Clinical experience of long-term use of dienogest after surgery for ovarian endometrioma

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Objective
Endometriosis is a common and recurring gynecologic disease which have afflicting females of reproductive age. We investigated the efficacy of long-term, post-operative use of dienogest for ovarian endometrioma.

Methods
We studied 203 patients who had undergone laparoscopic or robotic surgery for ovarian endometrioma, and were administrated dienogest 2 mg/day beginning in July of 2013, and continuing. We evaluated side effects of dienogest and ultrasonography was performed every 6 months to detect potential recurrence of endometrioma (2 cm) in these post-surgical patients.

Results
The follow-up observation periods were 30.2±20.9 months from surgery. The mean age was 34.1±7.2 years old. The mean diameter of pre-operative endometrioma was 5.6±3.0 cm². One hundred eighty-two (89.7%) women received dienogest continuously for 12.0±7.1 months. Of the subjects, 21 (10.3%) patients discontinued dienogest at 2.4±1.0 months. The most common side effect when dienogest was discontinued was abnormal uterine bleeding. The occurrence rate of vaginal bleeding was 15.8%, a number which did not differ significantly in patients with/without post-operative gonadotropin releasing hormone agonist administration. The other side effects were gastrointestinal trouble including constipation, acne, headache, depression, hot flush, weight gain, and edema. However, no serious adverse events or side effects were documented and recurrent endometriomas were diagnosed in 3 patients (1.5%).

Conclusion
The data indicates that dienogest was both tolerable and safe for long-term use as prophylaxis in an effort to obviate the recurrence of ovarian endometrioma post-operatively, as well as potential need for surgical re-intervention.

Keywords: Dienogest; Endometriosis; Recurrence
ment would be warranted for ovarian endometriomas >3 cm. Laparoscopic stripping of the cyst wall is considered as the “Gold Standard” treatment of endometrioma as that procedure has been associated with reduced relapse rate, diminished signs and symptoms, improved intimate relations and also, improves fertility by enhancing chances of spontaneous conception [5].

However, recurrent endometrioma is a common dilemma and the condition can become a chronic problem. A pooled analysis of 23 studies estimated recurrence rates of 21.5% at 2 years and 40.0% to 50.0% at 5 years after primary surgery [6]. ESHRE does not offer specific guidelines for management of “recurrence of endometrioma”. In view of the foregoing, it is, in some cases, difficult to make a determination as to whether conservative, office-based treatment modalities or surgical re-intervention would represent the most informed, practical and best treatment option [7,8]. Consideration of surgery must include consideration of potential, post-surgical damage of ovarian function associated with diminished ovarian reserve (DOR) has also been reported. In a pooled analysis of 237 patients, significant decrease in serum anti-Müllerian hormone (AMH) concentration was appreciated after an ovarian cystectomy, although antral follicle count (AFC) is not significantly affected after primary surgery (laparoscopic stripping of endometrioma) [9]. Recent studies report that there is marked decrease in ovarian reserve (evaluated by AFC) after a surgery for recurrent endometrioma [10]. It is also concluded that there is decrease in implantation rate, pregnancy rate and live birth rate in women with DOR caused by previous cystectomy for endometrioma. The success rate of in vitro fertilization (IVF) is decreased in such cases [11].

Repeated surgery for recurrent endometriomas is associated with evidence of a higher loss of ovarian tissue and is more harmful to the ovarian reserve evaluated by AFC and ovarian volume, if compared with endometriomas operated for the first time [12]. Surgical re-intervention should be considered only after more conservative therapies have been implemented, and then shown to be ineffective, or the cyst formation is expanding so rapidly that there is suspected malignancy. Before the second surgery for recurrent endometrioma is recommended, the patient should be informed about the potential risk of ovarian failure. In cases of persistent infertility, IVF should be considered after primary surgery [12].

Due to increased incidence of recurrent endometrioma postoperatively and other surgery related complications, it is necessary to consider the strategy for prophylaxis, or prevention. According to ESHRE revised guidelines in 2014, it has been recommended that all clinicians prescribe, to their post-operative patients, hormone-based contraceptives within the 6-month period following surgery, in an effort to obviate recurrence of the signs and symptoms of recurrent endometrioma [13].

Although dienogest (2 mg once daily), a fourth-generation progestin, has been implemented and thought to be useful by clinical trial for its long-term use (up to 65 weeks) in the treatment of endometriosis [14,15], there is still lack supportive evidence to approve the safety, efficacy, higher compliance and lower withdrawal rate for long-term use of dienogest.

Therefore, the present study was conducted to investigate the clinical experience of long-term use of dienogest after surgery for ovarian endometrioma.

**Materials and methods**

This study was conducted retrospectively on 203 patients who underwent laparoscopic or robotic surgery for ovarian endometrioma and subsequent treatment with dienogest (2 mg/day) at the Department of Obstetrics and Gynecology, Ewha Womans University Mokdong Hospital. The surgeries were performed by 4 experienced gynecologic surgeons. The enrolled study population had been prescribed dienogest from July 2013 through February 2016.

All patients were reproductive-aged women with regular menstruation and did not want to get pregnant promptly after surgery. The size of the ovarian endometriomas were varied, and when there were multiple ovarian endometriomas, the mean diameter was measured with the largest and total diameter of cysts by ultrasonography. All ovarian endometriomas seen during surgery were removed and combined pelvic adhesions were dissected. The stage of endometriosis was defined by revised American Society for Reproduction Medicine (rASRM) classification during operation and the diagnosis was confirmed by final histopathology. The patients who were tolerable for gonadotropin releasing hormone (GnRH) agonist were injected it monthly for the time as possible up to 6 months before administration of dienogest.

Baseline characteristics of patients were analyzed and the patients prescribed dienogest (2 mg/day) were seen tri-monthly thereafter, to evaluate for possible side effects. Ad-
verse events were investigated at all visits at the discretion of her doctor during and after treatment of dienogest.

Clinical characteristics of patients were compared between continued dienogest group and discontinued dienogest group. The long-term use was defined treatment for 6 months and more, otherwise, the discontinued group was discriminated a group that stopped before 6 months of starting medication.

Transvaginal or transrectal ultrasound obtained every 6 months, to detect recurrence of endometrioma (≥2 cm). The visualization of round-shaped homogeneous hypoechoic cyst of low-level echoes within the ovary was defined as characteristic ultrasonographic finding of endometrioma.

Statistical analysis was performed using IBM SPSS Statistics version 20 (SPSS Japan Inc., Tokyo, Japan). A Student’s t-test and an χ² test were used and 2-tailed P-values of <0.05 were considered to be significant.

This study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital.

### Results

The follow-up observation periods were 30.2±20.9 months from surgery for ovarian endometrioma. The mean age was 34.1±7.2 years old (range, 18 to 53 years) and body mass index was 20.8±3.0 kg/m². One sixty-one (79.3%) of patients were nulliparous women. The mean diameter of pre-operative endometrioma was 5.6±3.0 cm². Before surgery, serum cancer antigen (CA) 125, CA 19-9, and AMH levels were measured 113.4±428.6 U/mL, 44.1±116.3 U/mL, and 4.4±3.4 ng/mL, respectively. Sixty-nine point five percent of patients had unilocular type of endometrioma and 30.5% were multilocular ovarian cysts. Fifty-three point seven percent were unilateral endometrioma and 46.3% of patients had bilateral cysts. Sixty-nine percent of patients had documented presence of deep infiltrating endometriosis (DIE) according operation finding.

Of the total, 182 (89.7%) of the women received dienogest continuously for 12.0±7.1 months (range, 6 to 35 months) and 21 (10.3%) patients stopped at 2.4±1.0 months (range, 1 to 4 months). Clinical characteristics of patients were then compared between continued group and discontinued group (Table 1) and the following was noted.

### Table 1. Clinical characteristics of patients according to continuation of dienogest

| Characteristics                        | Continuous use (n=182) | Discontinuation (n=21) | P-value |
|----------------------------------------|------------------------|------------------------|---------|
| Age (yr)                               | 33.8±7.1               | 36.9±8.1               | 0.100   |
| BMI (kg/m²)                            | 20.7±2.9               | 21.4±4.0               | 0.406   |
| Pre-operative blood test               |                        |                        |         |
| CA 125 (U/mL)                          | 120.1±451.3           | 52.8±37.3              | 0.075   |
| CA 19-9 (U/mL)                         | 46.4±122.7            | 23.9±12.2              | 0.035   |
| AMH (ng/mL)                            | 4.5±3.4               | 3.6±3.2                | 0.484   |
| Diameter of endometrioma (cm)          | 5.6±3.0               | 5.6±2.8                | 0.953   |
| Type of endometrioma                   |                        |                        |         |
| Unilocular                             | 127 (62.6)            | 14 (6.9)               | 0.769   |
| Multilocular                           | 55 (27.1)             | 7 (3.4)                |         |
| Laterality of endometrioma             |                        |                        | 0.029   |
| Unilaterial                            | 93 (45.8)             | 16 (7.9)               |         |
| Bilateral                              | 89 (43.8)             | 5 (2.5)                |         |
| Presence of DIE                        |                        |                        | 0.450   |
| Absent                                 | 58 (28.6)             | 5 (2.4)                |         |
| Present                                | 124 (61.1)            | 16 (7.9)               |         |
| Post-operative GnRH agonist (mon)      | 3.7±2.5               | 2.8±2.7                | 0.170   |

Values are presented as mean±standard deviation or number (%).

BMI, body mass index; CA, cancer antigen; AMH, anti-Müllerian hormone; DIE, deep infiltrating endometriosis; GnRH, gonadotropin releasing hormone.
In continued dienogest group, the serum CA 19-9 level was significantly higher and the discontinuation rate was significantly lower in patients operated for bilateral endometriomas. The most common side effect, following discontinuation, was abnormal uterine bleeding. The occurrence rate of vaginal bleeding was 15.8%, which did not differ significantly in patients with/without post-operative GnRH agonist administration. One hundred forty-seven patients (72.4%) were injected GnRH agonists for 3.6±2.5 months before dienogest medication.

The other reported side effects included gastrointestinal trouble, constipation, depression, weight gain, edema, hot flashes, headache, and acne (Table 2). However, no serious side effects were documented.

The follow-up periods between recurrence and last dienogest treatment were 5.7±7.4 months. Three patients (1.5%) were diagnosed with recurrence of endometrioma. These patients had previously undergone surgeries which included laparoscopic ovarian cystectomies for bilateral and multilocular endometriomas with DIE relevant to stage IV by rASRM classification (Table 3). For all these patients, repeated surgery has not been performed. A couple of recurrent endometriomas decreased after dienogest re-administration for 6 months. The third patient has been treated for infertility to get pregnant instead of re-operation or medication of dienogest.

### Discussion

Due to increased post-operative recurrence rate of endometrioma and its related complications, a plan for prophylaxis which is to say, secondary prevention, is necessary to improve quality of life and enhance fertility of those suffering from chronic endometriosis. Usually, surgical re-intervention for

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**Table 2. Side effects of dienogest treatment**

| Side effects            | Occurrence rate |
|-------------------------|-----------------|
| Uterine bleeding        | 32 (15.8)       |
| GI trouble/constipation | 6 (3.0)         |
| Depression              | 6 (3.0)         |
| Weight gain/edema       | 5 (2.5)         |
| Hot flashes             | 5 (2.5)         |
| Headache                | 4 (2.0)         |
| Acne                    | 1 (0.5)         |

Values are presented as number (%). GI, gastrointestinal.

**Table 3. Three cases diagnosed as recurrence of endometrioma**

| Cases                              | 1                        | 2                      | 3                        |
|------------------------------------|--------------------------|------------------------|--------------------------|
| Sonographic findings of recurrent endometrioma (side/mean diameter, cm) | Right/2.1                | Left/2.0               | Left/3.4                 |
| Age (yr)                           | 34                       | 33                     | 30                       |
| Method of surgery                  | LOC                      | LOC                    | LOC                      |
| Duration of dienogest (mon)        | 18                       | 6                      | 9                        |
| Period between recurrence and last dienogest treatment (mon) | 6                        | 6                      | 0                        |
| Side effects of dienogest          | Depression               | Weight gain            | None                     |
| Post-operative GnRH agonist (mon)  | 3                        | 6                      | 6                        |
| Pre-operative blood test           |                           |                        |                          |
| CA 125 (U/mL)                      | 5,489                    | 29.6                   | 43.7                     |
| CA 19-9 (U/mL)                     | 945.3                    | 17.7                   | 41                       |
| AMH (ng/mL)                        | 3.88                     | 7.48                   | 5.7                      |
| Diameter of the previous endometrioma (cm) | 14.0                     | 7.5                    | 9.1                      |
| Type of endometriomas              | Multilocular             | Multilocular           | Multilocular             |
| Laterality of endometrioma         | Bilateral                | Bilateral              | Bilateral                |
| Presence of DIE                    | Present                  | Present                | Present                  |
| Stage of rASRM classification      | IV                       | IV                     | IV                       |

LOC, laparoscopic ovarian cystectomy; GnRH, gonadotropin releasing hormone; CA, cancer antigen; AMH, anti-Müllerian hormone; DIE, deep infiltrating endometriosis; rASRM, revised American Society for Reproduction Medicine.
recurrent endometrioma serves to produce greater loss of ovarian tissue and markedly decreased ovarian reserve [12]. Therefore, the risk of infertility increases and long-term medical therapy is the best option for prevention of recurrence.

Although several hormonal therapies are available, no consensus has been established as to which medication is the best option for long-term prevention of recurrence. Though oral contraceptive pills (OCPs) widely used is associated with several side effects, resistance to long-term therapy and has high rate of recurrence (55%) after discontinuation [16]. Danazol is not preferred as it causes masculinizing side effects including weight gain, edema, acne, vaginal dryness, hot flashes, hirsutism, liver toxicity, and breast atrophy. GnRH agonists are frequently used by many clinicians but are associated with accelerated loss of bone mineral density (BMD) causing osteoporosis. In absence of add back therapy their use is thus limited up to 6 months [17]. It also causes hot flashes and vaginal dryness, and these adverse symptoms are sometimes felt to be intolerable by those so afflicted. A number of progestins offer long-term efficacy but cause weight gain and androgenic effect at high doses [18].

Therefore, we need a medication that has minimal side effects, higher compliance and can be used as long-term therapy. One might consider dienogest with its tolerable profile, higher rate of patient compliance, low problematic withdrawal rate and safe for long-term use, it was chosen for the present study [17]. Strowitzki et al. [19] showed the results that dienogest can be safely used over a period extending up to 65 weeks.

In the present study, we found that rate of recurrence with dienogest therapy was only 1.5%. Our findings are comparable to the study of Ouchi et al. [13] who reported that no recurrence was seen in continual dienogest group whereas 25% recurrence was noted in GnRH group and 55.5% after discontinuation of OCP.

Our 3 patients with recurrence were in young age less than 35 years. Ouchi et al. [13] reported similar results, suggesting that the disease is more aggressive in young patients and with a higher rate of recurrence [20]. This perhaps explains why youth is considered an actual a risk factor, and greater effort should be made to obviate recurrence of the pathology in youthful patients after surgery.

Of the group studied, 89.7% of the women received dienogest continuously for 12.0±7.1 months without complaint of any intolerable symptoms, while 10.3% patients stopped at 2.4±1.0 months. Hence patient’s acceptance for dienogest therapy was fairly good. The medical indication for discontinuation can be explained by irregular bleeding (15.8%) and change of planning for conception. Unexpected irregular bleeding was common and troublesome side effect. Constipation (3.0%), depression (3.0%), weight gain (2.5%), hot flashes (2.5%), headache (2.0%), and acne (0.5%) were also noted but were minimal and did not adversely affect the quality of life. Takaesu et al. [17] reported that side effects were notably seen in GnRH agonist group as compared to dienogest group. In the dienogest group 100% of the patients had irregular bleeding but all were mild (i.e., spotting), and none developed anemia. Marked side-effects were observed in the goserelin group, when compared to the dienogest group [19].

We observed that in continued dienogest group, serum CA 19-9 level was significantly higher and discontinuation rate was significantly lower in patients operated for bilateral endometriomas. Endometriosis is significantly associated with elevated serum CA 125 and CA 19-9 concentrations, and CA 19-9 is increased further in the more advanced stages of disease. Serum CA 125 and CA 19-9 may represent useful biomarkers for the noninvasive diagnosis of endometriosis [21-23]. This relation could be explained that the patients with increased risk of recurrence might accept uncritically the post-operative medical treatment for prevention [24,25].

It was also noted that all recurrent endometriomas were bilateral, multicellular, associated with DIE and stage IV by rASRM classification.

The major strength of this study is that follow-up observation period extended over 30.2±20.9 months from surgery till recurrence of ovarian endometrioma. As other previous studies, our study has some limitations. This study was based on the results of small numbers in a single-center. The data from retrospective chart review lacks description of some clinical outcomes and the nature and duration of reported side effects might have been under-estimated. The change of endometriosis-associated pain using a visual analog scale and BMD could not be compared because the results were inadequate, depending on clinicians although long-term treatment with dienogest which seems effective in reducing pain and possible bone loss [26].

In the present study, we did not divide laparoscopic or robotic surgery. The meticulous surgical technique could provide complete destruction of endometriotic lesions to decrease the recurrence rate as well as preserving the remained ovarian re-
We suggest the clinical experience of post-operative long-term use of dienogest, which was safe and tolerable prevention to avoid reoperation for recurrence of ovarian endometrioma. Therefore, therapeutic application of dienogest could be extended for a longer time until the patient desires to become pregnant. Further studies are warranted to establish up to what age long-term dienogest therapy can be given in patients effectively.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Rogers PA, D’Hooghe TM, Fazleabas A, Gargett CE, Giudice LC, Montgomery GW, et al. Priorities for endometriosis research: recommendations from an international consensus workshop. Reprod Sci 2009;16:335-46.
2. Allen C, Hopewell S, Prentice A. Non-steroidal anti-inflammatory drugs for pain in women with endometriosis. Cochrane Database Syst Rev 2005:CD004753.
3. D’Hooghe TM. Endometriosis. In: Berek JS, Novak E. Berek & Novak’s gynaecology. 15th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2012. p.505-56.
4. Liu X, Yuan L, Shen F, Zhu Z, Jiang H, Guo SW. Patterns of and risk factors for recurrence in women with ovarian endometriomas. Obstet Gynecol 2007;109:1411-20.
5. Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometrioma. Cochrane Database Syst Rev 2008:CD004992.
6. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update 2009;15:441-61.
7. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D’Hooghe T, De Bie B, et al.ESHRE guideline: management of women with endometrioma. Hum Reprod 2014;29:400-12.
8. Leyland N, Casper R, Laberge P, Singh SS; SOGC. Endometriosis: diagnosis and management. J Obstet Gynaecol Can 2010;32:51-32.
9. Rizk B, Turki R, Lotfy H, Ranganathan S, Zahed H, Freeman AR, et al. Surgery for endometriosis-associated infertility: do we exaggerate the magnitude of effect? Facts Views Vis Obgyn 2015;7:109-18.
10. Ferrero S, Scala C, Racca A, Calannii L, Remorgida V, Venturini PL, et al. Second surgery for recurrent unilateral endometriomas and impact on ovarian reserve: a case-control study. Fertil Steril 2015;103:1236-43.
11. Roustan A, Perrin J, Debals-Gonthier M, Paulmyer-Lacroix O, Agostini A, Courbiere B. Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of in vitro fertilization outcome. Hum Reprod 2015;30:840-7.
12. Muzii L, Achilli C, Leccce F, Bianchi A, Franceschetti S, Marchetti C, et al. Second surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery. Fertil Steril 2015;103:738-43.
13. Ouchi N, Akira S, Mine K, Ichikawa M, Takeshita T. Recurrence of ovarian endometrioma after laparoscopic excision: risk factors and prevention. J Obst Gynaecol Res 2014;40:230-6.
14. Köhler G, Faustmann TA, Gerlinger C, Seitz C, Mueck AO. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. Int J Gynaecol Obstet 2010;108:21-5.
15. Schindler AE. Dienogest in long-term treatment of endometriosis. Int J Womens Health 2011;3:175-84.
16. Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbarra G, Fedele L. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reprod Biomed Online 2010;21:259-65.
17. Takaesu Y, Nishi H, Kojima J, Sasaki T, Nagamitsu Y, Kato R, et al. Dienogest compared with gonadotropin-releasing hormone agonist after conservative surgery for endometriosis. J Obstet Gynaecol Res 2016;42:1152-8.
18. Vercellini P, Fedele L, Pietropaolo G, Frontino G, Somigliana E, Crosignani PG. Progestogens for endometriosis: forward to the past. Hum Reprod Update 2003;9:387-96.
19. Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. Int J Womens Health 2015;7:393-401.
20. Sengoku K, Miyamoto T, Horikawa M, Katayama H, Nishiwaki K, Kato Y, et al. Clinicopathologic risk fac-
tors for recurrence of ovarian endometrioma following laparoscopic cystectomy. Acta Obstet Gynecol Scand 2013;92:278-84.

21. Somigliana E, Viganò P, Tirelli AS, Felicetta I, Torresani E, Vignali M, et al. Use of the concomitant serum dosage of CA 125, CA 19-9 and interleukin-6 to detect the presence of endometriosis. Results from a series of reproductive age women undergoing laparoscopic surgery for benign gynaecological conditions. Hum Reprod 2004;19:1871-6.

22. Harada T, Kubota T, Aso T. Usefulness of CA19-9 versus CA125 for the diagnosis of endometriosis. Fertil Steril 2002;78:733-9.

23. Shen A, Xu S, Ma Y, Guo H, Li C, Yang C, et al. Diagnostic value of serum CA125, CA19-9 and CA15-3 in endometriosis: a meta-analysis. J Int Med Res 2015;43:599-609.

24. Guzel AI, Topcu HO, Ekilinc S, Tokmak A, Kokanali MK, Cavkaytar S, et al. Recurrence factors in women underwent laparoscopic surgery for endometrioma. Minerva Chir 2014;69:277-82.

25. Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, et al. Recurrence of ovarian endometrioma after laparoscopic excision. Hum Reprod 2006;21:2171-4.

26. Park SY, Kim SH, Chae HD, Kim CH, Kang BM. Efficacy and safety of dienogest in patients with endometriosis: a single-center observational study over 12 months. Clin Exp Reprod Med 2016;43:215-20.