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Efficacy of Norethisterone in Patients with Ovarian Endometrioma

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ABSTRACT

Endometriosis is a chronic inflammatory disorder associated with pelvic pain and infertility. Because surgical and medical therapies control symptoms, but it is hard to cure completely endometriosis, long term of pharmacologic management is necessary. Norethisterone (NET), one of progestins, has safety profile and advantage that allow long-term use. In this preliminary report, we showed the efficacy of NET in 6 patients with endometriosis. The size of ovarian endometrioma was decreased after treatment with NET for 6 months, and all patients were relieved from dysmenorrhea pain within 6 months, suggesting that NET would be a suitable medication to treat endometriosis.

Key words endometriosis; norethisterone; progestin

Endometriosis occurs in 10% of women in their reproductive age. Over recent years, it is estimated to be increasing due to late marriage and delayed childbearing in Japan. This disorder causes dysmenorrhea, infertility, and chronic pelvic pain. Ovarian endometrioma is a common endometriotic lesion, affecting 55% of patients with endometriosis.[1] Management of endometrioma includes surgical and medical treatment, taking into consideration symptoms, desire for childbearing, lesion dimension, past treatment history, and ovarian reserve.

The commonly used medications to treat endometriosis are non-steroidal anti-inflammatory drugs (NSAIDs), low dose oral contraceptive pills (OCPs), GnRH agonists (GnRHa), and progestins, such as NET and dienogest (DNG). Hormonal drugs can control ovulation or menstrual cycle, in addition to possessing beneficial effects against pain. Because the medication for endometriosis usually takes long time, the drugs with favorable safety profile, efficacy, tolerability and cost profile should be preferable.

Recently, OCP as a first-line treatment is a simple way to manage endometriosis. The OCPs containing synthetic estrogen and progestin are effective for pelvic pain relief and control of endometriotic lesions. Only one randomized, controlled trial (RCT), which demonstrated the efficacy of an OCP (norethisterone/ethinylestradiol: NET/EE: 1 mg/35 μg) for dysmenorrhea associated with endometriosis and the reduction of the endometrioma volume larger than 3 cm in diameter after 4 cycles of OCP, has been reported. The OCP treatment resulted in about a 50% reduction in dysmenorrhea as determined by verbal rating pain scoring.[2]

However, there are some practical limitations to use the OCPs. The critical issues in managing endometriosis are side effects and recurrence of symptoms that require long-term or repeated courses of medication. For instance, OCPs are contraindicated in patients older than 35 years who smoke or have the risk of venous thromboembolism, whereas NET confers no increased risk. Moreover, the long-term use of OCPs for several years may result in endometrial thinning that is nonresponsive to estrogen.[3] This adverse effect of long-term use may be crucial for women with endometriosis who want to conceive.

In contrast to OCP, several investigators indicated the efficacy of progestins, such as NET or DNG in alleviating the chronic pelvic pain and dysmenorrhea associated with endometriosis.[4–6] NET, which is known and used as norethindrone or norethisterone acetate (NETA) in the foreign countries, is a steroidal progestin of the 19-nortestosterone group with additional weak androgenic and estrogenic activity. These compounds induce atrophy of eutopic and ectopic endometrium, have anti-inflammatory and proapoptotic properties. In the case of a contraindication to estrogen, OCPs could be the therapy of endometriosis-associated pain, followed by progestin-only treatment. In this study, we focused the efficacy of NET in the development of ovarian endometriomas and endometriosis-associated pain.

PATIENT REPORT

Study design

After obtaining informed consent, we recruited 6 wom-

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Abbreviations: BMI, body mass index; DNG, dienogest; DRSP, drospirenone; EE, ethinylestradiol; GnRHa, GnRH agonist; NET, norethisterone; NETA, norethisterone acetate; NSAID, non-steroidal anti-inflammatory drug; OCP, oral contraceptive pill; RCT, randomized controlled trial; VAS, visual analogue scale

Table 1. Summary for 6 cases

Case	1	2	3	4	5	6
Age (years)	39	48	39	44	47	43
G/P	0/0	0/0	0/0	0/0	1/1	0/0
VAS (mm)	52	100	58	80	50	51
Volume of endometrioma (cm^3)						
Pre-treatment	236.3	17.3	43.3	0.55	9.3	56.6
After 6 months	130.2	2.9	42.0	0.29	5.0	35.5
Incidence of amenorrhea (months)	6	3	3	3	3	1
Duration of NET therapy (months)	26	20	18	15	14	9
CA125 (U/mL)	29.8	11.3	20.1	22.4	33.5	14.4
Presence of adenomyosis		(+)		(+)	(+)	(+)
Age at diagnosis (years)	39	43	39	32	37	43
Other treatment until NET	(–)	(–)	(–)	Cystectomy	(–)	(–)

G/P, gravidity and parity; NET, norethisterone; VAS, visual analogue scale.

en with unilateral ovarian endometriomas from January to December 2015. Patient inclusion criteria included women 39 to 48 years old; regular menstrual cycles (28 ± 2 d); ovarian endometrioma diagnosed by transvaginal ultrasound or magnetic resonance imaging; moderate or severe dysmenorrhea; and no hormonal or surgical treatment for endometriosis within 1 year of entry into this study. The degree of dysmenorrhea was evaluated according to a visual analogue scale (VAS) from 0 mm "no pain" to 100 mm "the worst pain you could imagine." NET (5 mg/d: Norluten; Fuji Pharma, Tokyo, Japan) was administered every day for at least 6 months. The use of other hormonal treatments for pain and any kinds of analgesics was not allowed. The characteristics of this study population are shown in Table 1.

Patient monitoring

In this protocol, each patient underwent a pre-recruitment evaluation, consisting of a general medical and gynecologic history, physical and pelvic examination, patient evaluation of pain, and review of the menstrual records. Blood was drawn for pretreatment clinical laboratory determinations, including hematologic and biochemical tests, and CA125. Patients were followed every 4 weeks to evaluate pain, side effects, and other health concerns. After 6 four-week treatments, efficacy of NET was evaluated. Main outcome measures were the final measurement of the volume of ovarian endometrioma and the VAS score during treatment. The measures recorded at the initiation of NET therapy prescription were considered the baseline (pretreatment). Clinical and ultrasound examinations were performed at baseline and after 6, 9, and 12 months of treatment. Total volume of the endometrioma was obtained by calculating the three-dimensional diameters on a longitudinal and sagittal scan. When the endometrioma was multiocular, the size of largest cyst was measured. Data are shown as mean ± SD.

Analysis data

The characteristics of 6 patients with ovarian endometriomas were shown in Table 1. Ages ranged from 39 to 48 years (43.3 ± 3.8 years). Mean body mass index (BMI) of patients was 21.1 ± 2.0 kg/m^2. All patients had regular menstrual cycles. Five patients had never experienced childbirth. The mean largest diameter of ovarian endometrioma was 4.6 ± 2.4 cm (range: 1.1 to 8.3 cm) and pretreatment CA125 value was 21.9 ± 8.6 U/mL (range: 11.3 to 33.5 U/mL).

The maximum diameter of ovarian endometrioma was slightly decreased by NET treatment for 6 months (Mean: 3.9 cm vs. pretreatment: 4.6 cm). Accordingly, NET treatment for 6 months exhibited 37.2% reduction of volume of endometrioma (Mean: 37.9 cm^3 vs. pretreatment: 60.5 cm^3). After 9, and 12 months, the reduction rates of endometriomas were almost as much as those after 6 months. Before NET treatment, the mean of VAS scores indicating dysmenorrhea pain was 65.2 ± 20.4 mm. The state of amenorrhea and "no pain" were verified in 5 patients within 3 months, and in 1 patient at 6 months after NET treatment. Prior to the NET therapy, 5 patients were not treated with any drugs for endometriosis, and 1 patient was performed laparoscopic cystectomy for right ovarian endometrioma 12 years ago. Two patients (No. 2 and 5) were followed up for the expectant management until NET therapy, and 3 patients (No. 1, 3

and 6) were initially treated with NET after the diagnosis of endometriosis.

No *de novo* development of ovarian endometriomas occurred in this follow-up period. No serious adverse events related to NET use were observed. For example, the abnormal liver function results and skin problems did not occur.

DISCUSSION

Our present data revealed that NET was effective in treating dysmenorrhea, resulted in amenorrhea for at least 6 months, and reduced the size of ovarian endometriomas. It appears that women with endometriosis may be controlled well with oral progestin-only treatment as one of the first-line therapies. Progestin alone, in milligram per day doses, generally inhibit ovulation,[7, 8] and induce amenorrhea, which could prevent dysmenorrhea. The decrease of gonadotropin secretion induced by the action of potent progestins will result in a relatively hypoestrogenic state that could help suppress endometriosis lesions, and certainly should prevent progression of this disease.

Progestins do not increase the thrombotic risk, and have the anti-inflammatory and anti-angiogenic activity in endometriotic tissues. NET or DNG appear to be equally effective in alleviating pain and decreasing lesion size in endometriosis.[4] NET also has androgenic activity, whereas DNG is anti-androgenic. These two progestins do not exhibit substantial glucocorticoid or anti-mineralcorticoid actions, which several other hormonal drugs possess. Progestins themselves may have a positive effect on bone formation.[9] A hypothetic advantage of NET over DNG is that NET is partly metabolized to estrogens. This should prevent bone loss during prolonged periods of treatment.[10] In terms of these progestins, Vercellini et al. indicated the recent data to assess the proportion of patients satisfied with the treatment of NETA (2.5 mg per d, for 90 d) or DNG (2 mg per day, for 90 d) as the first-line progestin for symptomatic endometriosis. The overall satisfaction with treatment, such as pain relief, psychological status, and sexual function, was almost identical in both drugs.[4]

On the other hand, OCPs suppress ovulation and reduce the growth of endometrial tissue, thus reducing both menstrual flow and prostaglandins production. OCPs' possible side effects, such as headache, nausea, and atypical uterine bleeding, are known. In two recent studies, a significant reduction in the diameter of endometrioma after 6 months of an ultra-low dose OCP containing DRSP/EE (drospirenone/EE: 3 mg/20 μg) was shown.[11] We also showed that it alleviates dysmenorrhea, synthesizes proinflammatory cytokines, and preserves ovarian reserve.[11]

NET and DNG did not appear to differ with regard to safety profiles, but their cost did: DNG was more expensive compared with NET (approximately 100,000 vs. 4,000 Japanese yen, per a year). However, the patients were also informed that NET or DNG induce only temporary pain relief during treatment, and are not expected definitive cure of endometriosis. Even if the long-term management with these drugs is done, it is difficult to be eliminated completely the lesions of endometriosis. For the future, the long-term safety of these progestins remains to be investigated, because the medical treatments for endometriosis may be needed for years.

In conclusion, current data suggest that NET is a promising treatment not only for endometriosis-associated dysmenorrhea but it also reduces the size of ovarian endometriomas. Oral progestins alone can be used at any age, do not increase the risk of thrombosis, and are capable of inhibiting ovulation and inducing amenorrhea with very few side effects.

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