

Case Report

Traditional Chinese medicine combined with acupuncture improved diminished ovarian reserve

Lin Su^{1*}, Hai Xu^{2*}, Qing Tong³, Zhe Jin³, Hongmei Liu¹, Yunbo Li⁴

¹Rehabilitation Hospital, National Research Center for Rehabilitation Technical Aids, Beijing 100176, P. R. China;

²Department of Obstetrics and Gynecology, Huangjiahu Hospital, Hubei University of Chinese Medicine, Wuhan 430065, P. R. China; ³The Eastern Hospital of Beijing University of TCM, Beijing 100086, P. R. China; ⁴Gynecological Clinic, Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, P. R. China. *Co-first authors.

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Abstract: This study reported a 35-year-old female case with DOR was referred to this study and had a 3-year history of infertility. This case had failed three times to be pregnant by the treatment of multiple clomid cycles and IVF. Then, she came to the clinic in The Third Affiliated Hospital of Beijing traditional Chinese medicine University for seeking the TCM therapy. The Traditional Chinese Medicine (TCM) treatment-Chinese herbs combined with acupuncture lasted from April 2014 to July 2014. The main outcome was the improvement of the patient's reproductive hormone panel, including FSH level, estradiol level, and AFC amount; in addition a pregnancy outcome was desired. After receiving the 3-month TCM treatment, the patient had great improvement in her reproductive hormone panel, the level of FSH was decreased from 12.3 mIU/mL to 6.7 mIU/mL and the amount of AFC was improved from 1-2 to 6-8 total. When she returned to receive the treatment of IVF auxiliary fertility technology, she was successfully pregnant. The therapy of Chinese medicine combined with acupuncture was effective and practicable in IVF auxiliary fertility.

Keywords: Infertility, diminished ovarian reserve, acupuncture, chinese medicine, the therapy of nourishing the kidney and dredging the stagnation of liver

Introduction

Infertility, caused by diminished ovarian reserve (DOR), was mainly resulted from the endocrinological imbalance. There are some typical manifestations, including follicle stimulating hormone (FSH) rising and antral follicle count (AFC) decreasing for women under 40-year-old, pregnancy ratio under 5%, miscarriage ratio beyond 75%. For those infertility females, the IVF-ET technology is quite promising [1,2]. However, the success rate is still low, and the ovarian reserve function sharply diminished caused by excessively stimulating ovarian for repeatedly inducing ovarian and transplanting embryo. Compared with the IVF-ET technology, Chinese medicine and acupuncture display following advantages: improving the level of FSH and the amount of antral follicle, elevating the ratio of pregnancy, and decreasing miscarriage ratio. Now, more and more females with DOR accepted the treatment of Chinese medicine and

Acupuncture as the first choice of IVF auxiliary fertility technology.

The diagnosis of female infertility was based on the following criterias: woman had no conception for 1 year when she was under 35-year-old and woman had no conception for 6 months when she was 35 or beyond 35-year-old. In general, such woman firstly turned to assisted conception before they came to fertility specialists. The most common solution from gynecologist is to induce ovulation with drug followed by *in vitro* fertilization. Clomid, the medicine used to induce ovulation, should be taken once a day for 5 days. It is the fifth day of the menstrual cycle to start taking clomid. Clomid is thought as a selective estrogen-receptor modulator, but its mechanism of action is not completely understood. It can block the E₂ receptor in the hypothalamus, then the releasing of gonadotropin-releasing hormone (GnRH) is triggered to signal the anterior pituitary to release FSH. The

increased FSH in circulation will signal one or more follicles in ovaries to mature [3-5].

It has more than 2000 years history that the Traditional Chinese medicine and the acupuncture had been applied for the treatment of female infertility in China. Recently, studies indicated that the acupuncture can improve the outcome of assisted reproductive technology [6]. There is no descriptions for DOR disease in the Traditional Chinese medicine. However, the reproductive life-cycle has been elaborately described more than 2000 years ago in *Huang Di Nei Jing (The Yellow Emperor's Canon of Internal of Medicine)*, a classical medicine ancient text in China, in a close pattern of modern biomedicine. In the ancient text, a natural shift in female fertility had been defined as 7-year interval, which is close to what is cited in current biomedical literatures [7].

In Chapter 1 of the *Huang di Nei Jing*, there are two key opinions on the reproductive lifecycle: the kidney was thought as the governor of reproduction and reproductive potential was described with 7-year interval. The fertility of 28-year-old was defined as "apex" and entered the beginning of the vacuity shift. This is quite close to the result drawn from the biomedical statistics observation, and there is only one year difference in their predicted age of the beginning of the subtle decline of ovarian reserve. In *Fu Qingzhu Gynecology work*, another gynecology publication, the female with DOR was suggested to be referred to woman with the menopause who is under 49-year-old.

In Traditional Chinese Medicine, the governing role of Kidney in reproduction is quite critical for health fertility. On clinic, females undergoing *in vitro* fertilization (IVF) were usually diagnosed as kidney pathologies by the Traditional Chinese Physician. In terms of the TCM theory, kidney had to endure some etiologic factors like repeated reproductive-medicine intervention, and in turn those factors would deplete kidney and ultimately had a negative impact on reproductive outcome [8]. Based on the theory of Traditional Chinese Medicine, some exogenous treatments, including multiple clomid cycles and IVF, can deplete kidney blood and yin, and exert the negative effect on the reproductive lifecycle.

This article reported a DOR case treated with the TCM therapy of nourishing the kidney and

dredging the stagnation of liver combined with acupuncture. This DOR case was very common in the infertility acupuncture specialty practice. Before they received the TCM treatment, they often had failed several times to be pregnant by many consecutive clomid cycles and IVF.

Case report

A 35-year-old woman with infertility caused by DOR came to the clinic to see a doctor in April 2014. The patient was 165 cm high and 60 kg weigh. She went through the menarche at 14-year-old. Her menstrual cycle was 23-24 days. The menstrual bleeding of her menstrual cycle lasted for 4 days in recent three months. The menstrual flow was moderate. At the beginning of her cycle, the menstrual blood was thin, fresh, and red or pale red. On the fourth day of her cycle, the menstrual blood tapered off and became watery and pale brown. There was no clot in her menstrual blood. The mild-to-moderate cramping often appeared during the 5 days before her menses or the first 2 days of the menstrual cycle. In addition, there were also other symptoms to occur during the 5 days before menses, including irritability, bloating, and breast tenderness. By determining with an ovulation-predictor kit, she was predicted to ovulate on CD 10 or 11. The cervical fluid, which naturally appears on the normal female, did not occur, and she had the manifestation of vaginal dryness or dyspareunia. She not only had a smoking history but also drank alcoholic beverage less than 7 times a week.

Three years ago, her left Fallopian tube had been cut off because of the Ectopic pregnancy. She had no family history of the premature menopause. In the fall of 2013, she received the treatment of three consecutive clomid cycles with IVF prescribed by a woman's health nurse-practitioner (NP). Finally, she was not pregnancy. At the end of 2013, her FSH level was 12.3 mIU/mL, and the AFC amount was 1-2 bilaterally. She took 100 mg of clomid every month and generally had 1 primary follicle during the ovulation. She was suggested to receive IVF by the NP one day. There was no information of her endometrial thickness during the insemination. Except for that she was told her ovaries small by the NP during the ultrasound examination, there was no other information. In her medical record, her Fallopian tubes had been recorded to be blockages, and her uterus

to be abnormal. For her husband, the result of the sperm analysis was normal, including sperm counting and motility. There was no available morphology information came from any morphology test.

This patient was pale complexion and soft-spoken. When she spoke her fertility challenge accompanied by a series of demeanor, she became weepy, desperate, and frustrated. She often felt fatigued and moderately-to-highly stressed. She often lay in lethargy and was difficult to wake up. Gas and bloating after meals; sugar cravings; daily bowel movements that were occasionally loose or became urgent and/or crampy with stress; mild-to-moderate anxiety that manifested as chest palpitations, chest tightness and, shortness of breath; thirst; nocturia once nightly; frequent urination; no night sweats except for taking clomid; dull, "achey" headaches every 2 weeks; occasional dizziness; and a neutral core body temperature with cold hands and feet. Her pulses, overall, were slow and deep. On her left side, the pulse was especially deep, soft, and weak in the *guan* and *chi* positions. On her right side, the pulse was soft and weak in the *chi* position. Her tongue was pale purple, swollen and wet.

Her TCM diagnosis were: 1) Kidney Yang and Essence (*Jing*) deficiency, as evidenced by her low energy; frequent urination; nocturia; and weak, deep, soft pulses (according to poor response to medications, small ovaries, and infertility also indicate this diagnosis), 2) Liver Qi stagnation, evidenced by frustration/irritability, breast tenderness, bloating, and premenstrual cramping.

Treatment

According to this patient's initial consultation, she was firstly recommended to have a 3-month break from any reproductive interventions. Secondly, she was suggested to have a full reproductive physical examination for her and her husband in the biomedical opinion, because of the failure of conception after three attempts with clomid. In order to know what her husband's sperm morphology was, the third suggestion was to evaluate male factors. The patient agreed with the first treatment plan and declined to follow the last two recommendations.

According to the cycle phases, the treatment of Chinese herb and Weekly acupuncture was tailored for her. The needles used were 0.20×30 mm, Spring type (DBC, Korea) on body points, and 0.16×15 mm, D-type (Red Seirin, Japan) needles without guide tubes on the ears. Chinese herbal medicine (Kaiser Pharmaceutical Co., Ltd., Taiwan) was administered from April through July, 2014. All point functions were determined according to *A Manual of Acupuncture*, and all herb functions were determined according to *Chinese Herbal Medicine: Formulas and Strategies, 2nd ed.*,¹⁶ unless otherwise noted. When selecting points for treatment, great emphasis was placed on changes in pulse quality when acupuncture points were palpated. If the pulse improved when the point was palpated, it was selected for that treatment. All points were needed to elicit De Qi with a lifting thrusting technique and manipulated with an even rotation technique.

Herbal formula. The Yi Jing Zi Gui Yin was administered by combined with the premixed granular formula. This formula was prescribed to Kidney-nourishing Dispersing depression of the liver therapy. Formula base included: Duzhong, Shudi, Tusizi, Chaihu, Baishao, Shanyao, Baizhu, Dangshen, Huangqi, Maidong, Suanzaoren. These Herb were refined into decoction and granules. The dosage was 10 g twice daily, dissolved in warm water to be taken on CD 5-24 only.

Acupuncture treatments

Follicular Phase (CD 5-11): During this phase, Yin and Blood become most abundant. The treatment goals were to benefit the Kidney, nourish Yin and Blood, circulate Qi and Blood, and calm the *Shen*. Acupuncture was performed twice per week, alternating front and back treatments, to support follicle maturation and nourish Yin and Blood. Acupuncture was performed on her ear and manually on other parts of her body.

Six to eight body points, with no more than five ear points, were selected. Points were selected based on the patient's pulse and presentation on the day of treatment. Acupuncture of the ear included points involving Endocrine, Uterus, FSH, *Shenmen*, Liver, Kidney, or Heart areas as follows: Guanyuan CV 4 (Infant's Palace)-to

Table 1. Index before and after treatment

Index	Pre-treatment	Post-treatment
FSH (mIU/ml)	12.3	8.7
AFC (biaterly)	1-2	16-18

address Yin, Essence, Qi, and Yang; regulate the Uterus; tonify the Kidney; and calm the Shen; *Sanyinjiao* SP 6-to nourish Blood, circulate Qi, and calm the Shen; *Qichong* ST 30-to promotes Kidney Essence, improves Middle Jiao function, and regulate Qi and Blood in the lower abdomen; *Zi Gong* M-CA-18-to raise and regulates Qi around uterus and ovaries; *Zusanli* St 36-to nourish the Blood and Qi; *Taixi* KI 3-to tonify the Kidney and benefit the Essence; *Taichong* LV 3-to circulate Qi; *Neiguan* PC 6-to calm the Shen, open the chest, harmonize the Stomach, and regulate the Blood; *Lieque* LU 7 and *Zhaohai* KI 6-*Ren Mai* confluent points.

Ovulation Phase (CD 12-17): In this Phase, Yin transforms to Yang through the assistance of the Qi dynamic in the ovulation phase. Treatment goals during this phase were to circulate Qi and Blood, nourish the Heart, calm the Shen, promote ovulation, and tonify the Kidney. Six to eight points selected from the following: *Zusanli* ST 36-to tonify Qi, which may promote ovulation indirectly by supporting the transition to Yang; *Hegu* LI 4/*Taichong* LR 3-to move Qi to promote release of eggs; *Guanyuan* CV 4-to regulate the Uterus, tonify the Kidney, and calm the Shen; *Neiguan* PC 6-to relax the cervix and calm the Shen.

Luteal Phase (CD 18-Onset of Menses): In this Phase, Yang becomes most abundant. The treatment goals were to benefit the Kidney, support Kidney Yang by nourishing Qi and the Blood, raise Qi, circulate Liver Qi, and calm the Shen. This case required Yang support, through supplementation for the Qi and Blood. *Baihui* GV 20-to raise Yang/Qi and clears the mind; *Sishenchong* M-HN-1, with *Baihui* GV 20-to calm the Shen; *Zusanli* ST 36-to support Qi (and treat nausea with *Neiguan* PC 6); *Fuliu* KI 7-to tonify Kidney Yang and regulate sweating; *Neiguan* PC 6-to calm the Shen and nourish the Blood.

Results

The case had been treated for 3 months with the treatment plan prescribed above, From the follow-up phone call with the patient, her FSH

level was reported to be 8.7 mIU/mL in July 2014 and her AFC amount was reported to be 8-9 on each side. Then, She was prescribed to take 100 mg of clomid during CD 5-9. She was instructed to return for an ultrasound examination on CD 12. The result of examining was that 1 primary follicle had been developed and its diameter was 20 mm. Her endometrium was 10 mm thickness and trilaminar. Based on these results of examination, she was injected a human chorionic growth hormone (hCG) to trigger the ovulation and was instructed to come back for an IVF after 36 hours. She received the IUI on CD 14. And pregnancy result was gotten. Now, She has successfully conceived for 34 weeks (Tables 1-3).

Discussion

Based on the academic thoughts of Fu Qingzhu and combined with current pathological characteristic and surrounding, the therapy of nourishing the kidney and dredging the stagnation of liver was established. In the publication of *Fu Qingzhu Gynecology*, the female with DOR was suggested to be referred to woman with the menopause who is under 49-year-old, and it was considered that the menstrual was closely related with kidney, tiangui, Ren, du and viscera. In such environment, including life surrounding, natural and humanities environment, modern woman's mind was nervous and body was fatigue. More seriously, they often were suffered from emotional stimulation which was long-term and exceeded over the tolerance. The aforementioned situations would lead to the following outcomes, such as the imbalance of Yin and Yang, the disorder of Qi and Blood, the dysfunction of viscera, the insufficiency of kidney-Qi, the stagnation of Qi, and the stasis of meridians and collaterals. Its pathogenesis was the depletion of edema due to dysfunction of kidney and the failure of producing menstuous blood caused by the stagnation and retention of kidney meridian, which were resulted from the stagnation of liver and spleen and heart meridians, not the deficiency of liver-kidney. Based on the theory of meridians and collaterals, the pointer therapy was defined as the method which was to make meridians-collaterals, Zang-Fu organs, and Qi and blood dredging for achieving the therapeutic target by pushing the points. During the ovulation period and the

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Table 2. Chinese medicine symptoms, signs scale

Symptoms, signs	Coefficient	Degree			
		0	1	2	3
Menstrual cycle	4	Cycle regular 28-35 days	Menstruation in advance, cycle 21-27 days; menstrual delay, the cycle of 36-45 days menstrual delay	The cycle of 46-55 days after the delay	The cycle of 56 days or more
Menstrual volume, menstrual color	4	Normal	Menstrual volume for the previous 2/3, color dark red	Menstrual volume for the previous 1/2, color dark	Color dark menstrual vol- ume for the previous 1/3, color purple or light
Lumbar debility	2	No	Occasional	Intermittent appear	Sustain
Breast pain	2	No	Occasional	Intermittent appear	Sustain
Emotional depression or irritability	2	No	Occasional	Intermittent appear	Often affect the normal life
Dizziness and tinnitus	1	No	Occasional	Intermittent appear	Sustain
Heel pain	1	No	Occasional	Intermittent appear	Sustain
Sexual hypoactivity	1	No	Occasional	Intermittent appear	Often affect the normal life
Chest discomfort	1	No	Occasional	Intermittent appear	Sustain
Fatigue	1	No	Occasional	Intermittent appear	Sustain
Typical tongue and pulse	2	No	Low	Medium	High

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Table 3. Chinese medicine symptoms, signs score table

Symptoms, signs	Scores before treatment	Scores after treatment
Menstrual cycle	4	0
Menstrual volume, menstrual color	12	4
Lumbar debility	4	0
Breast pain	2	0
Emotional depression or irritability	4	0
Dizziness and tinnitus	2	1
Heel pain	3	0
Sexual hypoactivity	3	0
Chest discomfort	0	0
Fatigue	3	0
Typical tongue and pulse	4	0

post menstrual period, such points pushing could enhance the effect of Chinese herb on dredging stagnation and smoothing collaterals. If liver and spleen were smooth, heart and kidney were harmonious, the edema due to dysfunction of kidney was plenty, and the uterus was sufficient, the pregnancy would form.

In theory, the 3-month TCM treatment can improve reproductive outcomes as for the further biomedical interventions [9]. The TCM treatment not only can make the folliculogenesis cycle normal, but also can decrease FSH level and increase AFC amount [10, 11, 8]. That is to say, the TCM treatment can increase the ovarian reserve. Then, she was so wellbeing that she could receive biomedical *in vitro* fertilization (IVF).

In TCM opinion, it was problematic for female's reproductive health to continued use clomid which might exhaust Yin and stagnate Qi. Patients, who are Yang Deficiency, will respond best to this medication, while those patients, who are Yin and/or Blood Deficiency, or Qi Stagnation (just as the case in this article) will respond quite poorly, or even have been shown many adverse-effects. Taking clomid for several consecutive months, the latter patient will have several results, such as further depleted Kidney, damaged Yin, and engendered Empty Fire. The above is just the response of the case in this study to repeated usage of clomid. In brief, the most common manifestations were the poor development of follicular and the increased night sweats. Favorable reproductive

outcomes in patients with DOR-even with pharmaceuticals and reproductive technology-are substantially lower than other populations with the infertility diagnosis.

TCM fertility specialists frequently treat those patients who had underwent several rounds of clomid- or would undergo- the round of clomid. It is important to recommend the second suggestion to them who had obviously failed to have conceived through medication intervention after finishing three using cycles of clomid. In addition, it is a challenge that the Chinese herbal therapy was

used as an adjuvant of clomid, because Chinese herbs might promote clomid interventions.

Of course, another result is that the pregnancy still does not appear for those patients who took the additional three cycles of clomid after being treated for 3 months by the TCM therapy. However, their test results on the ovaries and the uterus, especially FSH level and follicle amount, had obviously been improved. More further research should be performed to investigate what and how acupuncture and Chinese herbs affect on ovarian physiology.

Conclusions

Clomid may not be ideal for all patients with DOR [12]. In this study, the patient had failed to have a pregnancy by three clomid cycles before she was treated with the 3-month treatment of TCM. At the end of the TCM treatment, her FSH level had been reduced and her AFC amount had been improved, which implies that her ovaries reserve have been greatly improved. However, she was still unable to conceive when she underwent another three cycles of clomid. It is an exception and very rare. Now, there is no more evidence to illustrate it. More further research should to be performed to discern which patient population would benefit best from several consecutive clomid intervention. In addition, ideal treatments for patients with DOR should be developed, including integrative treatment strategy combined with assisted reproductive techniques, acupuncture, and Chinese herbs.

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Disclosure of conflict of interest

None.

Address correspondence to: Yunbo Li, Gynecological Clinic, Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing 100029, P. R. China. Tel: +8618672779388; E-mail: yblll558@sina.com; Hongmei Liu, Rehabilitation Hospital, National Research Center for Rehabilitation Technical Aids, Beijing 100176, P. R. China. Tel: +8618672779388; E-mail: 930627227@qq.com

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