Dienogest, a new conservative strategy for extragenital endometriosis: a pilot study

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Abstract
Extragenital endometriosis severely impairs the quality of life for affected women but its standard management has not yet been well established because of its relatively low incidence. As extragenital organs, intestine, followed by urinary tract, is the most common place affected by endometriosis, for which surgical treatment is sometimes difficult and accompanied by severe complications. Recently, dienogest, a novel progestin, has emerged as a new alternative for endometriosis, especially for endometriosis-associated pain. In this report, we presented four cases with rectosigmoidal and one with bladder endometriosis, treated with oral 2 mg/day dienogest for over 6 months. For all cases, the measurable extragenital lesions exhibited the reduction in their size after 10 to 11 months of use, accompanied with immediate relief of subjective symptoms related with extragenital lesions. This report suggests that dienogest can be a novel conservative alternative for extragenital endometriosis.

Keywords: Endometriosis, extragenital endometriosis, dienogest, conservative therapy

Introduction
Endometriosis is a chronic and common condition, affecting 6–10% women of reproductive age [1]. It is defined as a presence of functionally and morphologically endometrium-like tissue outside of the uterine cavity, causing various symptoms. Although the site most commonly involved is ovary, extragenital organs are also affected. The intestine is involved in 5-37% of women with endometriosis [2]. Out of them, sigmoidal and rectal endometriosis concern 70% of cases of intestinal endometriosis [3]. Following the bowel, the urinary tract is also vulnerable, with 1–15% of reported prevalence of bladder endometriosis in patients with endometriosis [4]. The colorectal endometriosis lesion often causes defecation pain and hematochezia, typically most severe at menstrual phase. With the progression of disease, progressive constipation and diarrhea alternating with constipation occur. The bladder endometriosis, sometimes complicated with colorectal endometriosis, often causes pollakiuria and urodynia, sometimes hematuria, also typically pointed out at menstrual phase. These symptoms, together with dysmenorrhea caused by coincidental peritoneal endometriosis and/or adenomyosis [5], severely compromised quality of life of patients. Surgical treatment has its certain role but the surgical burden and complications, and incomplete removal of lesions, especially with lower rectal lesions, should be problems. As conservative therapies, gonadotropin releasing hormone (Gn-RH) agonists and oral contraceptives (OCs) are currently used, both of which have high therapeutic effects. However, both therapies have their own limitations. The therapeutic period of Gn-RH agonists is limited because of bone mineral loss as an adverse effect [6]. As for OCs, because the risk for thrombosis increases with age [7], we should be careful

and sometimes refrain from prescribing combined OCs for patients in their 40s or 50s. Dienogest, a novel 19-nortestosterone derivative, is a progestin that is highly selective for progesterone receptors [8]. In addition to its antiovulatory effect, which indirectly inhibits progression of endometriosis, dienogest has direct inhibitory effect on proliferation of endometriotic stromal cells [9] and inflammatory cytokine production from these cells [10]. Based on these findings, dienogest has been recently investigated as a new therapeutic agent against endometriosis. After 24 weeks of treatment with oral 2 mg/day dienogest, Momoeda et al. showed significant reduction in painful symptoms of endometriosis and in diameter of ovarian endometriomas [11]. Other studies showed that dienogest is as effective as buserelin acetate [12] or leuprolide acetate [13] and significantly more effective than placebo [14] in relieving the painful symptoms of endometriosis. But there is no report addressing the effect of dienogest on extragenital endometriosis.

In this context, we examined the effect of dienogest on patients with extragenital endometriosis as a pilot study.

Methods
Cases were collected from patients attending to our university hospital. A retrospective case analysis was undertaken by the authors.

Patients
Inclusion criteria were as follows: (i) ≥20 years of age; (ii) regular menstrual cycles before dienogest was given; (iii) extragenital endometriosis diagnosed with the use of...
imaging analysis (combination of magnetic resonance imaging and ultrasonography, sometimes with colon fiber or cystoscopy); (iv) presence of subjective symptoms associated with extragenital endometriosis (defecation pain or hematochezia for rectosigmoidal endometriosis and urodynia or pollakiuria for bladder endometriosis); (v) dienogest had been given in oral dose (1 mg twice daily) for at least 6 months before the case analysis was undertaken.

Exclusion criteria were as follows: (i) pregnant or nursing; (ii) use of Gn-RH agonists, testosterone derivatives, progestins, estrogens, estrogen antagonists, or aromatase inhibitors within 3 months prior to the start of administration with dienogest; (iii) having undergone surgical therapy or surgical examination for genital or extragenital endometriosis within a menstrual cycle prior to the start of dienogest.

**Measurements**

The size of extragenital endometriosis was evaluated by ultrasonography with the interval of 1–3 months [15,16]. After defining the largest sagittal view of the lesion, the longest part of the lesion (A) and the orthogonal part (B) were measured. A × B was calculated and defined as an ‘maximal area index’. The change in subjective symptoms was also assessed by interview.

**Results**

Five patients met criteria described above. Four cases had rectosigmoidal endometriosis and the other one had bladder endometriosis. Table I summarizes these cases. All the cases with rectosigmoidal endometriosis were complicated with genital endometriotic lesion. The changes in the size of extragenital lesions were shown in Figure 1. All the patients experienced the reduction in the size of the lesions after 10 to 11 months of oral dienogest. [6] Figure 2 shows the ultrasonographic images of rectosigmoidal endometriotic lesion in case 2. The response to dienogest appears to differ between individuals. The reduction rates in the size of the lesions at 10 or 11 months varied from 25% to 80% depending on individuals.

<table>
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<th>Table I. Summary for cases.</th>
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<td>Case</td>
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<td>Age, y</td>
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<td>G/P</td>
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<tr>
<td>Site of ex EMosis</td>
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<td>Maximal area index before treatment (mm²)</td>
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<td>Symptoms associated with ex EMosis</td>
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<td>Other endometriotic lesions</td>
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<td>ADR</td>
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Note: ex EMosis, extragenital endometriosis; defec. pain, defecation pain; EM cyst, endometriotic cyst; LH, laparoscopic hysterectomy; RSO, right salpingo-oophorectomy; EMoma, endometrioma; ADR, adverse drug reactions.

Figure 1. Changes in the size of extragenital endometriosis in each case. The size of the lesions was evaluated by ultrasonography as mentioned in methods. The graph shows the fold change in ‘maximal area index’ of each lesion.
In addition, the period during which the lesions kept shrinking differed between individuals. For case 3, 4, and 5, dienogest caused the lesions to shrink only up to couple of months after the start of treatment, while the lesions of case 1 and 2 kept shrinking until 6 to 8 months. For the both groups, dienogest was effective in maintaining the size of the lesions after the first shrinking period, at least up to 10 to 11 months of use. As for subjective symptoms associated with extragenital endometriosis, all the cases with rectosigmoidal endometriosis had defecation pain before treatment, complicated with hematochezia for case 1 and 2. Case 5 had urodynia. For all cases, painful symptoms were dramatically relieved within a month after the start of taking dienogest. Both case 1 and 2 experienced no more hematochezia after the start of dienogest. As for the compliance of dienogest, case 1, 2, and 5 still continued. Case 3 and 4 quitted taking dienogest after 10 to 11 months of use, because of gastralgia and depression, respectively.

Discussion
We experienced five cases with extragenital endometriosis, for those dienogest 2 mg daily orally was effective in reducing the size of the lesions and relieving the symptoms associated with these lesions. To our knowledge, this is the first series of extragenital endometriosis patients treated with the novel drug, dienogest.

Although the extragenital endometriosis is relatively rare, the quality of life for women with extragenital lesions is severely impaired. Because of its low incidence, standard management has not yet been well established. The effect of dienogest on shrinkage of the lesions shown in this report suggests its possibility as a novel approach to extragenital endometriosis. Although the effect of treatment with dienogest for more than 1 year is difficult to address in the present study, a patient who took dienogest over 1 year (case 2) showed no additional shrinkage of the lesion after 1 year. As for subjective symptoms such as defecation pain or urodynia, dienogest exerted its effect immediately within a month after start of treatment. In terms of the safety or tolerability, two out of five patients discontinued after 10 to 11 months because of adverse drug reactions. This rate is considerably high compared to the one (5.2%) reported in the only existing clinical trial assessing the safety of long-term use of dienogest [11]. This high withdrawn rate is probably due to the limited number of the patients in this report. All four cases with uterus experienced spotting, as expected, but it was tolerable.

In conclusion, dienogest may become a promising alternative for treatment against extragenital endometriosis. Further studies are necessary to establish the efficacy and safety of dienogest for patients with extragenital endometriosis.

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References
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