Accepted Manuscript

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PII: S0301-2115(17)30346-9
DOI: http://dx.doi.org/doi:10.1016/j.ejogrb.2017.07.014
Reference: EURO 9984

To appear in: *EURO*

Received date: 30-4-2017
Revised date: 1-7-2017
Accepted date: 9-7-2017

Please cite this article as: Yamanaka Akiyoshi, Hada Tomonori, Matsumoto Tsuyoshi, Kanno Kiyoshi, Shirane Akira, Yanai Shiori, Nakajima Saori, Ebisawa Keiko, Ota Yoshiaki, Andou Masaaki.Effect of dienogest on pain and ovarian endometrioma occurrence after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis.*European Journal of Obstetrics and Gynecology and Reproductive Biology* http://dx.doi.org/10.1016/j.ejogrb.2017.07.014

Effect of dienogest on pain and ovarian endometrioma occurrence after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis

Word count: Main text: 2105 words

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Consendation

Effect of dienogest after surgery with deep infiltrating endometriosis.

Abstract

Objectve: To evaluate the effect of dienogest (DNG) in preventing the occurrence of pain and endometriomas after laparoscopic resection of uterosacral ligaments (USLs) with deep infiltrating endometriosis (DIE).

Study design: This retrospective analysis included 126 patients who underwent laparoscopic resection of USLs with DIE followed by postoperative administration of DNG or no medication. Every 6 months postoperatively, patients answered questions and underwent ultrasound examination to identify pain and/or endometrioma.

Result: There were three (5.0%) cases of endometrioma in 59 patients from the DNG group and 21 (31.3%) cases in 67 patients from the no medication group (P = .0002). Pain returned to preoperative levels in eight (11.9%) cases in the no medication group. No recurrence of pain occurred in the DNG group (P = .0061).

Conclusion: The administration of DNG after resection of USLs with DIE significantly reduces the occurrence rate of endometriosis-related pain and endometriomas.

Keywords: dienogest; occurrence of pain; endometriomas; uterosacral ligaments; endometrioma occurrence

Introduction

Deep infiltrating endometriosis (DIE) is a form of endometriosis in which pathologic tissue can penetrate up to 5 mm under the surface of the affected structure (1). These lesions are considered very active and are strongly associated with pelvic pain. The incidence of DIE is reported to be 20% in all cases of endometriosis, with uterosacral ligaments (USLs) representing the most frequent location (2). Somigliana *et al.* reported that DIE occurs without disease at other sites in only 6.5% of patients (3). Surgical therapy in patients with endometriosis is effective for relieving pelvic pain, dyspareunia, painful defecation, and lower urinary tract symptoms. DIE is also required for complete excision of lesions to reduce endometriosis-related symptoms (4).

Busacca *et al.* reported that the postoperative recurrence rates of endometriosis were 30% and 43% at 4- and 8-years, respectively (5). Other reports have shown that symptom recurrence requiring reoperation is common and worsens over time: 21.5% at 2 years and 40–50% after 5 years (6, 7). Several randomised trials have reported that postoperative hormonal therapy increases the duration of pain relief and delays recurrence (8, 9, 10). Oral progestin therapy is safe and well tolerated (11). However, few studies have investigated the effect of progestin on the postoperative recurrence of endometriosis.

In the present study, we investigated the efficacy of long-term administration of a synthetic progestin, dienogest (DNG), in preventing pelvic pain or ovarian endometrioma occurrence after laparoscopic resection of USLs with DIE.

Materials and Methods

In total, 1,666 patients underwent laparoscopic surgery for endometrioma- or endometriosis-related pain at Kurashiki Medical Center between January 2008 and December 2013. Of these, 298 underwent laparoscopic resection of USLs with DIE during surgery.

Preoperatively, all patients had undergone magnetic resonance imaging (MRI) or ultrasound examination to confirm the presence of endometriosis lesions. In the present study, we included only patients who had DIE in USL and excluded patients who did not have other locations of DIE. Patients were excluded from the study if they underwent bilateral oophorectomy or surgery to remove both ovaries along with other procedures. Patients were also excluded if none of their medical records indicated their pain levels according to the visual analogue scale (VAS) and if they were receiving hormonal therapy for at least 3 months preoperatively or any other hormonal drugs postoperatively. The indication for surgery in patients who did not undergo preoperative hormonal therapy was the existence of endometriomas or predicted existence of obvious adhesions. Thus, 126 patients were analysed retrospectively. Patients were followed for at least 6 months. The average follow-up duration was 32 ± 16.3 months. The study was approved by the ethics committee of the Kurashiki Medical Center and written *informed consent was obtained* in *all cases*. All surgical procedures were carried out by the same investigator (Masaaki Andou) and the same protocol was used in all cases. All laparoscopic surgeries were performed under general anaesthesia in the dorsal lithotomy position. Patients were scored according to the r-ASRM classification of endometriosis during laparoscopy. First, we removed adhesions around the ovaries to return the ovaries to their correct anatomical location. After endometrioma rupture, the cyst wall was stripped using scissors to make it as thin as possible without removing normal ovarian tissue. The diagnosis of DIE in USLs was made during surgery and was based on the macroscopic appearance of the lesion, which was a palpable nodule or induration, or a dark blue nodule visible at the ULSs. After identifying the ureter, we displaced it as laterally as possible. Next, we opened the perirectal space bilaterally and made clearly outlined the rectum to clearly reveal the shape of the USLs. Finally, we removed the USLs with DIE. DIE was histologically proven in the presence of endometrial glands and the stroma. Pathological

examination confirmed the clinical diagnoses of endometriosis, endometriomas, and DIE in USLs in all cases.

Postoperatively, all patients were informed about the risk of endometriosis recurrence, and DNG was offered to provide potential prophylaxis. Fifty-nine patients accepted DNG, while 67 patients declined this treatment because they wished to become pregnant. The DNG group included patients who took 2 mg of DNG (Dienogest; Mochida Pharmaceutical, Tokyo, Japan) every day. Postoperative hormonal treatment was initiated from the first menstruation occurring at least 2 weeks postoperatively. The average duration of administration was 31 ± 17.6 months. About 1 month postoperatively, transvaginal ultrasonographic scans were performed in all patients to exclude subjects with persistent ovarian endometriomas. As part of the follow-up assessment, patients were asked about their pain levels based on a 10-point VAS for pain (i.e. dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and dyschezia) and whether occurrence of endometrioma had occurred. All patients underwent clinical and transvaginal ultrasonographic examination and were questioned about pain every 6 months to assess for the possible occurrence of pain and endometrioma. Pain recurrence was defined as the same severity of pain as that experienced preoperatively on the 10-point VAS. The occurrence of endometriosis-related symptomatic pain (i.e. dysmenorrhea, non-menstrual pelvic pain, dyspareunia, and dyschezia) was defined when patients had pain that scored > 4 points on the 10-point VAS. We defined non-menstrual pelvic pain as the pain not limited particular period like ovulation or before menstruation. A previous report defined the occurrence of endometrioma as the presence of a persistent ovarian cyst with a minimum diameter of > 15 mm based on non-invasive imaging (e.g. ultrasound and MRI) (12). We also defined the occurrence of endometrioma in the same way as in this previous report. Moreover, we used MRI to define the occurrence of endometrioma.

Statistical Analysis

The Mann-Whitney U-test was used to compare means values between the two groups, and the chi-square test was used to compare proportions between the two groups. The first occurrence rate of endometriosis-related symptoms (VAS score ≥ 4) and endometriomas were analysed using Kaplan-Meier survival analysis and the log-rank test. For all tests, $P < .05$ was considered statistically significant.

Results

The demographic and treatment data for the 126 patients are presented in Table 1. There were no significant differences between the two groups in terms of age, nulliparity, and parity. The revised American Society for Reproductive Medicine (ASRM) score was significantly higher in the DNG group ($P = .047$) than that in the no medication group. The number of patients with stage I–II endometriosis was significantly larger in the no medication group ($P = .046$) than that in the DNG group. Seven of 9 patients with stage I-II in the no medication group aged over 40. However, there were no significant differences in stage-III or -IV endometriosis between the two groups. There were no significant differences in the incidence of bilateral endometriomas and endometriosis in USLs between the two groups.

At the end of the observation period, 21 (31.3%) of 67 patients with endometriomas in the no medication group had an occurrence confirmed through MRI and transvaginal ultrasound examination. Endometriomas were observed in three (5.0%) of 59 patients in the DNG group ($P = .0002$). Pain recurrence at the same level preoperatively was observed in eight (11.9%) patients in the no medication group, and no patients had pain recurrence at the same level preoperatively in the DNG group ($P = .0095$) (Figure 1). The incidences of all endometriosis-related symptoms were not statistically significantly different between the two groups, except for dysmenorrhea ($P < .0001$) (Table 2). In both groups, no cases of pain

occurred in patients who had no pain preoperatively. The mean observation periods were 28 ± 1.7 months and 35 ± 2.1 months in the no medication group and DNG group, respectively.

The prevalence of endometriomas in the no medication group and DNG group were 0.172 ± 0.047 and 0.035 ± 0.24 at 2 years, 0.531 ± 0.122 and 0.077 ± 0.47 at 5 years. The rate was significantly lower in the DNG group than in the no medication group (log-rank test, $P < .05$) (Figure 2). The prevalence of endometriosis-related symptoms in the no medication group and DNG group were 0.369 ± 0.063 and 0.061 ± 0.034 at 2 years, and 0.726 ± 0.104 and 0.133 ± 0.076 at 5 years. The rate was significantly lower in the DNG group than that in the no medication group (log-rank test, $P < .01$) (Figure 3).

Comment

The present study showed that the occurrence rate of endometriosis-related pain and endometriomas after undergoing laparoscopic resection of USLs with DIE was significantly decreased in patients who received hormonal treatment with DNG postoperatively and were followed for > 6 months. The prevalence of endometriosis-related pain and endometriomas were significantly lower in the DNG group than those in the no medication group. Moreover, the prevalence of endometriosis-related pain (VAS score ≥ 4) was significantly lower in the DNG group than that in the no medication group.

DNG is an oral progestin that has been investigated systematically for treating endometriosis in many countries. DNG binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule. The pharmacological mechanisms of DNG may include antiovulatory activity, resulting in reduced serum estradiol levels, and direct antiproliferative and anti-inflammatory effects on endometriotic cells (13, 14). Dienogest modulated prostaglandin production and metabolism (PGE2, PGE2 synthase, cyclooxygenase-2, and microsomal PGE

synthase-1) in a way that is anti-inflammatory and inhibited growth of endometriotic tissue by reducing the growth factors (vascular endothelial growth factor and nerve growth factor) (15).

DNG has been reported to be effective in relieving patient-reported symptoms, including the intensity of dysmenorrhea, dyspareunia, and chronic pelvic pain in some clinical trials (16, 17). Furthermore, in a previous study, the prevalence of endometriomas 5 years postoperatively decreased more in the DNG group than in the no postoperative medication group (69% vs. 4%; odds ratio: 0.09; 95% confidence interval: 0.03–0.26; $P < .0001$) (18). However, few reports have indicated that DNG prevents the occurrence of endometriosis-related pain and endometriomas after the resection of DIE. DIE lesions are multifocal in numerous patients, and they are observed in the bladder, USLs, vagina, intestine, and colon. However, USLs are the most common location of DIE (52.1–65.6%) (19, 20).

In the present study, we also assessed whether the postoperative administration of DNG is useful for preventing endometriosis-related pain and endometrioma occurrence after laparoscopic resection of USLs with DIE. To the best of our knowledge, this is the first study to evaluate the efficacy of using DNG postoperatively to prevent endometriosis-related pain or endometriomas occurrence after laparoscopic resection of USLs with DIE.

Hormonal treatment of DIE with progestins or estroprogestins is effective in endometriosis-related pain in > 90% of patients (21). Therefore, hormonal therapy should be considered as the first-line treatment of DIE-associated pain in women who do not wish to become pregnant. However, hormonal treatment is ineffective or intolerable in approximately 30% of women, with the most common side effects being erratic bleeding, weight gain, decreased libido, and headache (22). Surgical resection of DIE is mandatory in the presence of symptomatic bowel stenosis, ureteral stenosis with secondary hydronephrosis, and when hormonal treatments fail. Surgical treatment is as effective as hormonal treatment in relieving

dysmenorrhoea, dyspareunia, and dyschezia associated with DIE. Surgical resection of the nodules may require resection of the bowel, ureter, or bladder, with possible severe complications such as rectovaginal or ureterovaginal fistula and anastomotic leakage. The patient should be thoroughly counselled in order to determine a therapeutic plan centred not on the endometriotic lesions themselves, but on the patient's symptoms, priorities, and expectations. In the present study, almost all patients experienced temporary improvement of pain immediately after surgery in the no medication group. However, many patients experienced an occurrence of endometriosis-related pain after surgery. Because of the risk of recurrence, endometriosis surgery without postoperative hormonal treatment should not be performed even if the resection of DIE performed.

Our study has some limitations. First, this was a retrospective study, and the results were limited by a lack of random assignment, patient selection, and incomplete data acquisition, although prospectively maintained databases were used. Second, the number of patients in the retrospective cohorts was insufficient to generalize the results to the general population.

In conclusion, there is a possibility that the administration of DNG is effective for reducing endometriosis-related pain and the occurrence of endometrioma after resection of DIE. However, this was a small retrospective study, and not a randomised control study. A prospective randomised control study is needed in order to clarify the effect of DNG after laparoscopic resection of USLs with DIE.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgements

We thank the entire staff of Kurashiki Medical Center for their valuable help in completing this study.

References

(1) Vercellini P, Frontino G, Pietropaolo G, Gattei U, Daguati R, Crosignani PG. Deep endometriosis: definition, pathogenesis, and clinical management. J Am Assoc Gynecol Laparosc 2004; 11: 153-61.

(2) Fauconnier A, Chapron C, Dubuisson JB, Vieira M, Dousset B, Bréart G. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil Steril 2002; 78: 719-26.

(3) Somigliana E, Infantino M, Candiani M, Vignali M, Chiodini A, Busacca M. Association rate between deep peritoneal endometriosis and other forms of the disease: pathogenetic implications. Hum Reprod 2004; 19: 168-71.

(4) Cao Q, Lu F, Feng W, Ding J, Hua K. Comparison of complete and incomplete excision of deep infiltrating endometriosis. Int J Clin Exp Med 2015: 8(11): 21497-506

(5) Busacca M, Chiaffarino F, Candiani M, et al. Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. Am J Obstet Gynecol 2006: 195: 426-32.

(6) Weir E, Mustard C, Cohen M, Kung R. Endometriosis: what is the risk of hospital admission, readmission, and major surgical intervention? J Minim Invasive Gynecol 2005; 12: 486-93.

(7) Vercellini P, Crosignani PG, Abbiati A, Somigliana E, Viganò P, Fedele L. The effect of surgery for symptomatic endometriosis: the other side of the story. Hum Reprod Update 2009; 15: 177-88.

(8) Vercellini P, Crosignani PG, Somigliana E, Berlanda N, Barbara G, Fedele L. Medical treatment for rectovaginal endometriosis: what is the evidence? Hum Reprod 2009; 24: 2504-14.

(9) Seracchioli R, Mabrouk M, Frascà C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril 2010: 94: 464-71.

(10) Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014; 29: 400-12.

(11) 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.

(12) Seracchioli R, Mabrouk M, Frascà C, et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil Steril 2010: 93: 52-56.

(13) Fu L, Osuga Y, Morimoto C, et al. Dienogest inhibits BrdU uptake with G0/G1 arrest in cultured endometriotic stromal cells. Fertil Steril 2008; 89: 1344-47.

(14) Yamanaka K, Xu B, Suganuma I, et al. Dienogest inhibits aromatase and cyclooxygenase-2 expression and prostaglandin E_2 production in human endometriotic stromal cells in spheroid culture. Fertil Steril 2012; 97: 477-82.

(15) Bedaiwy MA, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. Fertil Steril 2017; 107(3): 537-48.

(16) 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: 21-25.

(17) Harada T, Taniguchi F. Dienogest: a new therapeutic agent for the treatment of endometriosis. Women Health 2010; 6: 27-35.

(18) Ota Y, Andou M, Yanai S, et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. J Endometr Pelvic Pain Disord 2015; 7: 63-67.

(19) Chapron C, Fauconnier A, Vieira M, et al. Anatomical distribution of deeply infiltrating endometriosis: surgical implications and proposition for a classification. Hum Reprod 2003; 18: 157-61.

(20) Chapron C, Chopin N, Borghese B, et al. Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution. Hum Reprod 2006; 21: 1839-45.

(21) Berlanda N, Sonigliana E, Frattaruolo MP, Buggio L, Dridi D, Vercellini P. Surgery versus hormonal therapy for deep endometriosis: is it a choice of the physician? Eur J Obstet Gynecol Reprod Biol. 2017; 209:67-71.

(22) Vercellini P, Somigliana E, Consonni D, Frattaruolo MP, De Giorgi O, Fedele L. Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction. Hum Reprod 2012; 27:3450–9.

Figure Legends

Figure 1. Prevalence of pain at the same level as preoperatively after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis

DNG, dienogest

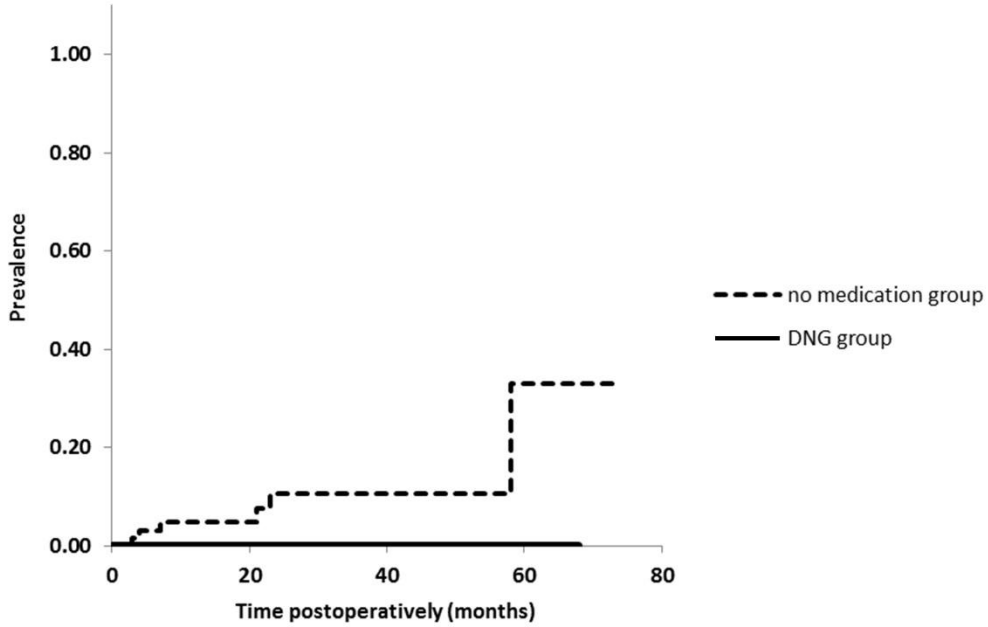
Figure 2. Prevalence of endometriomas after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis

DNG, dienogest

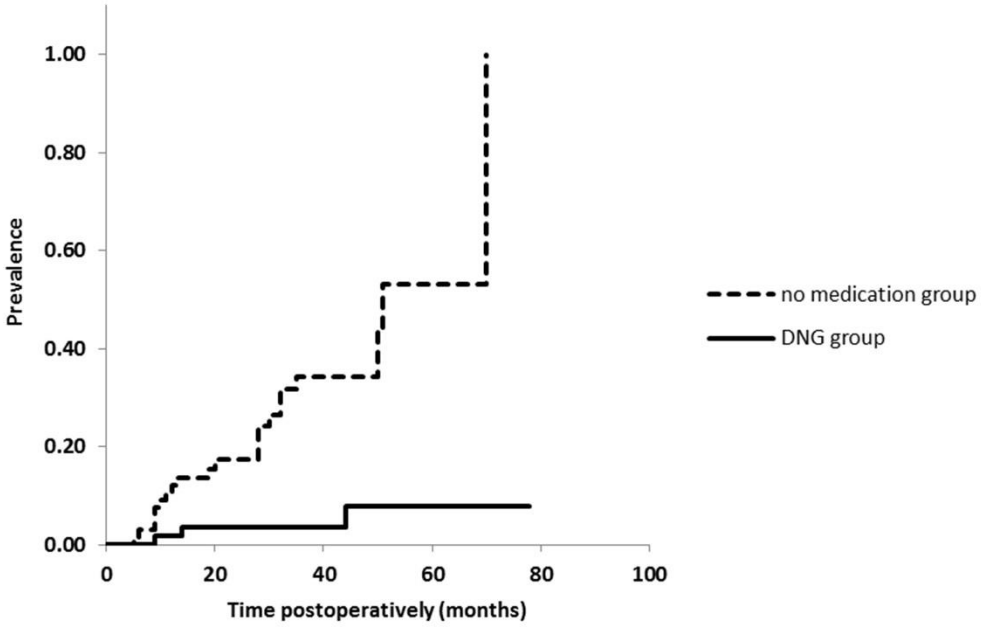
Figure 3. Prevalence of endometriosis-related pain (visual analogue scale score ≥4) after laparoscopic resection of uterosacral ligaments with deep infiltrating endometriosis

DNG, dienogest

Figr-1



Figr-2



Figr-3

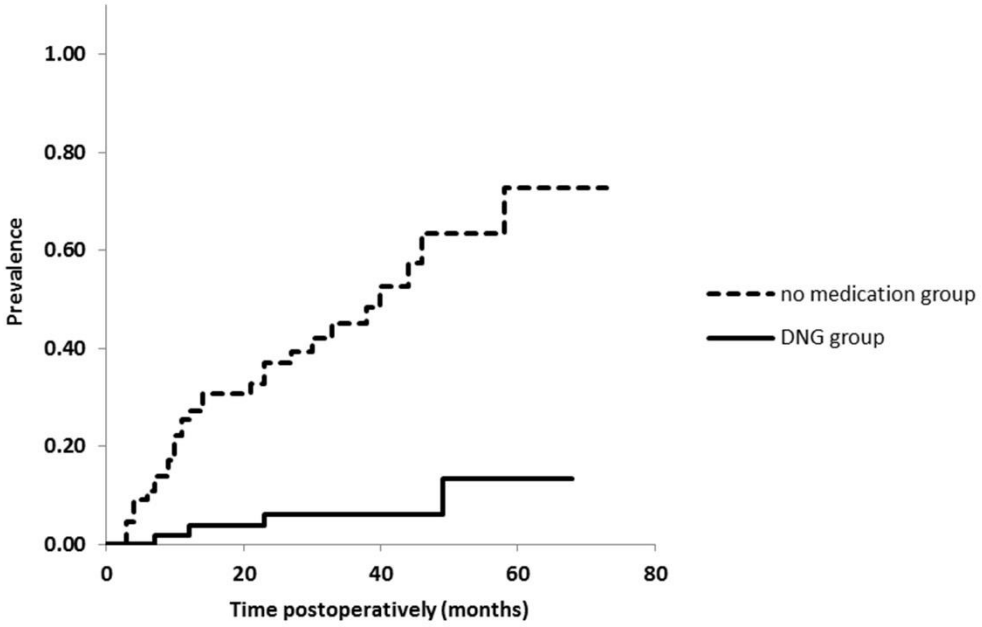


Table I. Patients' demographic data

	No medication group (%)	DNG group (%)	*P*-value
Number of patients	67	59	
Age (years), mean ± SE	36 ± 5.9	35 ± 6.8	.398
Nulliparous	40	41	.252
Parous	27	11	.0304
Infertile	11 (16.4)	1 (1.6)	.005
r-ASRM score, mean ± SD	54 ± 30.5	70 ± 28.2	.047
Stage of endometriosis			
I–II	9	2	.0463
III	16	13	.8059
IV	42	44	.1525
Presence of endometriomas	49 (73.1)	57 (96.6)	.0003
Bilateral endometriomas	16 (23.8)	19 (32.2)	.298
Bilateral presence of endometriosis in USL	47 (70.1)	43 (72.8)	.7348
Operative procedures			
Hysterectomy	16 (23.8)	9 (15.2)	.1944
Monolateral oophorectomy	16 (23.8)	16 (27.1)	.7504
Monolateral cystectomy	25 (37.3)	24 (40.6)	.6991
Bilateral cystectomy	17 (25.3)	18 (30.5)	.5208
Symptoms preoperatively			

Dysmenorrhea	57 (85.0)	44 (74.5)	.1404
Non-menstrual pelvic pain	23 (34.3)	11 (18.6)	.0478
Dyspareunia	8 (11.9)	3 (5.0)	.1737
Dyschezia	5 (7.4)	5 (8.4)	.0833

SE, standard deviation; r-ASRM, revised American Society for Reproductive Medicine; USL, uterosacral ligament

Table II. Recurrence of endometriosis-related pain and endometriomas

	No medication group (%)	**DNG group (%)**	***P*-value**
Number of patients	67	59	
Duration of observation (months, means ± SD)	28 ± 17.6	35 ± 17.6	.046
Pain recurrence at the same level preoperatively	8 (11.9)	0 (0)	.0061
Endometriosis-related symptoms after operation (VAS score ≥ 4)	29 (43.2)	4 (6.7)	<.0001
Dysmenorrhea	27 (40.2)	0 (0)	<.0001
Non-menstrual pelvic pain	8 (11.9)	4 (6.7)	.3248
Dyspareunia	0 (0)	0 (0)	
Dyschezia	2 (2.9)	1 (1.6)	.6355
Recurrence of endometrioma	21 (31.3)	3 (5.0)	.0002

SE, standard deviation; VAS, visual analogue scale