sup>120</sup>

Taken together, acupuncture therapies have demonstrated significant effects in the treatment of DOR, and as a relatively safe and low-cost non-pharmacological treatment, they have demonstrated unique advantages in improving ovarian reserve function, hormone levels, assisting in fertility, and enhancing the quality of life of patients with DOR by regulating the signalling pathway, inhibiting apoptosis, and improving the blood supply to the ovary through a variety of mechanisms. In addition, these acupuncture methods provide diverse options for the treatment of DOR and demonstrate their potential for wide application in reproductive health. See [Table 4](#).

## Summary and Prospect

Traditional Chinese medicine (TCM) has demonstrated unique advantages and potentials in the treatment of ovarian reserve decline. Through evidence-based treatment, traditional Chinese medicine (TCM) is able to achieve individualised holistic management of patients, with TCM, TCM compounds, acupuncture and therapies being used as adjuncts to IVF or hormonal therapies, intervening in the disease from multiple targets and pathways to further enhance the therapeutic effect (see [Figure 2](#) for details). Its core advantage is that it not only focuses on symptom relief but also on regulating the overall state of the body, improving serum hormone levels, improving the ovarian microenvironment, and delaying the decline of ovarian function. However, the application of TCM in the treatment of DOR still faces some challenges, such

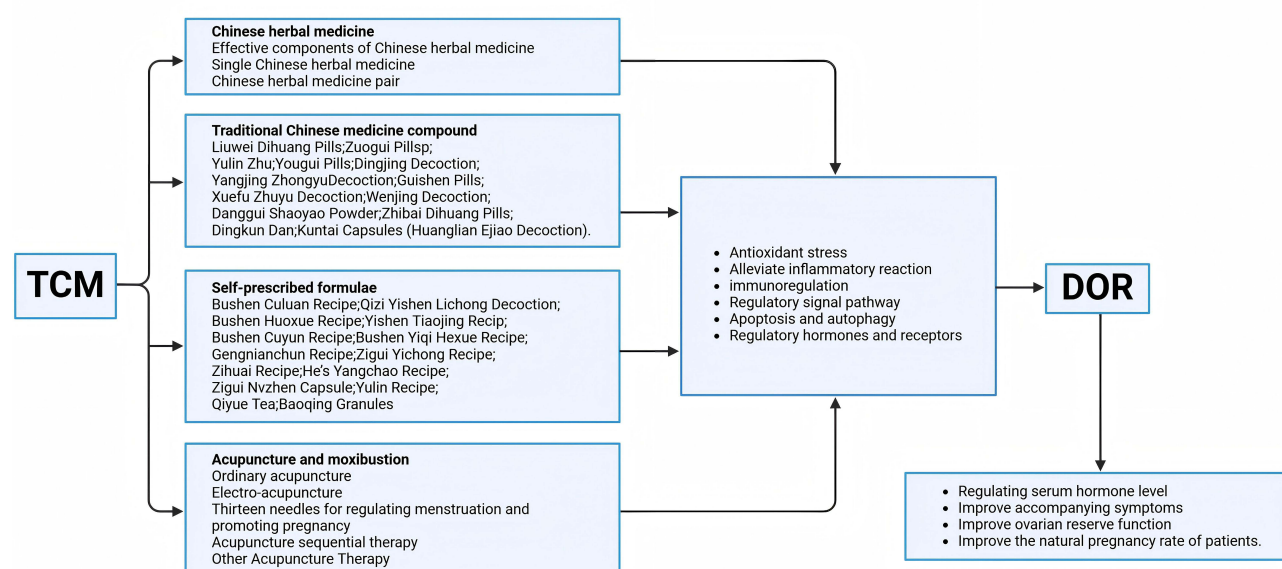
**Table 4** Summary of Acupuncture Intervention Strategies for DOR

Method	Acupuncture Point	Course of treatment	Principles of treatment	Indicator efficacy	Mechanism of action
Ordinary acupuncture	—	—	—	—	—
Electro-acupuncture	Tai-chong[LR3],Li-gou[LR5],Qu-quan[LR8],Ji-mai[LR12],Shen-shu[BL23],Zhong-liao[BL33]	Continuous wave, frequency 2Hz, current 0.5~ 1.0 mA, 30 min each time, once every other day, 3 times a week; Frequency 2Hz, 35 ma, once a day, 30min each time, and intervention for 14 days.	Soothing the liver, tonifying the kidney	Improve ovarian mass index. FSH↓, AMH↑, AFC↑	Regulate FSHR/AMHR and PI3K/AKT/FOXO3a cell signaling pathway downstream.
Thirteen needles for regulating menstruation and promoting pregnancy	A:Bai-hui[DU20],Shen-ting[DU24], Ben-shen[BG13],Zhong-wan[RN12],Tian-shu[ST25],Guan-yuan[RN4],Da-he[KI12],Zi-gong[EX-CA1],Zu-san-li[ST36],San-yin-jiao[SP6],Tai-xi[KI3].B:Tai-xi[KI3],Ci-liao[BL32].The two acupoint groups are used alternately. The operation sequence is head, abdomen, lower limbs and back.	30min sessions, once every other day,Group a and group b alternate,12 times per month, for a total of 3 months.	Tonifying the kidney and replenishing essence, regulating thoroughfare vessel and conception vessel, tranquilizing spirit to calm mind	Improve the number and quality of eggs and the number of available embryos. FSH↓, FSH/LH, E2, AFC↑	—
Acupuncture sequential therapy	Premenstrual period:Tai-chong [LR3],Yang-ling-quan[GB34],Guan-yuan[RN4],Qi-hai[N6].Late menstruation:Ge-shu[BL17],Tai-xi [KI3],Shen-shu[BL23],San-yin-jiao [SP6].Period of ovulation:Fu-liu [KI7],Zu-san-li[ST36],Zi-gong[EX-CA1],Guan-yuan[RN4],Qi-hai [RN6].Menstrual period:Shi-qi-zhui [EX-B7],Ming-men[DU4].	30min sessions,Once every two days,2 times per week.	Warming and unblocking meridians and vessels, regulating and harmonizing qi and blood	Improve egg quality, improve ovarian response, embryo implantation rate and clinical pregnancy rate of IVF-ET. Improve the number of eggs, fertilization and high-quality embryos. HCG day E2↑, AFC↑	—
Other acupuncture therapy	Pressing acupuncture therapy: Guan-yuan[RN4],Shen-shu[BL23], San-yin-jiao[SP6].	Take it off after 24 hours, once every other day, and intervene for 3 menstrual cycles.	Tonifying the kidney and resolving stasis, soothing the liver and fortifying the spleen	FSH↓, FSH/LH↓, AMH↑	—
	Expelling acupuncture from meridians: Ren meridian, Kidney meridian, Spleen meridian and Bladder meridian.	10 days is a course of treatment, with a total of 6 courses of treatment.	Tonifying the kidney and replenishing essence.	FSH↓, LH↓	Meridian needling: regulate the function of HPO axis

as the uncertainty of efficacy, the mechanism of action that has not been fully elucidated, and the lack of evidence support from large-scale, high-quality clinical trials. In addition, the complex composition of TCM complexes and their effects on multiple signalling pathways still need to be further explored. Future studies should focus on revealing the mechanism of action of TCM in treating DOR, especially its effects on various aspects such as PI3K/AKT/mTOR, hypothalamic-pituitary-ovarian axis (HPO axis), ovarian microcirculation, anti-oxidative stress, and immunomodulation. Meanwhile, high-quality, multicentre randomised controlled trials need to be promoted to assess the effectiveness and safety of TCM for DOR from a scientific perspective and to establish an evidence-based medical evidence system. In addition, combined Chinese and Western medicine therapy has shown unique potential and value in the treatment of DOR disease. By combining the holistic concepts and principles of evidence-based treatment in TCM with the precise diagnostic and therapeutic methods of modern medicine, TCM can not only effectively intervene for the specific etiology of DOR but also improve the systemic condition of patients to a certain degree and enhance the quality of life. The combination of TCM and modern medicine should be strengthened to explore the potential advantages of the synergistic treatment of DOR with Chinese and Western medicine, especially in improving fertility outcomes and delaying ovarian function decline. Moreover, emphasis should be placed on promoting the standardisation of TCM, including the whole process quality control of herbal medicines, standardisation of acupuncture protocols, and standardisation of evidence-based



## Flowchart of treating DOR with TCM



**Figure 2** Shows that traditional Chinese medicine can improve the hormone level and ovarian function of DOR patients and improve the natural pregnancy rate through the mechanisms of anti-oxidation, immune regulation and signal pathway regulation through acupuncture, traditional Chinese medicine compound and active ingredients of single traditional Chinese medicine.

treatment, as well as in-depth analyses of the mechanism of action of TCM compounding with the help of modern research tools such as cyberpharmacology, histological techniques and artificial intelligence, in order to provide a strong support for the modernisation and internationalisation of TCM.

Although TCM faces many challenges in the treatment of DOR, its concepts of holistic management, multi-target intervention and personalised treatment provide new treatment ideas for DOR patients. In the future, it is expected to further explore the potential of TCM in the treatment of DOR and provide patients with safer and more effective treatment options, as well as laying a scientific foundation for the recognition and application of TCM worldwide.

## Abbreviations

TCM, Traditional Chinese medicine; AFC, Antral Follicle Count; FSH, Follicle-Stimulating Hormone; bFSH, Basal Follicle-Stimulating Hormone; LH, Luteinizing Hormone; AMH, Anti-Müllerian Hormone; E2, Estradiol; FSHR, Follicle-Stimulating Hormone Receptor; INHB, Inhibin B.

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## Disclosure

The authors report no conflicts of interest in this work.

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