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Comparison of long-term use of combined oral contraceptive after gonadotropin-releasing hormone agonist plus add-back therapy versus dienogest to prevent recurrence of ovarian endometrioma after surgery

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ABSTRACT

Objective: The aim of this study was to compare long-term use of combined oral contraceptive (COC) after gonadotropin-releasing hormone (GnRH) agonist plus add-back therapy with dienogest (DNG) treatment as medical treatments after surgery for ovarian endometrioma.
Methods: This prospective cohort study analyzed 52 reproductive-aged women who underwent surgery for ovarian endometrioma and received postoperative medical treatment with either COC after GnRH agonist (n = 20) or DNG (n = 32) for 24 months. Changes in quality-of-life (QOL) and bone mineral density (BMD) were compared according to treatment. In addition, recurrence of pain and lesions were compared.
Results: Baseline characteristics did not differ in demographic profiles and factors associated with endometriosis or QOL. During 24 months of treatment, no differences in any component of QOL were found between the two groups. BMD at the lumbar spine significantly decreased after the first 6 months of treatment in both COC after GnRH agonist (−3.5%) and DNG (−2.3%) groups, but the groups did not differ statistically. After 6 months, further decrease in BMD was not observed until 24 months in both groups. In addition, no cases of pain or endometrioma recurrence were found.
Conclusion: Our results suggest that long-term use of COC after GnRH agonist plus add-back therapy is comparable to dienogest as a long-term postoperative medical treatment for endometriosis.

Introduction

Endometriosis is defined as the presence of endometrial tissue outside the uterine cavity. Since recurrence rates after surgery are reported to be 21.5% at 2 years and 40–50% at 5 years [1], long-term postoperative medical treatment is required to reduce recurrence [2,3] and avoid repetitive surgeries [4,5].

Combined oral contraceptive (COC) in either a cyclic or continuous schedule is widely used to prevent recurrence after conservative surgery [6], and postoperative gonadotropin-releasing hormone (GnRH) agonist followed by long-term COC is also effective [7,8]. Progestins have also been used to prevent recurrence of endometriosis [9–11]. Among them, dienogest (DNG) is considered an option for long-term postoperative management [12–14].

Although both COCs and progestins are used long-term until the patient wishes to conceive or reaches menopause, efficacy and tolerability may be different according to treatment. For example, unexpected vaginal bleeding, which affects QOL, is more common with the use of DNG [13,15]. However, long-term tolerability of DNG has seldom been compared with COCs, especially in the context of QOL.

Therefore, this study compared the tolerability of COC after GnRH agonist and DNG treatment as long-term postoperative medical treatments for prevention of recurrence.

Materials and methods

This study analyzed data from the Endometriosis Cohort at Samsung Medical Center, a prospective cohort designed to investigate the effects of postoperative medical treatment for prevention of endometriosis recurrence.

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Patients who received postoperative GnRH agonist followed by COC or those who received postoperative DNG for 24 months from 2012 to 2015 were selected from the cohort. Patients were excluded from analysis if they (1) underwent an oophorectomy or hysterectomy during the operation, (2) had a history of previous pelvic surgery for endometriosis, (3) had a history of preoperative hormonal treatment, (4) received both treatments, (5) were lost to follow-up before completing the 24-month assessment, or (6) had a history of disease or took other medications which affect bone density. The study protocol was approved by the institutional review board at Samsung Medical Center, and informed consent was obtained from all participants.

Operations were performed by the same surgeon. All recognized lesions were treated with excision or fulguration, and restoration of normal anatomy was achieved. After providing information on the day when pathologic diagnosis was confirmed, patients received either GnRH agonist followed by COC or DNG treatment according to the study period: patients were treated with GnRH agonist followed by COC from 2012 to 2013, and dienogest from 2013 to 2015, as dienogest was available at that time. A GnRH agonist (Leuprin® 3.75 mg; Takeda, Seoul, Korea) was administered subcutaneously every four weeks for six cycles and thereafter COC (YAZ®; Bayer, Seoul, Korea) was used. To prevent side effects related to GnRH agonist injection during administration, all patients received oral add-back therapy (1.0 mg/day of estradiol and 0.5 mg/day of norethisterone acetate [Cliovelle®; DR. KADE Pharma, Berlin, Germany]). DNG (Visanne®; Bayer) was taken orally at a dose of 2 mg/day DNG for at least 24 months.

Baseline and follow-up assessments consisted of a structured questionnaire and interview. Patients were asked about adverse events at every visit. QOL was determined by the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF), which consists of 24 questions covering four domains (physical health, psychological health, social relationships, and environment). QOL was estimated based on answers to each of the questions on a five-point scale, and the mean estimate for all items in each domain was transformed to a range of 0–100. Bone mineral density (BMD) was measured at the lumbar spine (L1–4) and femur using dual-energy X-ray absorptiometry (Delphi Q; Hologic Inc., Bedford, MA, USA) before and after 6, 12, and 24 months of treatment. The *in vivo* coefficient of variation was 1.3% for the lumbar spine and 1.4% for the femur at our center. In addition, pain was evaluated on a visual analog scale (VAS; 0 = no pain to 10 = extreme pain). Because chronic pelvic pain and dyspareunia were so rare, we assessed various kinds of pain in one, and pelvic ultrasound was performed annually to determine endometrioma recurrence.

Statistical analyses were performed with SPSS v.21.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviations or numbers (percentages). Clinical characteristics and changes in QOL and BMD were compared according to treatment regimen. The least 20 patients were required in each treatment group to ensure that this study would have a power of 60% to detect a 10% difference in the mean change with an alpha of 0.05. The Mann-Whitney test was used to compare non-parametric continuous variables and Student's or paired *t*-test were used to compare other parametric continuous variables. Chi-square of Fisher's exact test was used to compare categorical data as indicated. Serial changes in QOL and BMD were compared between the groups using repeated-measures analysis of variance after tests for normality. P-values of less than 0.05 were considered statistically significant.

Results

During the study period from 2012 to 2015, 108 women were eligible for the current study. Among them, 56 were excluded by criteria, and finally, a total of 52 patients (20 in GnRH agonist plus COC and 32 in DNG group) were included in the analysis as shown in the patient flow-chart (Fig. 1). Baseline characteristics of the study subjects are shown in Table 1. There were no significant differences in demographic profiles or characteristics regarding endometriosis such as size, laterality, stage, and serum level of CA-125 between the two treatment groups. In addition, factors associated with QOL, such as smoking, alcohol intake, exercise, and economic status, also did not differ by treatment.

Fig. 2 shows the physical, psychological, social, and environmental components of QOL.

No difference was found in values of these components at any time point between the two groups. In addition, patterns of change did not differ among components.

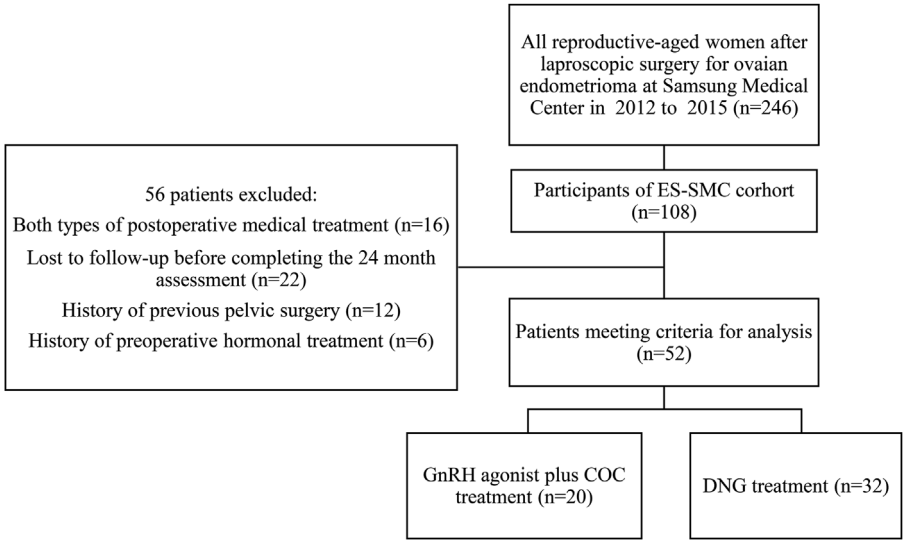

Fig. 1. Patient flow-chart.

Table 1
Baseline characteristics.

	GnRHa + COC (n = 20)	Dienogest (n = 32)
Age (yr)	29.2 ± 5.0	28.1 ± 5.9
Body mass index (kg/m^2)	20.7 ± 2.2	20.4 ± 3.3
Parity		
0	85.0	93.8
1-2	15.0	6.3
Menstrual cycle		
Regular	75.0	78.1
Irregular	25.0	21.9
Menstrual duration	6.1 ± 1.2	5.8 ± 1.5
Menstrual amount		
Large	5.0	28.1
Moderate	85.0	56.3
Small	10.0	15.6
Current smoking	10.0	3.1
Alcohol intake	65.0	53.1
Economic status*		
Middle	80.0	100
High	20.0	0
Level of education		
High school	6.3	16.1
College graduate	81.3	80.7
Graduate or above	12.5	3.2
Religion		
Yes	62.5	67.7
No	37.5	32.3
Marital status		
Single	80.0	93.8
Married	20.0	6.3
Endometrioma		
Size (cm)	5.1 ± 2.3	5.1 ± 2.0
Unilateral	80.0	65.6
Bilateral	20.0	34.4
ASRM stage		
III	35.0	18.8
IV	65.0	81.3
CA-125	34.7 ± 31.3	24.7 ± 19.0

Data are presented as mean ± SD or %.
* $P < 0.05$ between the two groups by *t*-test and Fisher's exact test or Chi-square test, as indicated.

Fig. 3 shows BMD changes according to treatment. In the lumbar spine, BMD significantly decreased compared to the baseline in the GnRH agonist plus COC group (-3.5%) and in the DNG group (-2.3%) after the first 6 months of treatment, and the amount of decrease did not differ between groups. However, in the GnRH agonist plus COC group, BMD increased with time after starting COC (at 12 and 24 months). In addition, BMD did not decrease further after the first 6 months in the DNG group. At the femur neck, BMD decreased significantly in both groups to 1 year from starting postoperative management, with no difference between groups. Thereafter, a further decrease in BMD was not observed until 24 months. During the 24 months of treatment, no cases of pain or disease recurrence were reported.

Discussion

This study compared two postoperative long-term medical treatments, GnRH agonist followed by COC and dienogest, for the prevention of recurrence of ovarian endometrioma. We demonstrated that both treatments were comparable in tolerability as well as efficacy. To the best of our knowledge, this is the first study to compare the long-term effects of COC with DNG as a postoperative medical treatment for recurrence prevention.

In this study, physical, psychological, social, and environmental components of QOL were not significantly different across treatment options. Although both COC and DNG treatment have been reported to improve QOL in patients with endometriosis in previous studies [16–18], these two treatment options have never been compared with each other, especially in an Asian population. Of note, although DNG induces low serum estrogen levels by inhibiting ovulation [19], QOL in all categories was not inferior to COC, which contains an estrogen component (20 μg of ethinyl estradiol). In addition, QOL did not decline with time in either treatment. These findings suggest that both COC and DNG are tolerable options for long-term maintenance.

BMD at the lumbar spine decreased significantly during the first 6 months of GnRH agonist treatment despite add-back therapy, but the degree of decrease (-3.5%) was smaller than that in other studies (4–8% of BMD decrease in 3–6 months of GnRH agonist without add-back therapy) [14,20,21]. However, when followed by long-term COC, BMD did not deteriorate at 12 and 24 months, and actually improved from 6 months. This finding is consistent with randomized studies reporting that COCs do not exert any clinically significant effect on BMD in the general population [22–25]. Meanwhile, lumbar spine BMD significantly decreased during the first 6 months of DNG treatment (-2.3%), consistent with previous Asian studies reporting BMD decrease from -1.7% to -2.8% within a year of DNG use [15,26]. However, similar to long-term COC, future significant decreases in BMD were not observed in this study. A discrepancy in the effect of DNG use on bone density between European and Asian populations [14] might be explained by differences in body mass index, serum estradiol level, or bone size [12,13,19]. The clinical importance of the BMD decrease observed in this study needs to be determined in a future long-term cohort study.

No recurrence was found in terms of either pain or lesions in the present study. Robust evidence has shown that COC effectively prevents both pain and endometrioma recurrence [27], and a continuous regimen of COC appears more efficacious than a cyclic regimen as to both dysmenorrhea and cyst recurrence rate. Also, COC use is more effective than levonorgestrel-releasing intrauterine system (LNG-IUS) in reducing pain and disease recurrence, although patient satisfaction was somewhat greater in LNG-IUS [10]. However, much lower recurrence rate of pain or endometrioma in the current study compared with a randomized trial might result from the small size and different criteria between the studies. The efficacy of dienogest to prevent postoperative pain recurrence also has been proven in randomized controlled trials [12–14,16]. Several retrospective studies have reported that cyst recurrence rate were 0-0.9% at 12 months, 3.5% and 7.7% at 2 years and 5 years, respectively [29–31], but research focusing on the effect of dienogest for the prevention of endometrioma recurrence is still limited [28]. Our findings add evidence for the efficacy of dienogest in prevention of endometrioma recurrence. In addition, feasibility about long-term use of dienogest should be also identified through further research due to possible bone loss in some women.

The present study has several limitations. First, despite a prospective design, this was not a randomized controlled trial. Second, the number of patients is relatively small. In addition, we used GnRH agonist before starting COC, and this might affect the efficacy and tolerability in some patients, compared with single use of DNG. However, we analyzed the effects of COC and GnRH agonist on quality of life and bone mass, since we measured values at serial time points.

In conclusion, long-term use of COC after GnRH agonist is comparable to dienogest as a long-term postoperative medical treatment for ovarian endometrioma. The treatment method should be determined according to the patient characteristics.

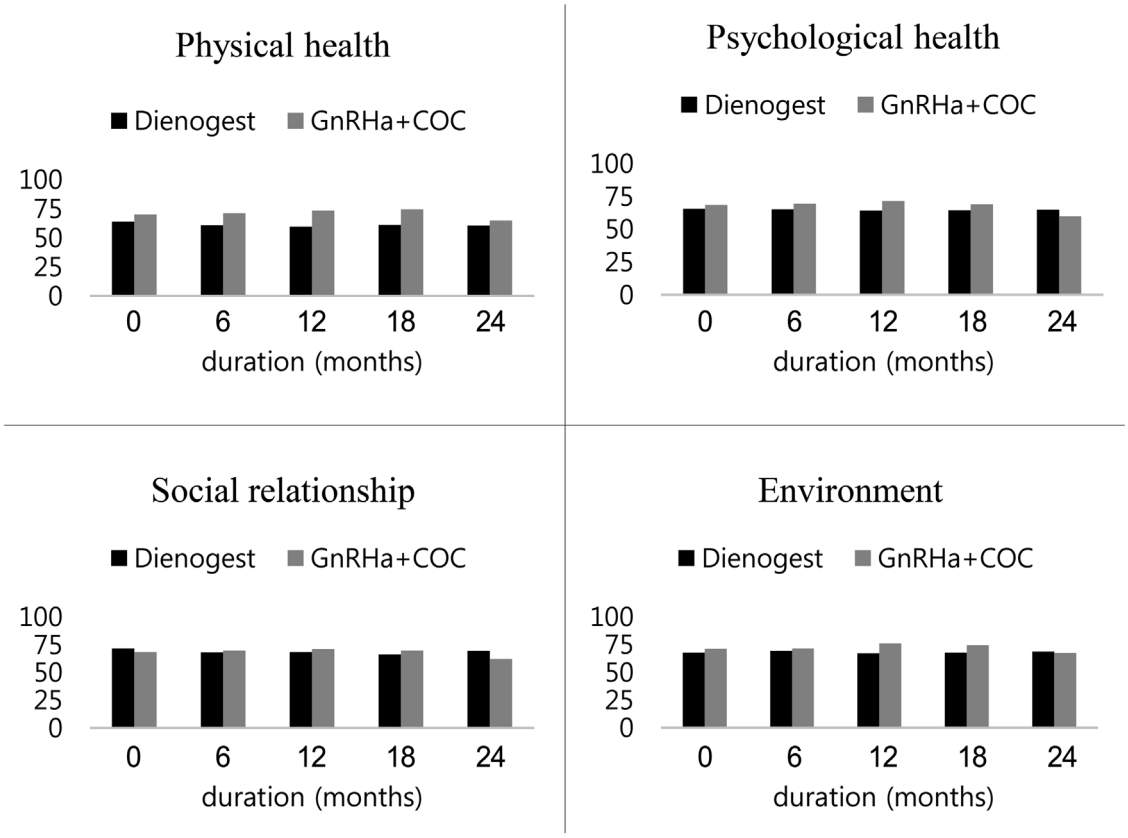

Fig. 2. Changes in the World Health Organization Quality of Life Questionnaire. No inter- or intra-treatment differences were found.

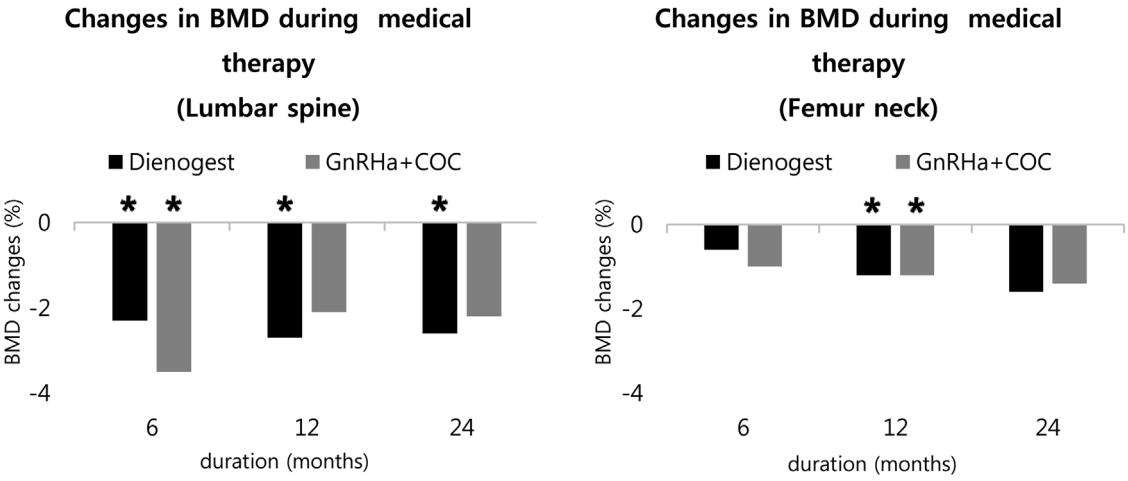

Fig. 3. Changes in bone mineral density (BMD) over 2 years. BMD in the lumbar spine and femur neck decreased significantly in both treatment groups, with no significant difference between groups. Asterisk indicates a significant difference from baseline within the same treatment.

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