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Efficacy and safety of Shen Que (RN8) moxibustion on reproductive outcomes in unexpected poor ovarian responders: a randomized controlled trial

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Abstract

Background Managing infertility patients with poor ovarian response (POR) to ovarian stimulation remains unmet clinically. Besides economic burdens, patients with POR have a poor prognosis during in vitro fertilization and embryo transfer (IVF-ET). In this study, we assessed the efficacy and safety of Shen Que (RN8) moxibustion on reproductive outcomes in POSEIDON patients (Group 2a).

Methods Women eligible for IVF were invited to participate in this randomized, open-label, superiority trial at an academic fertility center from January 2022 to December 2023. One hundred patients ≤ 44 years old equally divided between Shen Que moxibustion (SQM) and control groups were randomized. These patients must meet the POSEIDON criteria, Group 2a, which requires antral follicle count (AFC) ≥ 5 or anti-müllerian hormone (AMH) ≥ 1.2ng/ml, and a previous unexpected POR (< 4 oocytes). Twelve moxibustion sessions were conducted in the SQM group prior to oocyte retrieval, while only IVF treatment was performed in the control group. The primary outcome was the number of oocytes retrieved.

Results As compared with the IVF treatment alone, the SQM + IVF treatment significantly increased the number of retrieved oocytes (4.7 vs. 5.8, $p = 0.012$), mature oocytes (3.0 vs. 5.0, $p = 0.008$), and available embryos (2.0 vs. 4.0, $p = 0.014$) in unexpected poor ovarian responders aged more than 35 years. In the SQM group, the cumulative live birth rate was 27.3% (9/33) in comparison to 13.3% (4/30) in the control group, whereas no statistical significance was detected ($p = 0.172$). During the study, no significant adverse effects were observed.

Conclusions Women with unexpected POR who meet POSEIDON Group 2a can benefit from Shen Que (RN8) moxibustion treatment.

Trial registration ClinicalTrials.gov, NCT05653557.

Keywords Shen Que, Poor ovarian response, Moxibustion, IVF-ET, POSEIDON criteria

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Introduction

Worldwide childbearing postponement has been on the rise over the past few decades due to various socioeconomic factors, including contraceptive accessibility, economic prosperity, high education level, and female workforce engagement [1, 2]. This delay contributes to a higher average age at the first attempt at conception, proportionally more live births in their thirties, and higher miscarriage rates [2, 3]. Following-through effects are evident in the disproportionate use of assisted reproductive technology (ART) services among women of advanced reproductive age [4]. Besides, women are more susceptible to POR during ovarian stimulation (OS) in their mid to late thirties because of ovarian ageing. This illustrates the critical need to devote considerably more attention to these 'low-prognosis' patients undergoing IVF-ET [5, 6].

Large discrepancies in POR definition exist in the preceding studies [7]. Moreover, the estimated POR prevalence ranges from 6 to 43%, so management of patients with POR remains a challenge for reproductive experts [8–10]. Herein, the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) classification was developed to provide a homogeneous and refined POR definition, resulting in significant heterogeneity reduction in the Bologna POR population and individualized treatment promotion [11]. Among all POSEIDON patients, group 2 (age≥35 yrs. and AFC≥5 or AMH≥1.2 ng/ml) has been estimated to constitute 36% [8]. Furthermore, POSEIDON group 2a subpopulations have a lower prognosis due to an age-related increase in oocyte euploidy, resulting in more aneuploid embryos and higher ET cancellation rates. Despite the need for more evidence, this might be accomplished, perhaps by adding complementary treatment to the OS protocol or before OS is initiated [12]. Despite the different pretreatment strategies, which include coenzyme Q10 and dehydroepiandrosterone (DHEA), insufficient evidence has been found on the efficacy of these therapeutic agents to reverse low prognosis, particularly in women with POR [13].

Acupuncture and moxibustion, as an important complementary and alternative medicine (CAM), used to treat gynecological disorders for thousands of years, have been welcomed by many infertile couples in recent years [14]. As the name suggests, moxibustion involves igniting moxa velvet or sticks, after which they burn or fumigate the corresponding acupoints to achieve the purpose of treatment and prevention of disease. According to traditional Chinese medicine (TCM) theory, Shen Que (RN8) is the place where vitality converges under the navel, and is closely connected with the vitality generated by "Shen Qi". Therefore, stimulating Shen Que (RN8) may stimulate the essence stored in the "Shen", and improve the female fertility of "Wu Qi" (age≥35 yrs.) originating from the "Inner Canon of Huangdi". Moxibustion has been shown to improve ovarian functional reserve in patients with ovarian insufficiency in previous studies [15]. Moreover, a recent study demonstrates that moxibustion can enhance the antioxidant defense ability of naturally aging ovaries and inhibiting apoptotic events [16]. Nevertheless, studies on Shen Que (RN8) moxibustion in advanced-age women with unexpected POR who undergo IVF-ET are very limited. Consequently, we designed this randomized controlled trial (RCT) to evaluate the efficacy and safety of Shen Que (RN8) moxibustion on reproductive outcomes in POSEIDON patients (Group 2a).

Materials and methods

Study design

This was a randomized, open-label, superiority, controlled trial with a 1:1 allocation to either SQM or control groups. Following the study approval by Ethics Committees of the affiliated hospital of Shandong University of TCM, all couples provided voluntary written informed consent prior to participation. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Study population

In January 2022 through December 2023, participants were recruited from the public through daily outpatient services and posters and leaflets. Interested patients were referred to the study site or self-approached to undergo eligibility assessments. Pre-screening was conducted via telephone interview. Those who were potentially eligible for recruitment to the study were interviewed face-to-face. During the interview, assessors explained the overall objectives and nature of the study, demonstrated the informed consent process, and assessed the subjects' eligibility for enrollment in the study.

Eligibility criteria

POSEIDON Group 2a is known as ≥35 years old with normal pre-stimulation ovarian reserve parameters (AFC≥5 or AMH≥1.2 ng/ml) and with an unexpected POR (fewer than 4 oocytes) after standard OS. Patients meeting these criteria will be included in the study. The exclusion criteria were as follows: (1) patients with extremely advanced age (≥45 years old); (2) individuals with a body mass index (BMI)≥35 kg/m^2; (3) those using the natural cycle or mild stimulation for IVF treatment; (4) those with a history of unilateral oophorectomy or recurrent pregnancy loss, defined as ≥2 spontaneous miscarriage; (5) acceptors of donated oocytes or performed either in vitro maturation (IVM) or blastocyst biopsy for preimplantation genetic diagnosis (PGD) or

preimplantation genetic testing for aneuploidies (PGT-A); (6) those diagnosed with congenital (e.g., mediastinal uterus and double uterus) or acquired (e.g., submucosal myoma and adenomyosis) uterine abnormalities.

Randomization and masking

Randomization was implemented via sealed, sequentially numbered, opaque envelopes containing random assignment codes. Using R software, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), a statistician, unaware of the study's objectives, generated the codes using the block randomization method. Eligible patients were randomly assigned in a 1:1 ratio to either of the two groups: the IVF treatment group (control group) or the combined Shen Que (RN8) moxibustion and IVF treatment group (SQM group).

Interventions

Participants in the SQM group were required to undergo 12 sessions of herb-partitioned moxibustion administered at RN8 (Shen Que), with a 3-day (+1 day) interval between sessions from the previous menstrual cycle day 2 before OS until oocyte retrieval. First, to prepare the Wenqi Zhongzi formula, all drugs in the formula were ground into powder, mixed evenly, and then placed into a sealed bottle. This formula contained Wu Ling Zhi (Faeces Togopteri, 6 g), Bai Zhi (Radix Angelicae Dahuricae, 6 g), Da Qing Yan (lake salt, 6 g), Shu Fu Zi (Radix Aconiti Lateralis Preparata, 3 g), Chuan Jiao (Pericarpium Zanthoxyli, 3 g) and Bing Pian (Borneolum Syntheticum, 0.3 g). Ten moxa cones are used for this procedure, which takes 120 min, and abdominal irradiation with infrared rays will be used during moxibustion. Participants in the control group were not scheduled to visit the clinic until the OS. For the duration of the procedure, patients are recommended to close their eyes and rest. Following moxibustion, the umbilicus will be affixed and sealed with a medical applicator and removed after 24 h. For the subsequent steps, consult our previously published works [17, 18]. All eligible participants must commence the gonadotrophin releasing hormone antagonist (GnRH-ant) protocol 2–3 days into the subsequent menstrual cycle. Details of our controlled OS regimen, gamete handling, IVF, intracytoplasmic sperm injection (ICSI), embryo culture, ET, and luteal support were described elsewhere [19]. Hormone replacement treatment was used for FET endometrial preparation. Treatment with estradiol valerate (E_2, Progynova, Schering AG, Berlin, Germany) was commenced on the third day of the menstrual cycle at 6 mg daily for 10–12 days. Moreover, vaginal progesterone (90 mg per day, 8% Crinone, Merck-Serono, Switzerland) and dydrogesterone (20 mg twice a day, Abbott Laboratories biologicals) were administered, upon the endometrial layer reaching a thickness of 7 mm as revealed by pelvic ultrasound scanning.

Outcome measurements

Primary outcome measure

The primary outcome was the number of oocytes retrieved per OS cycle.

Secondary outcome measures

Cycle cancellation rate is defined as cycle cancelled before obtaining at least one viable embryo for any reason. Number of Metaphase II (MII) eggs are defined as eggs retrieved that reach the MII phase. Top quality embryos (TQE) are defined as embryos with more than six even blastomeres and <20% fragmentation. Embryo implantation rate per embryo defined as the percentage of the number of the gestational sac to the total transferred embryos. Cumulative live birth rate (CLBR) was defined as the proportion of live births delivered per initiated IVF cycle or per oocyte retrieval, including all fresh and frozen embryo transfers up to one live birth.

Sample size calculation and statistical analysis

In this study, the sample size was calculated using data from our reproductive center, combined with that from a recently published study [20]. The study was designed to detect a difference between the two groups in terms of one additional retrieved oocyte after human chorionic gonadotropin (hCG) trigger day at $p=0.05$ and power=80%, with a standard deviation (SD) of 1.5 retrieved oocytes. Assuming a 20% drop-out rate, the sample size of 100 was determined using Power Analysis and Sample Size (PASS) software 2021 (NCSS, LLC. Kaysville, Utah, USA), with 50 participants were in each group. For the primary statistical analysis, we followed the per-protocol principle. We compared continuous data utilizing a student t-test or a Wilcoxon rank-sum test, and the results are given as mean (SD) or median (IQR, interquartile range). Categorical data were assessed using chi-square analysis and Fisher's exact test for expected frequencies<5. A two-sided P value of <0.05 was considered statistical significance. All analyses were performed using SPSS version 26.0 and R statistical package version 4.0.0.

Results

Enrolled patients and baseline characteristics

The baseline characteristics of patients were comparable between the study groups (Table 1). A total of 14 patients deviated from the protocol, including 6 of 50 (12.0%) in SQM group and 8 of 50 (16.0%) in control group (Fig. 1). After OS, 4 of 45 (8.9%) in SQM group had no oocytes retrieved. Additionally, 7 of 45 (15.6%) in SQM group and

Table 1 Participants' baseline characteristics on menstrual cycle days 2–3

Characteristics	SQM group ($n=50$)	Control group ($n=50$)	*P* value
Age at inclusion (years; mean (SD))	38.3 (2.3)	38.4 (2.3)	0.726
Body mass index (kg/m^2; mean (SD)) ‡	23.2 (3.5)	23.7 (3.3)	0.448
Duration of infertility (years; median (P25, P75))	3 (2, 5)	2 (2, 5)	0.189
Nulliparous	11 (22.0)	13 (26.0)	0.640
Cause of infertility			0.884
Tubal factor	34 (68.0)	31 (62.0)	
Male factor	10 (20.0)	12 (24.0)	
Mixed factor	5 (10.0)	5 (10.0)	
Unexplained infertility	1 (2.0)	2 (4.0)	
AMH (ng/ml; median (P25, P75))	1.5 (1.3, 2.1)	1.6 (1.2, 2.1)	0.956
Total AFC (mean (SD))	7.7 (2.1)	7.3 (1.6)	0.319
Basal FSH (mIU/ml; median (P25, P75))	8.0 (6.6, 11.8)	8.6 (6.5, 11.0)	0.549
Basal LH (mIU/ml; median (P25, P75))	4.8 (3.1, 6.7)	5.6 (2.9, 7.0)	0.535
Basal Estradiol (pg/ml; median (P25, P75))	27.7 (23.1, 44.4)	26.0 (19.3, 31.1)	0.201

Data are presented as numbers (%) unless otherwise noted

In any of the baseline characteristics, no significant differences between groups were observed ($P<0.05$)

SQM=Shen Que Moxibustion; SD=standard deviation; P25=25th percentile; P75=75th percentile; AMH=anti-müllerian hormone; AFC=antral follicle count; FSH=follicle stimulating hormone; LH=luteinizing hormone

‡ Body mass index is weight (kg) divided by height squared (m^2)

15 of 46 (32.6%) in control group did not have an embryo available for transfer (Table S1).

OS and pregnancy outcomes

The primary statistical analysis was performed according to the per-protocol (PP) principle. Table 2 presents the primary outcomes. In the SQM group, the number of retrieved oocytes (5.8 vs. 4.7, $p=0.012$), mature oocytes (5.0 vs. 3.0, $p=0.008$), and available embryos (4.0 vs. 2.0, $p=0.014$) were significantly more than that in the control group. Furthermore, the SQM group has a higher percentage of patients with surplus frozen embryos after first ET (69.7% vs. 40.0%, $p=0.018$). Other secondary outcomes, including the frequency of top-quality embryos and cycle cancellation rate, were similar between the groups. The embryo implantation rate (29.5% vs. 19.2%, $p=0.116$), Live birth rate (LBR) per fresh ET (23.5% vs. 15.4%, $p=0.672$) or FET (26.7% vs. 15.2%, $p=0.224$), and CLBR (27.3% vs. 13.3%, $p=0.172$) in the SQM group was slightly higher, although not significantly more than that in the control group. As shown in Table S1, the intention-to-treat (ITT) analysis results were consistent with those from the PP analysis.

Safety outcomes

No adverse events occurred in either SQM group versus control group. Safety indicators of complete blood cell count and liver and kidney function before and after treatment were within reasonable limits in both groups.

Discussion

To our knowledge, this is the first RCT performed to examine herb-partitioned SQM effects on reproductive outcomes in patients undergoing IVF-ET who fulfilled POSEIDON group 2a. In this open-label RCT, we found no significant differences in LBR per ET and CLBR between SQM and control groups. However, herb-partitioned SQM resulted in more retrieved oocytes, mature oocytes, and available embryos than IVF treatment alone.

Over 40% of patients treated in fertility centers are POSEIDON patients, despite geographical variations in prevalence. [21]. A solid and independent predictor of live birth is the number of oocytes retrieved during OS. POSEIDON patients of groups 1 and 2 are therefore managed primarily with the aim of maximizing their ovarian reserve and subsequently, the number of oocytes and embryos, thus increasing the chance that at least one euploid embryo can be transferred [22]. POR results in decreased oocyte production, cycle cancellation, and poor pregnancy outcomes [23]. Several clinical and non-clinical studies have attempted to develop OS protocols for POR and to assess the effect of adjuvant therapy with hormone supplementation or acupuncture. [24]. Moreover, a recent study suggests that acupuncture may improve AMH, AFC and the number of retrieved oocytes among women undergoing IVF-ET with POR [25]. Acupuncture interventions have been shown to benefit poor ovarian responders in numerous studies [26].

However, very few scholars have evaluated the effects of moxibustion on patients with POR, especially those with herb-partitioned SQM. Moxibustion is commonly used in the treatment of gynecological diseases because

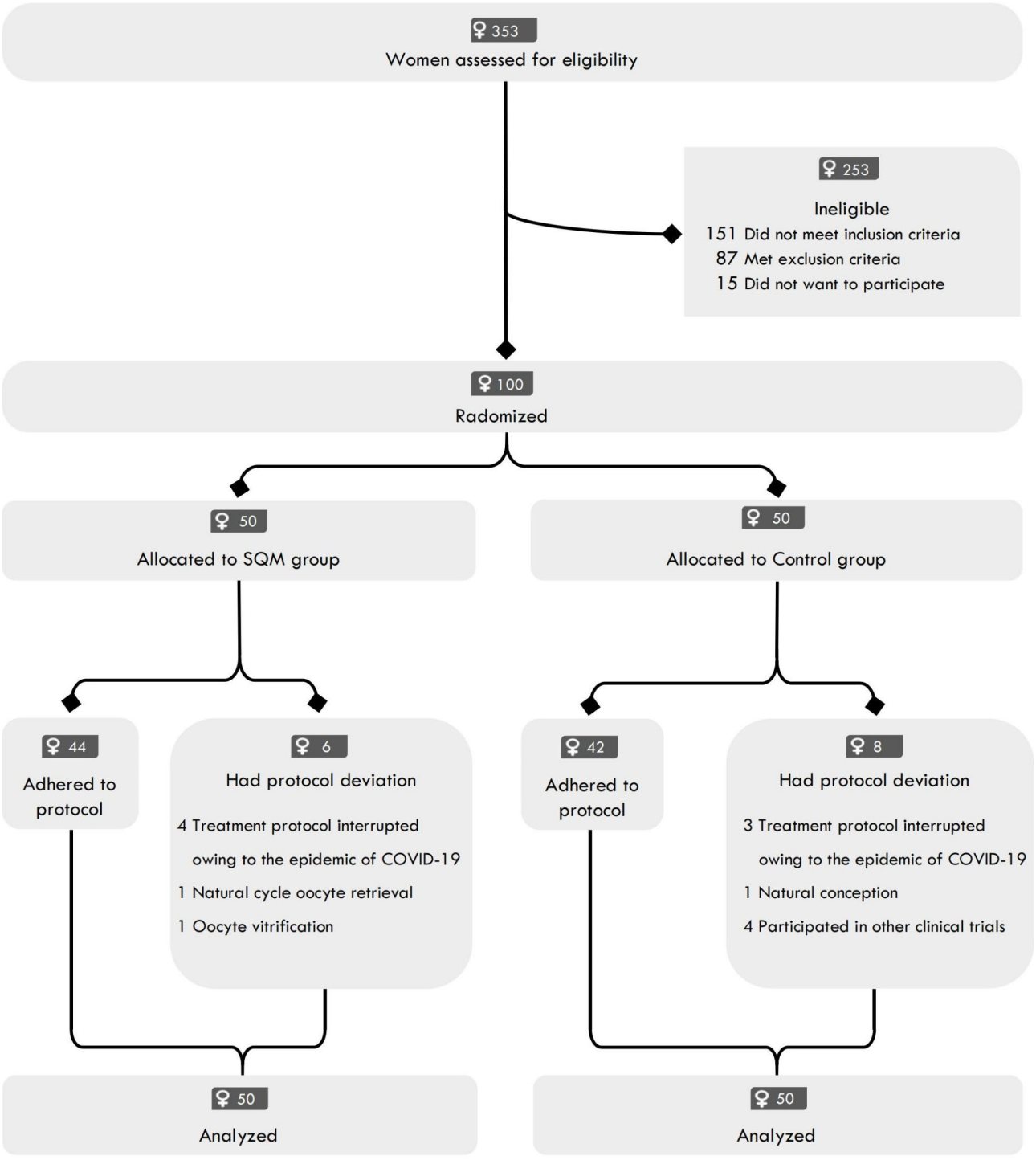

Fig. 1 Flow chart of the study design

of the development of CAM. There are several benefits of moxibustion, such as simple operation, long-lasting results, low cost, ease of acceptance, no discomfort from needles, and no side effects [26–28]. As a novel and pioneering clinical study, we have discovered for the first time that herb-partitioned SQM can increase the number of oocytes retrieved, mature oocytes, and transferable embryos for POSEIDON patients in group 2a.

Acupuncture and moxibustion have been employed as a treatment for infertility due to its ability to enhance the endometrium, stimulate ovulation, and alleviate discomfort during egg retrieval. Furthermore, acupuncture is

Table 2 IVF/ICSI outcomes and cumulative live birth rates in study population

Characteristics	SQM group (*n* = 44)	Control group (*n* = 42)	*P* value
No of days of COS (mean (SD))	9.1 (2.0)	9.4 (2.3)	0.529
Total Gn dose administered (IU; median (P25, P75))	2212.5 (1800.0, 2703.1)	2400.0 (1912.5, 3112.5)	0.143
E_2 on hCG trigger day (pg/ml; median (P25, P75))	2341.0 (1431.5, 2500.0)	2079.0 (1316.5, 2653.8)	0.887
P_4 on hCG trigger day (ng/ml; median (P25, P75))	0.8 (0.6, 1.2)	0.8 (0.4, 1.2)	0.577
Method of fertilization			0.573
IVF	29 (70.7)	32 (76.2)	
ICSI	12 (29.3)	10 (23.8)	
No of oocytes retrieved (mean (SD))	5.8 (1.9)	4.7 (1.9)	**0.012**
No of mature oocytes (median (P25, P75))	5.0 (3.5, 5.0)	3.0 (2.0, 5.0)	**0.008**
Embryos obtained (median (P25, P75))	4.0 (2.0, 5.0)	2.0 (1.0, 3.0)	**0.014**
Top-quality embryos ¶	28/112 (25.0)	15/73 (20.5)	0.483
Cycle cancellation rate †	11 (25.0)	12 (28.6)	0.708
Patients with surplus frozen embryos after first ET	23/33 (69.7)	12/30 (40.0)	**0.018**
Embryo implantation rate	33/112 (29.5)	14/73 (19.2)	0.116
Cumulative LBR	9/33 (27.3)	4/30 (13.3)	0.172
LBR per transfer fresh	4/17 (23.5)	2/13 (15.4)	0.672
LBR per transfer FET	12/45 (26.7)	5/33 (15.2)	0.224

Data are number/total number or number (%) unless stated otherwise

SQM = Shen Que Moxibustion; COS = controlled ovarian stimulation; SD = standard deviation; Gn = Gonadotrophin; E_2 = Estradiol; P_4 = Progesterone; P25 = 25th percentile; P75 = 75th percentile; hCG = human chorionic gonadotropin; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; ET = embryo transfer; LBR = live birth rate; FET = frozen embryo transfer

¶ Typically, a good, normally growing Day-3 embryos will contain between 6 and 10 cells

† Cycle cancellation is defined as cycle cancelled before obtaining at least one viable embryo for any reason

frequently used in conjunction with IVF to improve fertilization rates [29]. Based on previous studies by Ho et al. and Stener-Victorin et al., electroacupuncture has the potential to decrease uterine artery blood flow impedance in infertile women undergoing IVF [30, 31]. Given that ovarian stromal blood flow is commonly utilized to predict ovarian response prior to IVF, it is plausible that acupuncture or moxibustion could potentially influence ovarian response [32]. As indicated by previous research, moxibustion can enhance ovarian function by reducing mitochondrial dysfunction and NLRP3-induced inflammation [33], modulating PI3K/AKT signaling pathways to suppress granulosa cell death [34], activating the Nrf2/HO-1 pathway to mitigate inflammation [35], and augmenting antioxidant defense [16]. However, the acupoints for moxibustion in the above studies mainly focused on Shen Shu (BL23), Guan Yuan (CV4), and Zhong Wan (CV12), only one study addressed Shen Que (RN8) [33]. At present, the existing literature on moxibustion at Shen Que (RN8) point in the world mainly focuses on the treatment of primary dysmenorrhea [36], so this study provides robust evidence for the promotion of SQM in POR.

However, our study also has some limitations. Firstly, for POR patients, more oocytes mean more opportunities, so we chose the number of oocytes obtained as the primary outcome, rather than the ultimate goal of assisted reproduction, live birth, although we achieved positive results. Secondly, the sample size is not large, which is of course also related to the choice of retrieved oocytes as the primary outcome, which consequently led to no statistical significance despite higher LBR and CLBR in the SQM group. Perhaps a larger sample size would be a better choice in the future. Moreover, the results of this study cannot exclude the placebo effect, therefore, using nontreatment as a control may exaggerate the effect of SQM. Finally, we only used cleavage stage embryos for transfer, which affected the universality of this study.

Conclusions

For women with unexpected POR who meet POSEIDON Group 2a, herb-partitioned SQM (RN8) can improve their egg retrieval and embryo outcomes, which is worth recommending. However, future studies still need to expand the sample size to evaluate pregnancy outcomes.

Abbreviations

POR	Poor ovarian response
IVF-ET	In vitro fertilization and embryo transfer
SQM	Shen Que moxibustion
AFC	Antral follicle count
AMH	Anti-müllerian hormone
ART	Assisted reproductive technology
OS	Ovarian stimulation
POSEIDON	Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number
DHEA	Dehydroepiandrosterone
CAM	Complementary and alternative medicine

TCM	Traditional Chinese Medicine
RCT	Randomized controlled trial
CONSORT	Consolidated Standards of Reporting Trials
BMI	Body mass index
IVM	In vitro maturation
PGD	Preimplantation genetic diagnosis
PGT-A	Preimplantation genetic testing for aneuploidies
GnRH-ant	Gonadotrophin releasing hormone antagonist
ICSI	Intracytoplasmic sperm injection
TQE	Top quality embryos
CLBR	Cumulative live birth rate
hCG	Human chorionic gonadotropin
SD	Standard deviation
IQR	Interquartile range
PP	Per-protocol
ITT	Intention-to-treat
LBR	Live birth rate

Supplementary Information

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Supplementary Material 1

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Author contributions
Zhen-Gao Sun and Yu-Xia Ma conceived and designed the study; Jing-Yan Song was responsible for analysis and interpretation of the data and the drafting of the paper; Zhen-Gao Sun and Jing-Yan Song were responsible for data curation and supervision; Zhen-Gao Sun critically revised its intellectual content. All authors have approved the manuscript and agreed to be accountable for all aspects of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been reviewed by the Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (SDUTCM-2021-011), and written informed consent was obtained from all individuals involved in the study. And the study was registered at the ClinicalTrials.gov (NCT05653557, 08/12/2022).

Consent for publication
All the authors listed have approved the manuscript that is enclosed.

Competing interests
The authors declare no competing interests.

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