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ORIGINAL PAPER

Protocol of randomized controlled trial of potentized estrogen in homeopathic treatment of chronic pelvic pain associated with endometriosis

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Background: **Endometriosis is a chronic inflammatory disease that causes difficult-to-treat pelvic pain. Thus being, many patients seek help in complementary and alternative medicine, including homeopathy. The effectiveness of homeopathic treatment for endometriosis is controversial due to the lack of evidences in the literature. The aim of the present randomized controlled trial is to assess the efficacy of potentized estrogen compared to placebo in the treatment of chronic pelvic pain associated with endometriosis.**
Methods/design: **The present is a randomized, double-blind, placebo-controlled trial of a homeopathic medicine individualized according to program 'New Homeopathic Medicines: use of modern drugs according to the principle of similitude' (http://newhomeopathicmedicines.com). Women with endometriosis, chronic pelvic pain and a set of signs and symptoms similar to the adverse events caused by estrogen were recruited at the Endometriosis Unit of Division of Clinical Gynecology, Clinical Hospital, School of Medicine, University of São Paulo (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HCFMUSP). The participants were selected based on the analysis of their medical records and the application of self-report structured questionnaires. A total of 50 women meeting the eligibility criteria will be randomly allocated to receive potentized estrogen or placebo. The primary clinical outcome measure will be severity of chronic pelvic pain. Statistical analysis will be performed on the intention-to-treat and per-protocol approaches comparing the effect of the homeopathic medicine versus placebo after 24 weeks of intervention.**
Discussion: **The present study was approved by the research ethics committee of HCFMUSP and the results are expected in 2016.**
Trial registration: ClinicalTrials.gov Identifier: https://clinicaltrials.gov/ct2/show/NCT02427386. *Homeopathy* (2016) **105**, 240–249.

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Introduction

Endometriosis is a chronic inflammatory disease characterized by ectopic implantation and growth of endometrial tissue (ovaries, peritoneum, retrocervical region, rectosigmoid colon and bladder, among others). It affects about 10–15% of women of reproductive age, which corresponds to 70 million cases worldwide. The most common complaints among women with endometriosis are

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dysmenorrhea, deep dyspareunia, noncyclic pelvic pain and infertility, in addition to gastrointestinal and urinary problems (pain or bleeding upon passing stools or urine) during the menstrual period. Based on clinical parameters, endometriosis is classified as three distinct entities: superficial peritoneal endometriosis, ovarian endometriosis (endometrioma) and deeply infiltrating endometriosis, with increasing severity in this order. From the pathophysiological point of view, endometriosis is mainly an estrogen-dependent disease.[1,2]

The gold standard for diagnosis of endometriosis is visual inspection under surgery (preferably by means of laparoscopy) and biopsy of lesions. However, noninvasive methods, like magnetic resonance imaging (MRI) and transvaginal ultrasound (TVUS), exhibit high diagnostic accuracy in ovarian and deeply infiltrating lesions when specific protocols are applied by experienced professionals.[3–7]

The economic and social impacts of endometriosis are considerable. In the United States, endometriosis accounts for one third of hospital admissions for gynecological causes,[8] while one study conducted in Italy showed that the annual cost of inpatient treatment is about 54 million euros.[9]

Broadening the spectrum of the 'endometriosis disease' to the 'endometriosis syndrome', several studies demonstrate the association of other comorbidities with the most common complaints of the endometriosis (dysmenorrhea, deep dyspareunia, noncyclic pelvic pain and infertility), like autoimmune diseases (systemic lupus erythematous, rheumatoid arthritis, among others),[10–12] ovarian cancer,[10–14] psychiatric disorders (depression, anxiety, among others),[15–17] atopic diseases (asthma, sinus allergic rhinitis and dermatitis),[10,12,18,19] migraine,[20–23] sleep disorders,[24] urinary functional disorders,[25] visceral syndrome (constipation or diarrhea, nausea or vomiting, among others),[26] among others. Some of these comorbidities are not associated with chronic pain, and present genetic correlation with endometriosis.

In addition to surgical removal of lesions (laparoscopy), pharmacological treatment is indicated to induce anovulation, hypoestrogenism and amenorrhea, for which purpose combined contraceptives, gonadotropin-releasing hormone (GnRH) agonists, danazol and progestogens alone, as well as levonorgestrel-releasing intrauterine devices (LNg-IUD) are used. However, improvement of pain is not systematically achieved in an efficient manner, while it depends on the continuous use of medication, being that the rate of recurrence after discontinuation is over 50%.[27] In turn, continuous and prolonged use of those agents is associated with adverse events, like virilization and menopausal-like symptoms, among others.[28,29]

As a function of the side effects of conventional treatment and its failure to induce a systematic effective response, development of complementary therapeutic approaches is necessary to minimize the suffering of patients. Homeopathy might represent one such complementary therapeutic option. While the occurrence of placebo effects is similar among various modalities of therapeutic interventions[30,31] it is the ground for the current skepticism about homeopathy, whereby any clinical improvement is attributed to the nonspecific effects of homeopathic treatment.[32–34] To refute that hypothesis, hundreds of randomized controlled trials (RCTs) were performed in the past decades aiming at demonstrating the efficacy of homeopathic medicines compared to placebo.[35–40] Here we describe a specific research protocol elaborated to conduct a RCT to assess the efficacy of individualized homeopathic medication versus placebo for the treatment of chronic pelvic pain associated with endometriosis. To the best of our knowledge, no RCT has yet been performed assessing homeopathic medicines in the treatment of endometriosis.

Homeopathic therapeutics is grounded on four pillars: principle of therapeutic similitude (*similia similibus curentur*), pathogenetic testing of medicinal substances (similar to phase I pharmacological clinical studies), use of potentized (highly diluted and agitated) remedies and individualization of medicines (according to the full picture of characteristic signs and symptoms exhibited by the patient). The relevance of the highly diluted doses notwithstanding (which were introduced at a later stage in the early development of homeopathy to avoid the aggravation large doses could cause in patients subjected to treatment by similars), only therapeutic similitude and pathogenetic testing of medicines are the true pillars of the homeopathic model, whereas prescription of individualized medicines is indispensable for highly diluted doses to trigger a therapeutic response.

The clinical application of the principle of therapeutic similitude demands administering to patients medicines that induced similar signs and symptoms in human experimenters (primary action of drugs). The aim of this procedure is to awaken a vital reaction (organism's secondary action) in the patient against the organism's own disorders. According to a homeopathic aphorism, 'any substance able to cause symptoms in a healthy individual might be used to treat those very same symptoms in an ill person'. The effects caused by homeopathic medicines in several experimenters are compiled in the homeopathic materia medica, which thus contains the dataset required for the application of the principle of therapeutic similitude based on the full picture of characteristic signs and symptoms exhibited by each individual patient. Thus being, a specifically individualized medicine is selected for each particular patient, namely, the one that awakened a similar set of signs and symptoms in experimenters. It is worth to observe that any (natural or synthetic) substance might serve as a homeopathic medicine provided it produced pathogenetic effects in human beings.

The 'primary actions' or 'pathogenetic effects' of homeopathic medicines correspond, mainly, to the 'adverse/side effects' of conventional drugs. Similarly, the homeopathic 'secondary action' or 'vital reaction' corresponds to the organism's 'rebound effect' or 'paradoxical reaction'. Although poorly known among doctors, the rebound effect takes place following discontinuation or tapering of

hundred of modern drugs of many different types. It is defined as, "*the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it was used to treat may come back even stronger when the drug is discontinued or loses effectiveness*".[41] We started investigating the rebound effect in 1997 as an attempt to give modern scientific foundations to the principle of therapeutic similitude.[42–53]

A new therapeutic approach is currently evolving within modern pharmacology based on the use of substances that induce definite organic dysfunctions to treat similar disorders, being thus analogous to the therapeutic method homeopathy employs for more than 200 years.[54,55] Known as 'paradoxical pharmacology',[56–61] it assumes that, 'exacerbating a disease [can] make use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response',[56] thus suggesting the use of the paradoxical and bidirectional drug effects with therapeutic intention.

That therapeutic approach is exemplified by the use of beta-blockers and calcium channel blockers in the treatment of congestive heart failure (CHF), with consequent improvement of the ventricular contractility and reduction of the associated mortality.[56,60,62,63] Beta-blockers might also be used for chronic treatment of asthma, in which condition they promote bronchodilation and reduce the airway inflammation.[56,60,64] Similarly, arsenic trioxide (As_2O_3), a significant carcinogenic agent, showed much promise as anticancer drug (for instance, in acute promyelocytic leukemia).[65,66] These are just some examples among many.[67–71]

Aiming at bridging the gap between different therapeutic systems, as well as to broaden the scope of action of the treatment by similars, in 2003 we began to elaborate a systematic method of application of the curative rebound effect of drugs. Thus we suggest giving patients drugs that cause adverse events similar to the full picture of their characteristic signs and symptoms, but in highly diluted doses (homeopathic potencies) so as to stimulate a homeostatic reaction in the organism against its own disorders.[72–75]

To operationalize the aforementioned proposal, we elaborated a Homeopathic Materia Medica of Modern Drugs (HMMMD), which includes all the adverse events (primary or pathogenetic effects) of 1250 modern drugs as described in the United States Pharmacopeia Dispensing Information (USP-DI).[76] The entries follow the chapter distribution of the traditional works on homeopathic materia medica. In addition, to facilitate the selection of the individualized medication, to remind, the key for the success of homeopathic treatment, we elaborated a Homeopathic Repertory of Modern Drugs (HRMD) too. Also the organization of that work follows the one of the traditional homeopathic repertories, and thus pathogenetic manifestations and the corresponding medicines are distributed across anatomical-functional categories and their relative frequencies are indicated. This program, named 'New Homeopathic Medicines: use of modern drugs according to the principle of similitude', including theoretical and practical materials, is available at an open-access bilingual (English, Portuguese) website (http://www.newhomeopathicmedicines.com).[77]

Thus being, program 'New Homeopathic Medicines' not only introduces more than 1000 new medicines into the homeopathic therapeutic arsenal, but also broadens the scope of application of the principle of therapeutic similitude through the addition of countless signs, symptoms, clinical diagnoses, laboratory and anatomical pathology data, and modern clinical syndromes that are not described in the traditional homeopathic literature.

An illustrative example of the application of this new approach is provided by the treatment of chronic pelvic pain associated with endometriosis, namely, the target of the present study. The traditional homeopathic literature makes no mention of any remedy able to cause 'endometrial ectopic growth or proliferation' as a part of its primary action (pathogenetic effect). The reason is that in the past no diagnostic tests were available to identify such relevant anatomical and pathophysiological abnormality.

However, when the study of modern drugs is performed according to the criteria and methods described above,[75,77] one easily finds in USP-DI lists the typical description of endometriosis ('endometrial proliferation or hyperplasia') as an adverse event (pathogenetic effect) associated with the use of four types of modern drugs: estrogens, systemic and vaginal; tamoxifen; and toremifene. Any such drugs might prove useful to treat that very same problem or its consequences through the principle of therapeutic similitude and individualization of the symptom picture. It is worth to emphasize that in this regard, the use of conventional drugs in highly diluted doses (potencies) is crucial to avoid any aggravation of symptoms, as well as the side effects associated with large doses.

As a function of their high pathogenetic power, modern drugs cause a huge variety of adverse events (signs, symptoms, diseases and clinical syndromes), many of which are serious or even fatal. However, they might be used according to the homeopathic criteria (individualized selection of medicines based on the full symptom picture and prescribed in highly diluted doses) to treat disorders similar to the ones they cause.[73–75,77] The rationale underlying the protocol described here for the treatment of endometriosis, and that we describe below, might be also applied to any other condition and the drugs that cause them.

Aims

The aim of the present study is to assess the efficacy of individualized homeopathic treatment of chronic pelvic pain associated with endometriosis by means of a double-blind, placebo-controlled randomized clinical trial (RCT) and in compliance with the criteria and methods included in program 'New Homeopathic Medicines'.[72–75,77]

Methods and design

The present study consists in a medium-term RCT (24 weeks) in which three different potencies of estrogen (12cH, 18cH and 24cH) or placebo (1:1 ratio) will be administered sequentially every eight weeks to women with chronic pelvic pain associated with endometriosis and refractory to the conventional hormonal therapy. The participants were recruited at the Endometriosis Unit of Division of Clinical Gynecology, Clinical Hospital, School of Medicine, University of São Paulo, Brazil (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo − HCFMUSP), which is the study setting.

Choice of the homeopathic medicine to be tested in the RCT

According to a traditional approach in homeopathy, to select the most adequate individualized remedy, some peculiar and highly characteristic aspects of the patient are considered as 'elimination' factors. This means that such aspects must mandatorily belong to the set of signs and symptoms induced by the remedy in question in pathogenetic trials. As a function of the relevance of ectopic endometrial growths for the genesis and clinical manifestations of endometriosis, we chose 'endometrial proliferation or hyperplasia' from USP-DI list of adverse events (pathogenetic effects), and thus also in HRMD (chapter 'Genitalia female'),[77] as the primary elimination symptom. As a result, we located four types of modern drugs that caused that disorder in patients/experimenters (Table 1).

Next, we analyzed those four types of drugs to establish which one corresponded best (number and score of pathogenetic signs and symptoms) to the main manifestations of 'endometriosis syndrome' (endometrial proliferation, dysmenorrhea, dyspareunia, abdominal pain, depression, anxiety, insomnia, and migraine). Repertory analysis (Table 2) showed that 'Estrogens (Systemic)' was the most similar one and thus was selected for use in the present study.

Identification and recruitment of participants

Identification and recruitment of participants was performed at the Endometriosis Unit of Division of Clinical Gynecology, HCFMUSP, on the occasion of routine visits to the Endometriosis Outpatient Clinic. The women who met the inclusion criteria and signed an inform consent form were considered eligible for the present study.

Primary inclusion criteria: The participants were preselected based on the analysis of their medical records according to the following primary inclusion criteria: age 18−45 years old; confirmed diagnosis of endometriosis based on their clinical history and physical examination combined with MRI, TVUS with bowel preparation or laparoscopy (biopsy) evidencing the 'endometrial proliferation or hyperplasia'; absence of clinical or laboratory signs of menopause or premature ovarian failure; presence of chronic pelvic pain (persistent pelvic pain with no relation with the menstrual cycle for at least 6 months) in a score ≥5 on a visual analogue scale (VAS-Pain: 0−10 points). Patients who met the primary inclusion criteria were subjected to analysis as to the secondary (homeopathic) inclusion criteria, which was performed by means structured questionnaires as described below.

A total of 1112 medical records were analyzed in the course of one year, and 170 women were found to meet the primary inclusion criteria. That group was analyzed as to the secondary or homeopathic inclusion criteria, as follows.

Secondary or homeopathic inclusion criteria: individualization of the patients' symptom picture relative to the preselected remedy (a priori individualization of patients): As the number of drugs that caused the primary elimination symptom (endometrial proliferation) is very small (four only), in the present study, instead of the traditional technique of homeopathic individualization of the patient's symptom picture,[78,79] we chose to screen the patients so as to select the ones whose symptoms matched the pathogenetic manifestations of estrogen, which are quite similar to the clinical presentation of endometriosis (screening phase, pre-individualization or *a priori* individualization of patients). This represents the population of the RCT to test the efficacy of potentized estrogen compared to placebo.

It is worth to observe that *a priori* individualization of patients relative to one single preselected homeopathic remedy was previously used in other RCTs (screening phase prior to the randomized controlled phase),[80−82] and might also be applied to any other condition. In addition to complying with the homeopathic model criteria (therapeutic individualization based on the full picture of signs and symptoms), *a priori* individualization facilitates the performance of RCTs, as one single remedy is used. In addition, it shortens the duration of trials, which are usually quite long in the case of homeopathy, and makes the delivery of the medication to the participants simpler, among other advantages.

Selection of the medicine to be tested ⇨ *A priori* individualization of participants (set of signs and symptoms similar to the pathogenetic effects of the remedy) ⇨ RCT comparing the selected medicine versus placebo

In USP-DI, and consequently also in the HMMMD,[77] the adverse events (pathogenetic effects) attributed to 'Estrogens (Systemic)' are very similar to the clinical presentation of 'endometriosis syndrome' initially cited. Only patients exhibiting a set of signs and symptoms similar to the pathogenetic effects of estrogen were selected. For that purpose, the recruited volunteers answered a

Table 1 Endometriosis in HRMD (Chapter Genitalia Female)

Endometrium
endometriosis; disorder, endometrial; proliferation, endometrial; hyperplasia: *Estro-syst.*, *Estro-vag.*, *Tamo-syst.*, *Tore-syst.*

Estro-syst.: Estrogens (Systemic); Estro-vag.: Estrogens (Vaginal); Tamo-syst.: Tamoxifen (Systemic); Tore-syst.: Toremifene (Systemic).

Table 2 Repertory analysis of signs and symptoms of 'endometriosis syndrome'

Signs/Symptoms

(1) Chapter Genitalia Female − Endometriosis, endometrial proliferation
(2) Chapter Genitalia Female − Dysmenorrhea
(3) Chapter Genitalia Female − Dyspareunia
(4) Chapter Abdomen − Pain
(5) Chapter Mind − Depression
(6) Chapter Mind − Anxiety
(7) Chapter Sleep − Insomnia
(8) Chapter Head − Migraine

Drugs	*Number of signs/symptoms*	*Total score*	*Symptom score (1−4)*							
			(1)	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*
Estro-syst.	8/8	29	2	4	3	4	4	4	4	4
Estro-vag.	2/8	5	2	0	0	3	0	0	0	0
Tamo-syst.	2/8	6	3	0	0	0	3	0	0	0
Tore-syst.	1/8	3	3	0	0	0	0	0	0	0

The scores of symptoms correspond to the frequency of incidence (%) of the correlate adverse events (*USP-DI*, phase I−IV trials): score 4 (≥4%), score 3 (1−4%), score 2 (<1%), score 1 (overdose).

Table 3 Estrogens (systemic) − pathogenetic effects (HMMMD) − checklist

Estrogens (systemic) − HMMMD

Location	**Primary actions, pathogenetic effects or adverse events**
Mind	**anxiety; depression**; *emotional disturbance*; *dementia*; *irritability*; *nervousness*.
Vertigo	**dizziness, mild.**
Head	**headache; migraine headaches**; *embolic cerebrovascular events*; *hair, scalp, loss of*; *stroke*.
Eye	*infection, herpes simplex*; *intolerance to contact lenses*; *curvature, corneal, steepening of* (vision changes); *neuritis, optic*; *thrombosis, retinal*.
Vision	*disturbances, visual*.
Nose	**congestion, sinus; nasopharyngitis; rhinitis**; *congestion, nasal*; *infection, herpes simplex*.
Face	*acne*; *hirsutism*; *infection, herpes simplex*; *neuritis*; *chorea*.
Mouth	*chorea*.
Teeth	*abscess, tooth*.
Throat	**nasopharyngitis; pharyngitis.**
External Throat	**pain, neck.**
Stomach	**anorexia; dyspepsia; nausea**; *gastroenteritis*; *vomiting*; *appetite, changes in*.
Abdomen	**bloating; cramping, abdominal; flatulence; pain, abdominal**; *gastroenteritis*; *obstruction, gallbladder*; *hemangioma, hepatic, enlargement of*; *liver function, impaired, asymptomatic.*
Rectum	**constipation**; *diarrhea, mild*.
Bladder	**infection, urinary tract**; *dysuria*; *infection, bladder*; *cystitis*.
Kidneys	**infection, urinary tract.**
Genitalia Female	**bleeding, withdrawal; dysmenorrhea; vaginitis; vaginosis, fungal**; *bleeding, breakthrough*; *discharge, vaginal*; *hemorrhage, vaginal; infection, candidal*; *infection, herpes simplex*; *libido increase*; *menorrhagia*; *spotting*; *atrophy, endometrial*; *cancer, endometrial*; *cancer, ovarian*; *ectropion, cervical, change in*; *hyperplasia, endometrial; leiomyomata, uterine, increase in size*; *secretion, cervical, change in*.
Respiration	**bronchitis; infection, upper respiratory tract [URTI]**; *asthma, exacerbation of*.
Cough	*cough, increased*.
Chest	**bronchitis; enlargement of breasts; gynecomastia; pain or tenderness, breast**; *infection, pleural*; *pain, chest*; *tumors, breast*; *asthma, exacerbation of*; *cancer, breast*; *embolism, pulmonary*; *fibrocystic breast changes*; *galactorrhea*; *infarction, myocardial*; *palpitations* (irregular heartbeat); *thrombosis, coronary*.
Back	**pain.**
Extremities	**edema, peripheral**; *cramps, muscle*; *osteoarthritis*; *spasms, muscle*; *neuritis*; *cramps, leg*; *varicose veins, exacerbation of*.
Sleep	**insomnia.**
Skin	**irritation; pruritus; rash; redness**; *acne*; *hirsutism*; *chloasma*; *eruption, hemorrhagic*; *erythema multiform*; *erythema nodosum*; *melasma*.
Generalities	**asthenia**; **cyst**; **edema, peripheral**; **flu syndrome**; **fluid retention or edema**; **hypersensitivity reactions**; **infection**; **infection, fungal**; **infection, upper respiratory tract [URTI]**; **injury, accidental**; **pain**; **sinusitis**; **weight, increased**; *cramps, muscle*; *fatigue*; *hepatitis*; *hirsutism*; *hypertension*; *hypoesthesia*; *infection, herpes simplex*; *osteoarthritis*; *pancreatitis*; *spasms, muscle*; *thromboembolism or thrombus formation*; *epilepsy, exacerbation of*; *erythema multiform*; *hypocalcemia*; *jaundice, cholestatic*; *lupus erythematosus, exacerbation of*; *palpitations* (irregular heartbeat); *porphyria, aggravation of*; *retention, sodium*; *sugar levels, blood, increased or glucose tolerance, reduced*; *triglycerides, increased*; *varicose veins, exacerbation of.*

The scores of symptoms correspond to the frequency of incidence (%) of the correlate adverse events (USP-DI, phase I−IV trials): score 4/**bold** (≥4%), score 3/*underlined italic* (1−4%), score 2/*italic* (<1%), score 1/normal (overdose).

structured questionnaire (checklist) listing the pathogenetic effects (adverse events) of estrogen described in HMMMD (Table 3).

To prioritize emotional and mental aspects (mental symptoms) in the pre-individualization of patients, which are also highly relevant in endometriosis,[83–86] 'anxiety' and 'depression' were selected as secondary elimination symptoms. For that purpose, the Beck Anxiety Inventory (mild anxiety: score ≥8)[87] and the Beck Depression Inventory – II (mild depression: score ≥14)[88] were applied.

In addition to the already mentioned elimination symptoms ('endometrial proliferation or hyperplasia', 'anxiety' and 'depression'), the minimum syndrome for individualization further included five other signs or symptoms with high scores or frequency (3–4 points in Table 3) at least.

A priori individualization of participants (selection according to a set of signs and symptoms similar to the pathogenetic effects of estrogen): 'endometrial proliferation' + 'anxiety' + 'depression' + 'five other signs or symptoms with high scores or frequency'

It should be observed that the participants were selected based on the analysis of medical records (primary inclusion criteria) and application of self-report questionnaires (secondary inclusion criteria). Thus being, the possible nonspecific effects of homeopathic consultations (placebo effect, patient–doctor relationship or spending time with an empathetic practitioner) were ruled out, which as it was mentioned above, are often invoked to account for the possible beneficial effects of traditional homeopathic treatment.

The characteristics of the study will be explained to the women that met the criteria of inclusion who will manifest their agreement to participate by signing an informed consent form approved by the research ethics committee of HCFMUSP (ruling no. 448,607). The participants then will answer a quality of life questionnaire (SF-36), which was defined as secondary outcome measure in the global assessment of the response to treatment.

From 170 women who met the primary inclusion criteria, 50 also met the secondary inclusion criteria and were selected for the present study. The selected participants will be randomly allocated to receive homeopathic medication (potentized estrogen) or placebo along 24 weeks. Follow-up visits were scheduled every 8 weeks (visits 2, 3 and 4) to assess outcomes and deliver the medication.

Randomization and blinding

The participants will be randomly allocated to receive homeopathic medication (A) or placebo (B) in a 1:1 ratio. The randomization sequence was created by a supervisor, who does not participate in the treatment or assessment of the participants, using a random number generator. For that purpose, the code number of each participant (in order of recruitment, 01, 02, 03, 04, 05, etc.) was associated to an intervention code (A or B), e.g.: 01-A, 02-A, 03-B, 04-A, 05-B, etc. The vials containing homeopathic medicine or placebo are identical and were identified by means of an adhesive label with the participants' code numbers (01, 02, 03, 04, 05, etc.) according to the randomization sequence. Both physician-investigator and participants will remain blinded as to the nature of the interventions (potentized estrogen or placebo) for the duration of the study and through data analysis. The study flowchart is depicted in Figure 1.

Preparation of the homeopathic medicine (potentized estrogen)

The homeopathic remedy (potentized estrogen) was prepared from 17-beta-estradiol valerate (Pharma Nostra, Batch Number 12030691A, December 2011, São Paulo, Brazil) in compliance with the Brazilian Homeopathic Pharmacopeia.[89] In the preparation of the homeopathic potencies of 17-beta-estradiol used in the present study (12cH, 18cH and 24cH), the three first steps involved trituration with lactose, followed by centesimal dilutions (with 100 succussions). The medication will be delivered as drops (30% hydroalcoholic solution) in 30-ml vials including a dropper.

Interventions

Each participant allocated to the active treatment group (verum) is scheduled to receive a vial of potentized 17-beta-estradiol 12cH, 18cH and 24cH in visits 1, 2 and 3, respectively. To the participants in group placebo will be given identical vials containing hydroalcoholic solution only.

Following the initial assessment of outcomes and delivery of the first vial of homeopathic medication (potency 12cH) or placebo on visit 1, the participants will be evaluated by the physician-investigator every 8 weeks (visits 2, 3 and 4) along the duration of the study (24 weeks). On visits 2 and 3 the participants will be given new vials of homeopathic medicine (visit 2, week 8, potency 18cH; visit 3, week 16, potency 24cH) or placebo. The study will finish on week 24 (visit 4), when the final assessment of outcomes will be performed.

All the participants will remain under the care of their regular gynecologists at Endometriosis Outpatient Clinic (HCFMUSP) and will continue using their usual analgesics and hormonal therapy. No changes in conventional treatment will be allowed along the study period (recruitment/randomization/onset to end of study). The frequency of use of analgesics will be registered in the participants' medical records at each visit as a variable to validate self-reported improvement or aggravation of chronic pelvic pain (response to intervention).

The dose of homeopathic medicine or placebo will be 3 drops twice per day (every 12 h) to be taken all along the study period; however, the amount or frequency of intake might be reduced were homeopathic aggravation to occur. The content of 30-ml vials suffices for the indicated regimen. Possible occurrence of adverse events will be assessed at each visit and registered in an *ad hoc* adverse event form.

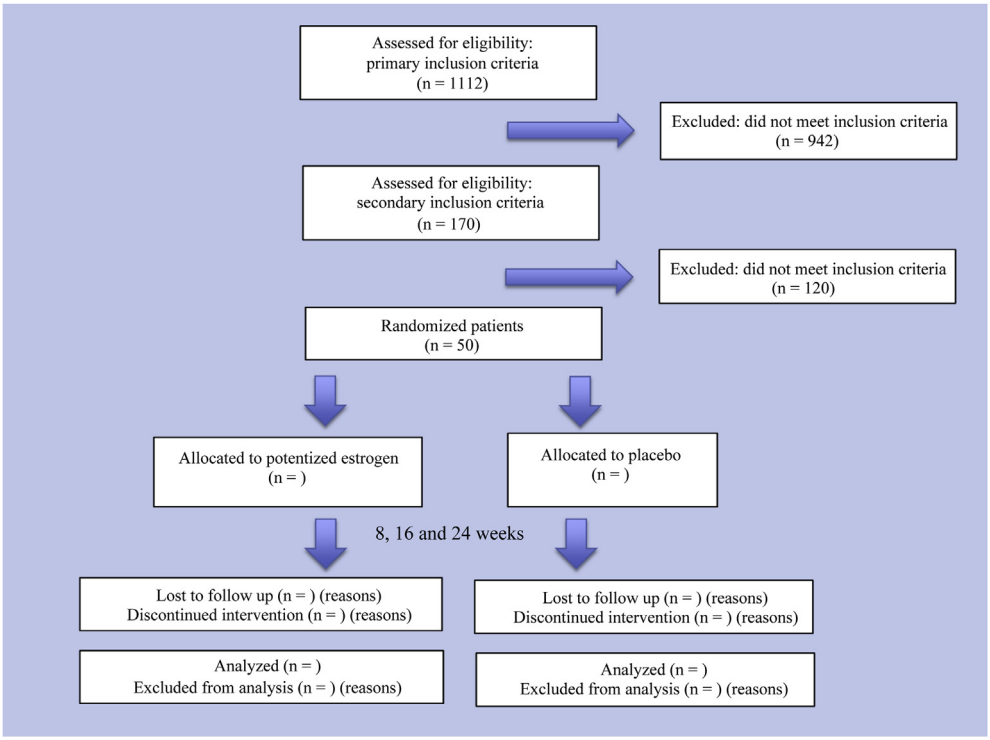

Figure 1 Flowchart of RCT showing the intervention arm.

Outcome measures

The primary outcome measure will be chronic pelvic pain that will be assessed on VAS-Pain, whereby scores 0 to 10 will be attributed to the intensity of pain. Other symptoms will be also verified with VAS scores: dysmenorrhea, deep dyspareunia, cyclical bowel complaints and/or cyclical urinary disorders. The secondary outcome measure will be the score on Short Form 36 Health Survey (SF-36).[90,91]

The primary outcome will be assessed at baseline (visit 1) and then on weeks 8 (visit 2), 16 (visit 3) and 24 (visit 4). The secondary outcome will be assessed at baseline and then at the end of the study (week 24). While the primary endpoint of the study corresponds to the outcomes on week 24, the intermediate assessments (weeks 8 and 16) of chronic pelvic pain might provide relevant data on the therapeutic response to the various potencies of 17-beta-estradiol (12cH, 18cH and 24cH) and the participants' clinical progression.

Sample size

The sample size was calculated based on the primary outcome, namely, changes in VAS-Pain (score 0—10 points) from baseline (visit 1) to week 24 (visit 4). The absence of similar studies in the literature makes calculating the sample size difficult. With conventional treatment,[92] the variation in the VAS for chronic pelvic pain was 2.58 points. To find a same difference in the present study (placebo controlled), the variation in VAS-Pain ought to be 2.16 points. With power 80% and significance level 5%, the minimum number of participants for a two-tailed test[93] ought to be 23 per group. Considering a loss to follow-up of 10%, the final sample size was estimated at 50 participants (25 patients in each group).

Data analysis

The data will be analyzed by means of descriptive statistics and a CONSORT-like flowchart[94,95] was plotted to describe the flow of participants through the study. The following basal characteristics of all the participants included in the RCT will be registered: age, type/severity of disease (localization of endometriotic lesions according to the diagnostic tests), VAS-Pain, score on SF-36 and use of analgesics and hormonal therapy. The basal data of the participants who complete or drop out from the study will be compared to investigate eventual differences between these groups.

The data will be subjected to intention-to-treat and per-protocol analysis at 5% significance level (95% confidence interval). In intention-to-treat analysis, the participants will be considered in the group of allocation, independently from having or not received the corresponding intervention. The primary outcome measure will be the average variation on VAS-Pain between the first (baseline) and last (week 24) assessments, which will be evaluated by means of analysis of covariance adjusted to the score at baseline. The same method will be used in the evaluation of the secondary outcome (score on SF-36). All the data will be tested for normality; the variables with non-normal distribution will be assessed by equivalent non-parametric tests.

Discussion

The present study was approved by the research ethics committee of HCFMUSP (no. 448.607, October 16 2013). Results are expected in 2016.

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

MZT had the lead role in drafting and revising the manuscript. MZT and SP designed the study protocol. SP and ECB made significant contributions to the development of the study protocol and to the critical revision of the manuscript. All the authors read and approved the final manuscript.

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