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GENERAL GYNECOLOGY

Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis

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Abstract
Objective A meta-analysis was conducted to determine the effectiveness of using gonadotropin-releasing hormone analogues (GnRH-a), both with and without hormonal add-back therapy, for the management of endometriosis.
Methods Cochrane library, Ovid (Embase) and Pubmed databases were searched between the years 1998 and 2013 for published, prospective, randomised controlled trials (RCT) that assessed the effectiveness of "add-back" therapy for EMs treatment. The meta-analysis was performed using RevMan V5.0. The main outcome measures were as follows: lumbar spine bone mineral density (BMD) immediately after treatment and after 6 months of follow-up; femoral neck BMD; serum estradiol levels; changes in the Kupperman index score; the pelvic pain score, including dysmenorrhoea and dyspareunia; and pelvic tenderness.
Results A total of 13 RCT, including 945 participants, were identified. The evidence suggested that "add-back" therapy was more effective for symptom relief than GnRH-a alone. BMD was significantly different when comparing "add-back" therapy to GnRH-a alone, both immediately after treatment and at 6 months. The "add-back" therapy increased serum oestrogen and did not reduce the efficacy of GnRH-a for treating dysmenorrhoea and dyspareunia. A variety of add-back regimens had a same effect for the treatment of endometriosis.
Conclusions "Add-back" therapy, based on the GnRH-a dose, does not reduce the efficacy of using GNRH-a for the management of endometriosis. "Add-back" therapy reduced the occurrence of side effects that can occur with GnRH-a therapy alone, such as osteoporosis and menopausal syndrome. There were no statistically significant differences when comparing the effectiveness of a variety of "add-back" regimens to each other.

Keywords Endometriosis · "Add-back" therapy · GnRH-a · Meta-analysis

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Introduction

Endometriosis (EMs) is a common gynaecological condition in which proliferative endometrial tissue is present outside the uterine cavity. EMs can cause pain and infertility and is invasive and recurrent. The main symptoms of endometriosis include dysmenorrhoea, chronic pelvic pain, primary or secondary infertility, menstrual disorders, changes in bowel function and urinary tract symptoms [1]. The incidence of endometriosis in women of reproductive age is about 10–15 % and the incidence of endometriosis in patients with infertility is 40 % [2].

EMs is oestrogen dependent and the removal of both ovaries has long been known to provide permanent symptomatic relief. However, this is often not an acceptable option in women of childbearing potential [3]. The disease is often treated medicinally or surgically. Gonadotropin-releasing hormone analogue (GnRHa) is commonly used to treat EMs. GnRHa has the same effect as removing the ovaries, inducing temporary menopause and very low levels of circulating oestrogens, leading to a decrease in the size of the ectopic lesion. However, some women experience adverse effects due to oestrogen deficiency, such as hot flushes, vaginal dryness and loss of libido. Low oestrogen levels can also accelerate bone mass loss [4], as often

occurs following menopause, thus treatment with GnRHa is usually administered for no more than 6 months [5].

To lengthen the period that GnRHa can be administered, so-called "add-back" therapy has been used in recent years to alleviate side effects. "Add-back" therapy, also known as hormone replacement therapy (HRT), refers to the replacement of hormones or non-hormonal substances to avoid some of the side effects that are caused by the GnRHa-induced suppression of oestrogen. "Add-back" therapy can cause premenstrual syndrome-like symptoms in women who suffer from or have suffered from premenstrual syndrome [6].

A systematic review was done to determine the efficacy of "add-back" therapy for the management side effects related to GnRHa and whether "add-back" therapy affected the efficacy of GnRHa for the treatment of EMs.

Methods

Study selection and data extraction

Medical databases were searched for reports of published clinical trials related to GnRHa and "add-back" therapy for the management of endometriosis. Searches were conducted in PubMed, Embase, and Ovid for English language articles published between January 1st, 1998 and February 28th, 2013. The keywords used were "add-back" or "HRT", "GnRHa" or "GnRH-a" or "GnRH agonist" or "GnRH analogues", and "endometriosis" or "EMs" or "EMT". A manual search was then performed using the references cited in the acquired articles. Previously published review articles were also searched to identify eligible studies. Prospective, randomised, controlled trials that compared GnRH analogues with placebo, that included no treatment or that included "add-back" therapies for the treatment of endometriosis were considered for inclusion. Only English and Chinese language articles were included.

The studies were included if (1) the subjects were women with endometriosis, as confirmed by laparoscopy or laparotomy, and had abdominal pain (including chronic pelvic pain and secondary dysmenorrhoea); (2) the subjects were of childbearing age and over the age of 18; and (3) the interventions considered were treatment with subcutaneous injections goserelin (3.6 mg, once every 4 weeks) or leuprorelin (3.75 mg, once every 4 weeks) or long-term treatment with goserelin (10.8 mg once every 3 months) or leuprorelin (11.25 mg once every 3 months). The "add-back" therapy studies included those that examined the use of daily oral supplements alone or in combination with oestrogen and progesterone and also included a control group treated with GnRHa alone or GnRHa plus an oral placebo. (4) Outcome measures had to be clearly reported for original studies, as well as the number of subjects in each group, whether subjects were lost to follow-up and the reason(s) that subjects were lost to follow-up.

The studies were excluded if (1) patients used hormone therapy 3 months prior to the study or if the patients were breastfeeding, pregnant or had other diseases for which hormone therapy was contraindicated. (2) Studies with incomplete or unavailable data, with sample sizes <10, from which data could not be extracted and those that were retrospective, were also excluded.

Two reviewers analysed the full text articles in a blinded fashion. The original research was reviewed using the Jadad scale, which assesses the randomisation, double blinding and dropout and withdrawal reports of the trials. A Jadad score of 4 or more was required for the trial to be designated "high quality" and to be included in the meta-analysis. Trials with scores of <4 were designated "low quality". Disagreements between reviewers were resolved via further discussion. If no consensus was reached, a third reviewer intervened to make a final decision. Data were extracted using a standardised form. One reviewer, who was blinded to the authors, examined the abstracts to ensure that all relevant studies were included.

Bone mineral densities, serum oestrogen levels, Kupperman index scores, dysmenorrhoea scores, dyspareunia scores, and pelvic tenderness scores were collected from, and compared between, groups that received GnRHa treatment alone and groups that received GnRHa + "add-back" treatment. Where continuous data were presented, a weight mean difference (or effect size) was calculated.

The differences between the "add-back" therapy group and GnRHa alone group are expressed as a weight mean difference with a 95 % confidence interval (CI). $P < 0.05$ was considered statistically significant. Statistical heterogeneity amongst randomised controlled trials (RCTs) was assessed by a χ^2 test and is expressed with a P value and I^2 statistics. I^2 is the proportion of the total variation contributed by between-study variability. In the presence of statistical heterogeneity, a random-effect model was used. In the absence of statistical heterogeneity, the fixed-effects model was used. Finally, a funnel plot was used to detect bias (such as publication and location bias) in the selection of included trials. A linear regression of the standard normal deviate (defined as the standardised mean difference divided by its standard error) was plotted against precision (inverse of the standard error) to quantitatively assess the asymmetry of the funnel plot. A regression line, which passes through the origin of the plot (within error limits), indicates symmetry and hence the absence of bias. The statistical software used was RevMan 5.0.

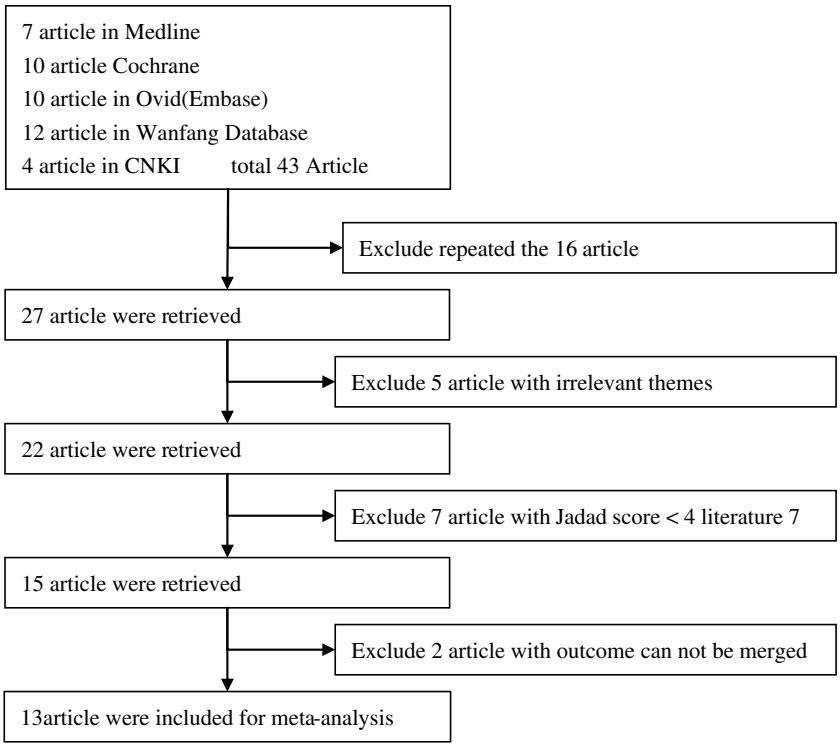

Fig. 1 Flow chart of search strategy for randomised controlled trials

Results

As shown in Fig. 1, 22 RCTs were identified that assessed the efficacy of GnRHa or GnRHa plus "add-back" therapy for the management of EMs. Seven trials had scores of <4 on the Jadad scale and were excluded from analysis. Two trials were excluded because outcomes cannot be combined analysis with outcomes of other studies. A total of 13 RCTs [7–19] were identified, including 11 published in English and 2 in Chinese. The characteristics of the included studies and the description and assessment of study quality are shown in Tables 1 and 2.

Assessment of study quality

In three trials [7, 8, 16], the method of allocation concealment was adequately described. Six trials [7–10, 12, 17] had adequate blinding, in which the participants and investigators were blinded, and eight trials [7–12, 15, 17] used an identical placebo. All studies adequately reported attrition. Overall, these 13 studies were considered to be of high methodological quality (Figs. 2, 3).

Meta-analysis of "add-back" therapy versus GnRH-a alone

Lumbar spine BMD after treatment

Twelve trials investigated lumbar spine BMD of the after treatment. These studies were significantly heterogeneous ($P = 0.06$, $I^2 = 42$ %), but could still be combined, thus, a random-effect model was used to summarise the weight mean difference (WMD). The summary WMD for the 12 trials was −0.03, with a 95 % CI of −0.05 to −0.02, and was significant ($P < 0.00001$). Lumbar spine BMD after treatment was superior with "add-back" therapy than with GnRH-a alone (Figs. 4, 5).

Lumbar spine BMD after 6 months of follow-up

Six trials investigated lumbar spine BMD after 6 months of follow-up. These studies at 6-month follow-up were not significantly heterogeneous ($P = 0.74$, $I^2 = 0$ %) and were combined. The summary WMD for the six trials was −0.02, with a 95 % CI of −0.03 to −0.01, and was significant ($P = 0.003$). Lumbar spine BMD was better with "add-back" therapy, compared to GnRH-a alone, after 6 months of follow-up (Fig. 6).

Femoral neck BMD after treatment

Three trials examined femoral neck BMD after treatment. These studies were not significantly heterogeneous ($P = 0.89$, $I^2 = 0$ %) and were combined. The summary WMD for the three trials was −0.01, with a 95 % CI of −0.02 to 0.01 and was not significant ($P = 0.28$). There was no statistically significant difference in femoral neck BMD when comparing "add-back" therapy to GnRH-a alone (Fig. 7).

Table 1 Characteristics of RCTs of effectiveness of GnRHa plus add-back therapy included into the meta-analysis

References	Participants	Characteristics of participants	Intervention	Outcome
AI-Azemi et al. [7]	25	Laparoscopically diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 14$: Zoladex (goserelin) 10.8 mg, iH, q3 months + tibolone 2.5 mg, po, qd Group B $n = 11$: Zoladex (goserelin) 10.8 mg, iH, q3 months + placebo, po, qd Treatment: 18 months	Bone mineral density of lumbar spine, femoral neck, hipbone Endometriosis health profile-30 (EHP-30)
Fernadez et al. [8]	78	Laparoscopically diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 39$: leuprorelin 3.75 mg, im, q28d + promegestone 0.5 mg + estradiol 2 mg, po, qd Group B $n = 39$: leuprorelin 3.75 mg, im, q28d + placebo, po, qd Treatment: 12 months	Bone mineral density of lumbar spine, femoral neck, hipbone
Franke et al. [9]	41	Laparoscopically diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain r-AFS: Stage II–IV	Group A $n = 18$: Zoladex 3.6 mg, iH, q28d + 17βE2 2 mg + NEt 1 mg, po, qd Group B $n = 23$: Zoladex 3.6 mg, iH, q28d + placebo, po, qd Treatment: 6 months, follow-up: 6 months	AFS score Bone mineral density of lumbar spine Serum oestrogen and FSH Kupperman index
Gnoth et al. [10]	27	Laparoscopically diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain r-AFS score >5	Group A $n = 14$: leuprorelin 3.75 mg, im, q28d + ethinyl estradiol 20 μg + desogestrel 0.15 mg, po, qd Group B $n = 13$: leuprorelin 3.75 mg, im, q28d + placebo, po, qd Treatment: 6 months	r-AFS score Bone mineral density of lumbar spine, femoral neck, Ward's triangle
Hornstein et al. [11]	201	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 51$:Lupron 3.75 mg, im,q4w + placebo for progestin and oestrogen, po, qd Group B $n = 55$: Lupron 3.75 mg, im, q4w + NEt5 mg + placebo, po, qd Group C $n = 47$: Lupron 3.75 mg, im, q4w + NEt5 mg + CEE 0.625 mg, po, qd Group D $n = 48$: Lupron 3.75 mg, im, q4w + NEt5 mg + CEE 1.25 mg, po, qd Treatment: 12 months	Pain Scores Bone mineral density of lumbar spine Vasomotor symptoms
Hurst et al. [12]	13	No hormone treatment in previous 3 months Symptomatic of pelvic pain Laparoscopically diagnosed endometriosis	Group A $n = 7$: leuprolide 3.75 mg, im, q28d + estradiol 1 mg, po, qd Group B $n = 6$: leuprolide 3.75 mg, im, q28d + placebo, po, qd Treatment: 6 months	Dysmenorrhoea Score Dyspareunia Score
Irahara et al. [13]	21	No hormone treatment in previous 3 months Symptomatic of pelvic pain Laparoscopically diagnosed endometriosis	Group A $n = 11$: leuprorelin 3.75 mg, im, q28d + CEE 0.625 mg + MPA 2.5 mg, po, qd Group B $n = 10$: leuprorelin 3.75 mg, im, q28d, po, qd Treatment: 6 months	Serum oestrogen Kupperman index Serum calcium levels Bone mineral density of lumbar spine

Table 1 continued

References	Participants	Characteristics of participants	Intervention	Outcome
Long et al. [14]	70	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 35$: Zoladex 3.6 mg, iH, q28d + estradiol valerate 0.5 mg + megestrol acetate 5 mg, po, qd Group B $n = 35$: Zoladex 3.6 mg, iH, q28d Treatment: 3 months	Serum oestrogen Kupperman index Dysmenorrhoea and dyspareunia Score Bone mineral density of lumbar spine, femoral neck, hipbone
Moghissi et al. [15]	345	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 119$: Zoladex 3.6 mg, iH, q28d + placebo for oestrogen and MPA, po, qd Group B $n = 113$: Zoladex 3.6 mg, iH, q28d + conjugated oestrogen 0.3 mg + MPA 5 mg, po, qd Group C $n = 113$: Zoladex 3.6 mg, iH, q28d + conjugated oestrogen 0.625 mg + MPA 5 mg, po, qd Treatment: 6 months, follow-up: 18 months	Total pelvic symptom score Total subjective symptom score Bone mineral density of lumbar spine
Pierce et al. [16]	45	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 14$: Zoladex 3.6 mg, iH, qM + estradiol 2 mg + NEt 1 mg, po, qd Group B $n = 31$: Zoladex 3.6 mg, iH, qM Treatment: 2 years, follow-up: 6 years	Bone mineral density of lumbar spine, femoral neck, Ward's triangle
Surrey et al. [17]	201	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 32$: leuprolide 3.75 mg, im, q28d + placebo, po, qd Group B $n = 31$: leuprolide 3.75 mg, im, q28d + NEt 5 mg, po, qd Group C $n = 34$: leuprolide 3.75 mg, im, q28d + NEt 5 mg + CEE 0.625 mg, po, qd Group D $n = 26$: leuprolide 3.75 mg, im, q28d + NEt 5 mg + CEE 1.25 mg, po, qd Treatment: 12 months, follow-up: 12 months	Pain score for dysmenorrhoea, dyspareunia and pelvic tenderness Serum estradiol levels Serum lipid levels Bone mineral density of lumbar spine
Wang et al. [18]	28	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 14$: Zoladex 3.6 mg, iH, q4W Group B $n = 14$: Zoladex 3.6 mg, iH, q4W + half hydrate estradiol 50 μg TDDS plus medroxyprogesterone acetate 6 mg, po, qd Treatment: 3 months, follow-up: once after menstruation	Serum estradiol levels and FSH Bone gla protein levels Bone mineral density of lumbar spine Kupperman index Pain score for dysmenorrhoea, dyspareunia
Zupi et al. [19]	133	Surgical diagnosed endometriosis No hormone treatment in previous 3 months Symptomatic of pelvic pain	Group A $n = 46$: enantone (leuprolide) 11.25 mg, iH, q3 months + E2 25 μg, transdermal, qd Group B $n = 44$:enantone (leuprolide) 11.25 mg, iH, q3 months Group C $n = 43$:ethinyl E2 30 μg plus gestodene 0.75 mg, po, qd Treatment: 12 months, follow-up: 6 months	The medical outcomes survey short-form 36 (SF-36) Pain score for dysmenorrhoea, dyspareunia Bone mineral density of lumbar spine

Table 2 Quality assessment of the studies included in this analysis

Include RCTs	Adequate sequence generation?	Allocation concealment?	Blinding?	Placebo control?	Incomplete outcome data addressed? Report reason?	Jadad
AI-Azemi et al. [7]	Computerised randomisation	Central control	Double blind	Yes	Yes, report reason	5
Fernandez et al. [8]	Random numbers	Central control	Double blind	Yes	Yes, report reason	6
Franke et al. [9]	No details	No details	Double blind	Yes	All completed	4
Gnoth et al. [10]	No details	No details	Double blind	Yes	All completed	4
Hornstein et al. [11]	Random numbers	No details	Blind for patient	Yes	All completed	4
Hurst et al. [12]	No details	No details	Double blind	Yes	All completed	4
Irahara et al. [13]	No details	No details	No	No	All completed	4
Long et al. [14]	Computerised randomisation	No	No	No	Yes, report reason	4
Moghissi et al. [15]	No details	No details	Blind for patient	Yes	Yes, report reason	4
Pierce et al. [16]	Computerised randomisation	Central control	Blind for patient	No	Yes, report reason	4
Surrey et al. [17]	No details	No details	Double blind	Yes	Yes, report reason	5
Wang et al. [18]	Computerised randomisation	No	No	No	All completed	4
Zupi et al. [19]	Computerised randomisation	No details	Blind for patient	No	All completed	4

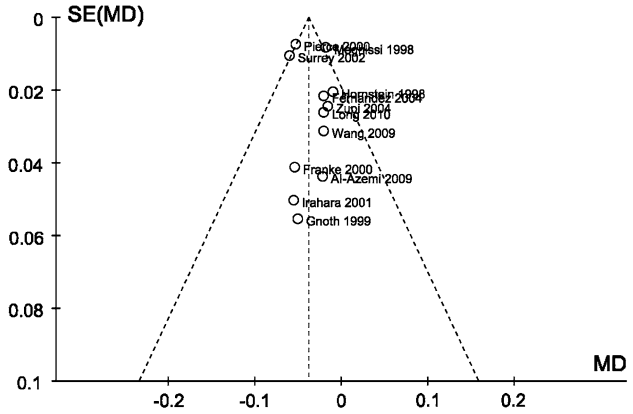

Fig. 2 Funnel plot of comparison: add-back therapy versus GnRH-a alone outcome: bone mineral density of lumbar spine after treatment

Serum oestrogen levels after treatment

Four trials investigated changes in serum oestrogen levels after treatment. These studies were significantly heterogeneous ($P = 0.01$, $I^2 = 73$ %), but could still be combined, so a random-effect model for summary weight mean difference (WMD) was applied. The summary WMD was 26.79, with a 95 % CI of 5.05–48.54, and was significant ($P = 0.02$). There was no statistically significant difference in serum oestrogen levels after treatment when comparing "add-back" therapy to GnRH-a alone (Fig. 8).

Kupperman index scores after treatment

Three trials investigated Kupperman index scores after treatment. These studies were not significantly heterogeneous ($P = 0.72$, $I^2 = 0$ %) and were combined. The summary WMD for the three trials was −5.13, with a 95 % CI of −5.77 to −4.48, and was significant ($P < 0.00001$). Kupperman index scores were better with "add-back" therapy as compared with GnRH-a alone (Fig. 9).

Dysmenorrhoea scores after treatment

Five trials examined dysmenorrhoea scores after treatment. These studies were significantly heterogeneous ($P = 0.04$, $I^2 = 60$ %), but could still be combined, thus a random-effect model for summary WMD was applied. The summary WMD in the five trials was −0.27, with a 95 % CI of −0.93 to 0.39 and was not significant ($P = 0.43$). There was no statistically significant difference in dysmenorrhoea scores when comparing "add-back" therapy to GnRH-a alone (Fig. 10).

Dyspareunia scores after treatment

Four trials analysed dyspareunia scores after treatment. These studies were significantly heterogeneous ($P = 0.51$, $I^2 = 0$ %), thus a fixed effect model for summary WMD was applied. The summary WMD in the four trials was 0.05, with a 95 % CI of −0.37 to 0.47 and was not

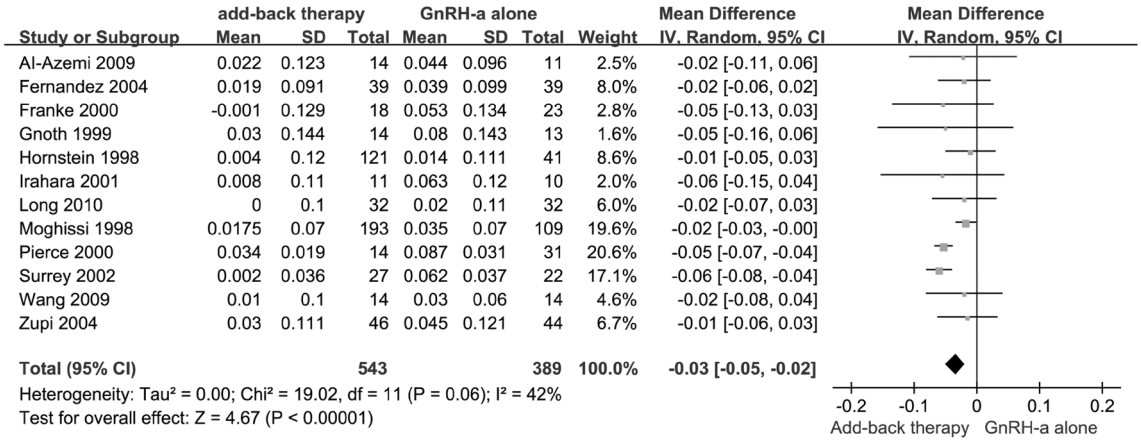

Fig. 3 Add-back therapy versus GnRH-a alone, outcome: bone mineral density of lumbar spine after treatment

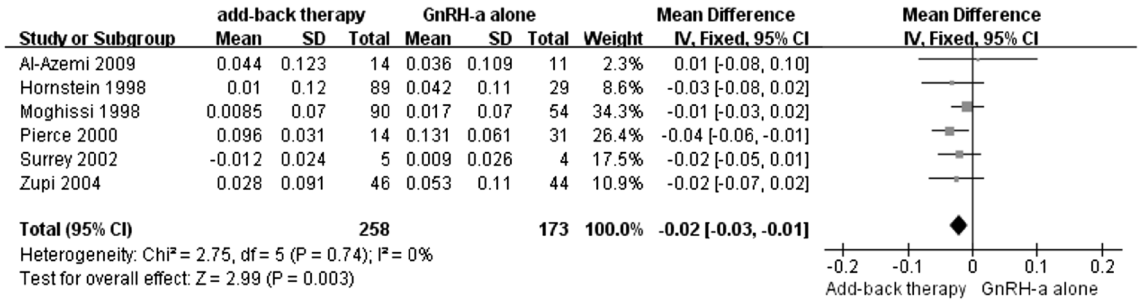

Fig. 4 Add-back therapy versus GnRH-a alone, outcome: bone mineral density of lumbar spine at 6 months follow-up

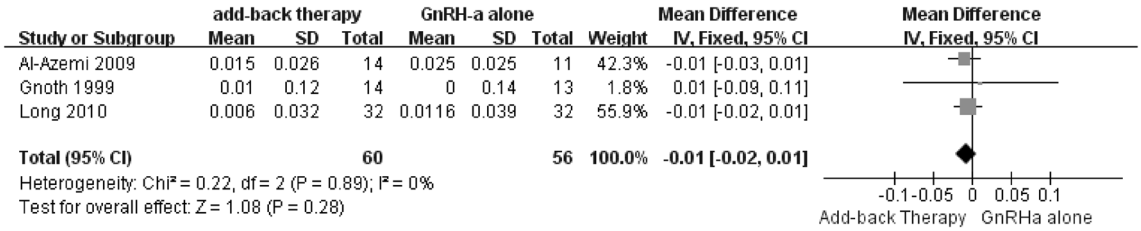

Fig. 5 Add-back therapy versus GnRH-a alone, outcome: bone mineral density of femoral neck after treatment

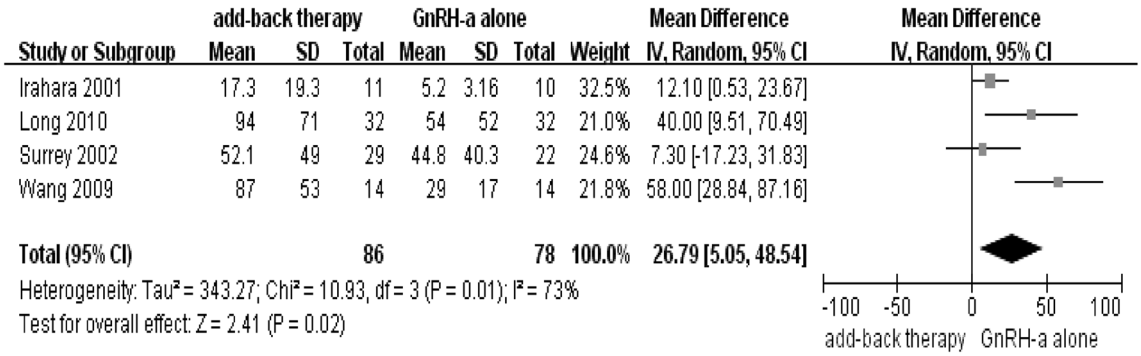

Fig. 6 Add-back therapy versus GnRH-a alone, outcome: changes in serum oestrogen levels after treatment

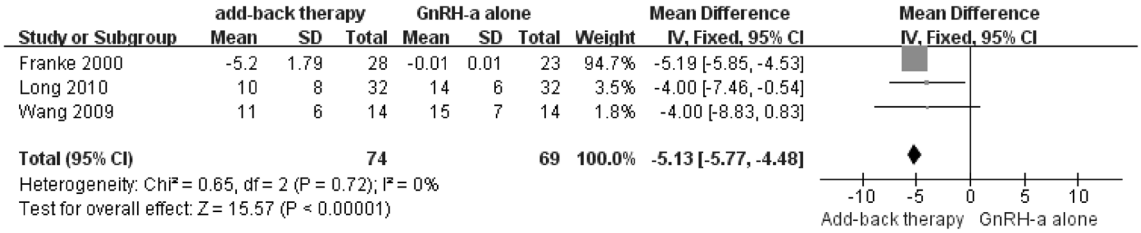

Fig. 7 Add-back therapy versus GnRH-a alone, outcome: Kupperman index after treatment

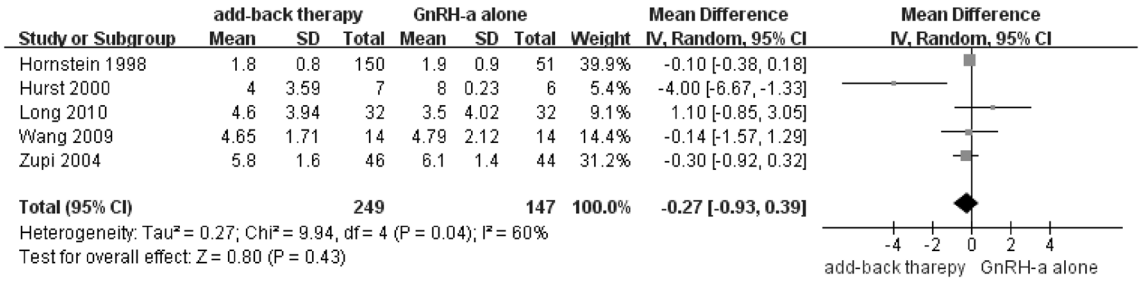

Fig. 8 Add-back therapy versus GnRH-a alone, outcome: dysmenorrhoea scores after treatment

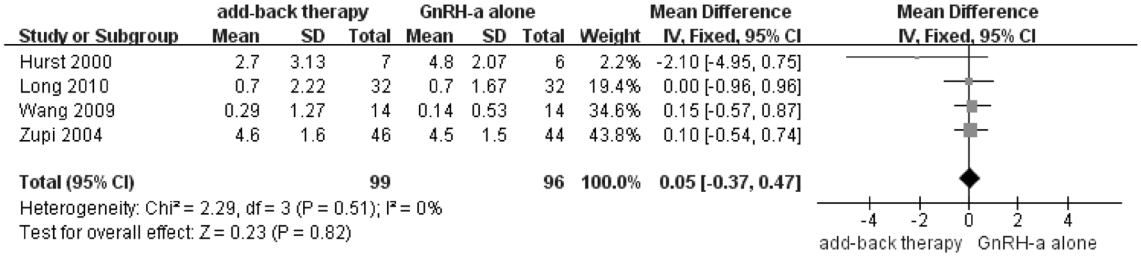

Fig. 9 Forest plot of comparison: add-back therapy versus GnRH-a alone, outcome: dyspareunia scores after treatment

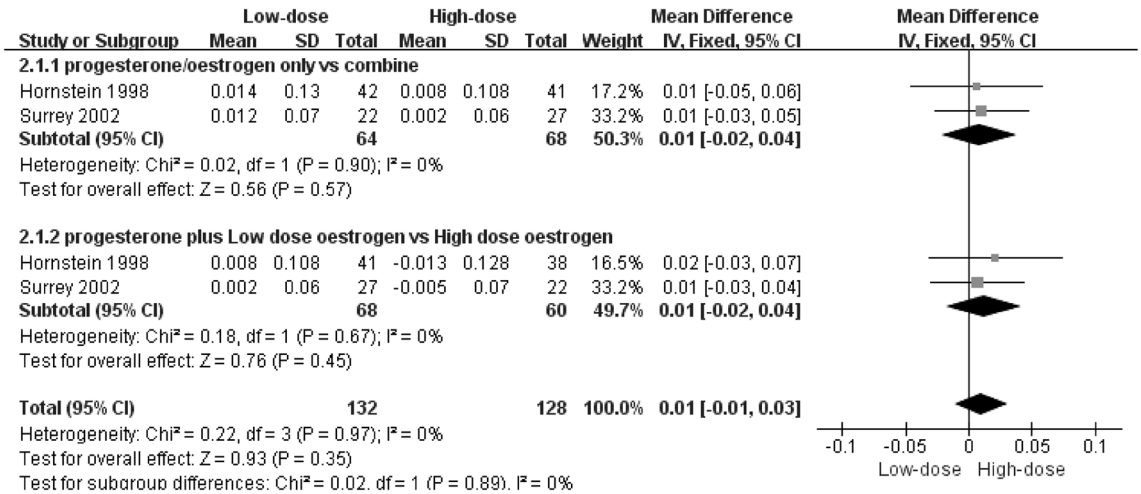

Fig. 10 Forest plot of comparison: low-dose add-back therapy versus high-dose add-back therapy outcome: bone mineral density of lumbar spine after treatment

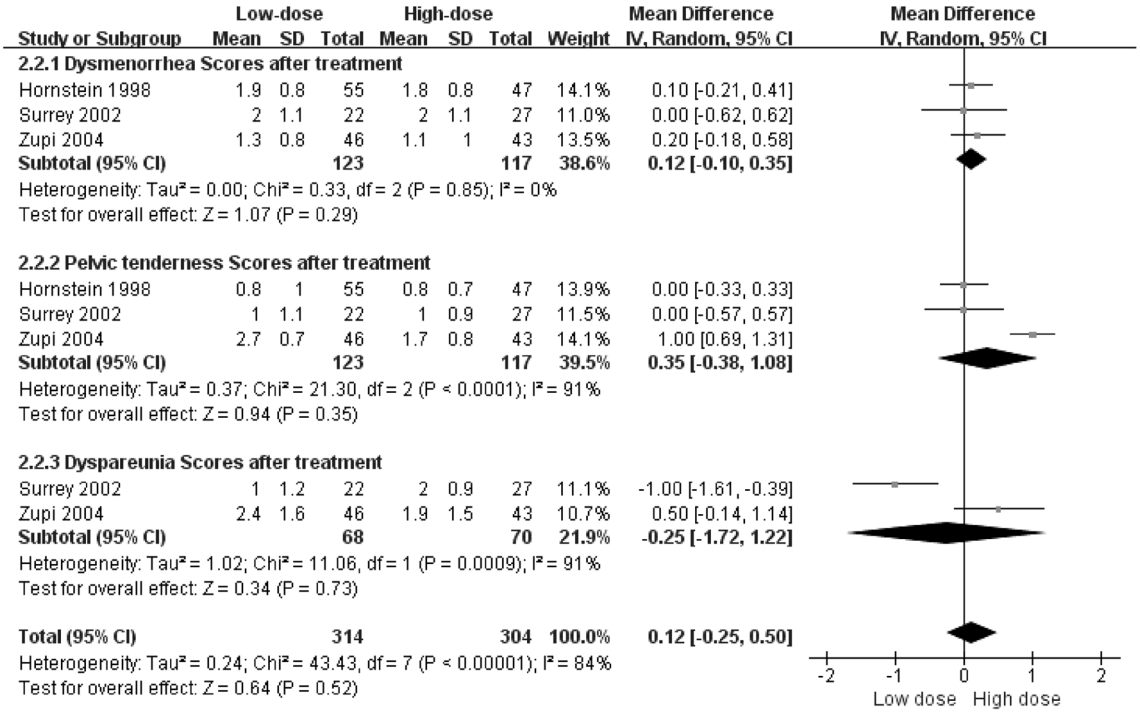

Fig. 11 Forest plot of comparison: low-dose add-back therapy versus high-dose add-back therapy outcome: changes of pain scores after treatment

significant ($P = 0.82$). There was no statistically significant difference in dyspareunia scores when comparing "add-back" therapy to GnRH-a alone.

Meta-analysis comparing varying dosages of "add-back" treatment

Lumbar spine BMD after treatment

Two trials investigated lumbar spine BMD after treatment with low- and high-dose "add-back" therapies. These studies were significantly heterogeneous ($P = 0.91$, $I^2 = 0\ \%$), thus a fixed effect model was applied. The summary WMD for the two trials was 0.01, with a 95 % CI of −0.01 to 0.03 and was not significant ($P = 0.35$). There appeared to be no significant difference in lumbar spine BMD when comparing low- and high-dose "add-back" therapies (Fig. 11).

Changes in pain scores after treatment

Three trials investigated changes in pain scores after treatment (including dysmenorrhoea, pelvic tenderness and dyspareunia). These studies were significantly heterogeneous ($P < 0.00001$, $I^2 = 84\ \%$), but could be combined, so a random-effect model for WMD was applied. The summary WMD for the three trials was 0.12, with a 95 % CI of −0.25 to 0.50 and was not significant ($P = 0.52$). There was no statistically significant difference in the changes in pain scores after treatment when comparing the low-dose "add-back" therapy and the high-dose "add-back" therapy.

Discussion

A search was conducted for published, randomised, controlled trials, relevant to the treatment of endometriosis with GnRH-a plus "add-back" therapy. The efficacy and safety of GnRH-a with and without an add-back therapy were examined. This meta-analysis demonstrates that treatment with "add-back" therapy is beneficial when compared with using GnRH-a alone. In subjects that received "add-back" therapy, loss of lumbar spine BMD and Kupperman index scores were reduced, indicating that "add-back" therapy can mitigate the side effects of GnRH-a; this could be especially beneficial for lumbar spine BMD. There was no significant difference in femoral neck BMD between those that received "add-back" therapy and those that received GnRH-a alone. However, this may have been due to the relatively small sample size and there may not have been sufficient follow-up time to see any changes in this indicator. "Add-back" therapy uses hormones and can, therefore, increase serum oestrogen levels. Oestrogen levels over 183 pmol/L (50 pg/mL) will stimulate endometrial growth, however, below this threshold, oestrogen will not aggravate

EMs [13]. Some patients in the included studies were using high doses of "add-back" therapy and their serum estradiol was over this threshold. However, there was no significant difference in lumbar spine BMD or in pain score changes when comparing low-dose to high-dose "add-back" therapies. Therefore, lower doses of "add-back" therapy should be used to avoid aggravation of EMs.

Some researchers considered that the "add-back" therapy maybe decreases the therapeutic effect of GnRH-a, mainly as poor pain relief and adverse lesions shrink. EMs lesions are mostly located in the abdominal cavity and shrinkage of lesions can generally only be accurately assessed via laparoscopy, however, this is an invasive surgical method. Therefore, the pain scale was used to evaluate abdominal pain. In this meta-analysis, dysmenorrhoea, dyspareunia, and the pelvic pain score index were selected to examine the effects of GnRH-a with or without "add-back" therapy. No significant difference was found in the above parameters between GnRH-a alone and with "add-back" therapy.

Ideal "add-back" therapy should eliminate bone loss and inhibit perimenopausal symptoms. There should be minimal emotional, blood lipid and endocrine side effects, whilst maintaining good GnRH-a efficacy. Therefore, further research should be done investigating different "add-back" therapy programmes. In earlier studies, single-use progesterone has generally been used for "add-back" therapy to avoid oestrogen stimulation of underlying disease. Medroxyprogesterone acetate (MPA) and norethindrone (NEt) have been demonstrated to be safe and effective for use in "add-back" therapy [19]. Potentially using low-dose oestrogen plus progestin as "add-back" therapy in the treatment of endometriosis has become a hot topic in recent years. Several studies have examined using a combination of oestrogen and progestogen for "add-back" therapy [7, 13, 15], thus RCTs that compared different "add-back" treatment regimens were included in the current study. Both oestrogen and progesterone alone, and in combination, inhibited the decrease in lumbar spine BMD, however, there was no significant difference in dysmenorrhoea or dyspareunia symptoms. Previous studies have shown no difference between treating with 0.625 mg conjugated equine oestrogen (CEE) and 1.25 mg CEE, though high oestrogen doses can potentially cause other oestrogen-dependent diseases.

Of course, in addition to oestrogen and progesterone, there are other "add-back" treatments such as the oestrogen receptor antagonist tamoxifen and the synthetic steroid, tibolone [20, 21]. Parathyroid hormone, bisphosphonates and other treatment programmes have also been used, but the efficacies of these programmes have to be evaluated via RCTs and meta-analysis.

In the current study, 13 RCTs had Jadad scale scores of more than 4, however, they did have flaws. Only seven RCTs reported specific stochastic methods in detail (computer-generated random number table method), only three RCTs reported clear allocation concealment (central control or opaque envelopes) and only seven RCTs used a placebo, thus there was the possibility of selection bias exists. In addition, BMD and serum oestrogen levels are objective indicators, however, the other indicators (e.g. pelvic pain scores) used were subjective, so there could have been selection bias and measurement bias, particularly if allocation concealment and blinding were used improperly.

In the current meta-analysis, the medications used in the included RCTs were different [GnRH-a (leuprolide, goserelin), oestrogen and progesterone (estradiol, norethindrone, medroxyprogesterone acetate)], as well as the dosages used and routes of administration. Currently, there is no uniform regimen for "add-back" therapy.

The current study and a new meta-analysis [22] demonstrate that "add-back" therapy can relieve the decrease in lumbar spine BMD, however, it does not provide a recommended dosing regimen. There were four included and one excluded RCTs [23] that compared different medication dosages for "add-back" therapy. The current meta-analysis incorporated the outcome of which can incorporate indicators dose regimen, but the results show no significant differences and some articles described the different outcome, cannot be merged. Therefore, further studies are necessary to determine the most suitable dosage for "add-back" therapy. One excluded RCT [24] used a non-universal scale assessment of pain scores and could not be included in the meta-analysis. Consequently, the current meta-analysis was not highly comprehensive since not enough RCTs were included.

Future studies on GnRH-a plus "add-back" therapy for the treatment of EMs should use internationally harmonised evaluation criteria and uniform data representation. This will allow more comprehensive systematic reviews in the future and contribute to the establishment of a safe and effective treatment programme for patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Tekin Y, Dilbaz B, Altinbas SK et al (2011) Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril 95(2):492–496
2. Denny E, Mann CH (2007) A clinical overview of endometriosis: a misunderstood disease. Br J Nurs 16(18):1112–1116
3. Kitawaki J, Kado N, Koshiba H, Honjo H (2002) Endometriosis: the pathophysiology as an estrogen-dependant disease. J Steroid Biochem Mol Biol 83:149–155

4. Sagsveen M, Farmer JE, Prentice A et al (2003) Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev (4):CD001297
5. Surry ES, Silverberg KM, Surry MW et al (2002) Prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization–embryo transfer in patients with endometriosis. Fertil Steril 78(4):699–704
6. Wyatt KM, Dimmock PW, Ismail KMK et al (2004) The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis. BJOG 111(6):585–593
7. Al-Azemi M, Jones G, Sirkeci F et al (2009) Immediate and delayed add-back hormonal replacement therapy during ultra long GnRH agonist treatment of chronic cyclical pelvic pain. BJOG 116:1646–1656
8. Fernandez H, Lucas C, HeÂdon B et al (2004) One year comparison between two add-back therapies in patients treated with a GnRH agonist for symptomatic endometriosis: a randomized double-blind trial. Hum Reprod 19(6):1465–1471
9. Franke HR, van de Weijer PH, Pennings TM et al (2000) Gonadotropin-releasing hormone agonist plus "add-back" hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. Fertil Steril 74(3):534–539
10. Gnoth CH, Gödtke K, Freundl G et al (1999) Effects of add-back therapy on bone mineral density and pyridinium crosslinks in patients with endometriosis treated with gonadotropin-releasing hormone agonists. Gynecol Obstet Invest 47:37–41
11. Hornstein MD, Surrey ES, Weisberg GW et al (1998) Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Obstet Gynecol 91(1):145–148
12. Hurst BS, Gardner SC, Tucker KE et al (2000) Delayed oral estradiol combined with leuprolide increases endometriosis-related pain. JSLS 4:97–101
13. Irahara M, Uemura H, Yasui T et al (2001) Efficacy of every-other-day administration of conjugated equine estrogen and medroxyprogesterone acetate on gonadotropin-releasing hormone agonists treatment in women with endometriosis. Gynecol Obstet Invest 52:217–222
14. Long QQ, Zhang SF, Han Y et al (2010) Clinical efficacy and safety of gonadotropin releasing hormone agonist combined with estrogen-dydrogesteronea in treatment of endometriosis. Chin J Obstet Gynecol 45(4):247–251
15. Moghissi KS, Schlaff WD, Olive DL et al (1998) Goserelin acetate (Zoladex) with or without hormone replacement therapy for the treatment of endometriosis. Fertil Steril 69(6):1056–1062
16. Pierce S, Gazvani R, Farquharson R (2000) Long-term use of gonadotropin-releasing hormone analogs and hormone replacement therapy in the management of endometriosis: a randomized trial with a 6-year follow-up. Fertil Steril 74(5):964–968
17. Surrey E, Hornstein M (2002) Prolonged GnRH Agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. Obstet Gynecol 99(5):709–719
18. Wang YQ, Zhang SF, Chen X et al (2009) Effects and safety of gonadotrophin-releasing hormone agonist combined with estradiol patch and oral medroxyprogesterone acetate on endometriosis. Chin J Obstet Gynecol 44(7):504–508
19. Zupi E, Marconi D, Sbracia M et al (2004) Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril 82(5):1303–1308
20. Cedars M, Lu J, Meldrum D, Judd H (1990) Treatment of endometriosis with a long acting gonadotropin-releasing hormone agonist plus medroxyprogesterone acetate. Obstet Gynecol 75:641–645
21. Surrey E, Gambone J, Lu J, Judd H (1990) The effects of combining norethindrone with a gonadotropin-releasing hormone agonist in the treatment of symptomatic endometriosis. Fertil Steril 53:620–626
22. Niu ZR, Yue XJ, Kong QY et al (2013) A meta-analysis of preventing bone mineral loss in patients with endometriosis treated by gonadotrophin-releasing hormone analogues with add-back therapy. Zhonghua Fu Chan Ke Za Zhi 48(5):338–343
23. Cheung TH, Lo KW, Yim SF et al (2005) Dose effects of progesterone in add-back therapy during GnRHa treatment. J Reprod Med 50(1):35–40
24. Guzick DS, Huang LS, Broadman BA et al (2011) Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil Steril 95(5):1568–1573