Accepted Manuscript

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

Authors: Akiyoshi Yamanaka, Tomonori Hada, Tsuyoshi Matsumoto, Kiyoshi Kanno, Akira Shirane, Shiori Yanai, Saori Nakajima, Keiko Ebisawa, Yoshiaki Ota, Masaaki Andou

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

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
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

Akiyoshi Yamanaka\textsuperscript{a,b}, Tomonori Hada\textsuperscript{b}, Tsuyoshi Matsumoto\textsuperscript{b}, Kiyoshi Kanno\textsuperscript{b}, Akira Shirane\textsuperscript{b}, Shiori Yanai\textsuperscript{b}, Saori Nakajima\textsuperscript{b}, Keiko Ebisawa\textsuperscript{b}, Yoshiaki Ota\textsuperscript{b}, Masaaki Andou\textsuperscript{b}

\textsuperscript{a) Department of Obstetrics and Gynecology, Shiga University of Medical Science\nSeta-Tsukinowa-cho Otsu Shiga 520-2192, Japan\n
\textsuperscript{b) Department of Gynecology, Kurashiki Medical Center, 250, Bakurocho, Kurashiki,\nOkayama 710-0824, Japan\n
Address all correspondence and requests for reprints to: Akiyoshi Yamanaka M.D., PhD.
Department of Obstetrics and Gynecology, Shiga University of Medical Science
Seta-Tsukinowa-cho Otsu Shiga 520-2192, Japan

Tel: +81 77 548 2267; Fax: +81 77 548 2406
E-mail: ykiyoshi@belle.shiga-med.ac.jp

\textbf{Consednation}\n
Effect of dienogest after surgery with deep infiltrating endometriosis.
Abstract

Objective: 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 to 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 antioovulatory 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


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
Figure 1

Prevalence

Time postoperatively (months)

- no medication group
- DNG group
Figure 2

The graph illustrates the prevalence of a certain condition over time postoperatively for two different medication groups: the no medication group and the DNG group. Prevalence is measured on the y-axis, with the x-axis representing time postoperatively in months. The graph shows a step-like increase in prevalence for both groups, with the DNG group generally exhibiting higher prevalence compared to the no medication group.
Table I. Patients’ demographic data

<table>
<thead>
<tr>
<th></th>
<th>No medication group (%)</th>
<th>DNG group (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>67</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SE</td>
<td>36 ± 5.9</td>
<td>35 ± 6.8</td>
<td>.398</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>40</td>
<td>41</td>
<td>.252</td>
</tr>
<tr>
<td>Parous</td>
<td>27</td>
<td>11</td>
<td>.0304</td>
</tr>
<tr>
<td>Infertile</td>
<td>11 (16.4)</td>
<td>1 (1.6)</td>
<td>.005</td>
</tr>
<tr>
<td>r-ASRM score, mean ± SD</td>
<td>54 ± 30.5</td>
<td>70 ± 28.2</td>
<td>.047</td>
</tr>
<tr>
<td>Stage of endometriosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>9</td>
<td>2</td>
<td>.0463</td>
</tr>
<tr>
<td>III</td>
<td>16</td>
<td>13</td>
<td>.8059</td>
</tr>
<tr>
<td>IV</td>
<td>42</td>
<td>44</td>
<td>.1525</td>
</tr>
<tr>
<td>Presence of endometriomas</td>
<td>49 (73.1)</td>
<td>57 (96.6)</td>
<td>.0003</td>
</tr>
<tr>
<td>Bilateral endometriomas</td>
<td>16 (23.8)</td>
<td>19 (32.2)</td>
<td>.298</td>
</tr>
<tr>
<td>Bilateral presence of endometriosis in USL</td>
<td>47 (70.1)</td>
<td>43 (72.8)</td>
<td>.7348</td>
</tr>
<tr>
<td>Operative procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>16 (23.8)</td>
<td>9 (15.2)</td>
<td>.1944</td>
</tr>
<tr>
<td>Monolateral oophorectomy</td>
<td>16 (23.8)</td>
<td>16 (27.1)</td>
<td>.7504</td>
</tr>
<tr>
<td>Monolateral cystectomy</td>
<td>25 (37.3)</td>
<td>24 (40.6)</td>
<td>.6991</td>
</tr>
<tr>
<td>Bilateral cystectomy</td>
<td>17 (25.3)</td>
<td>18 (30.5)</td>
<td>.5208</td>
</tr>
<tr>
<td>Symptoms preoperatively</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>57 (85.0)</td>
<td>44 (74.5)</td>
<td>.1404</td>
</tr>
<tr>
<td>Non-menstrual pelvic pain</td>
<td>23 (34.3)</td>
<td>11 (18.6)</td>
<td>.0478</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>8 (11.9)</td>
<td>3 (5.0)</td>
<td>.1737</td>
</tr>
<tr>
<td>Dyschezia</td>
<td>5 (7.4)</td>
<td>5 (8.4)</td>
<td>.0833</td>
</tr>
</tbody>
</table>

SE, standard deviation; r-ASRM, revised American Society for Reproductive Medicine; USL, uterosacral ligament
Table II. Recurrence of endometriosis-related pain and endometriomas

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

SE, standard deviation; VAS, visual analogue scale