Arch Gynecol Obstet (2016) 294:1257–1263
DOI 10.1007/s00404-016-4184-9

GENERAL GYNECOLOGY

Gonadotropin-releasing hormone agonist with add–back treatment is as effective and tolerable as dienogest in preventing pain recurrence after laparoscopic surgery for endometriosis

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Received: 25 March 2016 / Accepted: 18 August 2016 / Published online: 22 August 2016

Abstract
Purpose This study was performed to compare the efficacy and tolerability of GnRH agonist with add–back therapy versus dienogest treatment for preventing pelvic pain recurrence after laparoscopic surgery for endometriosis.
Methods Sixty-four reproductive-aged women who underwent laparoscopic surgery for endometriosis received post-operative medical treatment with either GnRH agonist plus 17β-estradiol and norethisterone acetate ($n = 28$) or dienogest ($n = 36$) for 6 months. The pre- to post-treatment changes in pain were assessed using a visual analogue scale, and changes in quality-of-life and menopausal symptoms were measured by questionnaire.
Results Visual analogue scale pain score decreased significantly for both treatments with no significant differences between groups. Neither physical, psychological, social, and environmental components of quality-of-life nor menopausal rating scale score were significantly different between the two groups. Bone mineral density at the lumbar spine declined significantly in both treatment groups (−2.5 % for GnRH agonist plus add–back and −2.3 % for dienogest), with no significant difference between the two groups.
Conclusion GnRH agonist and add–back therapy using 17β-estradiol and norethisterone acetate are as effective and tolerable as dienogest for the prevention of pelvic pain recurrence after laparoscopic surgery for endometriosis.

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Keywords GnRH agonist · Add–back therapy · Dienogest · Endometriosis · Pain · Quality-of-life

Introduction

Endometriosis is a chronic disease that affects about 10 % of reproductive-aged women, and is frequently associated with dysmenorrhea, dyspareunia, and chronic pelvic pain. Endometriosis-associated pain is the most common symptom; it has a severe impact on quality-of-life (QOL), and is the major indication for treatment of endometriosis. Although surgical treatment is effective at reducing endometriosis-associated pain [1], medical treatment is also necessary to prevent recurrence of painful symptoms after surgery, because the recurrence rate is high [2, 3].

Among different medical treatment options, gonadotropin-releasing hormone (GnRH) agonists are commonly used for pain relief [4]. These agonists effectively suppress endogenous gonadotropin secretion and result in a hypoestrogenic state [4–6]. However, concerns have been raised about side effects related to GnRH agonist-induced estrogen deprivation, such as bone loss and climacteric symptoms, which limit their long-term use and impair QOL during treatment [4, 7]. Therefore, add–back therapy should be considered during GnRH agonist treatment [8].

Dienogest is another treatment option that can reduce endometriosis-associated pain [9, 10]. Dienogest has been reported to improve quality-of-life compared with GnRH agonist-alone treatment [11]. Furthermore, serum estradiol concentration is maintained at the appropriate level to prevent hypoestrogenic side effects during dienogest treatment [12, 13].

Several studies have compared the efficacy of GnRH agonist versus dienogest at reducing pain and improving

the quality-of-life [11, 14–16]. However, dienogest and GnRH agonist with add–back therapy have not yet been compared, even though add–back therapy can minimize hypoestrogenic effects that can affect the efficacy and tolerability of GnRH agonist treatment.

Therefore, this study was aimed to compare the effects of GnRH agonist with add–back therapy using estradiol and norethisterone acetate with those of dienogest as post-operative medical treatment options for prevention of pelvic pain recurrence.

Methods

Patients

All reproductive-aged women (18–45 years) who underwent conservative laparoscopic surgery for pain and ovarian endometrioma (revised ASRM stage III or IV) in the endometriosis clinic at Samsung Medical Center from February 2012 to April 2015 were considered for this study.

Inclusion criteria were: (1) women with endometriosis confirmed by histology; (2) women who did not want to conceive immediately; (3) women who had no contraindications for either of the medical treatments; (4) women who completed the 6-month treatment; and (5) women who had the ability to complete a questionnaire and communicate clearly. The study protocol was approved by the Institutional Review Board of Samsung Medical Center, and informed consent was obtained from all participants.

Treatment

Conservative laparoscopic surgery was performed by one doctor (DC). All visible endometriotic lesions were removed or treated completely, adhesiolysis was performed, and finally, anatomical restoration was achieved.

After providing information, patients received either GnRH agonist with add–back treatment or dienogest treatment according to the study period: patients were treated with GnRH agonist with add–back therapy from February 2012 to February 2013, and dienogest from March 2013 to April 2015, as dienogest was available at that time. A GnRH agonist (leuprorelin acetate 3.75 mg, Leuprin®, Takeda, Japan) was administered subcutaneously on the day when pathologic diagnosis was confirmed and thereafter every 4 weeks for a total of six cycles. To prevent side effects related to GnRH agonist injection, patients also received oral add–back therapy (1.0 mg/day of estradiol and 0.5 mg/day of norethisterone acetate (Cliovelle®, DR. KADE Pharm, Germany). The other group of patients received oral dienogest (Visanne®, Bayer Schering, Germany) at a dose of 2 mg/day for 6 months.

Measurements

To compare the effects of GnRH agonist with add–back therapy versus dienogest on pelvic pain, a ten-point visual analogue scale (VAS) ranging from 0 for the 'absence of pain' to 10 for 'unbearable pain' was assessed before surgery and again after 3 and 6 months of treatment.

QOL and other variables were also assessed before surgery and again after 3 and 6 months of treatment. QOL was examined by means of 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 the 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 the range of 0–100.

Changes in hypoestrogenic symptoms were assessed by the menopause rating scale (MRS), which is composed of 11 items assessing menopausal symptoms divided into three subscales: somatic, psychological, and urogenital. Total MRS score is the sum of the scores of each five-point scale and ranges from 0 to 44 points, with a higher score reflecting more severe menopausal symptoms [17].

In addition, 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 the completion of treatment. The in vivo coefficient of variation was 1.3 % for the lumbar spine and 1.4 % for the femur at our center.

Statistical analysis

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). At least 23 patients were required in each treatment group to ensure that this study would have a power of 80 % to detect a 10 % difference in the mean change with an alpha of 0.05. Student's t test or the paired t test was used to compare continuous variables, while Fisher's exact test or the Chi-square test was used to compare categorical data. Serial changes in VAS, QOL, and MRS 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

Sixty-four patients (28 in the GnRH agonist with add–back therapy group and 36 in the dienogest group) were analyzed. Five patients in the GnRH agonist with add–back therapy and ten patients in the dienogest group stopped medication before 6 months of treatment and excluded from analyses.

Baseline characteristics of the study participants are shown in Table 1. There were no significant differences in age, body mass index, or menstrual history between the two groups. There was no difference in endometriosis characteristics or factors associated with QOL, such as smoking, alcohol intake, exercise, and economic status, between the two groups. Deep infiltrating endometriosis was not found in both groups.

VAS scores declined significantly in both groups compared with baseline, but there was no statistical difference at any time point between the two groups (Fig. 1). In addition, the pattern of change of VAS was similar for both groups. No case of pain recurrence was reported for either treatment.

Table 1 Baseline characteristics

	GnRHa + add–back ($n = 28$)	Dienogest ($n = 36$)
Age (years)	30.6 ± 6.1	29.0 ± 5.9
Body mass index (kg/m^2)	20.0 ± 3.0	20.6 ± 3.1
Age at menarche (yr)	13.6 ± 1.4	13.6 ± 1.2
Menstrual cycle		
Regular	24 (85.7 %)	32 (88.9 %)
Irregular	4 (14.3 %)	4 (11.1 %)
Menstrual duration	6.1 ± 1.1	5.5 ± 1.6
Menstrual amount		
Small	3 (10.7 %)	4 (11.1 %)
Moderate	19 (67.9 %)	21 (58.3 %)
Large	6 (21.4 %)	11 (30.6 %)
Size of endometrioma (cm)	5.1 ± 1.9	4.6 ± 1.4
Laterality of endometrioma		
Unilateral	15 (53.6 %)	22 (61.1 %)
Bilateral	13 (46.4 %)	14 (38.9 %)
ASRM stage		
III	21 (75.0 %)	22 (61.1 %)
IV	7 (25.0 %)	14 (38.9 %)
Current smoking	2 (7.1 %)	1 (2.8 %)
Alcohol intake	13 (46.4 %)	18 (50.5 %)
Regular exercise	10 (35.7 %)	13 (36.1 %)
Economic status		
Low	0	2 (5.6 %)
Middle	26 (92.9 %)	33 (91.7 %)
High	2 (7.1 %)	1 (2.8 %)
Level of education		
High school	1 (3.6 %)	4 (11.1 %)
College	24 (85.7 %)	28 (77.8 %)
Graduate or above	3 (10.7 %)	4 (11.1 %)
Religion		
Yes	20 (71.4 %)	23 (63.9 %)
No	8 (28.6 %)	13 (36.1 %)
Marital status		
Single	24 (85.7 %)	32 (88.9 %)
Married	4 (14.3 %)	3 (8.3 %)
Divorced	0	1 (2.8 %)

Data are presented as mean ± SD or number (%)

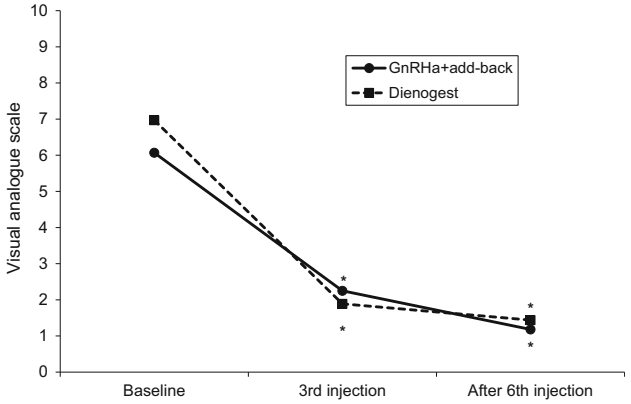

Fig. 1 Changes in visual analogue scale (VAS) between the two treatment groups. VAS score decreased in both groups with no significant difference between groups. The pattern of change in VAS also did not differ significantly between the two groups. *Asterisk* indicates a significant difference from baseline within the same group

Figure 2 shows that the physical, psychological, social, and environmental components of QOL did not differ significantly between the two groups. There was no difference in values of these components between the two groups at any time point or patterns of change in these components.

Although MRS increased from baseline to 3 or 6 months of treatment in the GnRH agonist plus add–back therapy group, this increase was not statistically significant. There was no change in MRS in the dienogest group (Table 2). The pattern of change of MRS did not differ between the two groups. In addition, there was no difference at any time point between the two groups.

Figure 3 shows changes in BMD at the lumbar spine and femur after treatment. BMD decreased significantly at the lumbar spine in both GnRH agonist plus add–back (−2.5 %, from 0.979 to 0.954 g/cm^2) and dienogest (−2.3 %, from 0.954 to 0.932 g/cm^2) groups compared with baseline, but there was no significant difference between the two groups. Change at the femur was also similar between the two groups (0.3 % in the GnRH agonist plus add–back group and −0.7 % in the dienogest group).

Adverse effects related to treatment are presented in Table 3. Menstruation-like bleeding and spotting were significantly more common in the dienogest group than in the GnRH agonist plus add–back group. Other adverse effects, such as hot flush and headache, were similar between the two groups.

Discussion

This study compared GnRH agonist with add–back therapy involving estradiol and norethisterone acetate to dienogest for the prevention of pelvic pain recurrence after laparoscopic surgery for endometriosis, and demonstrated that GnRH agonist with add–back therapy was as effective and tolerable as dienogest.

No significant difference was found in the change in VAS between the two groups in this study, consistent with the previous studies showing equivalent efficacy of GnRH agonist-alone and dienogest for treating endometriosis-associated pain [14–16]. As all visible lesions were removed or treated during laparoscopic surgery, VAS scores declined shortly in both groups after treatments, and changes of VAS after post-operative medical treatment were similar with the previous studies [14]. Although the

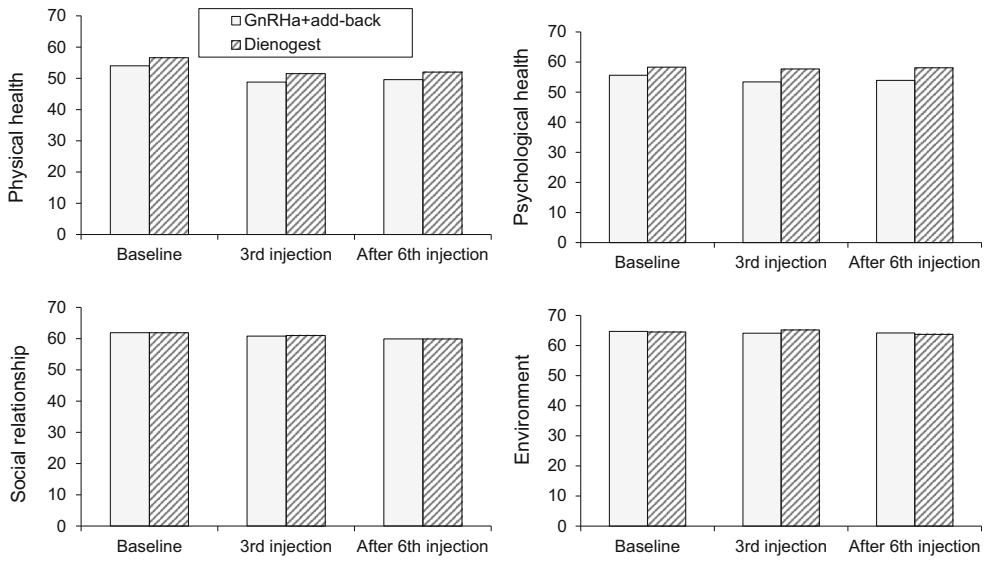

Fig. 2 Changes in quality-of-life. No difference was found between or within groups

Table 2 Changes in menopause rating scale

Regimen	Baseline	Third injection	Sixth injection
GnRHa + add–back ($n = 28$)	20.4 ± 9.2	25.1 ± 10.2	25.3 ± 7.8
Dienogest ($n = 36$)	22.7 ± 7.2	23.9 ± 8.0	23.7 ± 8.0

Data are presented as mean ± SD

No differences were seen between the two groups, at each time point

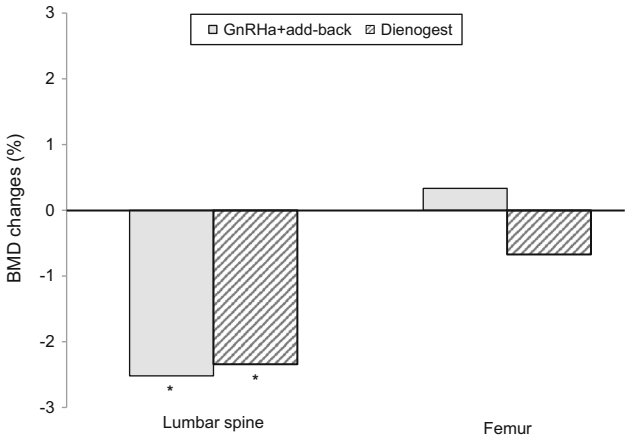

Fig. 3 Changes in bone mineral density (BMD). BMD at the lumbar spine decreased significantly in both groups, with no significant difference between groups. *Asterisk* indicates a significant difference from baseline within the same group

rationale for add–back therapy is based on the estrogen threshold hypothesis that there is a threshold of estrogen which hypoestrogenic symptoms are absent, while endometriosis is not stimulated [12], it is unclear whether add–back therapy reduces the effect of treatment on pain relief [18]. However, our results indicate that add–back therapy does not compromise the pain relief efficacy of GnRH agonist treatment.

Hypoestrogenic state induced by a GnRH agonist can impair QOL, and the previous studies demonstrated specific QOL benefits in terms of physical and mental health for dienogest treatment compared with GnRH agonist-alone treatment [11, 13]. However, we did not observe differences in QOL according to treatment option in this study. This discrepancy could be explained by the add–back component of GnRH agonist treatment. A recent study reported improvement in SF-36 scores during GnRH agonist with add–back therapy, especially when estrogen was added [19], supporting the efficacy of add–back therapy. However, it is not clear why QOL did not improve after surgery in our study, despite the significant pain relief reported by both treatment groups.

In this study, BMD at the lumbar spine decreased significantly (−2.3 %) in dienogest treatment, with no significant difference between the two groups. A previous study also demonstrated that BMD at the lumbar spine was significantly decreased (−1.6 %) after 24 weeks of dienogest treatment in patients with endometriosis [20]. However, our finding is not consistent with another study that reported minimal changes in bone turnover markers and lumbar spine BMD after 6 months of dienogest treatment [14]. Although the reduction in serum estradiol level during dienogest treatment is considered to be modest [14, 16, 21], dienogest usually inhibits ovulation, and therefore, the serum level of estradiol might not be sufficient to maintain

Table 3 Adverse effects (multiple choice)

	GnRHa + add–back ($n = 28$)	Dienogest ($n = 36$)
Uterine bleeding		
Menstruation-like bleeding*	1 (0.8 %)	14 (53.8 %)
Spotting*	8 (22.2 %)	20 (55.6 %)
Irregular bleeding	0	3 (8.3 %)
Hot flush	3 (11.5 %)	4 (11.1 %)
Genital dryness	3 (11.5 %)	1 (2.8 %)
Depression	1 (3.8 %)	4 (11.1 %)
Sleep disorder	2 (7.7 %)	4 (11.1 %)
Acne	1 (3.8 %)	3 (8.3 %)
Headache	1 (3.8 %)	2 (5.6 %)
Weight gain	0	1 (2.8 %)
Decreased libido	0	0

Data are presented as number (%)

* $P < 0.05$ by Fisher's exact test or Chi-square test, as indicated

bone density. Moreover, the high standard deviation of estradiol levels in studies indicates that there is a substantial degree of variability between individuals [22]. Because of the lack of studies regarding BMD changes in response to dienogest use, more data are needed to draw a clear conclusion.

Although lumbar spine BMD decreased significantly in the GnRH agonist with add–back therapy groups, the degree of decrease (−2.5 %) was smaller than that reported in other studies (4–8 % decrease in spine BMD over 3–6 months of GnRH agonist-alone treatment) [5, 14, 23, 24]. Serum estradiol levels were significantly higher in the add–back group using conjugated equine estrogen or estradiol compared with GnRH agonist-alone [25, 26], but still maintained at the level of less than 50 pg/mL. Norethindrone acetate is a preferred component of add–back therapy, because it is converted into ethinyl estradiol after oral ingestion [27]; this could be responsible for its beneficial effects on bone health [28]. These findings suggest that the combination of estrogen and norethisterone acetate could be an adequate add–back regimen for bone health. However, this conversion might lead to a high level of estrogen over the threshold in some patients, especially when combined with estrogen. Therefore, more studies are needed to determine the ideal add–back regimen.

In this study, both treatments were well tolerated and only seven (two in the GnRH agonist group and five in the dienogest group) patients discontinued medication due to side effects during the study period. Among side effects, uterine bleeding was the most common in both groups, and the incidence of uterine bleeding was significantly higher in the dienogest group, as expected. Other side effects were not significantly different between the two treatment groups. Hypoestrogenic side effects are common in GnRH agonist-alone treatment [28]; our results suggest that add–back therapy can effectively reduce hypoestrogenic symptoms induced by this treatment.

This study had some limitations. First, this is not a prospective, randomized controlled trial. Second, the treatment duration was relatively short, and the long-term effects of each treatment could, therefore, not be assessed. Third, levels of estradiol were not measured. However, to the best of our knowledge, this is the first study to compare the effects of GnRH agonist with add–back therapy versus those of dienogest alone as medical treatment options after surgery for endometriosis; the previous studies have focused on comparing GnRH agonist-alone treatment with dienogest treatment [15, 16, 28].

In conclusion, treatment with GnRH agonist plus estradiol and norethisterone acetate was as effective and tolerable as that with dienogest for preventing pelvic pain recurrence after laparoscopic surgery for endometriosis. A future large, long-term randomized trial is warranted to confirm our findings.

Compliance with ethical standards

Conflict of interest DYL declares that he has no conflict of interest. JYL declares that she has no conflict of interest. JWS declares that he has no conflict of interest. BKY declares that he has no conflict of interest. DC declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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