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ORIGINAL RESEARCH

The Effect of Traditional Chinese Medicine Treatment on the Cumulative Live Birth Rate of Patients with Poor Ovarian Response to the Patient-Oriented Strategies Encompassing Individualized Oocyte Number Criteria

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Objective: This study analyzed the role of traditional Chinese medicine (TCM) treatment on the cumulative live birth rate (CLBR) in women with poor ovarian response to the patient-oriented strategies encompassing individualized oocyte number (POSEIDON) criteria.

Methods: This cohort study selected 3347 patients with low ovarian response and divided them into four subgroups according to the POSEIDON criteria: Group 1 (n=947), Group 2 (n=778), Group 3 (n=164), and Group 4 (n=1458). Logistic regression analysis was used to evaluate the role of TCM treatment on the CLBR of patients with poor ovarian response to POSEIDON criteria.

Results: In the unadjusted model, TCM treatment might be related to the heightened CLBR (OR=2.052, 95% CI: 1.745–2.413). After adjusting for the POSEIDON group, a higher CLBR was identified in those with TCM treatment (OR=1.927, 95% CI: 1.615–2.300). In Model 3, covariates including the POSEIDON group, age, body mass index (BMI), anti-mullerian hormone (AMH), and/or antral follicle count (AFC) were adjusted, and TCM treatment was associated with elevated CLBR of patients with poor ovarian response to the POSEIDON criteria (OR=1.905, 95% CI: 1.586–2.289). This suggested that TCM increased CLBR by 19.05% in patients who used TCM compared with those who did not. Subgroup analysis indicated that TCM treatment might increase the CLBR of patients in POSEIDON criteria Group 1 (OR=1.83, 95% CI: 1.33–2.51), indicating that TCM elevated the CLBR by 8.3% in POSEIDON criteria Group 1.

Conclusion: TCM treatment was related to increased CLBR in patients with poor ovarian response to the POSEIDON criteria.

Keywords: Traditional Chinese medicine, live birth rate, the POSEIDON criteria

Introduction

At present, the management of fertility in women with poor ovarian response still poses a significant challenge in clinics.[1] Poor ovarian response is reported to be related to decreased pregnancy rates in assisted reproductive technology (ART).[2] Patient-oriented strategies, known as the Personalized Oocyte Number (POSEIDON) criteria, have been raised to offer improved stratification for patients with a low prognosis and enable more individualized therapeutic approaches for these individuals.[3] The patients are categorized into four groups based on their age, ovarian reserve markers such as anti-mullerian hormone (AMH) and/or antral follicle count (AFC), and the number of oocytes retrieved in a previous ovarian stimulation cycle.[4] The available evidence suggests that the cumulative live birth rate (CLBR) is lower in women with low ovarian response to the

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POSEIDON criteria compared to those who do not meet the POSEIDON criteria (33.7% vs 50.6%) and differed across POSEIDON groups.[5] However, previous evidence indicated that testosterone supplementation, dehydroepiandrosterone, and delayed start protocol significantly improved the total number of eggs collected, which seems to correlate with a better live birth rate in women with CLBR in women with low ovarian response to the POSEIDON criteria.[6] The prognosis of women with low ovarian response to the POSEIDON criteria is still unfavorable. Improving CLBR in patients with poor ovarian response to POSEIDON criteria is of great value.

Traditional Chinese medicine (TCM) treatments such as Chinese herbal medicine and acupuncture have gradually been accepted in the field of ART in recent years.[7–9] According to TCM, the diagnosis and treatment of disease are based on the concepts of "Qi" and "Blood". "Qi" represents the vital energy that sustains life and regulates normal physiological functions in the body.[10] The flow of blood within the vessels and meridians is synergistically accompanied by the circulation of "Qi" energy, which serves to energize it. Both "Qi" and blood supply essential nutrients to the uterus, thereby facilitating the normal functioning of the female reproductive system. The "Kidney" stores the vital energy known as "Qi", which plays a crucial role in growth and reproduction. Enhancing the function of the "Kidney" may potentially improve rates of implantation.[11] A growing body of evidence suggests that TCM has demonstrated efficacy in regulating hormone levels, enhancing implantation rates, and improving pregnancy outcomes in IVF cycles.[12,13] TCM can regulate the bone morphogenetic factor 15 (BMP15) and growth differentiation factor 9 (GDF9) expressions in the follicle fluids,[7] which belong to TGF-β superfamily and are two important oocyte-derived factors, acting as two paracrine regulators of the oocyte development and exhibit biological effects through Ser/Thr kinase.[14] Several systematic reviews demonstrated that Chinese herbal medicine and acupuncture may confer potential benefits in enhancing pregnancy rates in those receiving IVF.[15,16] However, the sample size of much of the existing evidence is relatively insufficient, and the results are not sufficiently robust or consistent for findings to be adopted with confidence.[17] Additionally, the impact of TCM treatments on CLBR, particularly among patients in different POSEIDON groups, has not been reported. Also, there are controversial findings regarding the effect of TCM on the improvement of pregnancy rates, indicating that adjuvant acupuncture did not improve pregnancy outcomes.[18]

In this study, the association between TCM treatments and the CLBR per oocyte retrieval cycle was analyzed, especially in women with low ovarian response to POSEIDON criteria, and the related factors affecting the CLBR of women with low ovarian response infertility were further analyzed based on a large cohort size. Subgroup analysis was also performed by stratified analysis by different POSEIDON groups, which may reinforce the importance of TCM in the broader context of ART research.

Materials and Methods

Study Design and Population

This was a cohort study that collected the data of 10662 infertility women who meet IVF/ISCI treatment indications at Shenzhen Zhongshan Obstetrics & Gynecology Hospital (formerly Shenzhen Zhongshan Urology Hospital) Hospital Information System (HIS) and the reproductive case system and completed the first cycle from January 1, 2019 to December 31, 2021. These two case systems are real-time case recording systems, which record all the data of assisted reproduction techniques and TCM treatment of patients. Among them, 3347 had poor ovarian response to the POSEIDON criteria. This study was conducted in accordance with the declaration of Helsinki. This study got the approval from the Ethics Committee of Shenzhen Zhongshan Obstetrics & Gynecology Hospital (formerly Shenzhen Zhongshan Urology Hospital) (SZZSECHU-F-2021014). All women were classified into four groups according to the POSEIDON criteria. Group 1: age <35 years and AMH≥1.2 ng/mL and AFC≥5 (n=947); Group 2: age ≥35 years and AMH≥1.2 ng/mL and AFC≥5 (n=778); Group 3: age <35 years and AMH < 1.2 ng/mL and AFC < 5 (n=164); Group 4: age ≥35 years and AMH < 1.2 ng/mL and AFC < 5 (n=1458).

Data Collection and Definitions

Age (years), body mass index (BMI, kg/m^2), AMH, AFC, number of retrieved oocytes, D3 embryos, duration of infertility (years), ovarian stimulation protocols long protocol, antagonist protocol, no stimulation protocol, and mild

stimulation protocol), trigger protocols (dual-trigger protocol or single trigger protocol), gonadotropin (Gn) duration (days), and Gn dose, human chorionic gonadotropin (hCG) day estradiol (E_2) level (pg/mol).

BMI = weight (kg) / height^2 (m^2) (<18 kg / m^2, 18–24 kg / m^2, and >24 kg / m^2). Trigger protocols were defined based on the type of trigger drug used on trigger day. Single trigger protocol used only one trigger drug, such as hCG or GnRH agonist (GnRH), while the dual-trigger protocol used both of the two trigger drugs.

Main and Outcome Variables

TCM treatment was the main variable. Participants received TCM decoction, acupuncture, or acupuncture combined with TCM decoction treatments. As for TCM decoction those with deficiency of spleen and kidney qi syndrome, Yu Linzhu was applied. For those with stagnation of liver qi syndrome, Kaiyu Zhongyu decoction was applied. Cangfu Daotan pill was applied for patients with phlegm-dampness internal obstruction syndrome. As for the syndrome of stagnation of uterus and uterus, Shaofu Zhuyu decoction was used. Patients with kidney Yin deficiency syndrome received Yangjing Zhongyu decoction, while patients with spleen and kidney Yang deficiency syndrome, Yangyang Yangkun prescription was applied. Patients received one dose per day with a decoction of 500mL, drank in the morning and evening after meals during a total of 1–3 menstrual cycles. TCM treatment occurred in the first to third menstrual cycles prior to the first oocyte retrieval cycle, with or without the entire induction cycle. As for patients receiving acupuncture, the points targeted were first group: Baihui (GV 20), Shenting (GV 24), Zhongwan (CV 12), Guanyuan (CV 4), bilateral Dahe (GV 24), Tianshu (ST 25), Zusanli (ST 36), and Sanyinjiao (SP 6); or second group: bilateral Shenshu (BL 23) and Ciliao (BL32). Patients were alternately treated with 0.25mm × 25mm and 0.25mm × 50 mm acupuncture needles, respectively. According to the degree of fat and thin of the according to the patient's fat and thin degree, different types of acupuncture needles and acupuncture depths were selected. The acupuncture was applied horizontally at Baihui (GV 20) and Shenting (GV 24) for 10–15 mm, straight at Zhongwan (CV 12), Guanyuan (CV 4), Dahe (GV he), Zigong (ST 36), Zusanli (ST 36), and Shenshu (BL 23) for 20–30 mm, straight at Sanyinjiao (SP 6) for 10–15 mm, and oblique at Ciliao (BL 32) for 40–50 mm. Lift and twist to obtain qi, all acupoints retained needles for 30 min. As for patients targeted at first group, ipsilateral Tianshu (ST 25) and uterine acupoints and, for the second group, ipsilateral Shenyu (ST 36), and Ciliao (BL 32) acupoints, were connected with electronic acupuncture instrument (SDZ-IIB, Zhejiang Chinese Medical University and Suzhou Medical Supplies Factory Co., LTD), disperse-dense wave was applied, and the patient's tolerance was considered. The acupuncture was conducted once every 3 days and suspended during menstrual periods.

The outcome was the CLBR with first cycle embryo transfer, which was calculated according to the number of first live births with fresh cycle and subsequent frozen cycle transfer/number of embryo transfer cycles with first cycle (ie, total number of retrieved oocyte cycles − number of embryos without transfer) ×100%.

Statistical Analysis

Data analysis was performed by two different statisticians. The data of IVF/ICSI cases were exported from the Reproductive Case System. The data of TCM treatment-related cases were exported from the HIS system. The two tables were compared and matched. Each covariate was checked for errors or missing data, and corrected. Patients with missing data were excluded. Kolmogorov–Smirnov test evaluated the normality of the data. Continuous variables with normal distribution were described as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) and least significant difference (LSD) *t*-test were applied to assess the statistical difference in these data. The categorical variables with normal distribution were described as case numbers and percentiles. Data that do not conform to the normal distribution were presented as median and quartiles [M (Q_1, Q_3)], and χ^2 test was employed to compare differences among groups. A binary Logistic regression model analysis was applied to identify potential covariates, and a multivariate Logistic regression analysis was conducted post adjusting covariates including POSEIDON group, age, BMI, AMH, and AFC. Subgroup analysis was performed in patients from different POSEIDON groups. SPSS 27.0 (IBM SPSS Statistics 27) was utilized for statistical analysis.

Results

Comparisons of the Baseline Data of Participants in Different POSEIDON Groups

In total, a total of 10662 patients completed the first cycle in our hospital. Among them, 3347 patients were eligible for poor ovarian response to the POSEIDON criteria. The participants were divided into four groups according to the POSEIDON criteria. Group 1 (n=947), Group 2 (n=778), Group 3 (n=164), and Group 4 (n=1458). The screen process of the participants is shown in Figure 1.

According to the data in Table 1, the mean age (30.75 years vs 38.10 years vs 30.91 years vs 39.82 years), BMI (21.32 kg/m^2 vs 22.07 kg/m^2 vs 20.81 kg/m^2 vs 22.25 kg/m^2) and duration of infertility (3.23 years vs 3.89 years vs 3.04 years vs 4.08 years) of participants were different among Group 1, Group 2, Group 3, and Group 4. The mean AMH (2.82 ng/mL vs 2.24 ng/mL vs 1.87 ng/mL vs 0.79 ng/mL), and AFC (10.73 vs 8.40 vs 3.34 vs 3.76) were statistically different among Group 1, Group 2, Group 3, and Group 4. Statistical difference was also observed among Group 1, Group 2, Group 3, and Group 4 concerning the mean Gn duration (9.14 days vs 8.96 days vs 8.91 days vs 8.79), Gn dose (30.47 vs 31.13 vs 26.38 vs 21.97), and hCG day E2 level (1832.27 pg/mol vs 1649.31 pg/mol vs 1463.13 pg/mol vs 1109.77 pg/mol). The CLBR of patients in Group 1, Group 2, Group 3, and Group 4 was 47.41%, 26.61%, 21.34%, and 6.93%, respectively (Table 1).

Potential Confounding Factors Associated with the CLBR of Patients with Poor Ovarian Response to the POSEIDON Criteria

Confounding factors associated with the live birth of patients with poor ovarian response to the POSEIDON criteria were evaluated. The regression coefficient of age was −0.207, which was negatively related to CLBR (OR=0.813, 95% CI: 0.797–0.829). The regression coefficient of BMI was −0.038, which was negatively associated with the CLBR (OR=0.962, 95% CI: 0.936–0.989). AMH was positively correlated with the CLBR (OR=1.705, 95% CI: 1.597–1.820). AFC was related to increased CLBR (OR=1.185, 95% CI: 1.162–1.208). Increased number of retrieved oocytes was correlated with higher CLBR (OR=1.539, 95% CI: 1.479–1.601). This means that the first CLBR increases 1.539 times for every increase in the number of retrieved oocytes. We also observed that the CLBR was elevated with the

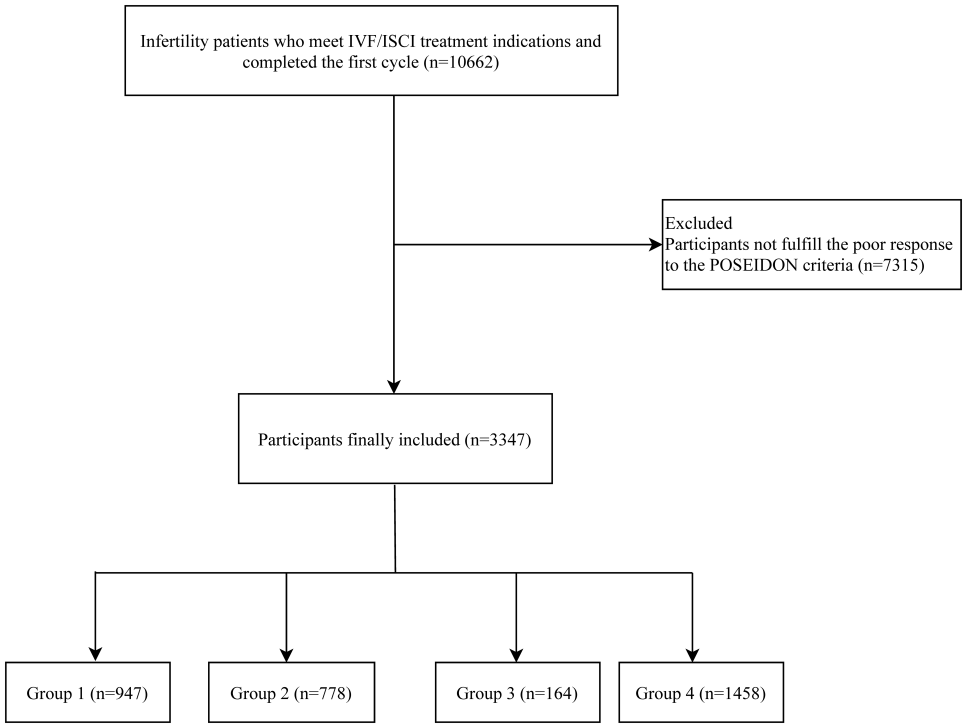

Figure 1 The screen process of the participants.

Table 1 The Baseline Data of Participants in Different POSEIDON Groups

Variables	Group 1 (n=947)	Group 2 (n=778)	Group 3 (n=164)	Group 4 (n=1458)	F/χ^2	*P*
Age (years), Mean ± SD	30.75±2.513	38.10±2.598	30.91±2.532	39.82±3.386	2098.626	<0.001
BMI (kg/m^2), Mean ± SD	21.32±3.087	22.07±2.927	20.81±2.745	22.25±3.107	25.820	<0.001
Infertility duration (years), Mean ± SD	3.23±2.218	3.89±3.339	3.04±1.948	4.08±3.858	16.061	<0.001
AMH (ng/mL), Mean ± SD	2.82±1.755	2.24±1.021	1.87±0.695	0.79±0.524	691.754	<0.001
AFC, Mean ± SD	10.73±5.657	8.40±3.094	3.34±1.420	3.76±2.354	751.450	<0.001
Ovarian stimulation protocol, n (%)					1249.009	<0.001
Long protocol,	145 (15.31)	87 (11.18)	24 (14.63)	18 (1.23)		
Antagonist protocol	655 (69.17)	488 (62.72)	36 (21.95)	221 (15.16)		
No stimulation protocol	3 (0.32)	1 (0.13)	1 (0.61)	6 (0.41)		
Mild stimulation protocol	144 (15.21)	202 (25.96)	103 (62.8)	1213 (83.20)		
Trigger protocols, n (%)					65.68	<0.001
Dual trigger protocol	748 (78.99)	617 (79.31)	133 (81.10)	1301 (89.23)		
Single trigger protocol	198 (20.91)	161 (20.69)	31 (18.9)	149 (10.22)		
Gn duration (day), Mean ± SD	9.14±2.269	8.96±1.910	8.91±2.436	8.79±3.382	3.071	0.027
Gn dose, Mean ± SD	30.47±9.930	31.13±9.470	26.38±12.347	21.97±10.210	198.362	<0.001
hCG day E_2 level (pg/mol), Mean ± SD	1832.27±888.928	1649.31±746.296	1463.13±815.631	1109.77±712.390	184.779	<0.001
Traditional Chinese medicine treatment, n (%)					16.673	<0.001
Yes	202 (21.33)	204 (26.22)	33 (20.12)	410 (28.12)		
No	745 (79.67)	574 (73.78)	131 (79.88)	1048 (71.88)		
Cumulative live birth rate, (%)	47.41 (449/947)	26.61 (207/778)	21.34 (35/164)	6.93 (101/1458)	538.671	<0.001

Abbreviations: POSEIDON, patient-oriented strategies encompassing individualized oocyte number; SD, standard deviation; BMI, body mass index; AMH, anti-mullerian hormone; AFC, antral follicle count; Gn, gonadotropin; hCG, human chorionic gonadotropin.

increase of D3 embryos (OR=1.732, 95% CI: 1.650–1.818). Different POSEIDON groups were also identified to be related to decreased CLBR (Table 2).

The Effect of TCM Treatment on the CLBR of Patients with Poor Ovarian Response to the POSEIDON Criteria

As exhibited in Table 3, in the unadjusted model, TCM treatment might be related to increased CLBR (OR=2.052, 95% CI: 1.745–2.413). After adjusting for the POSEIDON group, a higher CLBR was found in those with TCM treatment (OR=1.927, 95% CI: 1.615–2.300). In Model 3, covariates including the POSEIDON group, age, BMI, AMH, AFC were adjusted, and TCM treatment was associated with elevated CLBR of patients with poor ovarian response to the POSEIDON criteria (β=1.905, 95% CI: 1.586–2.289). Subgroup analysis indicated that TCM treatment might increase the CLBR of patients in POSEIDON criteria Group 1 (OR=1.83, 95% CI: 1.33–2.51) (Table 4, Figure 2). Sensitivity analysis was performed in patients receiving acupuncture combined with TCM decoction treatments (n=133). The results indicated that TCM was related to improved CLBP in patients from different POSEIDON group (OR=1.22, 95% CI: 1.03–1.44). Detailed data are shown in Supplementary Table 1.

Discussion

The present study assessed the role of TCM treatment on the CLBR of patients with poor ovarian response to the POSEIDON criteria. The results delineated that TCM treatment was associated with increased CLBR in these patients. Subgroup analysis showed that TCM treatment was associated with increased CLBR of patients in POSEIDON criteria Group 1. The findings might provide a reference for the treatment of infertility patients with poor ovarian response to the POSEIDON criteria.

Here in our study, TCM treatment was identified to be an independent influencing biomarker for the CLBR of the first oocyte cycle with an OR of 1.908, implying an approximately 0.9-fold increase in the live birth rate during the first oocyte cycle in patients using TCM treatment compared to those not. This was consistent with the results in previous

Table 2 Potential Confounding Factors Associated with the Cumulative Live Birth Rate

Variables	β	Wald	*P*	OR (95% CI)
Age	−0.207	417.958	<0.001	0.813 (0.797–0.829)
BMI	−0.038	7.500	0.006	0.962 (0.936–0.989)
AMH	0.534	256.152	<0.001	1.705 (1.597–1.820)
AFC	0.169	295.792	<0.001	1.185 (1.162–1.208)
Number of retrieved oocytes	0.431	456.269	<0.001	1.539 (1.479–1.601)
D3 embryos	0.549	494.925	<0.001	1.732 (1.650–1.818)
POSEIDON				
Group 1		427.270	<0.001	
Group 2	−0.911	76.736	<0.001	0.402 (0.328–0.493)
Group 3	−1.201	35.557	<0.001	0.301 (0.203–0.447)
Group 4	−2.494	418.319	<0.001	0.083 (0.065–0.105)

Abbreviations: BMI, body mass index; AMH, anti-mullerian hormone; AFC, antral follicle count; POSEIDON, patient-oriented strategies encompassing individualized oocyte number.

Table 3 The Effect of Traditional Chinese Medicine Treatment on the Cumulative Live Birth Rate of Patients with Poor Ovarian Response to the POSEIDON Criteria.

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	β (95% CI)	*P*
Traditional Chinese medicine treatment						
No	Ref		Ref		Ref	
Yes	2.052 (1.745–2.413)	<0.001	1.927 (1.615–2.300)	<0.001	1.905 (1.586–2.289)	<0.001

Notes: Model 1: unadjusted model, Model 2: adjusting for POSEIDON group, Model 3: adjusting for POSEIDON group, age, BMI, AMH, and AFC.

Table 4 The Effect of Traditional Chinese Medicine Treatment on the Cumulative Live Birth Rate of Patients in Different POSEIDON Criteria Groups

Poseidon criteria groups	Traditional Chinese medicine treatment	OR (95% CI)	*P*
Group 1	No	Ref	
	Yes	1.83 (1.33–2.51)	<0.001
Group 2	No	Ref	
	Yes	0.78 (0.55–1.11)	0.17
Group 3	No	Ref	
	Yes	0.39 (0.17–0.88)	0.02
Group 4	No	Ref	
	Yes	1.36 (0.85–2.18)	0.21

Notes: Multivariable Logistic regression analysis adjusting for Poseidon group, age, BMI, AMH, and AFC.

studies. A systematic review and meta-analysis indicate that acupuncture may offer benefits in improving IVF outcomes for women who have previously experienced unsuccessful attempts.[19] A multicenter, randomized, controlled clinical trial revealed that transcutaneous electrical acupoint stimulation obviously enhanced the clinical pregnancy rate in women undergoing IVF, particularly among older women, potentially attributed to improved endometrial receptivity.[20] Wu et al demonstrated that acupuncture could enhance the endometrial receptivity, regulate serum E2 levels on the day of hCG injection, and improve the pregnancy success rate in patients with infertility due to polycystic ovary syndrome undergoing IVF.[21] 1. The sequential therapy of activating blood circulation and regulating Gan (Liver) tonifying Shen (Kidney)

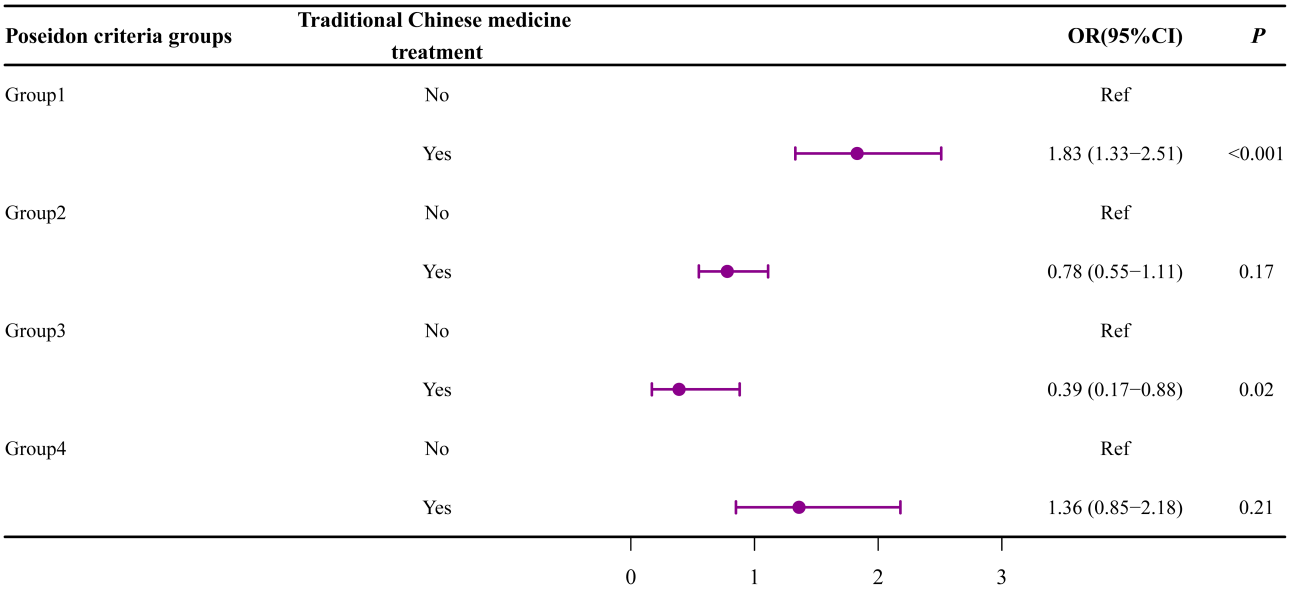

Figure 2 Forest plot of the effect of TCM treatment on the CLBR of patients in different POSEIDON groups.

strategies has been reported to effectively enhance the live birth rate in cases of endometriosis-associated infertility with qi stagnation and blood stasis after laparoscopy. Additionally, it improves follicular development, promotes ovulation, enhances endometrial receptivity while maintaining a safe treatment option.[22] Another multicenter randomized trial suggests that personalized acupuncture therapy may serve as a viable alternative treatment option for enhancing the live birth rate in infertile women with polycystic ovary syndrome, when compared to fixed acupuncture or placebo letrozole.[23] The administration of Zishen Yutai Pills has been reported to yield favorable outcomes in patients with diminished ovarian reserve undergoing IVF, leading to an increase in the number of oocytes and embryos retrieved, as well as an up-regulation of bone morphogenetic protein 15 and growth differentiation factor 9 expressions in the follicular fluid.[7] The study conducted by Li et al demonstrated that the combined administration of Shoutai Pill and western medicine may offer a superior approach compared to western medicine alone during the first trimester of pregnancy, for the prevention of miscarriage in women with unexplained recurrent spontaneous abortion.[24] There are also inconsistent conclusions about the effect of TCM treatment on the improvement in pregnancy rates. In a study that included patients with low ovarian response with traditional acupuncture therapy, Yang Ting et al found that traditional acupuncture treatment for 3 cycles could improve the MII egg rate of patients in POSEIDON 3 group, but could not improve the CLBR.[25] According to the 2017 Performing the embryo transfer guidelines, adjuvant acupuncture therapy has no improvement effect on pregnancy outcomes.[18] The inconsistent results might be due to the sample size, and the effects of different TCM treatments might differ.

A previous study on the live birth rate of patients with low ovarian response to POSEIDON criteria found that the CLBR of POSEIDON patients was lower than that of non-POSEIDON patients.[26] In a large 2019 retrospective analysis involving 18,455 cycles, CLBR showed a progressive decline in POSEIDON criteria: 44.6% in Group 1, 35.5% in Group 3, 24.5% in Group 2, and 12.7% in Group 4.[27] This is consistent with a multicenter observational cohort study in the Netherlands, which also observed differences in pregnancy rates between POSEIDON groups.[28] Chen et al demonstrated that it is recommended for all low-prognosis women to undergo assisted reproductive technology (ART) treatment for a minimum duration of 2 years or three frozen embryo transfer (FET) cycles, and they achieve improved outcomes when extending the ART treatment period to 3.5 years or 6 FET cycles (particularly applicable to POSEIDON groups 3 and 4).[29] In our study, the CLBRs were of statistical significance in different POSEIDON groups. The CLBR was 47.41% in Group 1, 26.61% in Group 2, 21.34% in Group 3 and 6.93% in Group 4. Subgroup analysis revealed that the CLBR was heightened in POSEIDON Group 1, Group 2, and Group 3 in patients receiving TCM therapy, while no significant association was found in TCM therapy and patients in POSEIDON Group 4. This might be because patients in

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POSEIDON Group 4 exhibit the most compromised ovarian responses, characterized by a diminished number of retrieved oocytes, limited embryo production, and an elevated risk of lacking high-quality embryos for transfer.[30]

The use of TCM therapy in reproductive centers has gradually increased.[31] In this study, a large sample size of data was used to analyze the association between TCM treatments with CLBR in patients with low ovarian response to POSEIDON criteria. A previous meta-analysis finds that acupuncture in IVF-ET trials appears to increase clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), and CLBR compared with no adjunctive treatment.[16] In 2015, a prospective randomized double-blind clinical study using Zishen Yutai Pill found that Zishen Yutai Pill had higher live birth rate and implantation rate in fresh cycle than the placebo control group, and the effect of the elderly group was more significant.[32] Some studies have found that electroacupuncture can improve the quality of oocytes, and the possible mechanism is to improve the DNA methylation level of follicular fluid.[33] TCM has been reported to enhance progesterone and E2 levels in patients with reproductive disorders, promote increased blood supply to reproductive organs, and improve overall reproductive performance.[34] In addition, according to TCM theory, the capability of reproduction is enhanced by tonifying Shen and Pi as well as nourishing blood.[35] TCM has demonstrated favorable outcomes in patients with diminished ovarian reserve undergoing IVF-ET, leading to an increase in the number of oocytes and embryos, as well as an up-regulation of BMP15 and GDF9 expressions in the follicle fluids.[7] Chinese medicine treatment has a positive impact on the CLBR of these patients, which make a meaningful contribution to the field of reproductive medicine. It builds on existing knowledge by providing evidence for the potential of TCM to enhance ART outcomes, particularly for specific subgroups of women with poor ovarian response. This stratified approach is essential for refining treatment strategies and may inform personalized medicine in ART by indicating that certain groups (like POSEIDON Group 1) could benefit more from TCM. The findings suggested the value of TCM treatments in the management of infertile women. There were some limitations in this study. Firstly, only a few cases of acupuncture treatments were found, and subgroup analysis of TCM treatments could not be carried out. This also indicated that the standardization of TCM protocols could improve the applicability of the findings in clinical practice. Secondly, this was a retrospective study, some of the data of participants might have bias. Thirdly, patients' physical and mental health conditions such as depression of anxiety-related disorders were closely related to the outcomes of CLBR,[36] which might affect the adherence to the TCM regimen, and further influence the CLBR.[37] However, the underlying health conditions of patients or their adherence to the TCM regimen were not analyzed in our study. Fourthly, the precise biological mechanisms by which TCM influences fertility outcomes were still unclear. In the future, a prospective design is required to strengthen the causal inference of the findings, and it would be helpful to discuss any potential biases and how they were mitigated.

Conclusions

The role of TCM treatment on the CLBR of patients with poor ovarian response to the POSEIDON criteria was evaluated in our study. The results showed that TCM treatment was associated with increased CLBR in these patients. The findings might provide a direction for future studies to identify more effective ways to improve the pregnancy outcomes of infertility patients.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study got the approval from the Ethics Committee of Shenzhen Zhongshan Obstetrics & Gynecology Hospital (formerly Shenzhen Zhongshan Urology Hospital) (SZZSECHU-F-2021014). The written informed consent was obtained from the participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Consent for Publication

The written informed consent was obtained from the participants.

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