

Research Article

Clinical Efficacy of Traditional Chinese Medicine Chaihu-Guizhi-Ganjiang Decoction Combined With Danggui-Shaoyao-San for the Treatment of Oligomenorrhea: A Prospective, Open-Label Clinical Study

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Objective: To assess the efficacy and safety of Chaihu-Guizhi-Ganjiang decoction (CGGJD) combined with Danggui-Shaoyao-San (DS) in oligomenorrhea treatment.

Methods: In this prospective open-label trial, 35 oligomenorrhea patients (30–40 years) received CGGJD-DS for 3 months, followed by a 2-month follow-up. Outcomes included clinical efficacy rate, menstrual pattern and frequency, serum hormones (E2, LH, and FSH), uterine spiral artery indices (RI, PI, and S/D), endometrial blood flow parameters (VI, FI, and VFI), and endometrial thickness assessed pre-/post-treatment and post-follow-up.

Results: Post-treatment menstrual pattern and frequency both significantly increased versus baseline ($p < 0.01$), with a 68.6% total efficacy rate. E2 levels significantly increased post-treatment and post-follow-up (both $p < 0.01$), while LH and FSH decreased significantly (both $p < 0.01$). Significant improvements occurred in spiral artery indices (all $p < 0.01$), endometrial blood flow parameters (all $p < 0.01$), endometrial blood distribution (Wald $\chi^2 = 20.8$, $p < 0.01$), and endometrial thickness ($p < 0.01$). No serious adverse events occurred.

Conclusions: CGGJD-DS effectively improves ovarian function and endometrial perfusion in oligomenorrhea, demonstrating potential as an alternative therapy.

Keywords: Chaihu-Guizhi-Ganjiang decoction; Danggui-Shaoyao-San; oligomenorrhea

1. Introduction

Oligomenorrhea, characterized by infrequent menstruation (cycle lengths > 35 days), affects 10%–15% of reproductive-aged women [1]. This condition increases risks of infertility, cardiovascular disease, anxiety, and other complications [2]. Key pathological factors include ovarian dysfunction [3], PCOS [4], hyperprolactinemia [5], stress, endometrial thinning [6], and estrogen deficiency [7]. Although

hormonal therapy remains first-line treatment [8], its adverse effects and high postdiscontinuation recurrence rates drive demand in China for safer alternatives with demonstrated efficacy [9].

With oligomenorrhea prevalence at 12.18% among Chinese women [10], alternative therapies are needed. Randomized trials support electroacupuncture for PCOS-related oligomenorrhea [11] and fennel seed infusion with cupping therapy [12]. Zhenqi Buxue Oral Liquid combined

with progesterone also shows promise [13]. Classical texts (e.g., Shang-Han-Za-Bing-Lun) suggest Chaihu-Guizhi-Ganjiang decoction (CGGJD) and Danggui-Shaoyao-San (DS) for gynecological disorders. CGGJD improves mood in menopausal women [14], while DS enhances ovulation in rats [15] and ameliorates luteal insufficiency without disrupting normal cycles [16].

Integrating traditional theory with modern evidence, CGGJD combined with DS (CGGJD-DS) may benefit oligomenorrhea patients. However, systematic clinical mechanistic studies are limited. This prospective open-label study therefore evaluated CGGJD-DS's therapeutic efficacy and safety for oligomenorrhea, generating data to inform future randomized controlled trials.

2. Materials and Methods

2.1. Study Design. This single-center clinical study (clinical trial registry: TCTR202204010) was conducted at the Tian-He hospital in Lin-Yi city, Shandong Province, China, from May 2022 to March 2024. This study was approved by the ethics committees of Tian-He Hospital (No: T20220402) on March 28, 2022, and conducted in accordance with the 1964 Helsinki Declaration. All patients provided written consent to participate.

This pilot study on the feasibility, safety, and preliminary efficacy of the CGGJD-DS intervention did not include a formal a priori sample size calculation. Instead, a pragmatic sample of 40 participants was targeted, reflecting the expected number of eligible patients recruitable over a 22-month period. This was deemed adequate for evaluating feasibility endpoints and collecting preliminary performance data. All enrolled oligomenorrhea patients received a physical examination (height, weight, hirsutism, and acne) and blood tests (complete blood count, liver, and kidney function).

2.2. Diagnostic Criteria for Eligible Patients

- (1) Oligomenorrhea was defined as 5–8 menstrual periods per year or cycle lengths of 35–90 days, persisting for ≥ 3 consecutive cycles [17].
- (2) TCM Syndrome Diagnosis (Liver Qi Stagnation with Qi-Blood Deficiency).

1. Required manifestations:

- ① Oligomenorrhea
- ② Pale tongue with thin white coating
- ③ Pulse: Weak/thready *and/or* wiry

2. Secondary manifestations (≥ 2 required):

- ① Irritability/mood swings
- ② Breast distension (especially premenstrual).
- ③ Persistent fatigue
- ④ Dizziness or lightheadedness
- ⑤ Pale or sallow complexion
- ⑥ Hypochondriac/lower abdominal distension

3. Supportive signs (strengthen diagnosis): Menstrual clots (small, dark), reduced menstrual flow (< 2 days duration), and dry nails/hair.

- (3) Hormonal Panel Assessment: Measurement of serum testosterone, dehydroepiandrosterone sulfate (DHEA-S), and androstenedione to exclude non-PCOS hyperandrogenism; thyroid-stimulating hormone (TSH) and free thyroxine (FT4) to exclude thyroid dysfunction; prolactin (PRL) to exclude hyperprolactinemia; and follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) to assess hypothalamic-pituitary-ovarian axis function. A diminished ovarian reserve was screened for based on age and FSH levels.
- (4) Pelvic Ultrasound: Transvaginal or transabdominal ultrasonography was performed to evaluate ovarian morphology (e.g., to exclude polycystic ovarian morphology based on the Rotterdam criteria if applicable) and to assess the uterus and endometrial lining for obvious pathologies.
- (5) Clinical History and Examination: A thorough clinical interview and examination were conducted to exclude other significant etiologies such as a recent history of breastfeeding, significant weight change, excessive exercise, or other systemic illnesses.
- (6) Aged 30–40.

2.3. Exclusion Criteria Were as Follows

- (1) Presented with other causes of hyperandrogenism
- (2) Had been breast feeding in the past 6 months
- (3) Received hormonal contraceptives within the past 3 months
- (4) Had a history of liver or kidney pathologies, or presented with abnormal liver and/or kidney function
- (5) Had a history of psychotic illness or eating disorders
- (6) Had currently active major depression
- (7) Thyroid disease, Cushing's disease, congenital adrenal hyperplasia, hyperprolactinemia, or anemia
- (8) Reported known allergies to herbal ingredients.

2.4. The Preparation and Treatment of CGGJD-DS Formulation. According to TCM theory, CGGJD combined with TS comprises 12 herbal materials (Table 1 shows the pharmaceutical composition and dosage). All herbs strictly conformed to Chinese Pharmacopoeia standards. The CGGJD-DS formulation, prepared by the hospital TCM Pharmacy, was subjected to an integrated quality control strategy: high-performance liquid chromatography (HPLC) quantified key bioactive markers (e.g., saikosaponins, paeoniflorin), and electrochemical fingerprinting characterized redox-active constituents. Statistical correlation analysis was then used to cross-validate these bioactive components, ensuring both compliance with

TABLE 1: Contents of standardized Chinese herbal medicine prescription of CGGJD combined with DS.

Chinese Pinyin name	Common name	Part used	Dried herbal daily dosage (g)	Percentage
Chai Hu	<i>Radix Bupleuri</i>	Root	12	8.7
Gui Zhi	<i>Cassia twig</i>	Twig	9	6.5
Gan Jiang	<i>Rhizoma zingiberis</i>	Rhizome	6	4.4
Huang Qin	<i>Scutellaria baicalensis</i>	Root	9	6.5
Mu Li	<i>Oyster</i>	Shell	15	10.9
Tian hua fen	<i>Radix trichosanthis</i>	Root	12	8.7
Dang Gui	<i>Angelica sinensis</i>	Root	15	10.9
Shao Yao	<i>Radix Paeoniae Alba</i>	Root	15	10.9
Chuan Xiong	<i>Ligusticum chuanxiong Hort</i>	Rhizome	12	8.7
Fu Ling	<i>Poria cocos</i>	Sclerotium	12	8.7
Ze Xie	<i>Alismatis Rhizoma</i>	Rhizome	9	6.5
Bai Zhu	<i>Atractylodes macrocephala Koidz</i>	Rhizome	12	8.7

pharmacopoeial specifications and batch-to-batch consistency of the formulation.

Within the first month of treatment, each dose of herbal medicine was added to 1000 mL of water at room temperature and soaked for 30 min. To make the decoction, fresh ginger (approximately 10 g, based on three slices of 2–3 cm diameter) and dried jujube fruits (approximately 12 g, based on three medium-sized fruits) were added at the same time. Each dose of herbal medicine was brought to a boil over high heat and then simmered for 15 min. The residue was filtered to obtain 400 mL of liquid, and the patients took 200 mL twice daily after meals. During the second and third months of the treatment period, participants were prescribed 60 g of granulated extracts per day: 30 g each time, taken with hot water as a tea, twice daily. The 3-month treatment period was followed by a 2-month follow-up, a duration selected to balance scientific assessment with practical feasibility and to minimize dropout risk.

2.5. Patient Evaluation

2.5.1. Menstrual Pattern Changes and Total Effective Rate. Menstrual frequency per 28-day interval was calculated using established methods from prior studies [18]. Through this menstrual data collection approach, we compared the following parameters before versus after treatment for each patient: the average number of menstrual periods during 3 months, cycle length changes, bleeding duration, and menstrual volume quantification; additionally, the average number of menstrual periods during the final 4 months (comprising the last two treatment months and two follow-up months) was included in statistical analysis. Clinically, a normal menstrual frequency constitutes 9–12 cycles annually, while oligomenorrhea is defined as 3–8 cycles per year; thus, experiencing three menstruations during the last four months (treatment and follow-up period) was considered treatment effectiveness, with the total effective rate calculated as (effective cases/total cases) \times 100%.

2.5.2. Sex Hormones Determination. Fasting blood samples were collected before and after treatment for sex hormone quantification. Serum E2, FSH, and LH levels were measured

using chemiluminescent immunoassay on Day 3 of the menstrual cycle for all patients. (Note: Day 1 of the menstrual cycle was defined as the first day of visible bleeding requiring sanitary protection.)

2.5.3. Ultrasound Examination of the Endometrium. At baseline and at the third and fifth months after treatment, patients underwent transvaginal ultrasonography using a 6 MHz probe with Envisor C Color Doppler Ultrasound (Royal Philips Electronics Inc., Amsterdam, Holland) 6–7 days after ovulation (confirmed by a positive urine LH test strip). Dr. Xiu-Liu performed all examinations with patients in the lithotomy position and with a completely empty bladder, comprehensively assessing the blood flow in the uterine spiral arteries and endometrial arteries, as well as the endometrial thickness. The uterus was visualized in the longitudinal section to visualize the entire endometrial and subendometrial areas, with the subendometrial region, situated 10 mm beneath the myometrial-endometrial junction, specifically assessed.

Using power Doppler in the two-dimensional (2-D) mode on selected areas, the following parameters of the uterine spiral arteries were electronically calculated: (i) resistance index (RI): the difference between peak systolic and end-diastolic flow velocities divided by the peak systolic velocity ((S-D)/S); (ii) pulsatility index (PI): the difference between peak systolic and end-diastolic flow velocities divided by the mean flow velocity throughout the cardiac cycle ((S-D)/mean); and (iii) the systolic/diastolic ratio (S/D). Following confirmation of continuous waveforms, an average of 3–5 cardiac cycles was selected for calculation of RI, PI, and S/D.

In addition to the above ultrasound parameters, the endometrial blood flow indices, including vascular index (VI), flow index (FI), and vascularization flow index (VFI), were also measured. Moreover, the endometrial–subendometrial blood flow distribution pattern was classified as follows [19]: Type A: No detectable endometrial or subendometrial flow; Type B: Presence of subendometrial flow only; and Type C: Presence of endometrial and subendometrial flow. Finally, endometrial thickness was measured at its thickest point between the two basal layers of the anterior and posterior uterine walls on sagittal plane images.

2.6. Statistical Analysis. Data were analyzed using SPSS 22.0 (IBM, Chicago, IL, USA). Continuous variables are expressed as mean \pm standard deviation (SD). Categorical data (e.g., endometrial blood distribution pattern) are expressed as frequencies.

Repeated Measures Analysis: Changes in the average number of menstruations, hormone levels (E2, FSH, LH), uterine spiral arterial flow indices (RI, PI, and S/D), endometrial blood flow indices (VI, FI, and VFI), and endometrial thickness before, during, and after treatment were analyzed using repeated-measures ANOVA. When the omnibus F-test indicated significance ($p < 0.05$), Bonferroni-adjusted post hoc tests were performed for pairwise comparisons between observation time points.

For cycle length, bleeding duration, and menstrual volume, 5-month average values before treatment were compared to 5-month post-treatment averages using paired *t*-tests.

Categorical Blood Flow Type Analysis: Uterine blood flow types (A, B, C) across three time points were compared using generalized estimating equations (GEE) with an exchangeable correlation structure and multinomial logit link, quantifying type transition odds ratios (OR) versus pre-treatment. Sensitivity analyses for blood flow type transitions included exact McNemar–Bowker tests (10,000 Monte Carlo replicates) and Fisher–Freeman–Halton tests ($\alpha = 0.05$ performed in R). A significance level of $p < 0.05$ was used throughout.

3. Results

All analyses adhered to intention-to-treat principles ($N = 35$). Six participants discontinued: three due to scheduling conflicts (unrelated to adverse events), two were lost to follow-up, and one due to an unrelated health issue (appendectomy). No discontinuations were intervention-related. Twenty-nine participants completed the protocol. Missing continuous data from noncompleters were imputed using last observation carried forward.

At baseline, 25 participants exhibited abnormal E2, LH, and FSH levels, and 19 had suboptimal endometrial thickness. Seventeen participants presented with concurrent hormonal abnormalities and reduced endometrial thickness.

3.1. Menstrual Outcomes

3.1.1. Treatment Efficacy. During treatment and follow-up months 2–5, 24 participants (68.6%, 24/35) experienced three menstruations.

3.1.2. Menstruation Frequency. The average number of menstruations increased significantly compared to pre-treatment baseline both 3 months post-treatment ($t = -6.765$, $p < 0.001$; Cohen's $d = -1.15$, 95% CI $[-1.58, -0.717]$) and during the final 4 months (months 2–5; $t = -6.606$, $p < 0.001$; $d = -1.06$, $[-1.48, -0.643]$; Table 2).

3.1.3. Cycle Length. Mean menstrual cycle length decreased significantly from 68.07 ± 20.74 days to 40.97 ± 8.93 days post-treatment ($T = 6.76$, $P < 0.001$; $d = 1.26$, $[0.760, 1.74]$).

3.1.4. Bleeding Duration. Mean bleeding duration increased significantly from 2.34 ± 0.64 days to 3.17 ± 0.66 days post-treatment ($t = -6.56$, $p < 0.001$; $d = -1.11$, $[-1.53, -0.681]$).

3.1.5. Menstrual Volume (Using Higham Pictorial Blood Assessment Chart). Scores increased significantly from 28.13 ± 4.83 to 38.66 ± 7.67 post-treatment ($T = -8.39$, $P < 0.001$; $d = -1.42$, $[-1.88, -0.941]$).

3.2. Hormonal Profiles. E2 levels increased significantly versus baseline at both end-of-treatment ($t = -9.36$, $d = -1.605$, $[-2.10, -1.096]$) and follow-up ($t = -5.64$, $d = -0.966$, $[-1.36, -0.558]$; both $p < 0.001$; Table 3). Both LH (end-of-tx: $t = 6.63$, $d = 0.988$, $[0.578, 1.39]$; Follow-up: $t = 5.07$, $d = 0.825$, $[0.436, 1.21]$) and FSH levels (end-of-tx: $t = 3.60$, $d = 0.610$, $[0.245, 0.968]$; follow-up: $t = 3.60$, $d = 0.615$, $[0.250, 0.974]$) decreased significantly from baseline (all $p < 0.01$; Table 3). Following treatment, 22 of the 25 participants with baseline hormonal abnormalities achieved normalization.

3.3. Uterine Hemodynamic Parameters. Significant bilateral improvements were observed in all uterine spiral arterial flow indices during treatment and follow-up compared to baseline (all $P < 0.001$; Table 4).

RI: Left ($t_1 = 5.61$, $d = 0.959$, $[0.552, 1.36]$; $t_2 = 5.10$, $d = 0.872$, $[0.477, 1.26]$), right ($t_1 = 8.81$, $d = 1.38$, $[0.907, 1.84]$; $t_2 = 7.17$, $d = 1.20$, $[0.757, 1.63]$).

PI: Left ($t_1 = 7.10$, $d = 1.21$, $[0.766, 1.64]$; $t_2 = 6.17$, $d = 1.06$, $[0.637, 1.47]$), right ($t_1 = 9.46$, $d = 1.61$, $[1.100, 2.11]$; $t_2 = 7.44$, $d = 1.26$, $[0.808, 1.70]$).

S/D: Left ($t_1 = 10.24$, $d = 1.69$, $[1.16, 2.20]$; $t_2 = 9.35$, $d = 1.55$, $[1.05, 2.04]$), right ($t_1 = 10.54$, $d = 1.79$, $[1.25, 2.33]$; $t_2 = 9.63$, $d = 1.64$, $[1.12, 2.14]$).

3.4. Endometrial Blood Flow. VI, FI, and VFI all showed significant improvements versus baseline at both time points (all $p < 0.001$; Table 5): VI: $t_1 = -9.80$, $d = -1.64$, $[-2.14, -1.12]$; $t_2 = -10.22$, $d = -1.68$, $[-2.19, -1.16]$. FI: $t_1 = -7.12$, $d = -1.181$, $[-1.61, -0.742]$; $t_2 = -4.73$, $d = -0.787$, $[-1.16, -0.402]$. VFI: $t_1 = -7.84$, $d = -1.310$, $[-1.76, -0.851]$; $t_2 = -4.72$, $d = -0.809$, $[-1.19, -0.422]$.

3.5. Endometrial Thickness. Endometrial thickness increased significantly at both assessment points versus baseline ($t_1 = -6.50$, $d = -0.996$, $[-1.40, -0.585]$; $t_2 = -7.63$, $d = -1.072$, $[-1.48, -0.650]$; both $p < 0.001$; Table 5). Consequently, 16 of 19 participants with baseline endometrial thickness achieved normalization following treatment.

TABLE 2: Comparison of average number of menstruations before and after treatment.

Time	Average number of menstruations ($n = 21$)	Statistical value
Three months before treatment (baseline)	0.44 ± 0.16	
Three months after treatment	0.62 ± 0.19*	$t = -4.35, p < 0.001$
The last four months (including 2 months of treatment and 2 months of follow-up)	0.70 ± 0.15*	$t = -7.64, p < 0.001$

*Represents statistical differences.

TABLE 3: Scores of E₂, LH, and FSH before and after the treatment.

Observation time	E ₂ (Pg/mL)	LH (IU/L)	FSH (IU/L)
Before treatment (T1)	24.96 ± 6.2	6.71 ± 2.05	10.80 ± 2.83
After treatment (T2)	31.49 ± 4.42	3.83 ± 0.61	8.20 ± 1.07
The end of follow-up (T3)	29.79 ± 2.16	3.80 ± 0.34	8.45 ± 0.78
Statistical value	F = 21.89* $p < 0.001$	F = 34.69* $p < 0.001$	F = 32.4* $p < 0.001$
T, p value			
T1-T2	$t = -10.09^*$ $p < 0.001$	$t = 6.918^*$ $p < 0.001$	$t = 5.88^*$ $p < 0.001$
T1-T3	$t = -5.24^*$ $p < 0.001$	$t = 8.249^*$ $p < 0.001$	$t = 5.25^*$ $p < 0.001$
T2-T3	$t = 2.37$ P = 0.085	$t = 0.202$ P = 1.000	$t = -1.01$ P = 0.609

*Represents statistical differences.

TABLE 4: Scores of uterine spiral arterial flow before and after the treatment.

Observation time	Uterine spiral arterial flow (left)			Uterine spiral arterial flow (right)		
	RI	PI	S/D	RI	PI	S/D
Before treatment (T1)	0.90 ± 0.12	2.74 ± 0.39	6.41 ± 0.56	0.91 ± 0.10	2.67 ± 0.24	6.48 ± 0.57
After treatment (T2)	0.72 ± 0.09	2.26 ± 0.31	5.52 ± 0.45	0.70 ± 0.10	2.18 ± 0.27	5.47 ± 0.46
The end of follow-up (T3)	0.77 ± 0.05	2.32 ± 0.31	5.48 ± 0.39	0.74 ± 0.07	2.30 ± 0.20	5.44 ± 0.38
Statistical value	F = 3.39* P = 0.044	F = 5.19* P = 0.010	F = 25.53* $p < 0.001$	F = 8.34* $p < 0.001$	F = 14.05* $p < 0.001$	F = 19.31* $p < 0.001$
T, p value						
T1-T2	$t = 6.45^*$ $p < 0.001$	$t = 6.792^*$ $p < 0.001$	$t = 12.673^*$ $p < 0.001$	$t = 9.30^*$ $p < 0.001$	$t = 9.44^*$ $p < 0.001$	$t = 12.177^*$ $p < 0.001$
T1-T3	$t = 4.52^*$ $p < 0.001$	$t = 6.330^*$ $p < 0.001$	$t = 11.227^*$ $p < 0.001$	$t = 6.47^*$ $p < 0.001$	$t = 8.62^*$ $p < 0.001$	$t = 10.214^*$ $p < 0.001$
T2-T3	$t = -2.34$ P = 0.092	$t = -0.937$ P = 1.000	$t = 0.728$ P = 1.000	$t = -1.43$ P = 0.503	$t = -2.16$ P = 0.131	$t = 0.318$ P = 1.000

*Represents statistical differences.

3.6. Blood Flow Distribution Type. Significant redistribution occurred over time (Wald $\chi^2 = 41.3, df = 4, p < 0.001$). Type B odds increased significantly versus pretreatment (2 months: OR = 30.6, [9.8, 95.4], $p < 0.001$; 5 months: OR = 36.9, [11.6, 117.5], $p < 0.001$). Transitions from Type A to B occurred in 57.1% (20/35) at 2 months and 60.0% (21/35) at 5 months (both exact $p < 0.001$). No significant differences existed between 2 and 5 months (exact McNemar-Bowker $p = 0.317$), indicating stability by month 2 (Table 5). Sensitivity analyses confirmed robustness (Fisher-Freeman-Halton $p < 0.001$).

3.7. Safety. No serious adverse events occurred. Mild, transient gastrointestinal symptoms were reported: bloating/nausea ($n = 3$) and loose stools ($n = 2$). Symptoms resolved

spontaneously or with massage. No participants withdrew due to adverse effects. No clinically significant abnormalities were detected in blood counts, liver function, or renal function during treatment or follow-up.

4. Discussion

4.1. CGGJD-DS Exhibits Phytoestrogenic Effects. Dysfunction of gonadal hormone secretion and disruption of the hypothalamus-pituitary-ovary (HPO) axis are primary causes of oligomenorrhea [20]. HPO axis impairment can lead to LH secretion disorders [21] and estrogen deficiency, resulting in menstrual disorders including amenorrhea and oligomenorrhea [22]. In this study, significant pre-/post-treatment estrogen changes in some patients demonstrate that CGGJD-DS regulates hormonal activity.

TABLE 5: Changes of endometrial blood flow and thickness before and after the treatment.

Observation time	Endometrial blood index			Endometrial blood distribution pattern			Endometrial thickness (mm)
	VI	FI	VFI	Type A	Type B	Type C	
Before treatment (T1)	1.53 ± 0.22	17.85 ± 1.93	0.34 ± 0.11	17	4	0	7.64 ± 0.48
After treatment (T2)	2.10 ± 0.25	20.70 ± 2.00	0.44 ± 0.07	5	14	2	9.56 ± 0.88
The end of follow-up (T3)	2.22 ± 0.21	20.26 ± 1.73	0.46 ± 0.09	4	15	2	9.33 ± 0.49
Statistical value	$F = 24.46^*$ $p < 0.001$	$F = 27.21^*$ $p < 0.001$	$F = 5.86^*$ $p = 0.006$	$\chi^2 = 20.8^*$	$p < 0.001$		$F = 13.18^*$ $p < 0.001$
<i>T, p value</i>							
T1-T2	$t = -9.13^*$ $p < 0.001$	$t = -6.54^*$ $p < 0.001$	$t = -6.41^*$ $p < 0.001$	$\chi^2 = 14.1^*$	$p < 0.001$		$t = -10.576^*$ $p < 0.001$
T1-T3	$t = -12.25^*$ $p < 0.001$	$t = -6.93^*$ $p < 0.001$	$t = -4.74^*$ $p < 0.001$	$\chi^2 = 16.4^*$	$p < 0.001$		$t = -13.905^*$ $p < 0.001$
T2-T3	$t = -1.98$ $p = 0.187$	$t = 0.173$ $p = 0.228$	$t = -1.05$ $p = 0.918$	$\chi^2 = 0.146$	$p = 0.930$		$t = 0.933$ $p = 0.627$

*Represents statistical differences.

Saikosaponin, extracted from *Radix Bupleuri*, structurally resembles estradiol, with studies confirming its estrogen receptor-mediated activity [23]. Modern pharmacology further validates the estrogenic activity of *Scutellaria baicalensis* [24]. Additionally, oyster extract alleviates ovarian dysfunction in female rats by elevating serum estradiol levels and reducing FSH receptor expression in ovarian tissues [25].

DS directly stimulates ovarian progesterone/estradiol production in vitro [26], yet restores uterine atrophy and plasma estradiol in vivo without activating estrogen receptors [27]. This supports its therapeutic potential for menopausal syndromes and oligomenorrhea. Furthermore, DS significantly stimulates 17 β -estradiol secretion and promotes ovulation in vitro [28], indicating dual stimulatory effects on steroidogenesis and ovulatory processes for treating ovulatory disorders. DS also induces bovine oviductal contraction via the G protein-coupled estrogen receptor, potentially accelerating embryo transport through longitudinal contraction [29]. Animal experiments confirm DS significantly enhances α -nucleotidyltransferase activity and cyclic AMP accumulation in ovarian tissue [30].

In conclusion, components of CGGJD-DS elevate estrogen levels in oligomenorrhea patients, facilitating menstrual recovery.

4.2. CGGJD-DS Improves Endometrial Blood Circulation.

Endometrial blood circulation impairment contributes to oligomenorrhea. Electron microscopy revealed reduced metabolic activity and diminished protein synthesis in 20 women developing oligomenorrhea/amenorrhea after 6 months of contraceptive treatment; 16 exhibited inactive endometrium, 1 had weakly proliferative endometrium, and 3 biopsies were insufficient for evaluation [7]. Pulsed Doppler studies further confirm impaired uterine perfusion causes endometrial dysfunction in polycystic ovary syndrome [31]. This study demonstrates CGGJD-DS improves endometrial blood circulation in oligomenorrhea patients.

Radix Bupleuri extract induces vasorelaxation by blocking sarcoplasmic reticulum Ca^{2+} channels [32]. *Cinnamomi Ramulus*, *Poria cocos*, and *Radix Paeoniae Alba*

demonstrate clinical efficacy in promoting blood circulation, resolving blood stasis, and exerting significant spasmolytic effects on uterine contractions [33]. *Cinnamomi Ramulus* additionally promotes menstruation and blood flow, traditionally treating blood-cold amenorrhea and palpitations; its extract attenuates ischemia/reperfusion injury by suppressing inflammasome activation and pyroptosis-related pathways [34]. *Scutellaria baicalensis* extract administration rescues memory impairments induced by chronic cerebral hypoperfusion [35].

Multiple studies confirm DS enhances endometrial circulation. By mitigating superoxide-mediated endometrial damage during implantation, DS significantly improves pregnancy rates [36]. It enhances leukemia inhibitory factor production in endometrial gland cells and increases uterine implantation sites in rats [37]. Furthermore, DS ameliorates hyperalgesia and lesion formation in endometriosis-like murine models, suggesting therapeutic potential for endometriosis-related dysmenorrhea [38]. These pharmacological findings confirm CGGJD-DS enhances endometrial blood flow, consequently increasing endometrial thickness.

4.3. Integrated Therapeutic Mechanism and Study Limitations.

This study demonstrates that the CGGJD-DS combination exerts a multifaceted therapeutic effect in oligomenorrhea, operating through both hormonal regulation and local endometrial improvement. While direct clinical evidence on the complete CGGJD formula remains limited, the established pharmacological profiles of its constituent herbs—such as the phytoestrogenic activities of *Radix Bupleuri* and *Scutellaria baicalensis* and the microcirculation-enhancing properties of *Cinnamomi Ramulus* and *Radix Paeoniae Alba*—collectively support its observed hormonal regulation and endometrial blood flow enhancement. These effects are further complemented by DS, which directly promotes ovarian steroidogenesis and endometrial receptivity, as evidenced by its stimulation of estradiol secretion, increase in uterine implantation sites, and mitigation of endometrial damage.

Notwithstanding these promising findings, several limitations merit consideration. The single-arm, self-controlled design precludes definitive causal attribution, as influences from natural fluctuations in emotion, weight, or diet cannot be fully excluded. Additionally, the modest sample size constrains statistical power and generalizability, and the relatively short follow-up period limits the assessment of long-term outcomes. We also explicitly recognized the lack of anti-müllerian hormone (AMH) assessment as a study limitation in the Discussion section. Future large-scale randomized controlled trials with extended follow-up to enhance participant retention are warranted to validate these preliminary efficacy signals, confirm the sustainability of the treatment effects, further elucidate the underlying mechanisms of CCGJD-DS combination therapy, and incorporate AMH measurements to more fully evaluate ovarian reserve and long-term treatment effects.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki Approval, and it was granted by the Medical Ethics Committee of Tian-He hospital (No. T20220402). This open-label randomized controlled trial (Trial Registration: TCTR202204010) was conducted at Tian-He Hospital, Linyi City, Shandong Province, China, between May 2022 to March 2024. Written informed consent was obtained from all participants and their guardians prior to enrolment.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Mei Yu (first author): methodology, investigation, and writing—original draft.

Gui-Yan Liu: data curation, investigation, and formal analysis.

Wen-Xuan Zhou: validation and visualization.

Zhao-Hua Liu: visualization and formal analysis.

Lian-Tao Li (corresponding author): conceptualization, resources, supervision, and writing—review and editing.

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