ORIGINAL RESEARCH ARTICLE

Randomized clinical trial of acupuncture in patients with poor ovarian response

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Abstract

This study investigated the effect of acupuncture in patients with poor ovarian response (POR) receiving controlled ovarian stimulation (COS). Sixty seven patients with POR were randomly divided into two groups: Group A (acupuncture+COS) and Group B (COS only). The results showed that the rate of high-quality embryos and rate of available embryos in group A were significantly higher than those in group B (P<0.01). In addition, the number of high-quality embryos in Group A also significantly increased (P<0.05). There was no significant difference in the number of available embryos between the two groups (P>0.05), but group A showed an upward trend compared to group B. Therefore, acupuncture can be considered as a safe and effective method to add to COS in the treatment of patients with POR. *(Afr J Reprod Health 2025; 29 [2]: 27-34).*

Keywords: acupuncture; Poor Ovarian Response; oocyte quality

Résumé

Cette étude a examiné l'effet de l'acupuncture chez des patientes présentant une mauvaise réponse ovarienne (POR) recevant une stimulation ovarienne contrôlée (COS). Soixante-sept patients atteints de POR ont été répartis au hasard en deux groupes : le groupe A (acupuncture + COS) et le groupe B (COS uniquement). Les résultats ont montré que le taux d'embryons de haute qualité et le taux d'embryons disponibles dans le groupe A étaient significativement plus élevés que ceux du groupe B (P < 0,01). De plus, le nombre d'embryons de haute qualité dans le groupe A a également augmenté de manière significative (P <0,05). Il n'y avait pas de différence significative dans le nombre d'embryons disponibles entre les deux groupes (P>0,05), mais le groupe A a montré une tendance à la hausse par rapport au groupe B. Par conséquent, l'acupuncture peut être considérée comme une méthode sûre et efficace à ajouter au COS dans le traitement des patients atteints de POR. *(Afr J Reprod Health 2025; 29 [2]: 27-34).*

Mots-clés: acupuncture; mauvaise réponse ovarienne; qualité des ovocytes

Introduction

The incidence of infertility has been on the rise, and increasingly couples with infertility need to achieve fertility through in vitro fertilization embryo transfer (IVF-ET) and its derivatives. Controlled ovarian stimulation (COS) is one of the treatment processes for IVF. One of the prerequisites for IVF success is that the female ovaries can produce a sufficient number of oocytes s in the natural state or after superovulation. One of the prerequisites for the success of IVF-ET is that the female ovaries produces a sufficient number of good-quality oocytes either naturally or after superovulation. Poor ovarian response (POR) is a pathological manifestation in which the ovaries are insensitive to gonadotropins(Gn), leading to a decrease in the number of retrieved oocytes and pregnancy rate[1] .Over the decades, modern medicine has taken several approaches to advance the outcomes in POR patients, including modification of COS regimens to increase Gn doses and pharmacological pretreatment prior to ovulation induction, such as growth hormone (GH) analogues, dehydroepiandrosterone (DHEA),etc[2,3]. However, the results of the available studies illustrate none of

these approaches has yet shown a significant clinical effects[4].Meanwhile,the high cost of assisted reproduction and the low oocytes -acquisition outcomes of POR patients has brought tremendous financial pressure and psychological burden to patients, as well as clinical dilemmas faced by reproductive medicine specialists. Therefore, the search for an effective complementary therapy has attracted the attention of the medical profession and the community. In recent years, studies by Chinese and foreign scholars have shown that Acupuncture may have significant clinical potential for patients with DOR in terms of improving sex hormones level and increasing Antral Follicle Counting(AFC),and it may improve Clinical Pregnacy Rate(CPR), anti-Müllerian hormone(AMH), and the number of retrieved oocytes in women with POR undergoing IVF[5-6].

Acupuncture, a natural therapy of Chinese origin, is safe, has few side effects and is inexpensive. The results of a meta-analysis[7] suggests that acupuncture can advance ovarian function in women with POR by improving the levels of hormone. Another study indicated that acupuncture can regulate the levels of FSH (Follicle Stimulating Hormone, FSH), LH (Luteinising Hormone,LH) and E2 (estradiol2,E2) in the peripheral blood through the regulation of neurotransmitters in the brain[8]. In addition, acupuncture may improve oocyte quality by decreasing inflammatory factors in follicular fluid and reducing granulosa cell apoptosis, thereby improving pregnancy rates in COS patients[9].In an exploratory randomized controlled trial on acupuncture intervention for POR conducted at Busan Hospital in South Korea from 2017 to 2020[10] it was shown that after 16 acupuncture treatments, more oocytes were retrieved from women over 37 years old who received COS than in those treated with COS alone. These findings suggested that acupuncture can be considered for the women over 37 years old.

Participants

After rigorous screening, 67 POR patients were included in this study. After the relevant explanations and risk notifications, the patients signed the informed consent form respectively. The patients in this study were obtained from the Department of Reproductive Medicine of West China Second Hospital of Sichuan University and the Center for Treatment of Future Diseases of Chengdu University of Traditional Chinese Medicine Hospital. After being evaluated by a reproductive medicine specialist and undergoing cautious laboratory examination, patients who met all the following criteria were included :(i) those diagnosed with POR and who provided informed consent[11](ii) female, aged 30-45 years old; (iii) Compliance with the 2011 ESHRE consensus on the diagnosis of POR1; and (v) No acupuncture treatment in the last two months.

The exclusion criteria are as follows: (i)abnormal reproductive function of the spouse; (ii) patients unable to express themselves independently; (iii) allergy to acupuncture; (iv) those with other severe genital lesions, malignant tumors, infectious diseases, etc; (v) patients with severe cardiovascular, digestive, and respiratory diseases who cannot withstand pregnancy;(vi) those had been exposed to teratogenic doses of radiation, toxins, drugs, or have bad habits such as alcohol and drug abuse; and (vii) those receiving acupuncture treatment within 6 months or participating in other clinical research projects.

Interventions

All patients were randomly divided into two groups: Group A received acupuncture andcontrolled ovarian stimulation (COS+acupuncture), while Group B received controlled ovarian stimulation only. In the COS cycle, both groups used minimal stimulation protocol. The micro stimulation regimen included taking 100mg/d clomiphene citrate capsules on the third day of menstruation, intramuscular injection of 150IU/d HMG starting from the fifth day, and intramuscular injection of 10000IU HCG when the subject develops one or more dominant follicles with a diameter of 15-18mm. The acupoints treated in Group A include DU20 (Baihui), LI4 (Hegu), RN4 (Guanyuan), ST36 (Zusanli), SP6 (Sanyinjiao), LR3 (Taichong), and KI6 (Zhaohai). To avoid excessive stimulation, the treatment plan was set to three times a week, once every other day, starting 2 months before the COS cycle and ending on the day of oocytes retrieval, for a total of 8 weeks.

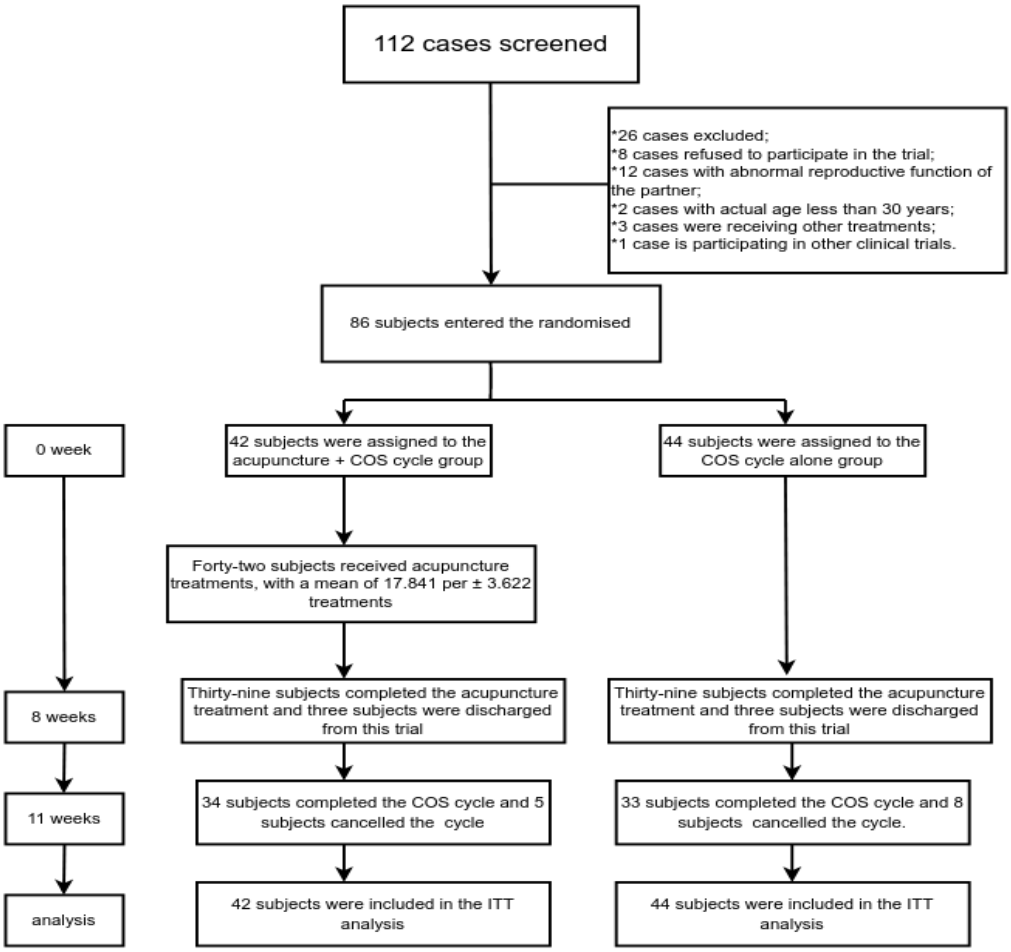


Figure 1: Completion of the trial

Basic information

The following information were obtained:
(i) demographic indicators - age, height and body mass index (BMI). (ii) Vital signs: heart rate, temperature, blood pressure, respiration. (iii) condition-related indicators: disease duration, menstrual cycle, AMH, basal FSH, LH, E2.

Primary Outcomes

(i) Rate of high-quality embryos[12]:After culturing embryos for 3d in vitro, the quality of embryos was assessed according to the number of embryonic cleavage globules, morphology, uniformity of size and the presence of fragments, and was divided into I, II, III, IV grade embryos, of which I and II grade embryos with 6 cells or more were considered to be high-quality embryos.

Secondary Outcomes

(i) Number of high-quality embryos,,(ii)Number of embryos available,(iii)Rate of available embryos

Safety evaluation

Record and evaluate adverse events during the implementation process of the subjects, such as dizziness, hematoma, needle breakage, needle retention, infection, burns, etc.

Table 1: AMH, FSH, LH, E2 in two groups of subjects

Group	No. of patients (n)	AMH （ng/ml）*	FSH （ng/ml）*	LH （ng/ml）#	E2（ng/ml）#
Group A	42	0.7±0.3	9.4±4.4	5.1±5.5	58.1±57.0
Group B	44	0.9±0.3	9.3±4.4	3.2±1.3	93.4±114.5
Statistic value		1.993	0.062	1.907	367.5
p-value		0.051	0.957	0.112	0.162

Note: *: Independent samples t-test; #: Mann-Whitney test

Comparison of laboratory measurements

As shown in Table 1, the differences in the basal FSH, LH, E2 and AMH indicators between the two groups were comparable (P>0.05).

Data analysis

All the count data were retained in two decimal places, and the data that conformed to normal distribution were expressed in the form of "mean ± standard deviation", and the data that did not conform to normal distribution were expressed in the form of "mean rank"; statistically relevant data, such as statistical quantities and P-values, were retained in four significant digits. Statistical data, such as statistics and P-values, are retained with four significant digits. Statistical data were analysed using SPSS22.0 statistical software, and the Chi-square test ($\chi 2$ Test) was used for counting data; the normal distribution test was performed for measuring data, and the independent samples t-test was used for measuring data that conformed to the normal distribution. The rank sum test (Mann-Whitney) was used for non-normally distributed data. A two-sided test was used, with P<0.05 as the criterion for significant difference.

This proposal was approved by the Ethics Committee of Chengdu University of Traditional Chinese Medicine Affiliated Hospital, with ethics approval number 2018KL-015. This study has been registered at the Chinese Clinical Trial Center with registration number: ChiCTR18000 (http://www.chictr.org/cn/).

Baseline results

Comparison of demographic characteristics

As shown in Table 2, after randomisation, age, disease duration, menstrual cycle and BMI of the two groups were comparable at baseline. (P>0.05).

Results

Safety evaluation results

The subjects in the Group A received a total of 571 acupuncture treatments, with 17.84±3.62 acupuncture treatments per capita. During the period, there were no adverse reactions such as dizziness, needle breakage, haematoma, infection and so on.

Primary outcomes

High quality embryo rate

As can be seen from Table 3 and Figure 2, the rate of high-quality embryos in GroupA was 43.5±30.1 (%), and it was 25.9±26.0 (%) in GroupB (P<0.01).

Secondary Outcomes

Number of high-quality embryos， Number of embryos available，Rate of available embryos

As shown in Table 4 and Figure 3, the number of high-quality embryos GroupA was1.8±1.1, and it was 1.0±1.3 in GroupB(P<0.05).As can be seen from Table 8 and Figure 7, the number of available embryos in GroupA was 2.5±1.8,and it was 1.2±1.2 in GroupB.(P＞0.05).

Table 2: Age, disease duration, menstrual cycle, BMI of subjects in both groups

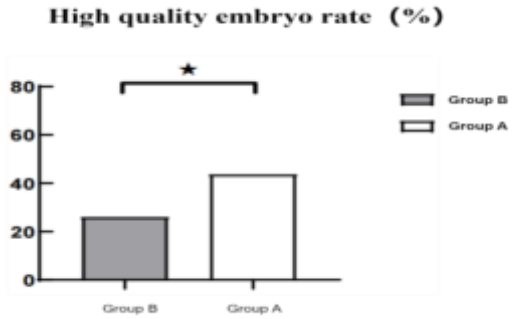
Group	No. of patients (n)	Age(years)	disease duration(months)	menstrual cycle(days)	BMI （kg/m^2）
Group A	42	34.3±3.1	53.3±25.4	27.3±3.4	22.5±2.4
Group B	44	35.5±3.4	52.0±50.8	28.1±3.4	22.3±3.2
Statistic value		390.5	422	0.978	453
p-value		0.102	0.225	0.350	0.051

Note: *: Independent samples t-test; #: Mann-Whitney test.

Table 3: Rate of good quality embryos

Group	No. of patients (n)	High quality embryo rate(100%)
Group A	42	43.5±30.1
Group B	44	25.9±26.0
Statistic value		322.5
p-value		0.009

Note: #: Mann-Whitney test



Note: ★: P < 0.01.

Figure 2: Rate of high-quality embryos (Mean±SD) in two groups of subjects

The rate of available embryos in GroupA was 66.3±21.2 (%), and it was 51.6±23.7 (%) in GroupB(P＜0.01).

Comparing Group A with Group B, acupuncture can significantly increase the rate of high-quality embryos, the rate of available embryos and the number of high-quality embryos, but it can not significantly increase the number of available embryos in the test group（GroupA.

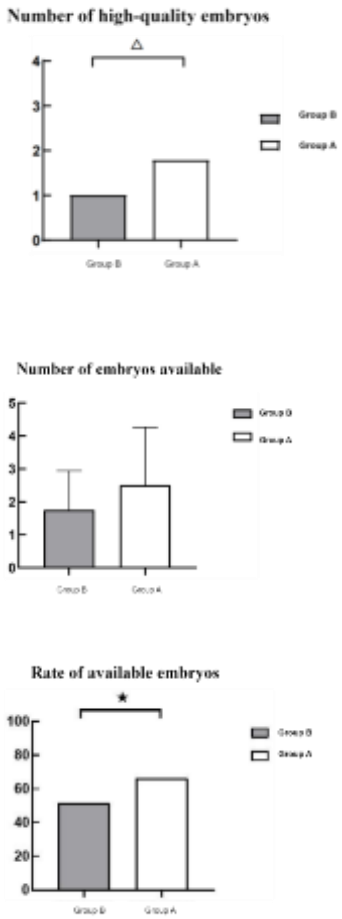
Discussion

Currently, different studies have reached inconsistent conclusions regarding the role of acupuncture in assisted reproductive technology; in addition to differences in the acupoints and forms of acupuncture used, there are also large variations in the duration of acupuncture interventions and treatment cycles between studies. For example, Smith, C. A. *et al.* compared the effects of acupuncture and sham acupuncture on the live birth rate during COS cycles in patients with Polycystic Ovary Syndrome (PCOS)[13], but the result showed no absolute difference between the effects of acupuncture and sham acupuncture on the live birth rate. However, it only performed one acupuncture treatment between days 6 and 8 of the follicular phase, as well as one treatment each before and after embryo transfer, for a total of three acupuncture treatments. Gu, S. pointed out[14] that the COS regimen and the acupuncture protocol did not take into account the individuality of the patients and were not individually adjusted, and the number of acupuncture treatments was too short, thus underestimating the real effect of acupuncture. The results indicated that the acupuncture group had a higher pregnancy probability and significantly lower pre-transplantation stress than the group that was not treated with acupuncture.Dehghani.[15] found that a single acupuncture session 25 minutes before transplantation increased the number of COS cycles compared to no acupuncture treatment improved biochemical, clinical and pregnancy outcomes in COS cycles, but this effect was not further improved by another acupuncture session 25 minutes after transfer.Hullender Rubin.[16] analysed the available evidence on this topic and suggested that just a few acupuncture treatments around the

Table 4: Number of high-quality embryos in the two groups of subjects,Number of available embryos, rate of available embryos in the two groups of subjects

Group	No. of patients (n)	Number of high-quality embryos	Number of embryos available	Rate of available embryos（100%）
Group A	42	1.8±1.1	2.5±1.8	66.3±21.2
Group B	44	1.0±1.3	1.2±1.2	51.6±23.7
Statistic value		337.5	1.929	329.5
p-value		0.0146	0.063	0.001

Note: #: Mann-Whitney test



Note: △: P < 0.05.

Figure 3: Number of high-quality embryos,number of available embryos and the rate of available embryos in the two groups of subjects

embryo transfer date is not enough to improve COS pregnancy outcomes, and that an increase in pregnancy probability,even live birth rate are associated with more acupuncture sessions. A systematic evaluation by Xie, Z. Y. *et al*[17] noted that acupuncture improved clinical outcomes in women whom had previous COS failure, and that the number of acupuncture treatments could be a potential influencing factor. In addition, a systematic evaluation[18] showed that, although further large-sample, high-quality studies are lacking, acupuncture may improve the number of oocytes retrieved, the pregnancy probability and live births rate in COS-treated patients with POR.In this study, based on the results of the team's previous research, the acupuncture treatment course was set at 8 weeks, aiming to obtain a more satisfactory outcome of oocytes acquisition.

The outcomes of this study are the rate of high-quality embryos, the number of high-quality embryos, the number of available embryos, and the rate of available embryos. POR patients need to observe and record all the above indicators after completing the COS cycle, so it is impossible to conduct self-control on the subjects before and after acupuncture.Therefore, this study adopted a two group control design. In addition, due to the particularity of acupuncture, the non blind design can only be used.The outcomes of test group in this study showed statistical significance compared to the control group, indicating that acupuncture can serve as a supplementary alternative therapy for POR. However, in order to obtain higher quality evidence, clinical studies still need to expand the sample size for further validation. At the level of mechanism research, this study collected follicular fluid from subjects for DNA methylation analysis. However, due to limited space, the methylation analysis results will be considered as a supplement to future clinical studies. In general, there are still some shortcomings in this study, and it is necessary to further explore higher quality methods to prove the therapeutic mechanism of acupuncture in POR.

Conclusion

From the research of this trial, it can be seen that acupuncture can improve the quality of oocytes in POR patients, thereby increasing the proportion of high-quality embryos. This is very important for the research on assisted reproduction.
In addition to traditional ovulation induction methods and oral nutritional supplements, acupuncture can be considered as a physical therapy for POR patients.

Conflict of interests

The authors declare no competing interests.

Authors' contributions

Rongli Yuan and Jie Wu conceptualized this study. Rongli Yuan, Xinyun Zhu, Yunzhu Liu, Mengjing Wang, Tianyu Wang, and Zhi Li worked on the literature review. Mengjing Wang, Rongli Yuan, and Xinyun Zhu worked on the data analysis and interpretation of results. All authors worked on the discussion of the findings. All the authors read and approved the final manuscript.

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