

Analysis of the Result of Korean Medicine Treatment for Female Subfertility Using Herbal Medicine, Acupuncture and Moxibustion Treatment

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Objectives: To report on the result of infertility treatment with Korean medicine in clinical settings.

Methods: This study was single arm, retrospective observational study. Analysis of the medical records on thirty four infertile women who were treated by acupuncture, moxibustion, herbal medicine(Jokjungjontang-gagambang, Sutaehwan-gagambang). Pregnancy rate(PR) and Live birth rate(LBR) were analyzed as the primary outcomes. Changes of AMH, FSH, LH, E₂, P₄, endometrial thickness, fat mass, and BMI were also analyzed as the secondary outcomes.

Results: A total of 34 patients were treated in the traditional Korean medical clinic. Nine patients were dropped, and 25 subjects completed the final examination at the end of this treatment schedule. Five of 25 subjects conceived during treatment, reaching 20% PR and LBR was also 20%. Except for FSH level, the results of the remaining outcome measures, including LFT, showed no significant changes. No serious adverse event has been reported.

Conclusion: Although no significant changes in bio-markers were observed, complex treatment using Korean medicine has shown effectiveness on women's infertility. In addition, the safety of the treatment has been verified.

Key Words : infertility, subfertility, pregnancy rate, acupuncture, herbal medicine, traditional Korean medicine

Introduction

South Korea is known as having one of the lowest birth rates in the world, and infertility has been thought to be an important factor causing the low birth rate. As this has become a social issue, the government has implemented policies to resolve it. The government reinforced economic support for infertile couples in taking assistant reproductive technology(ART) as a main program. This program has helped many infertile couples become pregnant;

however, the clinical pregnancy rate(PR) by this project only increased the success rate to around 30% per cycle. In addition, the ART program was associated with significant stress for infertile couples [1].

Traditional Korean medicine has a long history in treatment of infertility. The effect of Korean medicine has been verified not only in the traditional medical books [2-4], but also in recent studies [5,6]. Based on this supporting evidence and the medical environment, more than 70% of infertile couples

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visited traditional Korean medicine clinics [1]. Thus, we conducted retrospective study from our clinic data in order to overcome the limits of ART to help people suffering from infertility.

Herbal medicine Jokyungjongoktang-gagambang (JKJOT-GGB) and Sutaehwan-gagambang(STH-GGB), acupuncture, and moxibustion treatment were used in our clinic. JKJOT has been widely used in improving female infertility, especially that induced by stress [7]. Some studies have reported on the effect of JKJOT associated with immunological mechanism on stress, hormone changes, and ovulation [8-11]. STH is an herbal medicine used for prevention of miscarriage and some studies have reported that STH was effective for treatment of recurrent miscarriage, threatened abortion. The decoction worked as a positive influence on the maternal immune system for carrying on pregnancy [12-15].

Various studies on the relations between acupuncture and treatment of infertility have been reported. According to in vivo and clinical studies, acupuncture may regulate the function of the hypothalamic-pituitary-ovarian axis and change the concentration of neuropeptides such as β -endorphin, and also affect uterine blood flow and uterine motility [14]. Results of a meta-analysis study showed that acupuncture improved clinical PR and LBR among women undergoing IVF [5].

These evidence-based treatments have been well utilized in traditional Korean clinics. We provided infertile patients with complex and effective treatments.

Materials and Methods

1. Study design and participants

This study was conducted from the medical records of the infertile female patients who had visited at Dongguk University Ilsan Korean medicine

hospital(DUIH) between July 2011 and June 2012.

The inclusion criteria were as follows: women unsuccessful at conceiving for more than one year, even after many attempts to become pregnant; women diagnosed with unexplained infertility or ovulation related infertility from an infertility clinic; women who had intercourse with reasonable frequency at least twice or more per week, except during the menstrual period; women who approved of sharing the results.

The exclusion criteria were as follows: women who did not maintain the treatment with acupuncture and herbs for the duration of six months; taking medication for infertility, like hormonal drugs; diagnosed with polycystic ovarian syndrome(PCOS); male infertility; taking psychiatric medications.

Patients' visiting schedule was set by their own menstrual cycle day (MCD). Each patient visited the hospital four times per menstrual cycle, at MCD3, 8, 14, and 21. Assessments were performed and treatments were administered during six cycles, thus, each patient made a total of 24 hospital visits.

Each patient visited the hospital on MCD3 for the screening. Patients received acupuncture with moxibustion treatment and JKJOT-GGB was given on sight (MCD3). Blood chemistry test was performed for observation of changes of FSH, LH, estrogen, AMH, and LFT. BMI, fat mass, and endometrial thickness were also measured on the first visit.

Acupuncture and moxibustion treatments were administered on the first, second, and third visit (MCD 3, 8, and 14). On the third visit(MCD14), patients received STH-GGB and sonogram was performed for measurement of endometrial thickness (SA8000, SoNOAce PICO, Samsung medison, Korea). On the fourth visit(MCD21), blood chemistry test was performed for measurement of the progesterone level.

All the patients agreed with providing their medical information for this study. And information

of patients was used solely for the purposes of this study. This protocol was approved by DUIH IRB (2014-03)

2. Treatments

1) Herbal medicine

Both herbal medicines, JKJOT-GGB and STH-GGB, were purchased from Dongguk University Ilsan Korean medicine hospital. Participants took JKJOT-GGB for 10 days and STH-GGB for 15 days, twice per day. Each extract was prepared by decocting the dried prescription with water. The contents of the decoction are as follows.

JKJOT-GGB consists of 15 herbs; roots of *Rehmannia glutinosa*(GAERTNER) LIBOSCH (Scrophulariaceae) (12g), rhizomes of *Cyperus rotundus* L.(Cyperaceae) (12g), roots of *Angelica gigas* NAKAI(Umbelliferae) (8g), fruits of *Evodia rutaecarpa* BENTH(Rutaceae) (6g), rhizomes of *Cnidium officinale* MAKINO(Umbelliferae) (6g), roots of *Paeonia lactiflora* PALL.(Ranunculaceae) (8g), *Sclerotia* of *Poriacocos*(SCHW.) WOLF (Polyporaceae) (8g), fruit skins of *Citrus unshiu* MARKOVICH(Rutaceae) (6g), tubers of *Corydalis turtschaninovii* BESS(Papaveraceae) (6g), cortexes of *Paeonia suffruticosa* ANDREWS(Ranunculaceae) (4g), dried rhizomes of *Zingiber officinale* ROSC. (Zingiberaceae) (4g), cortexes of *Cinnamomum cassia* PRESL(Lauraceae) (4g), leaves of *Artemisia vulgaris* L.(Compositae) (6g), velvet antler of *Cervus nippon* TEMMINCK.(Cervidae) (8g), rhizomes of *Zingiber officinale* ROSC.(Zingiberaceae) (3g).

STH-GGB consists of six herbs; fruits of *Cuscuta chinensis* LAM.(Convolvulaceae) (12g), rhizomes of *Dioscorea japonica* THUNB.(Dioscoreaceae) (24g), roots of *Dipsacusaasper* WALL. (Dipsacaceae) (8g), roots of *Astragalus membranaceus* BUNGE (Leguminosae) (8g), roots of *Angelica gigas* NAKAI(Umbelliferae) (4g), roots of *Panax ginseng* C.A. MEY.(Araliaceae) (3g).

2) Acupuncture and moxibustion

Two doctors of Korean medicine administered all treatments. Both were qualified by the Korean ministry of health and welfare; one has had more than 20 years of clinical experience and the other has had more than two years of clinical experience. All patients were treated in the supine position and received acupuncture and moxibustion treatments three times during each cycle.

For the acupuncture treatment, 10 points were used, based on the traditional and contemporary literature reviews and consensus of doctors of Korean medicine who are experts in women's health(Table 1). Sterile disposable 0.25 x 40mm needles(Dongbang Acupuncture Inc., Korea) were used, and the retention time was 20±3min per treatment. Depths of needling varied from 5 to 30mm depending on the acupoints. The doctor manipulated the needles until the participant felt deqi sensation and electro-acupuncture stimulation was set to a continuous wave at 2Hz, which was applied on two sets, SP6 at one end and SP9 at the other as one set and M-CA-18 and N-CA-4 as another set. During acupuncture treatment, TDP(Teding diancibo Pu) was applied on the lower abdomen and participants were allowed to speak freely with doctors regarding their symptoms and conditions.

For the moxibustion treatment, Charcoal moxa (Dongbang Acupuncture Inc., Korea) was applied on

Table 1. Acupuncture Points of the Project

international number (WHO)	detail	Additional stimulation
GV20	unilateral	
CV4	unilateral	
SP6	bilateral	electro acupuncture
SP9	bilateral	(SP6-SP9, bilateral)
M-CA-18 [*] (Extra point)	bilateral	electro acupuncture
N-CA-4 [†] (Extra point)	bilateral	(Zigong-Tituo, bilateral)

(*JaGung: Its literal meaning is "uterus". On the lower abdomen, 4cun(≈6-8cm) below the center of the umbilicus and 3cun(≈4.5-6cm) lateral to CV3. †JeTak: Its literal meaning is "lift and support". 4cun(≈6-8cm) lateral to the anterior midline and 2cun(≈3-4cm) superior to the upper border of the pubic symphysis.)

the CV4 acupoint for 15mins per treatment, immediately after acupuncture treatment.

3. Outcomes

PR within the six menstrual cycle period and LBR were set as the primary outcome measures. The secondary outcome measure was the changes of hormone levels in FSH, LH, estrogen, and AMH. Hormone levels were checked during the first and sixth menstrual cycle periods. BMI, fat mass, and endometrial thickness were also measured during the same menstrual cycle periods.

4. Statistical method

SAS statistical package version 9.1 was used. Paired t-test was used for continuous variables. Differences of $P < 0.05$ were considered significant.

Results

1. Participant flow

Thirty four women were treated for infertility in our clinic. Nine women were excluded due to PCOS, spouse factor, drop out of the treatment schedule, resulting in 25 participants were analyzed. Data on blood chemistry test and LFT of five pregnant women were not acquired, thus, the analysis was performed using data from 20 women who failed to

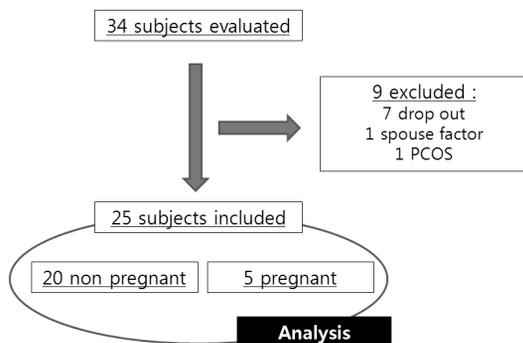


Fig. 1. Flow chart of Patients Disposition

conceive(Figure 1).

2. Baseline data

Baseline characteristics are shown in Table 2. Most patients, except for one patient, had undergone other types of treatment for infertility.

Table 2. General and Gynecological Characteristics of Participants

	n	M(SD)
General characteristics		
Age, yr	25	33(2.18)
Height, cm	25	162.12(4.26)
Body weight, kg	25	56.44(13.37)
Body fat, %	25	30.2(6.6)
BMI, kg/m ²	25	21.42(4.39)
Gynecological characteristics		
Duration of trying pregnancy, number.	25	41.36(24.98)
Duration of treatment, month	25	17.93(16.86)
Age of menarche, year	25	13.28(1.14)
Amount of menstruation, pad	25	17.88(6.48)
Duration of menstruation, day	25	4.96(1.4)
Menstrual cycle, day	25	29.36(2.38)

3. Pregnancy rate

Five of 25 patients succeeded in conceiving and the PR per treatment of six cycles was 20% (5/25*100).

Two women conceived during cycle 1 and another three women conceived during the following cycles: 2, 3, and 6 (Table 3).

Table 3. PR and LBR

Pregnancy Time (menstrual cycle)	Number	PR(%)	LBR(%)
Cycle1	2		
Cycle2	1		
Cycle3	1		
Cycle6	1		
within 6 cycles	5/25	20	20

4. Live birth rate

All of five pregnancies succeeded to result in

birth and the LBR was 20% (5/25*100). (Table 3). There were three cases of spontaneous labor, and two cases of cesarean section.

5. Changes of hormone level, BMI, body fat mass and endometrial thickness

Changes in hormone levels between cycles 1 and 6 were not statistically significant, except FSH. No significant differences were observed in AMH ($P=0.9477$), LH ($P=0.1247$), Estrogen ($P=0.7775$), and Progesterone ($P=0.5876$), however, significant difference was observed in FSH ($P=0.0366$).

BMI and body fat mass during cycles 1 and 6 showed no significant difference. Endometrial thickness measures on MCD 3 and 14 also showed no significant difference after treatment. The results are shown in Table 4.

6. Adverse events

There were four mild adverse events; one complaint of heartburn, two complaints of constipation after taking herbal medicine, and one complaint of nausea after acupuncture treatment. However, no severe adverse event was observed. The changes of LFT

were not statistically significant (Table 4).

Discussion

Through this project, five participants conceived within six menstrual cycles. Therefore, the PR was 20% in six cycles of this project. In comparison with the result of the national supporting program for infertile couples in Korea (31.2% in 2007, 31.9% in 2008, and 30.2% in 2009), the PR of our program was lower than the PR of past programs [1]. However, in our program, there was a limitation in controlling the number of times the subject had intercourse twice or more per week, referring to another study. For example, one study reported that patients with infertility had significantly low scores in the desire and arousal domains and low frequency of intercourse and masturbation; and another study reported that depression, erectile dysfunction, and problems in sexual relationships were prevalent among male partners of infertile couples [16,17].

It is important to increase the PR, however, ultimately, increasing LBR is more important for infertile couples. In addition, in this project, as

Table 4. Changes of Secondary Outcomes

	Cycle 1, M(SD)	Cycle 2, M(SD)	n	P-value
Changes of hormone level				
AMH(ng/ml)	3.65(3.16)	3.61(2.54)	20	0.9477
FSH(mIU/ml)	7.49(2.7)	8.76(4.34)	20	0.0366*
LH(mIU/ml)	4.9(2.23)	7.16(6.17)	20	0.1247
Estradiol(pg/ml)	43.15(19.49)	42.07(19.21)	20	0.7775
Progesterone(ng/ml)	10.87(7.05)	9.84(6.08)	20	0.5876
Changes of endometrial thickness, fat mass and BMI				
Endometrial thickness, MCD3 (mm)	3.68(1.61)	2.87(1.39)	20	0.0535
Endometrial thickness, MCD14 (mm)	7.93(2.42)	8.07(1.54)	20	0.7851
Fat mass(%)	29.16(6.34)	29.31(7.32)	20	0.9094
BMI(kg/m ²)	21.49(4.88)	21.71(5.08)	20	0.0794
Changes of LFT				
AST(IU/L)	19.45(10.28)	20.7(9.56)	20	0.5407
ALT(IU/L)	13.55(13.16)	19.65(17.29)	20	0.0743
ALP(IU/L)	50.05(12.28)	49.25(13.7)	20	0.3979

STH-GGB was prescribed for implantation and prevention of miscarriage, comparison of BR would be more reasonable than PR. In this project, there was no occurrence of miscarriage, therefore, LBR was the same as PR, that is, 20% in six cycles of pregnancy. Compared to the result of ART, 21.3% in 2006, 22.8% in 2007, this result demonstrated the potential of Korean medicine in prevention of miscarriage [1].

To determine influential factors for possible pregnancy in the future, hormone test, BMI, body fat mass, and endometrial thickness measurement were performed for participants who failed to conceive. FSH level only showed a significant increase, but the rest showed no significant change. This result indicated that the treatments might not lead to decrease of ovarian reserve and increase of BMI.

On the other hand, considering the increase of FSH and decreasing tendency(not statistical) of AMH, it appeared that traditional Korean treatments could not prevent or slow the process of aging of ovarian function [18]. Thus, it is necessary to consider the age factor of women and the duration of treatment at the beginning of treatment planning.

During the six-month treatment period, there was no occurrence of hepatotoxicity by LFT or severe adverse events and only four mild adverse events were observed. Although the duration of treatment was extensive, the treatment was safe for the participants.

Due to small sample size, lack of comparable objective measurement, measurement errors due to differences of menstrual cycle, and exclusion of successfully conceived women's post examination data, there are limitations to interpreting the findings. Regardless of such limitations, through this project, we achieved significant results, with a PR of 20%, and a LBR of 20%(no miscarriage). We also proved the safety of herbal medical treatment via hepatotoxicity, maintaining ovarian reserve and BMI.

Conclusion

Although no significant changes were observed in endometrial thickness, hormone levels, except FSH, the complex treatments using Korean medicine, JKJOT-GGB, STH-GGB, acupuncture and moxibustion, have shown effectiveness in management of women's infertility, especially PR and LBR. In addition, the safety of the treatment has been verified. Further clinical research is needed in order to evaluate the efficacy more objectively.

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