

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, rectosig-

moid 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 erythematosus, 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

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