International Journal of Gynecology and Obstetrics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Effects of low-dose combined drospirenone–ethinylestradiol on perimenstrual symptoms experienced by women with endometriosis

Yukiko Tanaka, Taisuke Mori, Fumitake Ito, Akemi Koshiba, Izumi Kusuki, Jo Kitawaki *

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form 11 May 2016
Accepted 11 July 2016

Keywords:
Chronic pelvic pain
Drospirenone
Dysmenorrhea
Dyspareunia
Endometriosis
Ethinylestradiol

ABSTRACT

Objective: To determine the effectiveness of a 24/4-day regimen of a low-dose combination drospirenone–ethinylestradiol oral contraceptive in alleviating perimenstrual symptoms among Japanese women with endometriosis. *Methods:* The present prospective, non-randomized study enrolled women diagnosed with endometriosis radiographically or surgically at the Kyoto Prefectural University of Medicine hospital, Japan, between December 1, 2010 and August 31, 2013. Patients received treatment with oral drospirenone–ethinylestradiol for six treatment cycles. Dysmenorrhea, chronic pelvic pain, and dyspareunia severity were assessed using visual analog scale scores after three and six treatment cycles, and changes in perimenstrual symptoms were assessed using the menstrual distress questionnaire (MDQ) scores. *Results:* In total, 46 patients were recruited for the study. Dysmenorrhea, chronic pelvic pain, and dyspareunia were all significantly reduced after both three and six treatment cycles in comparison with baseline ($P < 0.001$ for all comparisons). After six treatment cycles, significant reductions were observed for all menstrual MDQ measures and for the premenstrual water retention and negative-effect MDQ measures (all $P < 0.05$). *Conclusions:* Combination drospirenone–ethinylestradiol was effective in the treatment of dysmenorrhea, chronic pelvic pain, dyspareunia, and somatic/psychological symptoms in Japanese women with endometriosis.

1. Introduction

Endometriosis is a chronic estrogen-dependent disease characterized by the presence of endometrial-like tissue outside the uterus, primarily in the pelvic peritoneum and the ovaries. The incidence of endometriosis is approximately 10% among women of reproductive age and reduces following menopause. The main symptoms of endometriosis include dysmenorrhea, chronic pelvic pain, deep dyspareunia, and infertility [1]. Oral contraceptive pills (OCPs) containing low doses of estrogen and progestin have been shown to significantly alleviate dysmenorrhea in randomized controlled clinical trials when compared with a placebo [2] or a gonadotropin-releasing hormone agonist [3]. Generally, OCPs act by suppressing ovulation and prostaglandin synthesis, thereby reducing menstrual bleeding and relieving menstrual pain. OCPs can be administered for relatively long durations because they are safe and well tolerated with minimal severe adverse effects [4–7].

The 17α-spironolactone derivative drospirenone has antimineralocorticoid, anti-androgen, and progestational activity, and is less commonly associated with sodium and water retention than oral contraceptives, which cause adverse effects such as edema and weight gain [8]. OCPs consisting of low-dose estrogen–progestin combinations of drospirenone and ethinylestradiol have been used to treat pelvic pain not associated with endometriosis [9], and in 2010, the health insurance system of Japan approved the use of combination drospirenone–ethinylestradiol for the treatment of dysmenorrhea at doses of 3 mg and 0.02 mg, respectively. However, there is little evidence as to whether drospirenone–ethinylestradiol alleviates endometriosis-associated pelvic pain and other symptoms.

Owing to the low estrogen dose and short hormone-free interval, it is hypothesized that drospirenone–ethinylestradiol could relieve perimenstrual symptoms and minimize adverse events often associated with other OCPs including bleeding irregularities, nausea, edema, and headache. Endometriosis with severe menstrual symptoms imposes somatic, psychological, and economic burdens on patients and healthcare systems. These symptoms have often been assessed using the menstrual distress questionnaire (MDQ) [10]. Decreases in MDQ scores, indicating reduced distress, have been reported among women using OCPs [11] such as drospirenone–ethinylestradiol [12] to alleviate menstruation-related symptoms.

The aim of the present study was to assess the efficacy of combination drospirenone–ethinylestradiol (3 mg and 0.02 mg, respectively) administered for 24 days followed by placebo for 4 days (24/4-day regimen) for relieving endometriosis-associated pelvic pain and various perimenstrual symptoms associated with endometriosis. To the best of

* Corresponding author at: Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kamigyo-ku, Kyoto 602–8566, Japan. Tel.: +81 75 251 5560; fax: +81 75 212 1265.
E-mail address: kitawaki@koto.kpu-m.ac.jp (J. Kitawaki).

http://dx.doi.org/10.1016/j.ijgo.2016.05.004
0020-7292/

our knowledge, this is the first study to use MDQ scores to assess patients with endometriosis.

2. Materials and methods

The present prospective, nonrandomized, observational study enrolled women with dysmenorrhea due to endometriosis aged 20–49 years who visited the outpatient clinic of the Kyoto Prefectural University of Medicine Hospital in Kyoto, Japan (or affiliated hospitals) between December 1, 2010 and August 31, 2013. To be eligible for enrollment, patients had to have been diagnosed with endometriosis under surgical examination or using magnetic resonance imaging. Patients who had any contraindications to the use of low-dose estrogen–progestin combinations or who had received any hormonal medications within the 6 months prior to enrollment were excluded. The study protocol was approved by the Kyoto Prefectural University of Medicine's institutional review board, and written informed consent was obtained from all patients.

Patients were prescribed an oral drospirenone–ethinylestradiol (doses of 3 mg and 0.02 mg, respectively) combination tablet (YAZ; Bayer Yakuhin Ltd, Osaka, Japan) administered once a day using a 24/4-day regimen for 6 months. Efficacy and safety were assessed after three and six treatment cycles.

The primary outcomes were the severity of dysmenorrhea, chronic pelvic pain, and dyspareunia, assessed at each follow-up appointment using a visual analog scale (VAS), where 0 represented an absence of pain and 100 represented unbearable pain. The secondary end points included changes in the size of the ovarian endometrioma, evaluated using the longest diameter of the ovarian endometrioma, measured using two-dimensional transvaginal ultrasonography, tenderness and induration in the cul-de-sac, evaluated using a stepwise scale during pelvic examination, and changes in perimenstrual symptoms, assessed using MDQ scores. Serum CA-125 level was also recorded before treatment and after six treatment cycles.

The MDQ was used to assess the presence of perimenstrual, somatic, and psychological symptoms in each patient at baseline and after three and six treatment cycles; additionally, the presence of cyclic perimenstrual symptoms was evaluated. The MDQ, first described by Moos in 1968, classifies 46 symptoms into eight categories: pain, concentration, behavior change, autonomic reaction, water retention, negative effect, arousal, and control [10]. In this study, symptoms were assessed by assigning a score of 1 (no symptoms), 2 (minimal), 3 (mild), 4 (moderate), 5 (strong), or 6 (severe) to each of 35 items across six of the eight categories (pain, concentration, behavior change, autonomic reaction, water retention, and negative effect). The remaining two categories, arousal and control, were excluded because they were considered to be less common among Japanese patients than in patients from western countries. The MDQ was administered twice during both the premenstrual phase and menstrual phase. The premenstrual phase was defined as the 10 days before the first day of menstrual bleeding. The menstrual phase was defined as the period from the first to the last day of menstruation.

A minimum sample size of 40 patients was calculated as being necessary to detect a minimum difference of 20% ($\alpha = 0.05$, 80% power).

The crude data were fixed and sent to be analyzed independently (Kondo PP Inc, Data Research Section; Osaka Japan), with the authors masked to the analysis. Pairwise comparisons were made using the Wilcoxon signed-rank test for all evaluation items, except cul-de-sac induration, before and after (three and six cycles) treatment. The McNemar test was used to make pairwise comparisons of cul-de-sac induration before and after (three and six cycles) treatment. For all comparisons, P values of multiple tests were adjusted using the Bonferroni correction and $P < 0.05$ was considered statistically significant. All analyses were performed by using SPSS version 21 (IBM, Armonk, New York, USA).

3. Results

The trial enrolled 46 patients in total. The baseline clinical characteristics of the patients are listed in Table 1. Of the 46 patients, 38 (83%) experienced recurrent cases of laparoscopically diagnosed endometriosis, 35 (76%) had ovarian endometrioma, and 12 (26%) had adenomyosis. Reasons for performing laparoscopy included investigating the basis of infertility, resection of the endometrioma, and pain relief. Adenomyosis was diagnosed on the basis of a maximal junctional zone thickness of over 12 mm, a maximal junctional zone thickness to myometrial thickness ratio above 40% [13], or a maximum difference between the thinnest and thickest junctional zone of 5–7 mm [14].

No patients became pregnant during the treatment period. Of the 46 patients 10 (22%) had a history of prior treatment with hormonal medications, including oral contraceptives (6 [13%]), gonadotropin-releasing hormone agonists (3 [7%]), and dienogest (1 [2%]). There were 26 (57%) patients who had previously received non-steroidal anti-inflammatory drugs for the treatment of endometriosis.

Dysmenorrhea, assessed using VAS scores, significantly decreased from a median of 71 (interquartile range [IQR] 50–80) before treatment to 30 (IQR 12.5–55) after three cycles ($P < 0.001$), and to 24 (IQR 10–40) after six cycles of treatment ($P < 0.001$ compared with baseline) (Fig. 1A). Chronic pelvic pain significantly decreased from a median of 30 (IQR 10–60) before treatment to 10 (IQR 0–30) after three cycles ($P < 0.001$), and to 5 (IQR 0–21) after six cycles of treatment ($P < 0.001$ compared with baseline) (Fig. 1B). Dyspareunia significantly decreased from a median of 10 (IQR 0–35) before treatment to 0 (IQR 0–20) after three cycles ($P < 0.001$), and to 0 (IQR 0–10) after six cycles of treatment ($P < 0.001$ compared with baseline) (Fig. 1C).

Tenderness of the cul-de-sac significantly decreased after three ($P = 0.001$) and six cycles ($P < 0.001$) compared with the pre-treatment assessment (Fig. 2A). The proportion of patients with induration in the cul-de-sac decreased significantly, from 49% (22/45 patients) before treatment to 27% (10/37 patients) after three cycles ($P = 0.016$), and to 18% (7/39 patients) after six cycles of treatment ($P = 0.002$ compared with baseline) (Fig. 2B). Among the 35 patients with concurrent ovarian endometrioma, the endometrioma diameter significantly decreased from a median of 34.5 mm (IQR 0–44 mm) before treatment to 25.5 mm (IQR 0–36 mm) after three cycles ($P = 0.015$), and to 9.5 mm (IQR 0–31 mm) after six cycles of treatment ($P = 0.003$ compared with baseline) (Fig. 2C). The CA-125 level decreased significantly from a median of 24.2 U/mL (13.2–40 U/mL) before treatment to 13.3 U/mL (7.9–18 U/mL) after six cycles of treatment ($P < 0.001$ compared with baseline) (Fig. 2D).

The MDQ total score during the menstruation phase significantly decreased from a median of 69.0 (IQR 58–88) before treatment to 54.8 (IQR 47–75) after three cycles ($P < 0.001$), and to 54.0 (IQR 46–73) after six cycles of treatment ($P < 0.001$ compared with baseline) (Fig. 3A). During the menstruation phase, MDQ water-retention scores significantly improved from a median of 8.0 (IQR 6–11) before treatment to 7.5 (IQR 6–9) after three cycles ($P = 0.029$), and to 7.0 (IQR 6–8) after six cycles of treatment ($P = 0.002$ compared with baseline) (Fig. 3B).

Table 1
Patient characteristics at baseline (n = 46).[a]

Characteristics	Value
Age, y	34.4 ± 6.7 (22–45)
Height, cm	160.3 ± 4.3 (152–168)
Body weight, kg	53.1 ± 9.3 (42–80)
Body mass index[b]	20.8 ± 3.1 (16.4–29.0)
Duration of menstrual cycle, d	27.9 ± 2.0 (25–33)
No. of previous pregnancies	0.90 ± 1.32 (0–5)
Endometrioma	35 (76)
Adenomyosis	12 (26)

[a] Values are given as mean ± SD (range) or number (percentage).
[b] Calculated as weight in kilograms divided by the square of height in meters.

Please cite this article as: Tanaka Y, et al, Effects of low-dose combined drospirenone–ethinylestradiol on perimenstrual symptoms experienced by women with endometriosis, Int J Gynecol Obstet (2016), http://dx.doi.org/10.1016/j.ijgo.2016.05.004