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Long-term efficacy and safety of levonorgestrel-releasing intrauterine system as a maintenance treatment for endometriosis

Hye Yun Kim, MD, MS, Soo Youn Song, MD, PhD, Soo Hwa Jung, MD, MS, Hyun Jeong Song, MD, MS, Mina Lee, MD, PhD, Ki Hwan Lee, MD, PhD, Ye Won Jung, MD, MS, Heon Jong Yoo, MD, PhD*

Abstract

This study evaluated the efficacy and feasibility of long-term use of levonorgestrel releasing intrauterine system (LNG-IUS) in endometriosis patients after using LNG-IUS for >5 years as their postoperative maintenance therapy.

Data were obtained retrospectively from patients who maintained medical therapy for >5 years after surgical treatment of endometriosis from January 2008 to April 2015. Patients were divided into study group and control group according to the type of medication; the study group consisted of patients who received LNG-IUS as maintenance therapy, and patients in the control group received combined oral contraceptives (ethinyl estradiol 20 μg and drospirenone 3 mg) or dienogest 2 mg.

A total of 263 patients (94 patients in the study group, 169 in the control group) were included in the study. 91.5% (86/94) of the patients in the study group maintained the treatment for >5 years, whereas only 21.9% (37/169) of patients in the control group maintained the treatment for >5 years.

LNG-IUS significantly decreased the pain score for non-cyclic pelvic/back pain (from 4.0 ± 1.6 to 0.6 ± 1.3, $P < .001$), dysmenorrhea (from 6.5 ± 1.7 to 6.5 ± 1.7, $P < .001$), and dyspareunia/dyschezia (from 6.5 ± 1.7 to 1.3 ± 1.4, $P = .006$) after 1 year, and the effect was persistent for 10 years ($P < .01$). When compared with control group, the effect on pain reduction was comparable to the oral contraceptives or dienogest, with less systemic side effects such as mood change or nausea.

LNG-IUS for >5 years as a postoperative maintenance therapy for endometriosis patients is an effective and feasible treatment that shows significant effect on pain reduction with less systemic side effect compared with other types of treatment. Therefore, LNG-IUS can be recommended as a long-term postoperative therapy for endometriosis patients who do not plan to become pregnant for several years.

Abbreviations: EE/DRSP = cyclic combined oral contraceptives containing ethinyl estradiol 20 μg and drospirenone 3 mg, LNG-IUS = levonorgestrel-releasing intrauterine system.

Keywords: dysmenorrhea, endometriosis, levonorgestrel-releasing intrauterine systems, long-term efficacy

1. Introduction

Endometriosis is a gynecological disease defined as the presence of a functional endometrial epithelium and stroma outside the uterus. It is a relatively common disease known to occur in about 10% of women of childbearing age.[1–3] Women with endometriosis complain a variety of symptoms such as chronic pelvic pain, dysmenorrhea, and dyspareunia as well as subfertility.[1,3] Depending on the type and severity of symptoms, drugs (such as hormonal drugs and nonsteroidal anti-inflammatory drugs) and surgeries are treatment options.[4,5] Although surgery is effective for pain and subfertility by directly removing visible endometriosis lesions, recurrence rate after surgery is very high when surgical-only treatment is performed, reaching nearly 50% at 5 years after surgery. Therefore, a maintenance therapy is needed to prevent recurrence after surgery. Methods such as combined oral contraceptives, oral dienogest, and levonorgestrel-releasing intrauterine system (LNG-IUS) are commonly selected.[6–8]

The LNG-IUS (Mirena, Bayer Ag, Turku, Finland) is an intrauterine device that can steadily release levonorgestrel at a rate of 20 μg/day directly into the uterine cavity for 5 years.[9] Many clinical studies have demonstrated the efficacy of LNG-IUS as a first-line treatment[5,10] and a maintenance therapy after surgical treatment in endometriosis patients.[11,12] However,

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Department of Obstetrics and Gynecology, Chungnam National University School of Medicine, 33, Munhwa-ro, Jung-gu, Deajeon, Republic of Korea.

* Correspondence: Heon Jong Yoo, Department of Obstetrics & Gynecology, Chungnam National University School of Medicine, 33, Munhwa-ro, Jung-gu, Deajeon, 301-721, Republic of Korea (e-mail: bell4184@gmail.com).

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most of these studies had a short follow-up period of <30 months.[13]

Therefore, the objective of this study was to evaluate the efficacy and feasibility of long-term use of LNG-IUS in endometriosis patients after using LNG-IUS for >5 years as their postoperative maintenance therapy.

2. Methods

This was a retrospective study with approval from the Institutional Review Board of Chungnam National University Hospital (approval number: 2020-11-063). After reviewing medical records of patients diagnosed with endometriosis through histopathology from January 2008 to April 2015, patients who continued one of maintenance therapies for at least 5 years after surgery were included in this study. Those who did not visit the outpatient clinic after surgery and those who visited the outpatient clinic after surgery to receive the maintenance treatment but failed to maintain one maintenance therapy for >5 years were excluded from this study. The study group consisted of patients diagnosed with endometriosis after surgery who had LNG-IUS inserted as a maintenance therapy (LNG-IUS group). The control group consisted of patients who took cyclic combined oral contraceptives containing ethinyl estradiol 20 μg and drospirenone 3 mg (EE/DRSP), or continuous dienogest 2 mg as a postoperative maintenance therapy (EE/DRSP group and dienogest group, respectively). Patients chose their postoperative maintenance therapy after a doctor gave them an objective explanation regarding the insertion of the LNG-IUS device and the administration of EE/DRSP or dienogest drugs.

Demographic data, obstetric history, and medical history were obtained from medical records. The size of the ovarian cyst before surgery was determined as the longest measurement length. If there were multiple cysts or bilateral ovarian cysts, the longest diameter of each cyst was summed. The stage and score of endometriosis were calculated according to the American Society for Reproductive Medicine standards.[14] Pain caused by endometriosis was classified into 3 categories: non-cyclic pelvic pain/back pain, dysmenorrhea, and dyspareunia/painful bowel movements. The degree of pain was measured using a 10 cm visual analog scale. Recurrence of endometrioma was defined as the presence of a uniform, hypoechoic, thin-walled ovarian cyst larger than 2 cm seen on an ultrasound for >3 months.[13] Adverse events were defined as symptoms and signs related to the treatment of endometriosis recorded in the medical record. For patients who decided to discontinue the treatment, the reason for the discontinuation was collected at the same time.

SPSS version 24.0 (IBM, Armonk, NY, USA) was used for all statistical analyses. For continuous variables, the change in visual analog scale compared with the reference value was measured using the paired sample *t* test and the difference among 3 groups was measured using the Kruskal–Wallis test. Categorical variables were compared using the chi-square test. A *P* value of <.05 was considered significant.

3. Results

From January 2008 to April 2015, 696 patients underwent endometriosis surgery at the Department of Obstetrics and Gynecology, Chungnam National University Hospital. Of them, 263 patients met the requirements for this study. Of these 263 patients, 94 had LNG-IUS insertion after surgery and the rest took EE/DRSP or dienogest. The majority (n = 86, 91.5%) of the 94 of patients who chose LNG-IUS as a maintenance therapy maintained the treatment for >5 years, while 21.9% (37/169), 10.1% (10/99), and 38.6% (27/70) of patients in the control group, the EE/DRSP group, and the dienogest group, respectively, maintained the treatment for >5 years.

Table 1 compares basic characteristics of patients divided into 3 groups. Age and birth history were significantly higher in the LNG-IUS group than in the EE/DRSP or the dienogest group ($P < .001$). In terms of disease severity such as cyst size ($P = .072$), surgical type ($P = .651$), endometriosis stage ($P = .873$), and score ($P = .598$), there was no significant difference among the 3 groups. For values of visual analog scale of non-cyclic pelvic pain/low back pain ($P = .793$) and dysmenorrhea ($P = .068$), there was no statistically significant difference among the 3 groups either. Endometrioma recurred in 2 patients of the LNG-IUS group and 1 patient of the EE/DRSP group, showing no statistically significant difference between the 2 groups ($P = .171$).

Figure 1 indicates the effect of LNG-IUS on pain reduction. The pain score was significantly decreased in all 3 symptoms categories after LNG-IUS insertion. The visual analog scale score was 4.0 ± 1.6 for non-cyclic pelvic pain/back pain, 6.5 ± 1.7 for dysmenorrhea, 4.1 ± 1.1 for dyspareunia/painful bowel movements. After 1 year, pain score was decreased to 0.6 ± 1.3 ($P < .001$) for non-cyclic pelvic pain/back pain, 0.8 ± 1.4 ($P < .001$) for dysmenorrhea, and 1.3 ± 1.4 ($P = .006$) for dyspareunia/painful bowel movements. This effect remained consistent throughout the study. The pain score remained lower than reference values throughout this study ($P < .01$).

The effect of LNG-IUS on pain reduction was compared with those of other types of treatment on an annual basis. Table 2 shows effects of LNG-IUS, EE/DRSP, and dienogest treatment on the reduction of dysmenorrhea at 1-year interval. Decrease in pain score was noted in the LNG-IUS, the EE/DRSP, and the dienogest group at only 1 year after initiating the treatment. There was no statistically significant difference in the effect among the 3 groups. After the first year, visual analog scale scores remained lower than those at baseline in all 3 groups.

Table 3 shows side effects associated with LNG-IUS, EE/DRSP, or dienogest. The number of patients who complained of side effects after the treatment was 106 out of 123 (86.2%). In the LNG-IUS group, no patient complained of systemic side effects such as mood changes, nausea, hair loss, or headache, while the percentage of localized side effects was higher in the LNG-IUS group than in the EE/DRSP or dienogest group (64.0% for vaginal discharge, 29.1% for leukorrhea, and 20.9% for transient ovarian cyst). When comparing side effects occurred within 5 years and after 5 years in the LNG-IUS group, the percentage of side effects occurred within 5 years was 95.3% (82/86), while that after 5 years was decreased to 24.4% (21/86).

Reasons for the discontinuation of treatment before the fifth year are described in Table 4. It was found that 8.5% (8/94) of subjects in the LNG-IUS group, 89.9% (89/99) of subjects in the EE/DRSP group, and 61.4% (43/70) of subjects in the dienogest group discontinued before the fifth year of treatment. In the LNG-IUS group, abnormal uterine bleeding and vaginal discharge, both with an incidence rate of 25% (2/8), were the most common reasons for the discontinuation. One patient discontinued the treatment due to persistent discomfort in the lower abdomen. Another one discontinued the treatment due to recurrence of endometriosis. Compared with the EE/DRSP or the dienogest group, patients in the LNG-IUS group did not express any concerns about the long-term safety of the treatment.

Table 1

Baseline characteristics of patients with endometriosis who were treated with levonorgestrel releasing intrauterine system or oral pills (oral contraceptives or dienogest) after the surgery.

Characteristics	LNG-IUS (n = 86)	EE/DRSP (n = 10)	Dienogest (n = 27)	*P*
Age	36.95 ± 4.52	29.3 ± 4.67	27.48 ± 6.308	<.001
BMI	21.95 ± 2.86	18.71 ± 5.65	21.49 ± 3.13	.089
Parity				<.001
0	6 (5.88%)	10 (100%)	26 (96.3%)	
1	26 (25.49%)	0 (0%)	1 (3.7%)	
2	67 (65.68%)	0 (0%)	0 (0%)	
Size of the cyst	5.35 ± 2.66	13.07 ± 20.14	6.71 ± 3.53	.072
rASRM stage				.873
1	2 (2.0%)	0 (0%)	0 (0%)	
2	3 (3.0%)	0 (0%)	2 (7.4%)	
3	35 (34.7%)	4 (40%)	10 (37%)	
4	61 (60.4%)	6 (60%)	15 (55.6%)	
rASRM score	47.86 ± 26.26	57.89 ± 34.24	52.48 ± 30.46	.598
Type of surgery				.651
Unilateral ovarian cystectomy	66 (64.7%)	6 (60%)	16 (59.3%)	
Bilateral ovarian cystectomy	23 (22.5%)	4 (40%)	10 (37.0%)	
Unilateral salpingo-oophorectomy	7 (6.9%)	0 (0%)	0 (0%)	
Baseline VAS score				
Non-cyclic pelvic/back pain	4.03 ± 1.55	5.00 ± 4.24	4.00 ± 3.66	.793
Dysmenorrhea	6.52 ± 1.74	5.86 ± 2.91	6.71 ± 2.69	.068
Dyspareunia/dyschezia	4.10 ± 1.08			
Recurrence of endometioma	2 (2.0%)	1 (10.0%)	0 (0%)	.171

Data are presented as mean ± standard deviation or number (percent).

BMI = body mass index, EE/DRSP = combined oral contraceptives with ethinyl estradiol 20 μg and drospirenone 3 mg, LNG-IUS = levonorgestrel releasing intrauterine system, rASRM = Revised American Society of Reproductive Medicine, VAS = visual analogue scale.

4. Discussion

This study found that LNG-IUS used as a long-term maintenance therapy for >5 years after endometriosis surgery was effective in relieving pain symptoms given that pain scores measuring the degree of non-cyclic pelvic pain/back pain, dysmenorrhea, and dyspareunia/painful bowel movements were lower than those at baseline even after 5 years. Continuity of LNG-IUS treatment was also significantly higher than that of other drug treatments such as EE/DRSP and dienogest.

Several studies have suggested that LNG-IUS is effective in endometriosis patients as a postoperative maintenance therapy. According to a recent systematic literature review of randomized controlled studies, LNG-IUS can significantly reduce the risk of recurrence of pain symptoms[15] and endometrioma compared with place.[16] Many cohort studies comparing with other types of hormonal therapy have found that effects of LNG-IUS on pain relief and recurrence prevention are similar to those of combined oral contraceptives or dienogest.[17–19] The present study found that LNG-IUS was effective in preventing the recurrence of dysmenorrhea throughout a 10-year period and that its effect was similar to those of other types of hormone therapy.

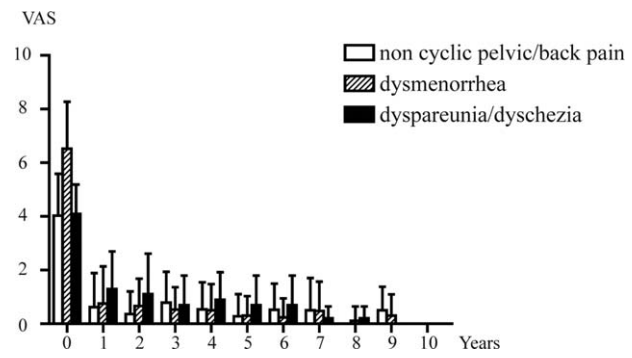

Figure 1. Changes in visual analog scale in non-cyclic pelvic/back pain, dysmenorrhea, and dyspareunia/dyschezia during 10 year of LNG-IUS treatment. LNG-IUS = levonorgestrel-releasing intrauterine system.

Endometriosis is a recurrent disease showing a recurrence rate of nearly 50% within 5 years after surgery. It is difficult to undertake resurgery due to adhesions caused by endometriosis itself as well as postoperative adhesions.[20] According to a recent study, a short-term hormone therapy of <6 months is not effective in preventing recurrence.[16] Therefore, recent guidelines recommend implementing a maintenance therapy for at least 18 to 24 months after surgery.[21] For successful long-term maintenance therapy, not only the efficacy of treatment, but also the tolerability of treatment and the compliance of patients must be considered. In this study, 21.9% of patients in EE/DRSP and dienogest groups maintained the treatment for >5 years, while 91.5% of those in the LNG-IUS group maintained the treatment for >5 years. In the EE/DRSP group, many patients discontinued their treatment within 5 years due to difficulties such as concerns about safety of long-term use and inconvenience of daily use. Therefore, LNG-IUS can be one of important long-term treatment methods for patients with endometriosis.

Localized side effects such as irregular uterine bleeding, vaginal bleeding, and vaginal discharge occurred more frequently in the LNG-IUS group. However, the incidence of all these symptoms significantly decreased after 5 years, consistent with another cohort study in which the incidence of adverse events decreased after 5 years in patients using LNG-IUS for endometriosis.[22] In the present study, systemic side effects such as mood changes, nausea, hair loss, acne, headache, and decreased bone density did not occur in the LNG-IUS group.

Table 2

Comparison of visual analogue scale of dysmenorrhea in each year before and after levonorgestrel releasing intrauterine system and hormonal pills (combined oral contraceptives or dienogest).

Year	LNG-IUS (n = 86)	EE/DRSP (n = 10)	Dienogest (n = 27)	*P*-value
0	6.52 ± 1.69	5.86 ± 2.91	7.00 ± 2.69	.019
1	0.68 ± 1.32	0.43 ± 1.13	0.45 ± 1.07	.110
2	0.67 ± 1.02	0.29 ± 0.76	0.24 ± 0.59	.055
3	0.50 ± 0.80	1.0 ± 1.29	0.11 ± 0.32	.131
4	0.47 ± 0.93	0.29 ± 0.76	0.58 ± 1.87	.621
5	0.26 ± 0.69	0.0 ± 0.0	0.29 ± 0.77	.988
6	0.19 ± 0.65	0.43 ± 1.13	0.33 ± 0.84	.248
7	0.40 ± 1.00	0.86 ± 2.27	0.50 ± 1.24	.989
8	0.10 ± 0.50	1.40 ± 3.13	0.50 ± 1.24	.365
9	0.28 ± 0.77	1.75 ± 3.50	0.88 ± 1.81	.705
10	0.25 ± 0.79	2.33 ± 4.04	1.25 ± 2.50	.629

Data are presented as mean ± standard deviation.

EE/DRSP = combined oral contraceptives with ethinyl estradiol 20 μg and drospirenone 3 mg, LNG-IUS = levonorgestrel releasing intrauterine system.

In our study, patients in LNG-IUS group were older than patients in EE/DRSP or dienogest group. As for parity, only 5.9% (6/86) patients in LNG-IUS group were nulliparous whereas only one patient in EE/DRSP or dienogest group was parous. This disparity in age and parity is due to the fact that young women who are single or who want to conceive in the near future are more reluctant in inserting intrauterine device. Based on these findings, LNG-IUS can be recommended in parous women who do not wish for further pregnancy.

Table 3

Adverse events of levonorgestrel releasing intrauterine system (before 5 years and after 5 years) and hormonal pill (combined oral contraceptives and dienogest).

	LNG-IUS before 5 years (%) N = 86	LNG-IUS after 5 years (%) N = 86	EE/DRSP (%) N = 10	Dienogest (%) N = 27	*P*
Person with side effects	82 (95.3)	21 (24.4)	7 (70.0)	17 (55.5)	<.001
Irregular bleeding	11 (12.8)	4 (4.7)	1 (10.0)	5 (18.5)	.131
Leukorrhea	25 (29.1)	9 (10.5)	2 (20.0)	0	<.001
Spotting	55 (64.0)	15 (17.4)	2 (20.0)	8 (19.7)	<.001
Low abdominal pain	2 (2.3)	3 (3.5)	0	0	.717
Breast tenderness	2 (2.3)	0	1 (10.0)	1 (3.7)	.127
Weight gain	1 (1.2)	2 (2.3)	2 (20.0)	1 (3.7)	.009
Coital discomfort	2 (2.3)	1 (1.2)	0	0	.785
Transient ovarian cyst	18 (20.9)	6 (7.0)	3 (30.0)	1 (3.7)	.008
Mood change	0	0	2 (20.0)	2 (7.4)	<.001
Nausea	0	0	3 (30.0)	0	<.001
Hair loss	0	0	1 (10.0)	0	<.001
acne	0	0	2 (20.0)	1 (3.7)	<.001
Headache	0	0	2 (20.0)	2 (7.4)	<.001
Leg edema	0	0	1 (10.0)	0	<.001

EE/DRSP = combined oral contraceptives with ethinyl estradiol 20 μg and drospirenone 3 mg, LNG-IUS = levonorgestrel releasing intrauterine system.

Table 4

Reason for cessation of levonorgestrel releasing intrauterine system, combined oral contraceptives or dienogest treatment before 5 years.

	LNG-IUS (n = 8)	EE/DRSP (n = 89)	Dienogest (n = 43)
Abnormal uterine bleeding	2 (25%)	1 (1.1%)	7 (16.3%)
Leukorrhea	2 (25%)	0	0
Low abdomen discomfort	1 (12.5%)	0	0
Recurrence	1 (12.5%)	0	2 (4.7%)
Attempt to conceive	0	15 (16.9%)	6 (14.0%)
Decreased bone mineral density	0	0	2 (4.7%)
Breast mass	0	2 (2.2%)	2 (4.7%)
Headache	0	0	2 (4.7%)
Liver dysfunction	0	1 (1.1%)	0
Hard to follow schedule	0	8 (8.9%)	9 (20.9%)
Concerns about long term safety	0	21 (23.6%)	7 (16.3%)

Data are presented as number (percent).

EE/DRSP = combined oral contraceptives with ethinyl estradiol 20 μg and drospirenone 3 mg, LNG-IUS = levonorgestrel releasing intrauterine system.

This study has several limitations. First, due to the retrospective nature of this study, there was a risk of bias from missing values for some results. Second, there was no direct comparison between LNG-IUS and placebo after surgical treatment of endometriosis. Third, pain was measured with the visual analog scale, which was a subjective measurement. Lastly, there were significant differences in birth history and age of basal characteristics among the 3 groups. Despite these limitations, this is the first-ever study to evaluate the long-term efficacy as well as the effectiveness of LNG-IUS as a postoperative maintenance therapy in endometriosis patients who have used LNG-IUS for >5 years after surgery. In addition, its effects on various pain symptoms such as dysmenorrhea, non-cyclic pelvic pain, and dyspareunia were evaluated.

In conclusion, LNG-IUS treatment is an effective and feasible method to control pain as a long-term postoperative maintenance therapy for endometriosis patients. It exhibited the best continuity for >5 years. Therefore, LNG-IUS can be considered as a long-term postoperative therapy for endometriosis patients who do not plan to become pregnant for several years.

Author contributions

Conceptualization: Ye Won Jung, Heon Jong Yoo.
Data curation: Hye Yun Kim, Soo Youn Song, Ki Hwan Lee, Heon Jong Yoo.
Formal analysis: Hye Yun Kim, Soo Youn Song, Heon Jong Yoo.
Funding acquisition: Heon Jong Yoo.
Investigation: Hye Yun Kim, Soo Youn Song, Ki Hwan Lee, Ye Won Jung.
Methodology: Hye Yun Kim, Soo Youn Song, Ye Won Jung.
Project administration: Heon Jong Yoo.
Resources: Heon Jong Yoo.
Software: Soo Youn Song.
Supervision: Soo Youn Song, Soo Hwa Jung, Hyun Jeong Song, Mina Lee, Ki Hwan Lee, Ye Won Jung, Heon Jong Yoo.
Validation: Hye Yun Kim, Soo Hwa Jung, Hyun Jeong Song, Mina Lee, Ki Hwan Lee, Ye Won Jung, Heon Jong Yoo.
Visualization: Hye Yun Kim.
Writing – original draft: Hye Yun Kim, Ki Hwan Lee, Ye Won Jung, Heon Jong Yoo.
Writing – review & editing: Hye Yun Kim, Soo Youn Song, Soo Hwa Jung, Hyun Jeong Song, Mina Lee, Ki Hwan Lee, Ye Won Jung, Heon Jong Yoo.

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