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Thread Embedding Acupuncture versus Classical Medical Therapy for Endometriosis-Associated Pain: A Randomised Controlled Trial

Sanaz Solati Sadati[1], Maliheh Mahmoudinia[2], Mohammad Hossein Ayati[3], Ehsan Mosa Farkhani[4,5], Mohammad Nematshahi[1], Malika Vaez Tehrani[1], Masoumeh Zibandeh Gorji[1], Hamid Reza Bahrami-Taghanaki[1*]

1- Department of Acupuncture, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2- Department of Obstetrics and Gynecology, School of Medicine, Omolbanin Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.
3- Department of Persian Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran.
4- Department of Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran.
5- Social Determinants of Health Research Center Mashhad University of Medical Sciences, Mashhad, Iran.

***Corresponding authors:** Dr. Hamid Reza Bahrami-Taghanaki, Department of Acupuncture, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: bahramihr@mums.ac.ir

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Abstract

Background: Endometriosis-associated dysmenorrhea and dyspareunia are common and difficult to manage with conventional pharmacotherapy; polydioxanone (PDO) thread embedding acupuncture (TEA) has been increasingly studied for its analgesic and anti-inflammatory effects in this setting.

Objectives: To compare TEA with classical medical therapy for dyspareunia and dysmenorrhea in women with endometriosis, and to evaluate effects on hormonal profile, antral follicle count, and quality of life.

Methods: This prospective, randomised, parallel-group, assessor- and analyst-blinded trial enrolled 80 women with endometriosis, allocated to embedding (n = 38) or classical therapy (low-dose combined oral contraceptives or dienogest; n = 42). Embedding involved subcutaneous implantation of 40 absorbable PDO threads at 22 standardised acupoints in two sessions six weeks apart. Dyspareunia, dysmenorrhea (VAS, 0–10), serum FSH and LH, antral follicle count, and quality of life (WHOQOL-BREF) were assessed at baseline and 1, 2, 3, and 6 months.

Results: Both interventions produced large, significant within-group reductions in dyspareunia and dysmenorrhea at every follow-up (all $p < 0.001$). For dyspareunia, the omnibus group×time interaction was not significant ($F = 0.14$, $p = .968$), indicating parallel improvement in both arms; a modest overall between-group difference favoured classical therapy (main effect of group, $p = .036$, partial $\eta^2 = 0.055$). None of the exploratory, non-normality-adjusted time-point comparisons remained significant after Bonferroni correction ($\alpha = .0125$ across four comparisons), including the 2-month comparison (nominal $p = .015$). Dysmenorrhea trajectories did not differ between groups at any time point (interaction $F = 0.61$, $p = .653$). FSH and LH fell significantly in both groups (all within-group $p < .001$) with no between-group difference after treatment; AFC decreased and quality of life improved comparably across groups. Adverse events with TEA were mild, transient, and local; comparative safety versus classical therapy was not systematically assessed.

Conclusions: TEA achieved dyspareunia and dysmenorrhea control with no statistically significant difference in trajectory from classical therapy across six months, with adverse effects limited to mild, transient local reactions, supporting its potential role as a complementary intervention for endometriosis-associated pain.

Keywords: Endometriosis; TEA; polydioxanone; dyspareunia; dysmenorrhea; gonadotropins; randomised controlled trial

1. Context

Endometriosis is a chronic, oestrogen-dependent gynaecological disorder in which endometrial-like tissue occurs outside the uterine cavity, most commonly on the ovaries, posterior cul-de-sac, uterosacral ligaments, and rectovaginal septum, with extra-pelvic sites also reported (1). It affects approximately 10% of women of reproductive age and up to 50% of women

with infertility (2), causing chronic inflammation, fibrosis, and adhesions that impair quality of life (3) and, despite its benign classification, can behave in an invasive, angiogenic, recurrence-prone manner (4). Dysmenorrhea and dyspareunia are its most debilitating symptoms, the latter affecting up to 50% of women and linked to increased nerve fibre density and local inflammation (5). Management options — hormonal therapy (combined oral contraceptives, dienogest, GnRH agonists, aromatase inhibitors), NSAIDs, and surgery — each have notable limitations: hormonal treatments are often unsuitable for women desiring fertility and carry side effects including hypoestrogenism and bone loss (6), while surgery carries a 40–50% five-year recurrence risk (7). This has driven growing interest in complementary therapies.

Acupuncture, a core modality of traditional Chinese medicine, has shown promise in pain management and modulation of reproductive health (8), with acupoint injection producing systemic effects on pain in gynaecological conditions such as labour and dysmenorrhea (9,10). Polydioxanone (PDO) thread embedding acupuncture (TEA) is an advanced technique involving subcutaneous insertion of absorbable threads at acupoints, providing prolonged mechanical and biochemical stimulation (11). PDO itself appears biologically active: prolonged exposure increases IL-10 in vivo, while human studies report reductions in IL-1β and TNF-α, suggesting an anti-inflammatory tendency without adverse immune effects (12,13), and PDO implantation at acupoints has also been shown to change levels of inflammatory cytokines such as IL-6 (14). Used for chronic, treatment-resistant conditions, PDO provides continuous stimulation akin to a retained needle, potentially enhancing and prolonging acupuncture's therapeutic effects (15). Compared with conventional acupuncture, TEA offers stronger, sustained stimulation with fewer sessions and improved cost-effectiveness (16), and may influence the nervous, endocrine, and immune systems implicated in endometriosis-related pain and inflammation (11).

Acupuncture-based approaches have been increasingly studied for endometriosis-associated pain specifically. A multicentre, single-blind, placebo-controlled trial found that acupuncture significantly reduced such pain relative to sham acupuncture (17), with a similarly designed protocol subsequently developed for pelvic pain in endometriosis (18). A systematic review and meta-analysis of 14 randomised trials confirmed that acupuncture significantly improves endometriosis-related pain (19), and two recent network meta-analyses — one of 42 trials and 3635 participants, the other of 23 trials — likewise found acupuncture-related therapies effective and safe, without identifying a clearly superior technique (20,21). High-quality trials evaluating TEA specifically against standard medical therapy nonetheless remain limited.

This trial aimed to compare the efficacy of TEA with classical medical therapy (low-dose combined oral contraceptives or dienogest) for dysmenorrhea and dyspareunia in women with endometriosis. Secondary objectives were to assess effects on serum FSH and LH, antral follicle count, and health-related quality of life.

2. Methods

2.1. Study design

This was a prospective, randomised, parallel-group, assessor- and analyst-blinded trial comparing TEA with classical medical therapy in women with endometriosis-associated dysmenorrhea and dyspareunia (see Section 3.3 for blinding details), conducted at the Acupuncture Clinic of Imam Reza Hospital, Mashhad University of Medical Sciences, Iran, between June 2022 and June 2024. The protocol was approved

by the institutional Ethics Committee (IR.MUMS.REC.1402.020), registered with the Iranian Registry of Clinical Trials (IRCT20121228011912N5), and conducted in accordance with the Declaration of Helsinki; written informed consent was obtained from all participants.

2.2. Participants

Women of reproductive age with a confirmed diagnosis of endometriosis (clinical and imaging criteria, assessed by a specialist obstetrician-gynaecologist) and moderate-to-severe dysmenorrhea and/or dyspareunia were eligible. Key exclusion criteria were contraindications to hormonal therapy, pregnancy or desire for immediate pregnancy, severe comorbidities, and previous TEA within six months. A blinded research collaborator screened all referrals.

2.3. Randomisation and blinding

Eligible participants were randomly allocated (1:1) to the TEA or classical therapy group using block randomisation generated in SPSS version 16, with concealed allocation. The data analyst and the researcher recording outcome data were blinded to allocation; complete blinding of participants and treating clinicians was not feasible given the nature of the interventions, but outcome assessors remained blinded.

2.4. Interventions

2.4.1. Classical medical therapy group

Participants received standard first-line hormonal therapy: either a low-dose combined oral contraceptive taken continuously daily for three months (from the first day of the menstrual cycle) or dienogest (2 mg daily), per international clinical guidelines.

2.4.2. TEA group

Participants received two sessions of TEA, six weeks apart, using absorbable polydioxanone (PDO) monofilament thread, size 0, 2 cm in length. Forty threads were implanted at each session at the following acupoints: BL17, BL18, BL20, BL22, BL23, SP4, SP6, SP9, SP10, CV3, CV4, CV6, CV12, ST25, ST29, ST40, LU7, LV3, LV8, KI3, KI6, and LI4. Both the acupoints and the treatment schedule were selected on the basis of the supervising practitioner's clinical experience in gynaecological disorders and a review of the literature (17). After skin disinfection with povidone-iodine, threads were implanted subcutaneously at the de qi level, in accordance with standardized manipulation procedures for TEA (24). Following each session, participants received oral cephalexin antibiotic prophylaxis (500 mg every 6 hours for 2 days), administered per the internal post-procedural protocol of Imam Reza Hospital for sessions involving more than ten deep thread implantations. All procedures were performed by a highly experienced practitioner (PhD in Acupuncture and Massage Therapy, full professor, Beijing University of Chinese Medicine) under sterile conditions. No additional acupuncture modalities were used.

Unlike fast-absorbing materials such as chromic catgut, which lose most tensile strength within 7–10 days, PDO retains approximately 74% of its tensile strength at 2 weeks, 50% at 4 weeks, and 25% at 6 weeks, with minimal mass loss before 90 days and complete absorption over 6–7 months (22,23), continuing to act as an embedded needle for roughly 4–6 weeks — approximating the duration of a conventional acupuncture course (around 12 sessions over one month) and thus broadly equivalent to one (11,15,16). Two implantations six weeks apart were used here because comparable extended courses (approximately 10–12 weeks) have proved effective for endometriosis-associated pain (17) and a single ~6-week implant would not cover the full three-month comparator period; together the two sessions approximate a

~24-session-equivalent course and renew the anti-inflammatory stimulus (increased IL-10; reduced IL-1β and TNF-α) (12,13) before the first thread's integrity substantially declines.

2.4.3. Safety monitoring protocol

A multi-stage protocol monitored participant safety across immediate, intermediate, and ongoing phases. Participants were observed for 30 minutes after each procedure for immediate events such as vasovagal reactions, acute pain, or localised bleeding, and underwent a structured telephone interview 48 hours later screening for delayed hypersensitivity, localised inflammation, or persistent discomfort. A 24-hour emergency contact number was provided throughout follow-up for reporting any delayed or unexpected event. All adverse events were recorded on structured case report forms, including type, severity, onset, duration, management, outcome, and assessed relationship to the intervention.

2.5. STRICTA reporting for TEA

The TEA intervention is reported in accordance with the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) guidelines (25) (Supplementary Table S1).

2.6. Outcome measures

The primary outcomes were changes in dyspareunia and dysmenorrhea intensity, evaluated using the Endometriosis-Associated Pelvic Pain (EAPP) scale for baseline qualification and the Visual Analogue Scale (VAS, 0–10) for pain intensity, assessed at baseline and 1, 2, 3, and 6 months.

Secondary outcomes were serum FSH and LH (IU/L), antral follicle count in each ovary (transvaginal ultrasound), and health-related quality of life via the WHOQOL-BREF questionnaire (26) — a widely validated instrument with established internal consistency and test–retest reliability (26). Hormonal, ultrasound, and quality-of-life assessments were performed at baseline and three months post-intervention.

2.7. Sample size

Sample size was calculated to detect a clinically meaningful difference in pain scores between groups, with a two-sided significance level of 0.05 and statistical power of 80%, based on the effect size reported in a comparable prior acupuncture trial for gynaecological pain. This yielded a minimum requirement of a specific number of participants per group; accounting for an anticipated attrition rate, a final enrolment target per group was set. (Authors: please insert the specific reference and the calculated per-group N and attrition assumption actually used.)

2.8. Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and cross-checked in Python (SciPy 1.17, pingouin 0.6). Continuous variables are presented as mean ± standard deviation (SD) or as mean with 95% confidence intervals (95% CI), while categorical variables are expressed as frequencies and percentages. The normality of data distributions was assessed using the Shapiro–Wilk test. Age and BMI were normally distributed in both groups and were compared using independent-samples t-tests. Dyspareunia, dysmenorrhea, FSH, LH, and AFC were non-normally distributed at every assessment in both groups (all Shapiro–Wilk $p < .05$); between-group comparisons for these variables therefore used Mann–Whitney U tests, and within-group change from baseline used Wilcoxon signed-rank tests. Categorical variables were compared using chi-square tests, with Fisher's exact test substituted where expected cell counts were below 5.

The time course of dyspareunia and dysmenorrhea across the five assessment

points was analysed using a mixed-design (group×time) ANOVA, with treatment group as the between-subjects factor and time as the within-subjects factor. Mauchly's test indicated a violation of sphericity for the time effect in both outcomes (both $p < .001$), so Greenhouse–Geisser-corrected p-values are reported for the time main effect. Where the omnibus interaction was significant, Bonferroni-adjusted pairwise contrasts would have been used; because neither interaction reached significance (Section 4.2), the individual time-point comparisons in Table 2 are presented as exploratory secondary analyses, with a Bonferroni-corrected threshold of $\alpha = .0125$ applied across the four post-baseline comparisons per outcome. All tests were two-sided; analyses followed intention-to-treat, and as there were no missing data or loss to follow-up, no imputation was required.

3. Results

3.1. Participant flow and baseline characteristics

A total of 80 women with confirmed endometriosis and associated dysmenorrhea and dyspareunia were enrolled in this randomised clinical trial (Fig. 1). Participants were randomly allocated to the TEA group (n = 38) or the classical medical therapy group (n = 42). All participants completed the 3-month intervention and the 6-month follow-up assessments, with no dropouts.

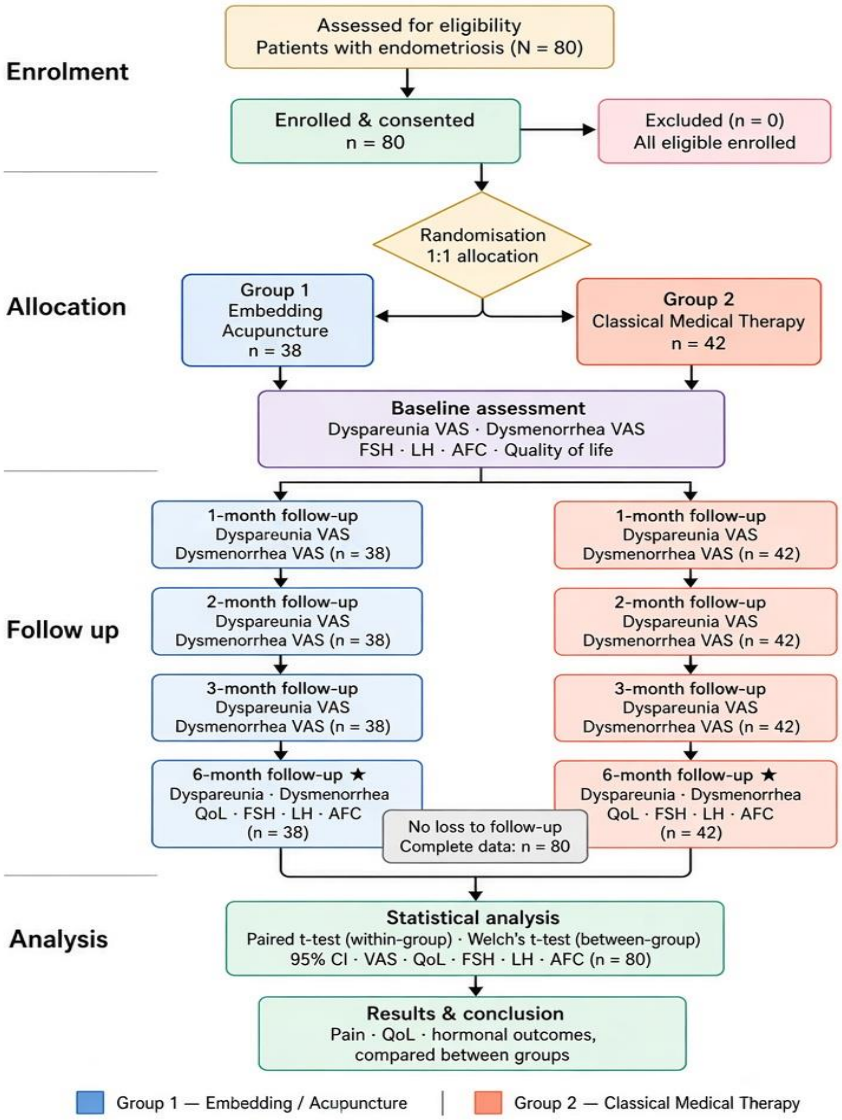

Figure 1. CONSORT flow diagram of participant enrolment, randomisation, allocation, follow-up, and analysis.

The two groups were well balanced at baseline (Table 1). There were no significant differences in mean age (31.84 ± 5.62 vs 31.77 ± 4.45 years, p = .95) or body mass index (24.52 ± 4.11 vs 24.70 ± 4.18 kg/m², p = .85). The distribution of comorbidities was similar between groups (p = .79 by chi-square across six categories; owing to small expected cell counts in some categories, we also confirmed this with a Fisher–Freeman–Halton-type comparison collapsed to 'any comorbidity vs none', p = .76). Family history of endometriosis was also balanced between groups (10.5% vs 16.7%, p = .64).

One imbalance is noted for transparency: participants in the classical therapy group reported more previous pregnancies on average than those in the embedding group (mean 1.00 vs 0.55; Mann–Whitney U, p = .025); the number of previous pregnancy losses did not differ significantly (mean 0.40 vs 0.24, p = .11).

Table 1. Baseline characteristics of study participants

Variable	TEA (n = 38)	Classical Medical Therapy (n = 42)	p-value
Age (years), mean ± SD	31.84 ± 5.62	31.77 ± 4.45	.95†
BMI (kg/m²), mean ± SD	24.52 ± 4.11	24.70 ± 4.18	.85†
No comorbidity — n (%)	31 (81.6%)	36 (85.7%)	.79‡
Neurological disorder	3 (7.9%)	2 (4.8%)	—
Diabetes mellitus	2 (5.3%)	2 (4.8%)	—
Hypertension	1 (2.6%)	0 (0%)	—
Hormonal disorder	1 (2.6%)	1 (2.4%)	—
Cardiovascular disease	0 (0%)	1 (2.4%)	—
Family history of endometriosis — n (%)	4 (10.5%)	7 (16.7%)	.64‡
Previous pregnancies, mean ± SD	0.55 ± 0.83	1.00 ± 0.94	.025§
Previous pregnancy losses, mean ± SD	0.24 ± 0.43	0.40 ± 0.50	.11§

† Independent two-sample t-test (Age and BMI were normally distributed, Shapiro–Wilk p > .05). ‡ Chi-squared test. § Mann–Whitney U test (non-normal distribution). Data shown as mean ± SD or n (%). Bold indicates p < .05.

3.2. Pain outcomes

Both interventions resulted in clinically meaningful and statistically significant reductions in pain intensity over the 3-month treatment period, sustained (with partial rebound) to 6 months (Table 2, Fig. 2).

Dyspareunia. Dyspareunia scores decreased substantially in both groups (Wilcoxon signed-rank p < .001 for within-group change from baseline at every follow-up). A mixed-design ANOVA testing the full time course found a highly significant main effect of time ($F(4,312) = 234.3$, Greenhouse–Geisser-corrected p < .001, partial $\eta^2 = .75$), a modest but significant main effect of group ($F(1,78) = 4.56$, p = .036, partial $\eta^2 = .055$, favouring lower overall scores in the classical therapy group), and — critically — no significant group×time interaction ($F(4,312) = 0.14$, p = .968, partial $\eta^2 = .002$). This means the shape of improvement over time did not differ between the two treatments: both groups improved and partially relapsed in parallel.

Exploratory time-point comparisons (Mann–Whitney U, appropriate given the confirmed non-normal distribution of VAS scores) are shown in Table 2. Applying a Bonferroni-corrected threshold of $\alpha = .0125$ across the four follow-up comparisons, none of the individual time-point differences remained statistically significant: the 2-month comparison showed a nominal difference (p = .015) that did not survive correction, and the 1-month (p = .052), 3-month (p = .108), and 6-month (p = .428) differences were likewise non-significant. We interpret the apparent early advantage

suggested by the uncorrected 2-month comparison as non-robust rather than a reliable time-specific effect, consistent with the null omnibus interaction above.

Dysmenorrhea. Both treatments produced comparable and highly significant reductions in dysmenorrhea (Wilcoxon signed-rank p < .001 within each group at every follow-up). The mixed-design ANOVA showed a highly significant main effect of time ($F(4,312)=332.2$, Greenhouse–Geisser-corrected $p < .001$, partial $\eta^2 = .81$), no significant main effect of group ($F(1,78) = 0.02$, $p = .89$), and no significant group×time interaction ($F(4,312) = 0.61$, $p = .653$). Exploratory time-point comparisons showed no statistically significant between-group difference at any time point (all Mann–Whitney U $p \geq .23$; Table 2, Fig. 2).

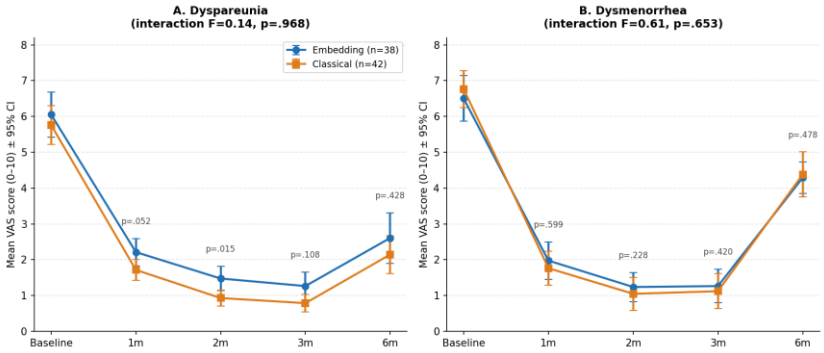

Figure 2. Mean VAS scores (± 95% CI) over time by treatment group for (A) dyspareunia and (B) dysmenorrhea. Annotated p-values are exploratory Mann–Whitney U comparisons at each follow-up (Bonferroni-corrected significance threshold α = .0125); the omnibus group×time interaction was not significant for either outcome.

Table 2. Pain outcomes across time points: descriptive statistics and exploratory between-group / within-group tests.

Time point	Embedding (n=38) Mean (95% CI)	Within-group p†	Classical (n=42) Mean (95% CI)	Within-group p†	Between-group p‡
Dyspareunia (0–10)					
Baseline	6.05 (5.42–6.69)	—	5.76 (5.22–6.30)	—	.601
1 month	2.21 (1.83–2.59)	<.001	1.71 (1.42–2.01)	<.001	.052
2 months	1.47 (1.13–1.81)	<.001	0.93 (0.71–1.15)	<.001	.015
3 months	1.26 (0.87–1.66)	<.001	0.79 (0.54–1.03)	<.001	.108
6 months	2.61 (1.90–3.31)	<.001	2.14 (1.62–2.67)	<.001	.428
Dysmenorrhea (0–10)					
Baseline	6.50 (5.86–7.14)	—	6.76 (6.25–7.28)	—	.681
1 month	1.97 (1.45–2.49)	<.001	1.76 (1.29–2.24)	<.001	.599
2 months	1.24 (0.83–1.64)	<.001	1.05 (0.59–1.51)	<.001	.228
3 months	1.26 (0.79–1.73)	<.001	1.12 (0.63–1.61)	<.001	.420
6 months	4.29 (3.84–4.73)	<.001	4.38 (3.75–5.01)	<.001	.478

† Wilcoxon signed-rank test, follow-up vs baseline within the same group. ‡ Mann–Whitney U test between groups at each time point (exploratory secondary analysis; Bonferroni-corrected significance threshold α = .0125 across the four post-baseline comparisons for each outcome). No individual time-point comparison remained significant after correction. Dash (—) = not applicable (baseline row). CI, confidence interval; VAS, Visual Analogue Scale. Omnibus mixed-design ANOVA results (main effects of time and group, and the group×time interaction) are reported in the text of Section 4.2.

3.3. Hormonal parameters and antral follicle count

Both interventions led to statistically significant within-group reductions in serum FSH and LH levels at 3 months (Table 3; Supplementary Fig. S1). In the embedding

group, FSH decreased from 21.88 (95% CI 20.29–23.48) to 20.13 (95% CI 18.62–21.64) mIU/mL (p < .001); in the classical group it decreased from 21.09 (95% CI 19.66–22.53) to 19.99 (95% CI 18.70–21.27) mIU/mL (p < .001). Between-group differences in FSH were not significant either before or after treatment (both p > .4). LH showed a significant baseline imbalance (embedding 10.26 vs classical 10.91 mIU/mL, p=.011) that resolved by the post-treatment assessment (p = .32), after significant within-group reductions in both arms (both p<.001). Mean baseline FSH in both groups (~21 mIU/mL) exceeds typical early-follicular-phase reference ranges. Elevated FSH is reported in endometriosis-associated diminished ovarian reserve, consistent with this cohort's low AFC (35).

Total antral follicle count (right + left) declined modestly but significantly within both groups (embedding: 3.53 to 3.13, p=.003; classical: 3.31 to 2.62, p < .001), with no significant between-group difference at either assessment (both p > .2). This cohort's low baseline AFC (~3 in both groups) is consistent with reduced ovarian reserve reported in endometriosis relative to unaffected populations (30), likely reflecting disease severity in this treatment-seeking population rather than a treatment effect, since values were already low at baseline. We note that the right- and left-ovary AFC values reported separately in the original draft of this table did not match the underlying per-ovary data, although they summed correctly to the (correct) combined total; the right- and left-ovary rows below have been recalculated directly from the source data. On this recalculation, the within-group decline in left-ovary AFC was not statistically significant in the embedding group (p=.257), unlike the originally reported figure; all other within-group and between-group conclusions in this section are essentially unchanged.

Table 3. Hormonal parameters and antral follicle count before and after treatment (recalculated).

Parameter	Embedding (n=38) Mean (95% CI)	Within p†	Classical (n=42) Mean (95% CI)	Within p†	Between p‡
FSH (mIU/mL)					
Baseline	21.88 (20.29–23.48)	—	21.09 (19.66–22.53)	—	.425
After treatment	20.13 (18.62–21.64)	<.001	19.99 (18.70–21.27)	<.001	.791
LH (mIU/mL)					
Baseline	10.26 (9.84–10.68)	—	10.91 (10.43–11.39)	—	.011
After treatment	10.04 (9.62–10.46)	<.001	10.30 (9.84–10.77)	<.001	.323
AFC — right ovary					
Baseline	1.76 (1.40–2.13)	—	1.71 (1.28–2.15)	—	.547
After treatment	1.45 (1.13–1.77)	.001	1.26 (0.81–1.71)	<.001	.182
AFC — left ovary					
Baseline	1.76 (1.26–2.27)	—	1.60 (1.21–1.98)	—	.870
After treatment	1.68 (1.17–2.20)	.257	1.36 (0.98–1.74)	.008	.429
Total AFC (right + left)					
Baseline	3.53 (2.71–4.34)	—	3.31 (2.51–4.10)	—	.648
After treatment	3.13 (2.37–3.89)	.003	2.62 (1.83–3.40)	<.001	.203

Values are mean (95% CI). † Wilcoxon signed-rank test, post-treatment vs baseline within the same group. ‡ Mann–Whitney U test between groups. Bold indicates p < .05. Dash (—) = not applicable. FSH, follicle-stimulating hormone; LH, luteinising hormone; AFC, antral follicle count. Non-parametric tests were used throughout this table because Shapiro–Wilk testing confirmed non-normal distributions for all four parameters in both groups at both assessments.

3.4. Quality of life

Quality of life scores measured by the WHOQOL-BREF questionnaire improved substantially in both groups at 3 months (embedding group: from 55.66 ± 7.66 to 77.05 ± 7.10; classical group: from 57.52 ± 7.35 to 76.12 ± 5.81; both within-group $p < .001$). The between-group difference was not statistically significant either at baseline ($p = .13$) or after treatment ($p = .41$).

3.5. Adverse events and safety

Adverse events were monitored throughout the study period in both groups using the multi-stage protocol described in Section 3.4.3. No severe adverse events were observed in the immediate post-procedure (30-minute) assessment. At the structured 48-hour follow-up in the TEA group, participants reported transient pain in approximately 30% of cases, a sensation of a foreign body at the implantation site in approximately 20%, localised bruising at some injection sites in approximately 55%, and a sensation of weakness in approximately 5%. No persistent or serious adverse event requiring medical intervention — including massive bleeding, allergic reaction, or granuloma formation — was reported at any point during follow-up. In the classical medical therapy group, no adverse events beyond those already well described for combined oral contraceptives and dienogest in the product literature were reported by participants during the study period.

4. Discussion

4.1. Principal findings

The present study compared TEA and classical medical therapy in women with endometriosis, evaluating pain, hormonal profile, ovarian reserve, and quality of life over six months. Both interventions produced clinically meaningful, statistically significant reductions in dyspareunia and dysmenorrhea from baseline at every follow-up. For dyspareunia, a mixed-design ANOVA found no significant group×time interaction — no statistically significant difference in trajectory was observed between treatments — with only a small overall main effect of group favouring classical therapy; no individual time-point comparison remained significant after correction for multiple testing, including the 2-month comparison (nominal $p = .015$). We interpret this as a non-robust signal rather than a diverging trajectory. Dysmenorrhea scores followed closely parallel trajectories, with no significant group effect, interaction, or between-group difference at any time point. Both groups showed partial pain rebound at six months, a pattern consistent with (though not independently validated against) the chronic, relapsing course of endometriosis once active treatment ends.

Both interventions produced significant within-group reductions in serum FSH and LH (all $p < .001$), with no significant between-group differences in magnitude. Antral follicle count declined modestly and significantly within each group after treatment, though between-group differences were not significant — a finding warranting cautious interpretation given the sample size. Quality of life improved substantially in both groups (approximately 19–21 points from baseline); the between-group difference was not significant, possibly reflecting limited statistical power.

4.2. Pain and quality of life

The reductions in dyspareunia and dysmenorrhea observed here are broadly consistent with the existing acupuncture literature: Li et al., in a multicentre, single-blind, placebo-controlled trial, found acupuncture significantly reduced endometriosis-associated pain relative to sham acupuncture, corroborating the analgesic effects seen in the present embedding group (17).

Unnisa et al. similarly found non-pharmacological management of dysmenorrhea to be safe and effective, and that dysmenorrhea meaningfully affects quality of life (27) — consistent with the within-group improvements observed in both arms here. The quality-of-life gains in both groups, while clinically meaningful, did not reach between-group significance, which we attribute to a small effect size relative to the available sample size.

4.3. Hormonal changes and ovarian reserve

The significant within-group FSH and LH reductions in both arms are consistent with known suppressive effects of endometriosis management on the hypothalamic-pituitary-ovarian axis. Endometriosis is an oestrogen-dependent, progesterone-resistant condition driving ectopic endometrial implantation, reduced apoptosis, and heightened oxidative stress and peritoneal inflammation (6,28); a primary goal of hormonal and complementary treatments alike is to suppress gonadotrophin secretion, reducing menstrual flow and disease activity. The equivalence of FSH and LH reductions between groups suggests TEA may exert a modulatory effect on this axis broadly comparable to conventional pharmacotherapy, consistent with Lin et al.'s report of meaningful AFC and hormonal improvements with acupuncture-based approaches to diminished ovarian reserve, a condition sharing hypothalamic-pituitary-ovarian pathways with endometriosis (29).

Evidence for hormonal assessment in acupoint-based studies remains limited: Chen et al.'s meta-analysis of 14 trials found acupuncture significantly improved endometriosis-related pain (19) but did not assess hormonal parameters. AFC is known to be reduced in endometriosis relative to unaffected controls (30), relevant background for this cohort's low baseline AFC (Section 4.3). AFC declined significantly within both groups, with no significant between-group difference; without an untreated control arm, these data do not establish whether either intervention affects ovarian reserve, and should not be read as evidence that TEA preserves or improves it.

4.4. Safety profile and clinical implications

In this trial, adverse effects attributable to TEA were limited to localised, transient reactions at the implantation site — mild stiffness, erythema, bleeding, and oedema — all resolving without intervention (Section 4.5). The actual comparator, combined oral contraceptives and dienogest, has its own recognised tolerability profile (breakthrough bleeding, headache, mood-related effects), though a recent meta-analysis found the two agents broadly comparable in tolerability for endometriosis treatment (34). (Other first-line agents such as NSAIDs and COX-2 inhibitors, not used as the comparator here, carry their own gastrointestinal and cardiovascular risk profiles (31,32). Adverse-event ascertainment was not fully symmetric between groups — TEA events followed the structured protocol in Section 3.4.3, while classical-therapy events relied on open-ended participant report — so comparative safety conclusions should be interpreted cautiously; TEA's localised, self-limiting profile may still make it worth considering where conventional therapy is poorly tolerated or contraindicated.

These findings extend prior evidence supporting acupuncture-based interventions in endometriosis management (17,18), showing that TEA achieved no statistically significant difference in trajectory from classical medical therapy across pain, hormonal, and quality-of-life domains, with fewer sessions than conventional manual acupuncture (11,16). This is consistent with two recent large network meta-analyses of acupuncture-related therapies for endometriosis-associated pain (42 trials/3635 participants; 23 trials) that likewise found such therapies effective and

safe without a clearly superior technique (20,21). Given the chronic, relapsing nature of endometriosis, interventions offering durable control with minimal systemic risk carry substantial clinical value.

4.5. Implications for fertility

Although fertility outcomes were not assessed here, the interaction between acupuncture-based interventions and the neuroendocrine system warrants further study; the broader literature on acupuncture as an adjunct to assisted reproduction, including IVF-embryo transfer, shows mixed results, likely reflecting heterogeneity in protocols and populations (33). Future studies should prospectively evaluate TEA's impact on fertility outcomes — live birth rate, implantation rate, ovarian reserve — in women with endometriosis seeking conception.

4.6. Limitations

Several limitations should be acknowledged. First, the relatively small sample size (n = 80) may have reduced statistical power — particularly for AFC and quality of life, where between-group effect sizes were small — and limits the precision of the exploratory time-point contrasts in Table 2, which should be read as hypothesis-generating rather than confirmatory, since none of the individual time-point comparisons survived correction for multiple comparisons. Second, the absence of a sham-embedding control precludes definitive attribution of effects to the specific physiological action of TEA versus non-specific therapeutic factors. Third, the six-month follow-up cannot characterise long-term recurrence or fertility outcomes. Fourth, the standardised point prescription used across all patients, irrespective of individual TCM pattern, may not reflect optimal individualised practice. Finally, the unblinded design for participants and clinicians introduces potential observer and performance bias, and because parity was not a randomisation stratification factor, the baseline imbalance in previous pregnancies (Section 4.1) should be regarded as a chance finding typical of a modestly sized trial; this imbalance was not adjusted for in the primary analyses and should be considered a residual confounder. Fertility outcomes (e.g., pregnancy rate, need for assisted reproduction) were not assessed and remain an important target for future research (Section 5.5). Future trials should be larger, multicenter, sham-controlled, and longer in follow-up.

5. Conclusion

Both TEA and classical medical therapy produced significant, clinically meaningful reductions in dyspareunia, dysmenorrhea, and gonadotrophin levels in women with endometriosis. For dyspareunia, no statistically significant difference in trajectory was observed between groups over six months (non-significant group×time interaction); a modest overall difference favoured classical therapy on omnibus testing, though no individual time-point comparison survived correction for multiple testing. Dysmenorrhea showed no significant between-group difference at any level of analysis. TEA achieved these effects with adverse effects limited to mild, transient local reactions and fewer treatment visits, though safety ascertainment was not fully symmetric between groups; TEA's promise as a safe, effective complementary intervention warrants confirmation with matched safety monitoring. The comparable FSH and LH suppression across groups suggests a shared modulatory effect on the hypothalamic-pituitary-ovarian axis, though the precise mechanisms warrant further investigation.

These findings support TEA's promise as a lower-risk alternative or adjunct to conventional treatment for endometriosis-associated pain. Future research should prioritise larger randomised trials with sham

controls, extended follow-up, and fertility-outcome assessment to establish TEA's full therapeutic scope and optimal clinical application.

Abbreviations

AFC: antral follicle count
ANOVA: analysis of variance
CI: confidence interval
CONSORT: Consolidated Standards of Reporting Trials
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone
IL: interleukin
IRCT: Iranian Registry of Clinical Trials
LH: luteinising hormone
NSAID: non-steroidal anti-inflammatory drug
PDO: polydioxanone
SD: standard deviation
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
TCM: traditional Chinese medicine
TEA: thread embedding acupuncture
TNF-α: tumour necrosis factor alpha
VAS: Visual Analogue Scale
WHOQOL-BREF: World Health Organization Quality of Life-BREF

Ethical considerations: This study adhered to all ethical standards required for clinical research. The research was reviewed and approved by the relevant institutional Ethics Committee on 7 April 2023 (18/01/1402), under approval code IR.MUMS.REC.1402.020. Written informed consent was obtained from all participants following a comprehensive explanation of the study objectives, procedures, and potential risks. Patient data were anonymised using unique identification codes, and access was restricted exclusively to authorised project investigators.

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References

1. Kalbi DP, Al Sbihi AF, Manasrah N, Chaudhary AJ, Iqbal S. A thoracic endometriosis-related catamenial hemopneumothorax in a woman with premature ovarian failure. Cureus. 2021;13(8):e17110. https://doi.org/10.7759/cureus.17110
2. Nezhat C, Agarwal S, Lee DA, Tavallaee M. Can we accurately diagnose endometriosis without a diagnostic laparoscopy? J Turk Ger Gynecol Assoc. 2022;23(2):117-119. https://doi.org/10.4274/jtgga.galenos.2022.2022-2-2
3. Marcinkowska A, Górnicka M. The role of dietary fats in the development and treatment of endometriosis. Life (Basel). 2023;13(3):654. https://doi.org/10.3390/life13030654
4. Rizk RC, Yasrab M, Weisberg EM, Chu LC, Fishman EK. Deep pelvic endometriosis causing ureteral obstruction. Radiol Case Rep. 2024;19(9):3845-3849. https://doi.org/10.1016/j.radcr.2024.06.012
5. Peng B, Alotaibi FT, Sediqi S, Bedaiwy MA, Yong PJ. Role of interleukin-1β in nerve growth factor expression, neurogenesis and deep dyspareunia in endometriosis. Hum Reprod. 2020;35(4):901-912. https://doi.org/10.1093/humrep/deaa017
6. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: the endocrine background. Rev Endocr Metab Disord. 2022;23(3):333-355. https://doi.org/10.1007/s11154-021-09666-w
7. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update. 2009;15(4):441-461. https://doi.org/10.1093/humupd/dmp007
8. Wang JS, Yang J, Deng S, Yu XD, Bao BH, Liu RJ, et al. Acupuncture combined with tamsulosin hydrochloride sustained-release capsule in the treatment of chronic prostatitis/chronic pelvic pain syndrome: A study protocol for a randomized controlled trial. Medicine (Baltimore). 2020 Mar;99(12):e19540.. https://doi.org/10.1097/MD.0000000000019540
9. Chao MT, Wade CM, Booth SL. Increase in plasma phylloquinone concentrations following acupoint injection for the treatment of primary dysmenorrhea. J Acupunct Meridian Stud. 2014;7(3):151-154. https://doi.org/10.1016/j.jams.2014.01.004
10. Liu X, Wu L, Yi W. [Clinical research of analgesic for labor with acupoint injection and electroacupuncture]. Zhongguo Zhen Jiu. 2015;35(11):1155-1158. Chinese.
11. Kazemi AH, Adel-Mehraban MS, Jamali Dastjerdi M, Alipour R. A comprehensive practical review of acupoint embedding as a semi-permanent acupuncture: a mini review. Medicine (Baltimore). 2024;103(23):e38314. https://doi.org/10.1097/MD.0000000000038314
12. Gollapudi S, So CS, Formica M, Agrawal S, Agrawal A. Safety and efficacy of polydioxanone nano-fibers as anti-inflammatory agents. J Nanomed Biother Discov. 2014;4(2):1000127. https://doi.org/10.4172/2155-983X.1000127
13. Le LTT, Chien PN, Trinh TTT, Seo JW, Giang NN, Nga PT, Zhang XR, Jin YX, Nam SY, Heo CY. Evaluating the efficacy of intra-articular polydioxanone (PDO) injections as a novel viscosupplement in osteoarthritis treatment. Life Sci. 2025;361:123303. https://doi.org/10.1016/j.lfs.2024.123303
14. Nematshahi M, Mirhamidi M, Farkhani EM, et al. Comparison of three therapeutic methods of transcutaneous electrical nerve stimulation, embedding acupuncture, and drug therapy on interleukin-6 and pain levels in patients with knee osteoarthritis. Clin Rheumatol. 2026;45:4557-4568. https://doi.org/10.1007/s10067-026-08197-6
15. Cho S, Kim E. A narrative review of clinical studies on thread embedding acupuncture treatment for spasticity after stroke. J Korean Med. 2022;43(4):131-144. https://doi.org/10.13048/jkm.22050
16. Cho Y, Lee S, Kim J, Kang JW, Lee JD. Thread embedding acupuncture for musculoskeletal pain: a systematic review and meta-analysis protocol. BMJ Open. 2018;8(1):e015461. https://doi.org/10.1136/bmjopen-2016-015461
17. Li PS, Peng XM, Niu XX, Xu L, Hung Yu Ng E, Wang CC et al. Efficacy of acupuncture for endometriosis-associated pain: a multicenter randomized single-blind placebo-controlled trial. Fertil Steril. 2023;119(5):815-823. https://doi.org/10.1016/j.fertnstert.2023.01.034
18. Liang R, Li P, Peng X, Xu L, Fan P, Peng J, et al. Efficacy of acupuncture on pelvic pain in patients with endometriosis: study protocol for a randomized, single-blind, multi-center, placebo-

controlled trial. Trials. 2018;19:1-6. https://doi.org/10.1186/s13063-018-2684-6
19. Chen C, Li X, Lu S, Yang J, Liu Y. Acupuncture for clinical improvement of endometriosis-related pain: a systematic review and meta-analysis. Arch Gynecol Obstet. 2024;310(4):2101-2114. https://doi.org/10.1007/s00404-024-07675-z
20. Li H, Wang X, Wang Y, Gao Y, Zheng X, Zhang X, et al. Acupuncture and related therapies for endometriosis: a network meta-analysis of randomized controlled trials. J Pain Res. 2024;17:3197-3216. https://doi.org/10.2147/JPR.S488343
21. Su Y, Ji R, Zheng X, Jia Y, Zhu H, Li C, et al. Efficacy and safety of acupuncture-related therapies in symptomatic endometriosis: a systematic review and network meta-analysis. Arch Gynecol Obstet. 2025;311(3):697-714. https://doi.org/10.1007/s00404-025-07979-8
22. Ray JA, Doddi N, Regula D, Williams JA, Melveger A. Polydioxanone (PDS), a novel monofilament synthetic absorbable suture. Surg Gynecol Obstet. 1981;153(4):497-507.
23. Dart AJ, Dart CM. Suture material: conventional and stimuli responsive. In: Ducheyne P, editor. Comprehensive Biomaterials II. Vol 7. Amsterdam: Elsevier; 2017. p. 746-771. https://doi.org/10.1016/B978-0-12-803581-8.10135-3
24. Standardization Administration of the People's Republic of China. Standardized Manipulations of Acupuncture and Moxibustion: Part 10: Thread-Embedding Therapy; GB/T 21709.10-2021. Beijing: Standards Press of China; 2021. Chinese.
25. MacPherson H, Altman DG, Hammerschlag R, Li Y, Wu T, White A, et al; STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med. 2010;7(6):e1000261. https://doi.org/10.1371/journal.pmed.1000261
26. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998;28(3):551-558. https://doi.org/10.1017/S0033291798006667
27. Unnisa H, Annam P, Gubba NC, Begum A, Thatikonda K. Assessment of quality of life and effect of non-pharmacological management in dysmenorrhea. Ann Med Surg (Lond). 2022;81:104407. https://doi.org/10.1016/j.amsu.2022.104407
28. Chen S, Liu Y, Zhong Z, Wei C, Liu Y, Zhu X. Peritoneal immune microenvironment of endometriosis: role and therapeutic perspectives. Front Immunol. 2023;14:1134663. https://doi.org/10.3389/fimmu.2023.1134663
29. Lin G, Liu X, Cong C, Chen S, Xu L. Clinical efficacy of acupuncture for diminished ovarian reserve: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne). 2023;14:1136121. https://doi.org/10.3389/fendo.2023.1136121
30. Tian Z, Zhang Y, Zhang C, Wang Y, Zhu HL. Antral follicle count is reduced in the presence of endometriosis: a systematic review and meta-analysis. Reprod Biomed Online. 2021;42(1):237-247. https://doi.org/10.1016/j.rbmo.2020.09.014
31. Stiller C, Hjemdahl P. Lessons from 20 years with COX-2 inhibitors: importance of dose-response considerations and fair play in comparative trials. J Intern Med. 2022;292(4):557-574. https://doi.org/10.1111/joim.13505
32. Dey R, Dey S, Samadder A, Saxena AK, Nandi S. Natural inhibitors against potential targets of cyclooxygenase, lipoxygenase and leukotrienes. Comb Chem High Throughput Screen. 2022;25(14):2341-2357. https://doi.org/10.2174/1386207325666210917111847
33. Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis. Reprod Biomed Online. 2019;38(3):364-379. https://doi.org/10.1016/j.rbmo.2018.12.038
34. Piacenti I, Tius V, Viscardi MF, Biasioli A, Arcieri M, Restaino S, et al. Dienogest vs. combined oral contraceptive: a systematic review and meta-analysis of efficacy and side effects to inform evidence-based guidelines. Acta Obstet Gynecol Scand. 2025;104(8):1424-1432. https://doi.org/10.1111/aogs.15145
35. Tan Z, Gong X, Wang CC, Zhang T, Huang J. Diminished ovarian reserve in endometriosis: insights from in vitro, in vivo, and human studies-a systematic review. Int J Mol Sci. 2023;24(21):15967. https://doi.org/10.3390/ijms2421159