



Effectiveness and safety of Korean medicine for treating women with unexplained infertility: A multi-center observational study

Su-Ji Choi^a, Dong-Il Kim^{a,*}, Sang Ho Yoon^b, Chi-Yeon Lim^c, Jin-Moo Lee^d, Chang-Min Choe^e

^a Department of Korean Obstetrics and Gynecology, Dongguk University Ilsan Hospital of Korean Medicine, Goyang, Republic of Korea

^b Department of Obstetrics and Gynecology, Dongguk University Ilsan Hospital, Goyang, Republic of Korea

^c Department of Biostatistics, School of Medicine, Dongguk University, Goyang, Republic of Korea

^d Department of Korean Gynecology, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

^e Department of Korean Gynecology, College of Korean Medicine, Wonkwang University, Iksan, Republic of Korea

ARTICLE INFO

Article history:

Received 13 November 2020

Revised 25 April 2021

Accepted 3 May 2021

Available online 30 May 2021

Keywords:

Acupuncture
Korean medicine
Herbal medicine
Infertility
Pregnancy rate

ABSTRACT

Background: This study was conducted to demonstrate the effectiveness and safety of herbal medicine and acupuncture treatment in unexplained infertile females.

Methods: One hundred patients were recruited from 3 Korean Medicine hospitals in Korea and they voluntarily signed informed consent agreements. Participants took the *Onkyeong-tang* (120cc) twice daily between menstrual cycle day (MCD) 3 and 12, and *herbal medicine for ovulation and implantation* (120cc) twice daily between MCD 13 and 28. They also received acupuncture and moxibustion treatment during 4 menstrual cycles. After the 4 menstrual cycle treatment period, there were 3 menstrual cycle observation periods. The primary outcome is signified by clinical pregnancy rates (CPR) and the secondary outcomes were implantation rates (IR), ongoing pregnancy rates (OPR), and live birth rates.

Results: 90 patients completed the study. 13 of the 90 subjects became pregnant. The CPR and IR was 14.44%. 7 of 13 pregnant subjects had continuing pregnancy for over 12 weeks, so that the OPR was 53.85%. The birth rate was 7.78%. All 7 pregnant patients gave birth to their babies and all the babies were live singletons and healthy. There were no serious adverse events.

Conclusions: The findings of this study may provide the possibility of effectiveness and safety of Korea medicine treatment for unexplained infertile women. Further study is required due to lack of control and small sample size in this study.

© 2021 Published by Elsevier B.V. on behalf of Korea Institute of Oriental Medicine.
This is an open access article under the CC BY-NC-ND license
(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

1. Introduction

Approximately 9–18% of normal couples are infertile, and about 15% of infertile patients are classified as unexplained infertility.^{1–3} Unexplained infertility is diagnosed when the basic infertility evaluation fails to reveal an obvious abnormality. The basic evaluation includes evaluation of ovulation, adequate sperm production and patency of the fallopian tubes. There are no standardized treatment of unexplained infertility yet. Lifestyle changes or timed intercourse, clomiphene citrate (CC), intrauterine insemination (IUI),

gonadotropin injections, in vitro fertilization (IVF) are suggested as treatments. The American Society for Reproductive Medicine recommended unexplained infertile couples to consider simple treatment before complex treatment and to balance what is known about effectiveness against cost and adverse effects of treatments.⁴

From 2017, ART has been covered by the national health insurance in Korea. From July 2019, the age limit for receiving support for infertility treatment expenses has also been removed. IVF tries are supported up to 12 times and artificial insemination 5 times.⁵ Although expenses for ART have greatly increased, the success rate of ART has remained constant during the last 10 years.^{6,7} Furthermore, there are concerns regarding the side effects associated with ART, such as ovarian hyper-stimulation syndrome (OHSS), preterm labor, premature birth, and low birth weight.^{8–10}

* Corresponding author at: Department of Korean Obstetrics and Gynecology, Dongguk University Ilsan Hospital of Korean Medicine, Goyang, Republic of Korea.
E-mail address: obgykdi@hanmail.net (D.-I. Kim).

In Korea, 71.6% of infertile couples receive Korean Medicine (KM)-based treatments.¹¹ This demand has resulted in local-government-level support programs, including financial assistance for infertile couples using Korean medicine. However, since there are no prospectively designed clinical trials confirming the effectiveness and safety of standard KM therapies for infertility. The lack of evidence also caused the weak trust of Western medicine researchers and government health policy managers in KM infertility treatment. Therefore, the aim of this trial is to investigate the potential effectiveness and safety of KM for unexplained infertility in women.

2. Methods

2.1. Study registration

This study was registered with the Korean Clinical Trial Registry (CRIS), Republic of Korea: KCT0002235. The trial protocol has been published and can be consulted for detailed information.¹²

2.2. Study design

This study was a single-arm, multi-center, before-and-after study conducted at 3 hospitals: Dongguk University Ilsan Korean Medicine Hospital, Kangdong Kyunghee Korean Medicine Hospital, and Wonkwang University Kwangju Korean Medicine Hospital.

The treatment protocol was designed by reflecting the clinical status and references of clinical practice guidelines and textbooks.^{13,14} After enrollment, participants visited 3 times per 1 menstrual cycle for 4 cycles of 'treatment periods'. After each treatment period, participants visited 1 time per 1 menstrual cycle for 3 cycles of 'observation period' (Supplement 1). If participants became pregnant during the study, they visited 4 more days, when they got positive pregnancy urine tests, 15 days for Intrauterine pregnancy (IUP), 12 weeks for IUP, and after delivery or miscarriage (Supplement 2).

2.3. Study population

Participants were recruited by advertisements on buses, subways, and bulletin boards at each medical center. The first participant enrolled on October 12, 2016, and the last participant on January 9, 2018. Signed informed consent forms were obtained from all patients before enrollment.

The eligible criteria for the study participants are detailed below.

2.3.1. Inclusion criteria

We included the participants according to following criteria: (1) female aged 20-44 years; (2) unexplained infertile female with a medical certification from a doctor of obstetrics-gynecology (including both primary and secondary infertility); (3) has sexual intercourse more than twice a week.

2.3.2. Exclusion criteria

We excluded the participants as following criteria: (1) unable to take herbal medicine, acupuncture, and moxibustion treatment during the 4 menstrual cycle treatment periods of this study; (2) unable to participate in this clinical trial for 7 months; (3) takes pregnancy-related medicine; (4) planning to undergo artificial insemination or In Vitro Fertilization (IVF); (5) has irregular menstruation, occurring at intervals of less than 21 days or more than 40 days; (6) male factor infertility; (7) has ovulation factor infertility; (8) has tubal or peritoneal or uterus factor infertility; (9) is diagnosed with dampness heat, kidney yin deficiency which means not appropriate for this trial's medication; (10) has taken IVF more

than 5 times; (11) has history of severe neuropsychological disease; (12) has other severe disease related to infertility (e.g., hypertension, diabetes, chronic/acute hepatitis, hyperlipidemia, cardiovascular disease, cancer, chronic/acute inflammatory disease, etc.); (13) has cancer history within past 5 years; (14) has a skin disease over an acupuncture/moxibustion point; (15) has an allergy or hypersensitivity to treatment (herbal medicine, acupuncture, moxibustion); (16) is planning to participate in another clinical trial within 3 months; (17) does not have the ability to fill out forms.

The exclusion criteria included the limit of the number of previous unsuccessful IVF treatments. Many studies found out the fecundity decreased significantly with increasing number of previous treatment cycles.¹⁵⁻¹⁷ The livebirth rate per treatment cycle fell down dramatically after 4 times of previous unsuccessful IVF cycle.^{16,17} We set this exclusion criteria (10) in this reason.

2.4. Interventions

The contents and durations of treatment and observation were determined according to opinions of experts working on Obstetrics and Gynecology practice of Korean medicine by referring to the guidelines.^{14,18}

2.4.1. Herbal medicine

All participants were treated for 4 menstrual cycles and underwent observation periods of 3 menstrual cycles. Based on their menstrual cycles, participants were administered the herbal medicine *Onkyeong-tang* and the *Prescription for Ovulation and Implantation (POI)*, twice daily, as follows: *Onkyeong-tang* between menstrual cycle day (MCD) 3 and 12, and *POI* between MCD 13 and 28. The detailed herbs in the prescriptions are listed in [Table 1](#). *Onkyeong-tang* is a popular prescription in Donggubogam that regulates the menstrual cycle and infertility.¹⁹ The *POI* was made by Dong-Il Kim on the basis of Yuklin-ju, Ontoyuklin-ju and Sutaehwan and has been patented for the promotion of implantation based on animal experimental research. These two prescriptions are representative infertility treatment prescriptions that are widely used in Korean medicine clinics with *Ongyeong-tang*, *Yukrinju*, and *Sue Tae-hwan*, which have been used for infertility treatment for a long time. They are prescriptions that have been used for more than 3 years and more than 200 cases, so we can assume the clinical effects and safety. They were used as interventions in this clinical study with the recommendation of the Korean Oriental Gynecological Association.

If the patient conceived during the treatment period, the *POI* was administered for 10 more days to stabilize the fetus ([Fig. 1](#)). All herbal medicines were manufactured by Jaseng-medical decoction facility, where there are semi-good manufacture practice (GMP) facilities and GMP herbs are used.

2.4.2. Acupuncture and moxibustion

All participants received acupuncture treatment for 20 minutes at 14 acupoints, GV20, CV4, bilateral Ex-CA7, ST29, SP6, SP9, ST36, and PC6, using acupuncture needles of 0.3mm diameter and 30mm length (DongBang, Gyeonggi-do, Korea). A group of experts working on Obstetrics and Gynecology practice of Korean medicine selected acupuncture points which promote pelvic blood flow, regulate menstruation and relieve stress based on textbooks and published references.¹¹ During the acupuncture treatment, electro stimulation was applied for maintaining the de-qi at low-continuous 2 Hz, indirect moxibustion using smokeless moxa cones (DongBang, Gyeonggi-do, Korea) applied on CV4, and infrared on the lower abdomen. All participating practitioners have had more than 1 year of clinical experience since completing 6 years of study majoring in Korean Medicine and have received Korean Medicine

Table 1
Contents of Onkyeong-tang and Prescription for ovulation and implantation.

Onkyeong-tang	Dose (g/day)	Prescription for Ovulation and Implantation	Dose (g/day)
Liriopsis tuber	16	Cuscutae semen	16
Angelica gigantis radix	12	Dioscorea rhizome	32
Ginseng radix	8	Rubi fructus	20
Pinelliar rhizome	8	Ginseng radix	8
Paeoniae lactiflorae radix	8	Lycii fructus	8
Chidii rhizome	8	Angelica gigantis radix	4
Moutan radidis cortex	8	Perillae folium	8
Gellatin	6	Amomi fructus	8
Achyranthis radix	6	Artemisiae argyi folium	8
Evodiae fructus	4	Zingiber officinale	6
Cinnamomum chingii	4	Zizyphi fructus	4
Zingiber officinale	12		
Total	100	Total	122

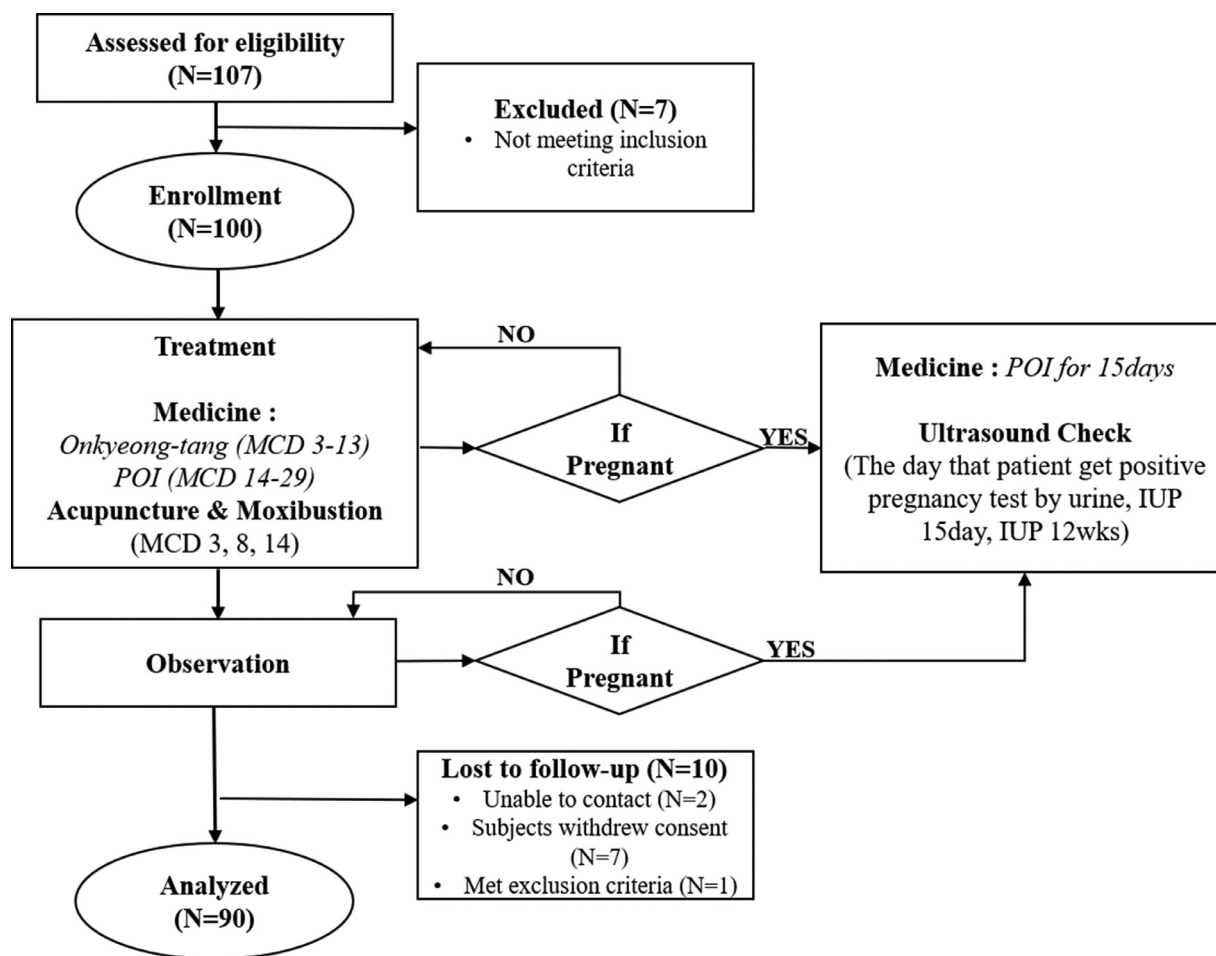


Fig. 1. Flow chart of study. MCD, Menstrual Cycle Day; POI, Prescription for Ovulation and Implantation.

Doctor licenses. Acupuncture and moxibustion therapy were performed on MCD 3, 8, and 14 during the 4 menstrual cycles. If the patient conceived during the treatment period, acupuncture and moxibustion therapy stopped.

2.5. Outcome measures

2.5.1. Primary outcomes

The primary outcome is shown as clinical pregnancy rates (CPR). Clinical pregnancy is considered to be at least 1 gestational sac with fetal heart rate confirmed by ultrasound, at 5–6 weeks of pregnancy. The CPR was calculated as the ratio of the number of

successful participants to clinical pregnancy to the total number of participants.

2.5.2. Secondary outcomes

- Implantation rates (IR)
- Ongoing pregnancy rates (OPR)
- Live birth rates
- Adverse events

Implantation is confirmed by at least 1 gestational sac after human chorionic gonadotropin positive. IR is calculated as the ratio of the number of participants who confirmed the implantation to the total number of participants.

Ongoing pregnancies are defined as the presence of fetal cardiac activity beyond 12 weeks of gestation. OPR is defined as the number of ongoing pregnancies divided by the number of clinical pregnancies.

Live birth is defined as the delivery of 1 or more living infant (have heart beats or have beats of umbilical cord or have definite movement of voluntary muscles). Live birth rates are calculated as the ratio of the number of participants who delivered and confirmed the live birth of infant to the total number of participants.

The occurrence of adverse events was monitored throughout the study. We monitored adverse events whether related to Korean medicine treatment or not, and we collected the TEAE (treatment-emergent adverse event). TEAE is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. Patients visiting the hospitals were asked about the presence of any adverse events or uncomfortable symptoms. Clinical laboratory tests were also performed before and after the treatment period.

2.6. Sample size calculation

The target sample size was 100 subjects. The sample size was determined by the experts considering that this pilot study is to explore the effectiveness and safety of KM infertility treatment. The sample size of this study was determined by Ministry of Health and Welfare and Korean Health Industry Development Institute in accordance with study budget, period, and purpose. Since there was no existing RCT research of Korean medicine treatment for unexplained infertility, the Korean national supporting project was selected as a reference in that the infertility treatment was conducted in the same environment in Korea and under the national control. Since age is a relatively manageable factor, age distribution of the population was designed similar to that of participants in the Korean national supporting project in 2012. This study recruited the target population accordingly.²⁰

2.7. Statistical methods

Statistical analysis was conducted using SAS program (version 9.4; SAS Institute Inc., Cary, NC) by an independent researcher who did not perform any process of intervention and outcome measure. The analysis for effectiveness evaluation was per-protocol group analysis in principle, and the analysis of the full analysis group was also performed. The per-protocol analysis included only those patients who had completed at least 80% of the treatment sessions and for whom there were no serious violations of the protocol. For safety assessments, we analyzed a safety group, which included all participants who had received at least one session treatment.

Descriptive analyses including the mean, standard deviation, and frequency were undertaken describing the baseline characteristics of participants. Continuous variables of primary and secondary outcomes were presented in descriptive statistics and categorical data will be presented in frequency and percentage. When comparing and analyzing the level of specific variables such as demographic variables, continuous data were tested using a Student's *t*-test or Wilcoxon's rank sum test. Categorical data were analyzed using a chi-squared test or Fisher's exact test. For before and after comparisons, the paired *t*-test or Wilcoxon's signed rank test were applied. ANOVA was used on repeated measures (e.g. menstrual condition), and McNemar's test performed on categorical data (e.g. presence of menstrual pain and premenstrual syndrome). All statistical analyses were conducted at a significance level of 0.05.

Table 2
Patient characteristics at baseline

Demographic characteristics (N = 90)	Value
	Mean ± SD
Age (yr)	35.91±3.7
Age of husband (yr)	38.12±4.10
Height (cm)	161.38±5.12
Weight (kg)	55.93±7.34
Duration of marriage (mo)	65.74±39.38
Duration of trying pregnancy (mo)	44.27±28.32
Frequency of sexual intercourse (per wk)	2.20±0.56
	N (%)
Experience of delivery	
Yes	16 (17.78)
No	74 (82.22)
Experience of abortion	
Yes	32 (35.56)
No	58 (64.44)
Alcohol intake	
Yes	34 (37.78)
No	56 (62.2)
Smoking status	
Non-smoker	89 (98.89)
Current smoker	1 (1.11)

3. Results

3.1. Patients' flow and baseline characteristics

A flow diagram of the overall study is provided in Fig. 2. A total of 100 patients were enrolled in the study: 44 at the Dongguk University Ilsan Korean Medicine Hospital, 37 at the Kangdong Kyunghee Korean Medicine Hospital, and 19 at the Wonkwang University Kwangju Korean Medicine Hospital. There were 10 dropouts, and the remaining 90 patients were included in the per protocol analyses. 90 subjects showed a good medication compliance of 97.96%. The baseline characteristics of the 90 patients are described in Table 2.

3.2. Outcome measures

3.2.1. Primary outcome

- Clinical pregnancy rate (CPR)

Pregnancy was achieved in 13 out of 90 subjects (CPR 14.44%). Additionally, 2 more participants got pregnant spontaneously after finishing the trial, but were not considered as an outcome of this trial (Fig. 2).

3.2.2. Secondary outcome

- Implantation rate (IR)

The IR achieved is about 14.44%. 13 of 90 subjects confirmed the gestational sac through ultrasound examination. There was one case of ectopic pregnancy.

- Ongoing pregnancy rate (OPR)

Out of 13 pregnant participants, 7 patients had continuing pregnancy of over 12 weeks. The OPR is about 53.85% (7 of 13 subjects). 6 patients miscarried.

- Live birth rate

All 7 pregnant patients gave birth to their babies and all the babies were live singletons. The live birth rate is about 7.78% (7 of 90 subjects).

3.3. Safety evaluation

Although 33 cases of TEAE (treatment-emergent adverse event) were reported, there were no serious adverse events (Table 3). No statistically significant changes were observed for clinical laboratory tests including liver function test, and for all vital signs before and after treatment (Supplement 3). There were statistically

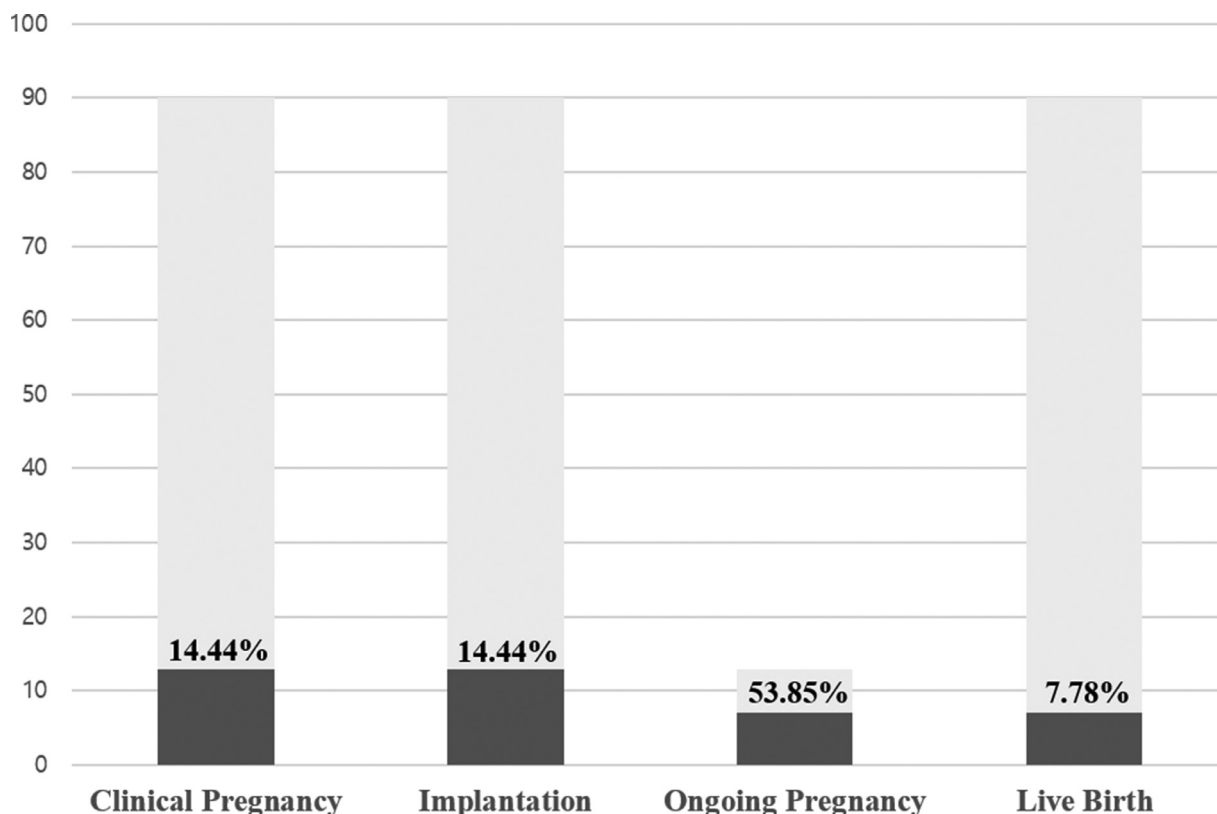


Fig. 2. Pregnancy Outcome (N = 90).

Table 3
Adverse Events (N = 100).

Classification	Diseases or Symptoms	Patients N	Events N
Dental Disease	Paradentitis	1	1
Respiratory Disease	Acute Bronchitis and Laryngitis	1	1
Disease	Influenza	4	4
	Common cold	10	10
Nervous Disease	Trigeminal Neuropathy	1	1
Musculoskeletal Disease	Headache	5	5
	Shoulder Pain	1	1
Disease	Cervical Disc Disease	1	1
	Diarrhea	2	2
Gastrointestinal Disease	Dyspepsia	1	2
	Vomiting	1	1
Urogenital Disease	Vaginitis	3	3
	Cystitis	3	3
Pregnancy Consequences of External Causes	Increasing the Size of Endometrial Polyp	1	1
	Abnormal Bleeding	1	1
	Ectopic Pregnancy	1	1
	Muscle Pain because of the Accident	2	2

significant changes in alanine aminotransferase, temperature and diastolic blood pressure, but they were changes within the normal range so that have no clinical significance. None of the children delivered presented congenital anomalies.

4. Discussion

4.1. Summary of the main results

Acupuncture and herbal medicine treatment is widely used in East Asian countries as a low cost and less invasive alternative to IVF for couples with unexplained infertility. There are some studies on effects of Korean medicine treatment (especially acupuncture) for infertile women.²¹⁻²³ However, there have been no previous prospective studies of Korean medicine single treatment on

unexplained infertile women. Therefore we designed this trial to confirm the effectiveness and safety of Korean medicine infertility treatment through controlled observational study.

In the process of designing the study, we standardized KM infertility treatment. As a result of study, 90 patients completed the study. The CPR was 14.44, IR was 14.44%, OPR was 53.85% and the birth rate was 7.78%. 13 of 90 patients got pregnant, and 7 pregnant patients gave birth to their babies. There were no serious adverse events.

4.2. Agreements and disagreements with other studies

We compared the result of this trial with the results of IUI (Intrauterine Insemination) from the latest report of Korean national supporting project for infertility couples in 2016.²⁴

The clinical pregnancy rate of IUI by the 2016 project for infertility supported by the Korean government was 13.9%, with the maximum cause of infertility in IUI cases being unexplained infertility (72.9% of total IUI cases). The clinical pregnancy rate of IUI in unexplained infertile couples was 13.6%.²⁴ In the case of patients who had experienced failed fertilization at IVF, the IUI success rate was 6.9% at the supporting project. In this study, the clinical pregnancy rate of unexplained infertile couples was 14.44% and the clinical pregnancy rate of whom had experienced failed IVF was 10.52% (4 of 38).

Since the success of pregnancy is affected by various factors, such as the age of couples, duration of infertility, use of medication, and treatment types and methods, the success rate is comparable only when these conditions are controlled.²⁵ Therefore, there is a limitation to the efficacy comparison in this simple result comparison.

4.3. Potential mechanism and implication for research

The significance of this study is that it is a prospective study of Korean medicine infertility treatment. This study is meaningful in that it standardized various KM infertility treatments and explored the effectiveness and safety for them. This trial showed the possibility of effectiveness and the safety of KM comprehensive treatment for unexplained infertility in women and the results could provide grounds for national policy projects.

Through this pilot study, we obtained the pregnancy rate of standard Korean traditional fertility treatment. Also we were able to identify additional advantages. In additional analyses, we found that the number of people complaining of menstrual pain and premenstrual syndrome significantly decreased after treatment. We also found value differences in AMH for specific groups before and after treatment. These findings show the possibility that KM infertility treatment improves reproductive health. It also shows the need for additional study on other biomarkers such as AMH, high quality of embryo rate, high quality of oocyte rate, endometrial thickness, which can be used as predictors for successful pregnancy. In addition, since there were no significant side effects, safety was confirmed. These advantages are the basis for choosing KM treatment despite the shortcoming of the lack of clinical trial evidence. On the other hand, the standard outcomes are predictable as there are many studies published on western medicine treatment for infertility. However, there are problems such as stress, anxiety, and side effects of the procedure. Therefore, utilizing these two medical treatments depending on patients' need and circumstances may be able to complement each other's shortcomings.

4.4. Limitations

This study had some weaknesses and limitations. This study has a design limitation as a single group study. Because people usually do not want to wait to conceive, it is not easy to set up a control group in infertility studies. There could be ethical problems to make infertile people wait to conceive for long time without treatment. Moreover, since 2017, ART has been supported by the national health insurance.⁷ Accordingly, these days, infertile patients tend to first choose a medical procedure that is subsidized by the government finance. Given the national financial support for ART, it would be practically difficult to recruit infertile patients who become the untreated control group. Also, there was a cost limit to using ART as a control. In addition, this study does not include an economic evaluation. According to survey results among participants before participating in this study, 58% of the respondents answered 'treatment cost' as the most unsatisfactory or uncomfortable factor expected about infertility treatment

of Korean medicine. It showed that the necessity to analyze cost effectiveness of treatments. However, it was difficult to compare the effectiveness between western medicine treatment and Korean medicine treatment through this clinical trial results, making it difficult to evaluate the economic evaluation precisely. Accordingly, only a simple cost comparison was made. The small size of participants can also be the limitation of the study.

4.5. Conclusions

Due to above described limitations, well designed further studies are needed. Well-designed, peer-reviewed RCTs are the golden standard of evidence-based medicine. Nevertheless, many researchers agree that not all treatments need an RCT and suggest to lower the golden standard of evidence-based medicine.^{26,27} Despite the weakness of study design, this study has its own value as it showed possibilities on the effectiveness and the safety of KM comprehensive treatment for unexplained infertility in women.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This study is supported by the Korea Health Industry Development Institute (grant number: HI15C0169).

Ethical statement

The study protocol was approved by the Institutional Review Board of Dongguk University Ilsan Korean Medicine Hospital (2016-01), Kangdong Kyunghye Korean Medicine Hospital (KHNMCOH2016-04-004-002), and Wonkwang University Kwangju Korean Medicine Hospital (2016/1). Informed consent was obtained from all participants.

Data availability

The data that support the findings of this study are available from the corresponding author upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.imr.2021.100751](https://doi.org/10.1016/j.imr.2021.100751).

CRediT authorship contribution statement

Su-Ji Choi: Data curation, Formal analysis, Writing – original draft. **Dong-Il Kim:** Data curation, Investigation, Supervision, Formal analysis, Writing – review & editing. **Sang Ho Yoon:** Investigation. **Chi-Yeon Lim:** Formal analysis. **Jin-Moo Lee:** Investigation. **Chang-Min Choe:** Investigation.

References

1. Aghajanova L, Hoffman J, Mok-Lin E, Herndon CN. Obstetrics and gynecology residency and fertility needs. *Reproduct Sci (Thousand Oaks, Calif)*. 2017;24(March(3)):428–434. doi:[10.1177/1933719116657193](https://doi.org/10.1177/1933719116657193).
2. Aboulghar MA, Mansour RT, Serour GI, HG Al-Inany. Diagnosis and management of unexplained infertility: an update. *Arch Gynecol Obstet*. 2003;267(February(4)):177–188. doi:[10.1007/s00404-002-0300-0](https://doi.org/10.1007/s00404-002-0300-0).
3. Ray A, Shah A, Gudi A, Homburg R. Unexplained infertility: an update and review of practice. *Reprod Biomed Online*. 2012;24(June(6)):591–602. doi:[10.1016/j.rbmo.2012.02.021](https://doi.org/10.1016/j.rbmo.2012.02.021).
4. *Medicine PCotASrEffectiveness and treatment for unexplained infertility. Fertil Steril*. 2006;86(5):S111–S114.

5. MiHee O. Current status and issues of assistance for infertile couples in South Korea and Japan. *Japanese Cultural Stud.* 2020;73:241–259.
6. EuiSeongDang; 2012:203–224.
7. 64 Analysis and evaluation of supporting project for infertility couples in 2013 (Korea Institute for Health and Social Affairs) 46 (2014).
8. NASTRI CO, FERRIANI RA, ROCHA IA, MARTINS WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. *J Assist Reprod Genet.* 2010;27(2-3):121–128.
9. Durant T, Anderson J, Goldfarb J, Macaluso M. Trends and correlates of good perinatal outcomes among singleton infants conceived through ART in the US, 2000–2005. *Fertil Steril.* 2010;94(4):S53.
10. Qin JB, Wang H, Sheng X, Xie Q, Gao S. Assisted reproductive technology and risk of adverse obstetric outcomes in dichorionic twin pregnancies: a systematic review and meta-analysis. *Fertil Steril.* 2016;105(5):1180–1192.
11. Hwang N, Hwang J, Kim J. *Evaluation of the national supporting program for infertility couples and future policy directions in Korea.* Sejong: Korea Institute for Health and Social Affairs; 2010.
12. Kim S-H, Jo J, Kim D-I. The effectiveness, safety, and economic evaluation of Korean medicine for unexplained infertile women: a multi-center, prospective, observational study protocol. *Medicine (Baltimore).* 2017;96(51).
13. . Seoul: EuiSeongDang; 2012:203–224.
14. Kim DI. *Oriental medicine clinical practice guideline of infertility.* Ass Korean Med. 2010:46.
15. Stern JE, Brown MB, Luke B, et al. Calculating cumulative live-birth rates from linked cycles of assisted reproductive technology (ART): data from the Massachusetts SART CORS. *Fertil Steril.* 2010;94(4):1334–1340.
16. Fukuda J, Kumagai J, Kodama H, et al. Upper limit of the number of IVF-ET treatment cycles in different age groups, predicted by cumulative take-home baby rate. *Acta Obstet Gynecol Scand.* 2001;80(1):71.
17. Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilization treatment. *Lancet.* 1996;348(9039):1402–1406.
18. Kim DI, Jang J, Choi SJ, et al. *Korean medicine clinical practice guideline of female infertility.* The association of Korean Medicine; 2018.
19. Jun Heo. *Dongeuibogam.* Seoul: Eui Seong Dang; 2010:1751.
20. Hwang N. Analysis and evaluation of supporting project for infertility couples in 2012. *Korea Inst Health Soc Affairs.* 2013;77:26.
21. Xie ZY, Peng ZH, Yao B, et al. The effects of acupuncture on pregnancy outcomes of in vitro fertilization: a systematic review and meta-analysis. *BMC Complement Altern Med.* 2019;19:131.
22. Rashidi BH, Tehrani ES, Hamedani NA, Pirzadeh L. Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome. *Acupunct Med.* 2013;31(2):151–156.
23. Xu J, Zuo Y. Efficacy of acupuncture as adjunctive treatment on infertility patients with polycystic ovary syndrome. *Zhongguo Zhen Jiu.* 2018;38(4):358–361.
24. Hwang N, Lee S, Jang I. Analysis and evaluation of supporting project for infertility couples in 2016. *Korea Inst Health Soc Affairs.* 2017:93–113.
25. Speroff L, Fritz MA. *Clinical gynecologic endocrinology and infertility.* 8th ed. Lippincott Williams & Wilkins; 2010.
26. Evers JLHH. Do we need an RCT for everything? *Hum Reprod.* 2017;32(3):483–484.
27. Griffin D, Sheldon S. PGS in the clinic. *Focus Reprod.* 2017;1:22–26.