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Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study

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ABSTRACT

Objective: To evaluate the efficacy and safety of potentized estrogen compared to placebo in homeopathic treatment of endometriosis-associated pelvic pain (EAPP).
Study design: The present was a 24-week, randomized, double-blind, placebo-controlled trial that included 50 women aged 18–45 years old with diagnosis of deeply infiltrating endometriosis based on magnetic resonance imaging or transvaginal ultrasound after bowel preparation, and score ≥ 5 on a visual analogue scale (VAS: range 0 to 10) for endometriosis-associated pelvic pain. Potentized estrogen (12cH, 18cH and 24cH) or placebo was administered twice daily per oral route. The primary outcome measure was change in the severity of EAPP global and partial scores (VAS) from baseline to week 24, determined as the difference in the mean score of five modalities of chronic pelvic pain (dysmenorrhea, deep dyspareunia, non-cyclic pelvic pain, cyclic bowel pain and/or cyclic urinary pain). The secondary outcome measures were mean score difference for quality of life assessed with SF-36 Health Survey Questionnaire, depression symptoms on Beck Depression Inventory (BDI), and anxiety symptoms on Beck Anxiety Inventory (BAI).
Results: The EAPP global score (VAS: range 0 to 50) decreased by 12.82 ($P < 0.001$) in the group treated with potentized estrogen from baseline to week 24. Group that used potentized estrogen also exhibited partial score (VAS: range 0 to 10) reduction in three EAPP modalities: dysmenorrhea (3.28; $P < 0.001$), non-cyclic pelvic pain (2.71; $P = 0.009$), and cyclic bowel pain (3.40; $P < 0.001$). Placebo group did not show any significant changes in EAPP global or partial scores. In addition, the potentized estrogen group showed significant improvement in three of eight SF-36 domains (bodily pain, vitality and mental health) and depression symptoms (BDI). Placebo group showed no significant improvement in this regard. These results demonstrate superiority of potentized estrogen over placebo. Few adverse events were associated with potentized estrogen.
Conclusions: Potentized estrogen (12cH, 18cH and 24cH) at a dose of 3 drops twice daily for 24 weeks was significantly more effective than placebo for reducing endometriosis-associated pelvic pain.
Trial registration: ClinicalTrials.gov Identifier: NCT02427386.
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Introduction

Endometriosis is an estrogen-dependent condition characterized by presence of extrauterine endometrial tissue and it affects 10 to 15% of women of reproductive age [1,2]. While diagnostic certainty requires surgery, the accuracy of non-invasive methods for diagnosis of deep endometriosis, such as magnetic resonance imaging (MRI) and transvaginal ultrasound (TVU), is quite high when performed by experienced professionals [3–10].

Endometriosis-associated pelvic pain (EAPP) encompasses dysmenorrhea, deep dyspareunia, non-cyclic pelvic pain, cyclic bowel pain and/or cyclic urinary pain. The most common treatment includes nonsteroidal anti-inflammatory drugs, combined oral contraceptives, and progestins. Although partially effective, most of these options are associated with systemic side effects, while the need for repeated or regular administration impairs long-term acceptability, resulting in decreased efficacy [11,12].

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Just as other complementary and alternative therapies [13], homeopathy might represent an option for women with symptomatic endometriosis. The theoretical-practical model underlying homeopathic therapeutics is based on four pillars: therapeutic similitude (*similia similibus curentur*, likes heal likes); homeopathic pathogenetic trials (similar to phase 1 clinical pharmacological trials); use of potentized medicines (prepared through serial dilution and agitation); and individualization of treatment (drug selection based on the full picture of signs and symptoms exhibited by each patient). In clinical practice, patients are prescribed medicines previously shown to elicit similar signs and symptoms on healthy subjects (so-called primary, direct or pathogenetic effects of medicines) to trigger a homeostatic reaction (secondary, rebound or paradoxical effect) in the body against its ongoing disorders [14,15]. Any (natural or synthetic) substance might be used as homeopathic medicine provided it elicits similar pathogenetic effects (or adverse events, in the terms of modern pharmacology) on healthy subjects.

To broaden the scope of action of similitude-based treatment, starting 2003, we developed a systematic method of application of the curative rebound effect of modern drugs. Within this context, we suggest giving patients drugs that induce adverse events similar to the full picture of their signs and symptoms, but in highly diluted doses (i.e., homeopathic potencies) to trigger a curative (homeostatic, rebound or homeopathic) reaction [16–18]. The resulting proposal is available at an open-access website (http://www.newhomeopathicmedicines.com) [19].

In the present article, we describe the results of the just mentioned method to individualized homeopathic treatment of EAPP according to a pre-set protocol [20,21]. There we consider using potentized estrogen for EAPP treatment, because this hormone elicits, as adverse events (or pathogenetic effects), a set of signs and symptoms very similar to the one of endometriosis, including endometrial hyperplasia, pelvic pain, depression, anxiety, insomnia and migraine, among others.

Materials and methods

Study design

The study consisted of a 24-week randomized clinical trial in which we investigated the efficacy and safety of three homeopathic potencies of estrogen (12cH, 18cH and 24cH) or placebo (1:1 ratio). The potencies were administered sequentially every eight weeks to women with pelvic pain associated with deep endometriosis lesions (totally or partially) refractory to conventional treatment (hormonal therapy and/or nonsteroidal anti-inflammatory drugs). The participants were recruited in 2014 at Endometriosis Unit of Gynecology Division, Clinical Hospital, School of Medicine, University of Sao Paulo, which was the study setting. The study protocol had institutional research ethics committee approval and all the participants provided written informed consent.

Participants

Table 1 shows the primary (endometriosis-related) inclusion criteria. Patients who met these criteria were analyzed for secondary (homeopathic-related) inclusion criteria (*a priori* or pre-individualization of patients vis-a-vis the adverse events caused by estrogen, i.e., pathogenetic effects of estrogen). Among patients who met the primary inclusion criteria, only the ones who exhibited a set of signs and symptoms similar to the one corresponding to the adverse events caused by estrogen (anxiety, depression, insomnia, migraine and constipation, among others) were selected to participate in the study. Described in full detail in the aforementioned protocol [21], individualization of treatment according to similarity of signs and symptoms is a *sine qua non* requisite for the development of curative homeostatic response (clinical efficacy) and must mandatorily be included in all homeopathic clinical trials [22].

Preparation of the homeopathic medicine (potentized estrogen)

Potentized estrogen was prepared from 17-beta-estradiol valerate (batch #12030691A, Pharma Nostra, Sao Paulo, Brazil, 2011) in compliance with the Brazilian Homeopathic Pharmacopeia [23]. The first three steps consisted in serial grinding of 17-beta-estradiol mixed with lactose, followed by dilution 1:100 (each dilution agitated 100 times) until reaching potencies 12cH, 18cH and 24cH. The medication was delivered as drops (30% hydro-alcoholic solution) in 30-ml vials including a dropper.

Randomization and blinding

The participants were randomly allocated to receive potentized estrogen or placebo in 1:1 ratio. The randomization sequence was created by an independent supervisor using a random number generator. Both physician-investigator and participants were blinded as to the interventions (potentized estrogen or placebo) for the full duration of the study and throughout data analysis. To preserve blinding, both interventions were indistinguishable in appearance and taste.

Interventions

Each participant allocated to active treatment group (verum) was scheduled to receive a vial of potentized 17-beta-estradiol, while participants in the placebo group were given identical vials containing hydroalcoholic solution only. After initial assessment and delivery of the first vial of homeopathic medication (potency 12cH) or placebo on visit 1, the participants were evaluated by the physician-investigator every eight weeks (visits 2, 3 and 4) along the duration of the study (24 weeks). On visits 2 and 3 the participants were given new vials of homeopathic medicine (visit 2, week 8, potency 18cH; visit 3, week 16, potency 24cH) or placebo. The study finished on week 24 (visit 4), when the final outcomes were assessed. Potentized estrogen or placebo was

Table 1
Primary (endometriosis-related) inclusion criteria.

Age 18–45 years old.
Diagnosis of deeply infiltrating endometriosis based on clinical history and demonstration of lesions on MRI or TVU after bowel preparation.
Absence of clinical or laboratory signs of menopause or premature ovarian failure.
Presence of chronic pelvic pain refractory to conventional therapy (one year of use at least).
Score $\geq$ 5 on a visual analogue scale (VAS: range 0 to 10; were 0 represents absence of pain and 10 indicates unbearable pain) for EAPP.

MRI, magnetic resonance imaging; TVU, transvaginal ultrasound; VAS, visual analogue scale; EAPP, endometriosis-associated pelvic pain.

administered in a dose of three drops twice daily (every 12 h). Compliance with treatment was assessed based on the return of the used vials.

All the participants remained under the care of their gynecologists and no changes in the concomitant medication (hormonal therapy and/or nonsteroidal anti-inflammatory drugs) were allowed along the study period to avoid a possible interference of this variable with the assessed outcomes.

Outcome measures

Primary outcome measure was change in severity of pelvic pain as determined by modifications of the VAS score (range 0 to 10) for five modalities of EAPP (dysmenorrhea, deep dyspareunia, non-cyclic pelvic pain, cyclic bowel pain and/or cyclic urinary pain). The score was analyzed per individual modalities (EAPP partial score: range 0 to 10) and globally (EAPP global score: range 0 to 50) at baseline (visit 1) and weeks 8 (visit 2), 16 (visit 3) and 24 (visit 4).

Secondary outcome measures were changes in the scores for quality of life, assessed with SF-36 Health Survey Questionnaire [24,25]; depressive symptoms on Beck Depression Inventory (BDI; range 0 to 63) [26]; and anxious symptoms on Beck Anxiety Inventory (BAI; range 0 to 63) [27]. The secondary outcomes were assessed at baseline and at the end of the study (week 24).

Adverse events

The incidence and severity of adverse events were assessed at each visit and registered in an ad hoc form. Only adverse events absent in the participants' previous medical history were considered as potentially related to the drugs and/or withdrawal of treatment.

Sample size

Sample size was calculated based on the primary outcome, namely, changes in VAS score for EAPP from baseline (visit 1) to week 24 (visit 4). With conventional treatment [28] the score reduced by 2.58, on average. In the present (placebo-controlled) study, the pain score ought to decrease by 2.16 to obtain the same difference. With 80% power and 5% significance level the minimum number of participants for a two-tailed test [29] ought to be 23 per group. Considering an expected dropout rate of 10% the final sample size was estimated as 50 participants (25 patients per group).

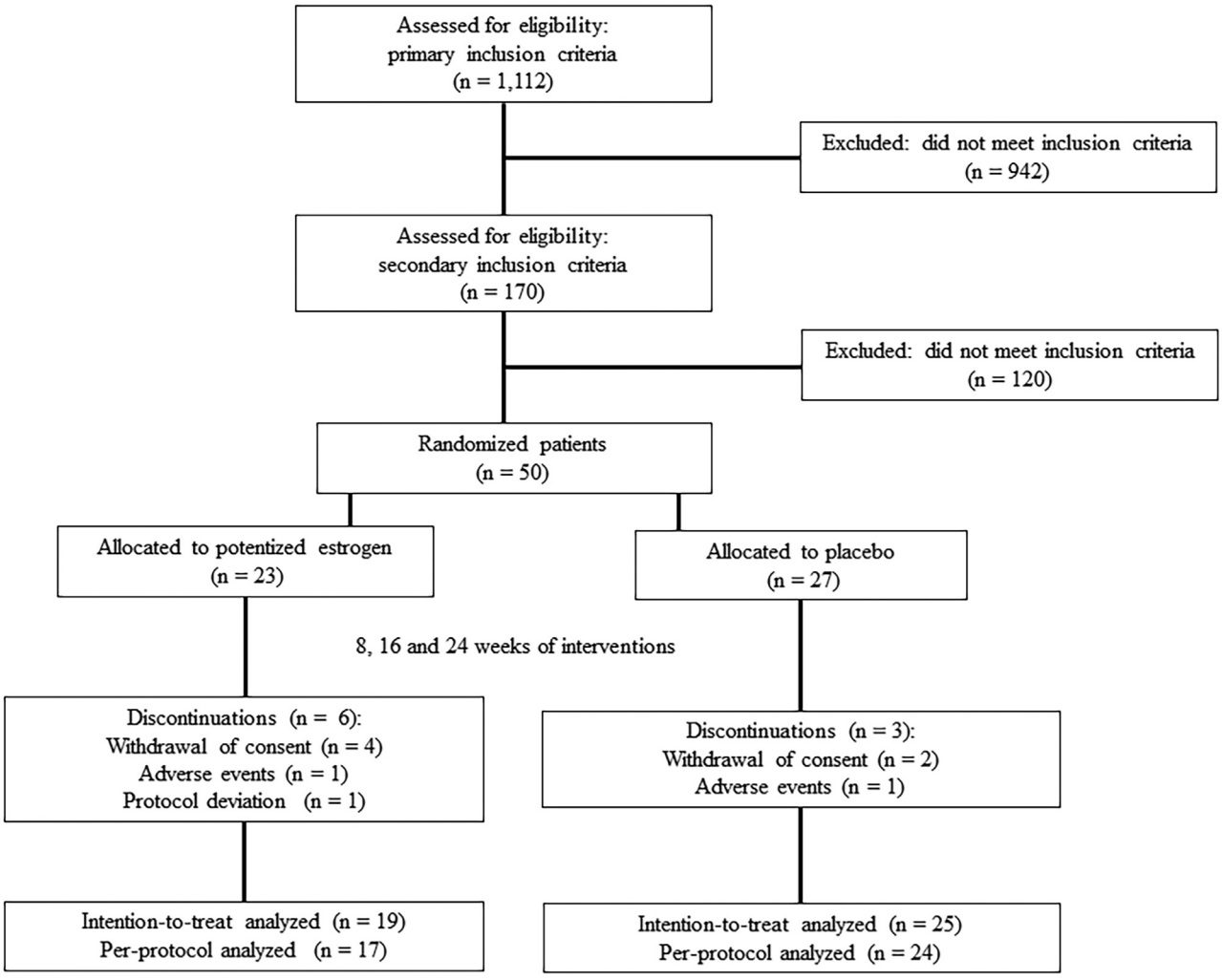

Fig. 1. Flowchart showing the intervention arms of the randomized clinical trial.

Data analysis

Data were analyzed by means of descriptive statistics, and a CONSORT-like flowchart [30,31] was plotted to describe the flow of participants through the study. The data were subjected to intention-to-treat (ITT) analysis and per-protocol (PP) analysis at 5% significance level (95% confidence interval). The primary outcome measure was average variation of pain score from first (baseline) to last (week 24) assessment, which was assessed by means of analysis of covariance adjusted to the scores at baseline. The same method was used for evaluation of the secondary outcomes (scores on SF-36, BDI and BAI).

The data were analyzed per group and along follow up using mean and standard deviation [29]. Comparison between groups and time points was performed by means of generalized estimating equations with first-order autoregressive structure, normal marginal distribution and identity link function [32]. Outcome measures that showed statistical significance were subjected to Bonferroni test [33] to establish between which groups and time-points differences in symptoms and scales occurred. The results are described as mean (mean difference – MD) and standard deviation unless stated otherwise.

Results

Participants' characteristics

A total of 1112 medical records were analyzed and 170 patients met the primary inclusion criteria. Fifty of them also met the secondary inclusion criteria and were randomized to receive treatment ($n = 23$, potentized estrogen; $n = 27$, placebo). Of these, 44 participants were included in ITT analysis ($n = 19$, potentized estrogen; $n = 25$, placebo). With a dropout rate of 18%, the study was completed by 41 participants ($n = 17$, potentized estrogen; $n = 24$, placebo) who were included in PP analysis. Fig. 1 shows the main reasons for study discontinuation.

Demographic and disease characteristics, including mean VAS scores (EAPP global and partial scores) were broadly similar at baseline between the two groups (Table 2). Most participants from both groups exhibited high pain scores and deep endometriosis lesions affecting the rectosigmoid. The participants exhibited complete compliance with treatment, as evidenced by the returned vials.

Primary outcome measure

Potentized estrogen was significantly superior to placebo in reducing the EAPP global and partial scores on ITT and PP analysis.

Change in EAPP global score (VAS: range 0 to 50)

On ITT analysis for the full treatment period (from baseline to week 24), potentized estrogen was associated with clinically significant reduction of the EAPP global score (MD 12.82; 95% CI 6.74-18.89; $P < 0.001$). Placebo was not associated with any significant change. Similar results were also observed on PP analysis (MD 12.03; 95% CI 5.32-18.74; $P < 0.001$) (Fig. 2).

Also in the intermediate assessments, potentized estrogen was associated with reduction of the EAPP global score on ITT analysis: 0–8 weeks (MD 9.93; 95% CI 6.23-13.63; $P < 0.001$), and 0–16 weeks (MD 10.60; 95% CI 5.51-15.68; $P < 0.001$). Similar results were observed also on PP analysis. Placebo showed no significant changes.

Changes in EAPP partial scores (VAS: range 0 to 10)

On ITT analysis of the full course of treatment (24 weeks), potentized estrogen was associated with clinically significant reduction of the partial scores in dysmenorrhea (MD 3.28; 95% CI 1.04-5.52; $P < 0.001$), non-cyclic pelvic pain (MD 2.71; 95% CI 0.36-5.05; $P = 0.009$), and cyclic bowel pain (MD 3.40; 95% CI 1.12-5.68; $P < 0.001$). Similar results were also observed on PP analysis. Placebo showed no significant changes (Fig. 3).

Secondary outcome measures

The secondary outcome measures were subjected to PP analysis (0 and 24 weeks).

Table 2
Demographic characteristics and disease severities at baseline.

Parameters	Potentized estrogen (n = 23)	Placebo (n = 27)
Age (years, mean ± SD)	34.3 ± 5.0	35.3 ± 4.9
Main site of endometriotic lesions (% women)		
Retrocervical	30	41
Rectosigmoid	70	59
EAPP partial scores (VAS: 0–10 points; mean ± SD)		
Dysmenorrhea	8.3 ± 2.5	7.6 ± 2.2
Deep dyspareunia	8.0 ± 2.7	6.9 ± 2.0
Acyclical pelvic pain	8.1 ± 2.5	7.1 ± 1.7
Cyclical bowel pain	7.7 ± 2.3	5.9 ± 3.2
Cyclical urinary pain	4.1 ± 3.6	3.9 ± 3.6
EAPP global score (VAS: 0–50 points; mean ± SD)	33.7 ± 8.5	29.4 ± 7.7
SF-36 (points, mean ± SD)		
Physical functioning	46.3 ± 23.6	54.6 ± 21.9
Role physical	40.2 ± 40.4	22.2 ± 32.8
Bodily pain	23.4 ± 15.3	28.3 ± 11.6
General health	34.5 ± 14.5	35.9 ± 14.6
Vitality	26.5 ± 17.1	25.6 ± 12.0
Social functioning	32.1 ± 19.9	40.7 ± 15.7
Role emotional	26.1 ± 34.8	25.9 ± 37.4
Mental health	30.6 ± 18.5	36.9 ± 14.5
BDI (0–63 points, mean ± SD)	30.0 ± 13.2	22.8 ± 6.6
BAI (0–63 points, mean ± SD)	27.0 ± 11.1	26.1 ± 12.2
Concomitant medication (% women)		
Hormonal therapy	83	78
NSAIDs	100	100

EAPP score, endometriosis-associated pelvic pain score; VAS, visual analogue scale; SD, standard deviation; SF-36, SF-36 Health Survey Questionnaire; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NSAIDs, nonsteroidal anti-inflammatory drugs.

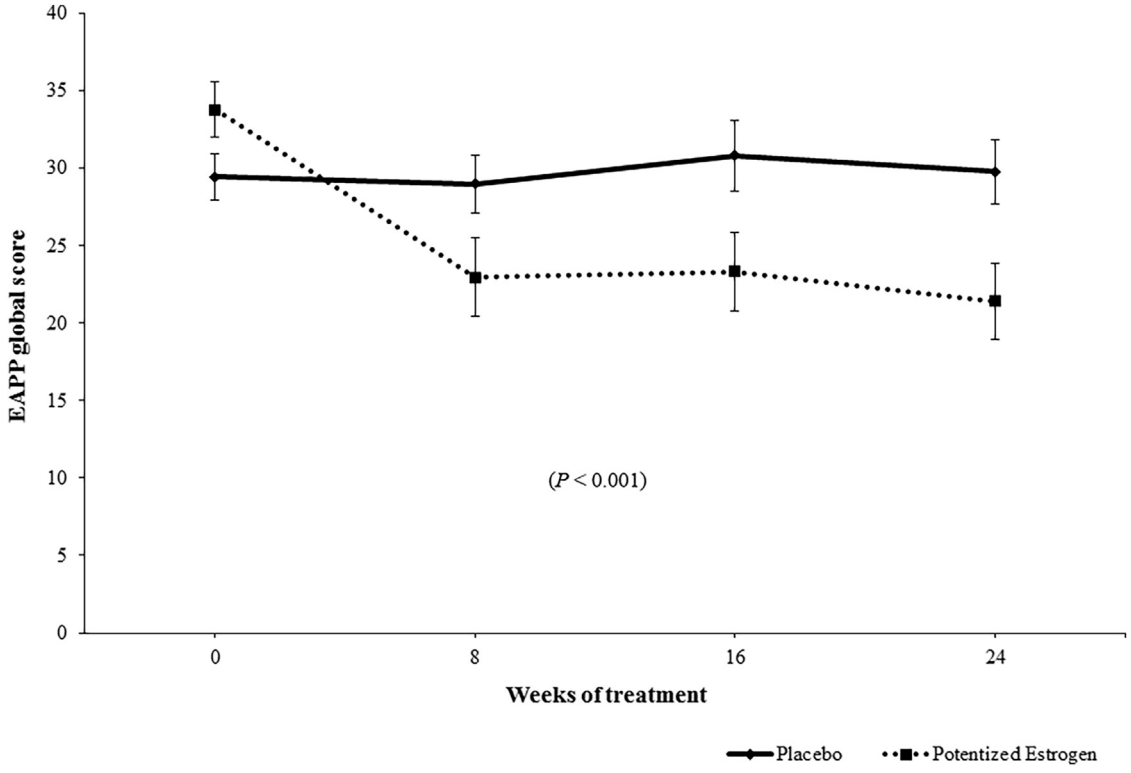

Fig. 2. Change in EAPP global score (mean difference – MD) from baseline to week 24 in groups potentized estrogen and placebo (intention-to-treat analysis).

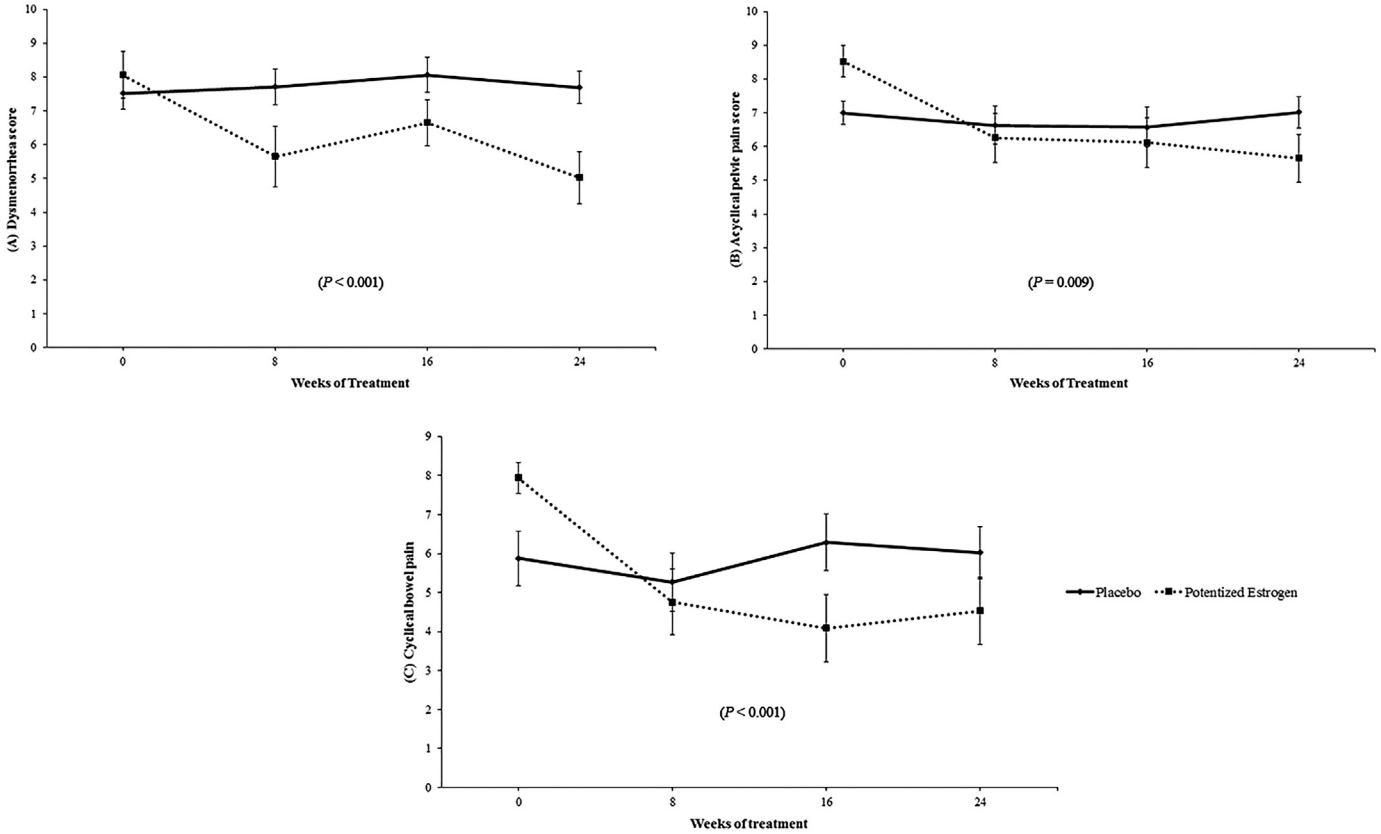

Fig. 3. Changes in partial scores (mean difference – MD) of three EAPP modalities from baseline to week 24 in groups potentized estrogen and placebo (intention-to-treat analysis): (A) dysmenorrhea, (B) non-cyclic pelvic pain, and (C) cyclic bowel pain.

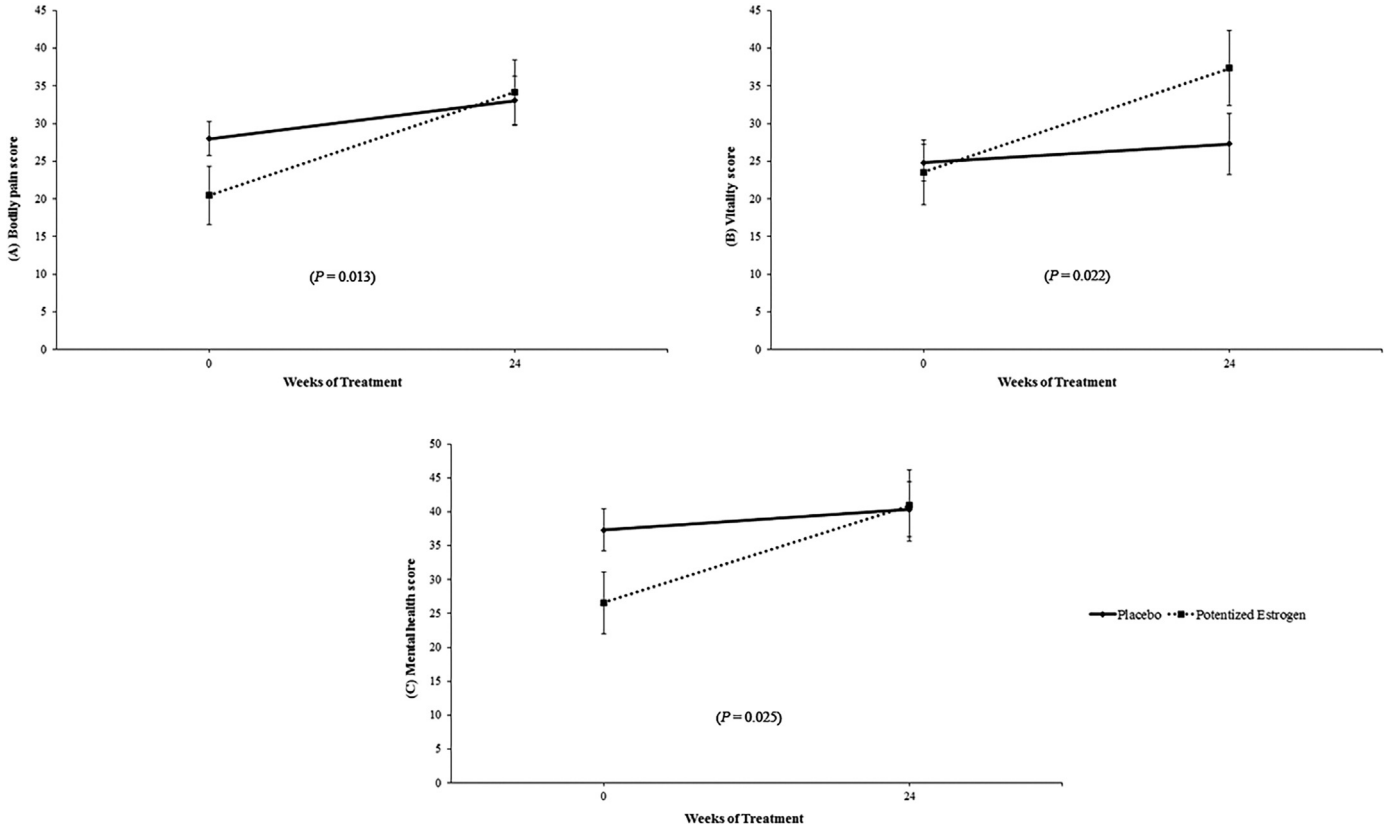

Fig. 4. Changes in scores (mean difference – MD) of three SF-36 domains from baseline to week 24 in groups potentized estrogen and placebo (per-protocol analysis): (A) bodily pain, (B) vitality, and (C) mental health.

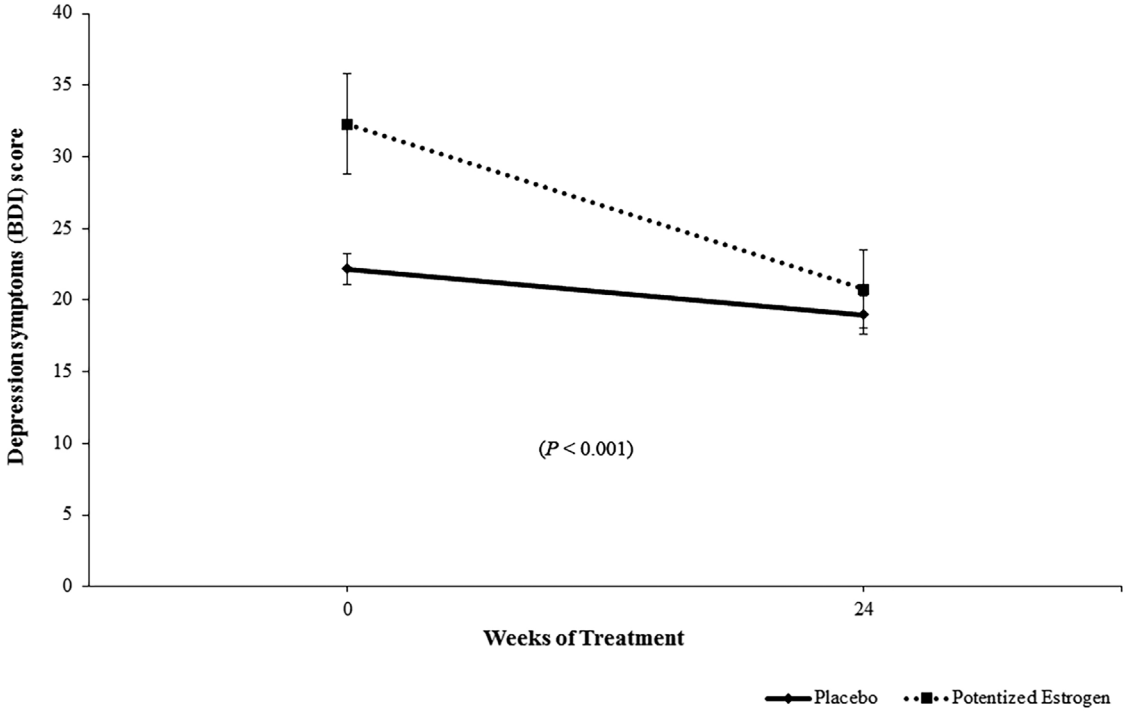

Fig. 5. Change in the score (mean difference – MD) of depression symptoms (BDI) from baseline to week 24 in groups potentized estrogen and placebo (per-protocol analysis).

Regarding quality of life, the potentized estrogen group exhibited improvement in three out of eight SF-36 domains: bodily pain (MD −13.71; 95% CI −25.49 to −1.92; $P = 0.013$), vitality (MD −13.82; 95% CI −26.38 to −1.27; $P = 0.022$), and mental health (MD −14.35; 95% CI −27.58 to −1.12; $P = 0.025$). Placebo group showed no significant improvement (Fig. 4).

Depression symptoms (BDI score) showed significant improvement in the potentized estrogen group only (MD 11.53; 95% CI 4.16-18.90; $P < 0.001$) (Fig. 5). It is worth stressing that this group presented significantly higher score on BDI at baseline compared to placebo group (MD 10.13; 95% CI −18.04 to −2.21; $P = 0.004$). Anxiety symptoms (BAI score) showed significant improvement in both groups (MD 5.43; 95% CI 2.11-8.74; $P = 0.001$).

Adverse events

Adverse event-related withdrawal occurred in only one patient from the potentized estrogen group (spotting). Possible drug-related adverse events occurred in four patients from the potentized estrogen group (nasopharyngitis, leucorrhea and diarrhea) and 11 patients from placebo group (headache, nasopharyngitis, canker sores, nausea, stomach pain, leucorrhea, cystitis, constipation, lichen planus and herpes simplex).

Discussion

In the present study, both intention-to-treat and per-protocol analysis demonstrated significant reduction of EAPP in women with endometriosis after 24 weeks of treatment with three homeopathic potencies of 17-beta-estradiol (12cH, 18cH and 24cH) compared to placebo based on the VAS results (EAPP global and partial scores). Presence of deep endometriosis, high EAPP scores at baseline and refractoriness to conventional treatment denote a high degree of severity of disease before treatment and also point to the relevance of the therapeutic response obtained.

As a function of the need for global treatment of endometriosis [34], the improvement found in the participants' quality of life (SF-36) and depression symptoms (BDI) indicate that potentized estrogen might be beneficial for the treatment of this condition. Taking also the safety (few adverse events with mild-to-moderate intensity) and low cost of homeopathic treatment, homeopathy might be added to routine conventional treatment of endometriosis as a complementary therapeutic resource [13], analogous to what occurs with other disorders (upper respiratory tract infections, respiratory allergies, childhood diarrhea, acute otitis media, premenstrual syndrome, menopause, fibromyalgia, chronic fatigue syndrome, attention deficit hyperactivity disorder, among others) and in accordance with favorable evidences demonstrated in systematic reviews and meta-analysis [35–40].

Relative to the therapeutic response to the three assessed potencies of 17-beta estradiol used consecutively, we found initial greater improvement (12cH) followed by continuous and progressive effect (18cH and 24cH), indicating therapeutic efficacy regardless of the potency used.

As study limitations, sample size was small and duration of treatment and follow up was short. Another point concerns the inclusion criteria, as they required diagnosis of endometriosis based on imaging methods, namely, TVU after bowel preparation or MRI, which were selected as a function of their high accuracy when performed by experienced radiologists [5–10]. While the limitations derived from the small sample size might be minimized by replicating the protocol used in larger and/or multicenter studies, the dropout rate (18%) points to the difficulty of keeping patients with severe disease and refractory to treatment in a randomized clinical trial over a long period of time. Future observational studies with larger samples and conducted over longer periods of time might consolidate the results found. In addition, imaging methods might also be included in longer lasting studies to quantify the possible reduction of lesions along treatment.

While the lack of similar studies in the literature made the calculation of sample size difficult, the results reported here will facilitate this estimation in future studies. As a particular strength, we might stress our concern with the methodological quality of the assessed protocol, which led us to strictly comply with inclusion/exclusion criteria, randomization/blinding methods and techniques for data collection, record and analysis.

To conclude, in the present 24-week, randomized, double-blind, placebo-controlled study, potentized estrogen was associated with significant improvement of EAPP, quality of life and depression symptoms among women with endometriosis. Potentized estrogen might represent an effective and well-tolerated complementary treatment for the pain and mental symptoms of endometriosis.

Competing interests

The present study is the postdoctoral research project of Marcus Zulian Teixeira at Department of Obstetrics and Gynecology, School of Medicine, University of Sao Paulo.

Authors' **contributions**

All the authors participated in the study design, manuscript writing and critical discussion, assuming equal responsibility for the manuscript. MZT, SP and ECB performed the applications for required approvals. MZT recruited and treated patients. MZT, SP and ECB have access to all the data and participated in the analysis and interpretation of the data.

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The present study had no funding source.

Conflict of interest statement

MZT, SP, and ECB have no commercial interest, financial interest, and/or other relationship with manufacturers of pharmaceuticals, laboratory supplies, and/or medical devices or with commercial providers of medically related services.

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