Estrogen Plus Progestin versus Estrogen after Definitive Surgery for Endometriosis: A Study of Pain Recurrence

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Objective: *To compare the cumulative recurrence rate of endometriosis-associated pain in women receiving estrogen plus progestin and in those using estrogen following definitive surgery for endometriosis.*

Material and Method: *A prospective cohort study was conducted in a university hospital. Consecutive premenopausal women with symptomatic endometriosis received hormone therapy following definitive surgery. Before November 2008 conjugated equine estrogen 0.625 mg per day was used in all patients. After that time, all patients received conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg per day. Patients came for a follow-up visit every six months to ascertain if they had any recurrent pain.*

Results: *The cumulative recurrence rates of pain at months 12, 24 and 36 were 0%, 2.9% and 2.9%, respectively in the estrogen plus progestin group (n = 68) and 4.4%, 6.0% and 8.2%, respectively in the estrogen group (n = 93). No significant difference in cumulative recurrence rates of pain between the two groups was observed. It could not be demonstrated that the hormone regimen was an independent risk factor of recurrence of pain.*

Conclusion: *There was a marginally lower recurrence rate of pain in patients receiving estrogen plus progestin than in those using estrogen. However, no statistically significant difference was demonstrated.*

Keywords: *Endometriosis, Hormone therapy, Pain, Recurrence, Surgery*

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Medical and conservative surgical therapies are the current options for symptomatic endometriosis patients as well as for those who wish to preserve their fertility or ovarian function. When medical and conservative treatments fail to relieve the symptoms associated with endometriosis and childbearing has been completed, definitive surgery and the resulting surgical menopause is indicated. Since these patients are often relatively young at the time of surgery, prolonged estrogen deficiency status may cause significant morbidity and have a major impact on their quality of life. Benefits of hormone therapy (HT) in terms of controlling menopausal symptoms, preventing urogenital atrophy, loss of libido, and bone protection are particularly important[1]. However, when using HT, there is a small underlying yet undefined risk of recurrence or malignant transformation of endometriosis[1,2]. Estrogen therapy (ET) has been used in patients with endometriosis after radical surgery for many decades. However, unopposed estrogen may be more likely to promote the growth of endometriosis and disease recurrence than estrogen plus progestogen therapy (EPT), but unfortunately, no studies have directly compared the two treatments[3].

In the past all patients after definitive surgery for endometriosis in our hospital received ET. In year 2003, the authors believed that ET was not associated with malignant transformation of residual endometriosis and planned to prospectively determine the cumulative recurrence rate of endometriosis-associated pain in women using ET. However, because of a rapidly increasing number of cases reported in the literature of malignancy developing in residual endometriosis after prolonged unopposed estrogen[1], EPT has been used instead of ET in all of our patients since November 2008. Thus, the authors found the opportunity to compare the cumulative recurrence rate of endometriosis-associated pain in women receiving EPT and in those using ET following definitive surgery for endometriosis.

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Material and Method

The present prospective cohort study was approved by the institutional review board and

conducted in our university hospital. Patients were enrolled between July 2003 and August 2011. The data were collected prospectively from the beginning of the study in July 2003. All of the patients included in the present study were consecutive premenopausal women with endometriosis-associated pain who had undergone a total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) and in whom the foci of the endometriosis had been removed without taking the risk of damaging the involved visceral organs. All of the subjects had endometriosis-associated pain that was refractory to previous medical and surgical treatments. The patients who had completed their child bearing and were at least 40-years-old were invited to have definitive surgery. The others were advised to consider more medical therapy, repetitive conservative surgery, or definitive surgery. Pathological diagnoses were confirmed in all of them. Severity of dysmenorrhea, non-menstrual pain, and deep dyspareunia were evaluated using a verbal rating scale (VRS). The VRS was modified from the pain measurement tool of Biberoglu and Behrman[4] and consisted of scores 0, 1, 2 and 3 (i.e. dysmenorrhea score 0 = no pain, 1 = no absence from work but decreased efficiency, 2 = absence from work less than one day per cycle, 3 = absence from work one day or more per cycle; non-menstrual pain score 0 = no pain, 1 = occasional pain but no analgesic needed, 2 = analgesic needed in some cycles, 3 = analgesic needed in every cycle; deep dyspareunia score 0 = no pain, 1 = pain tolerated, 2 = painful intercourse to point of interruption, 3 = avoidance of intercourse because of pain). Patients with known gastrointestinal, urologic, and orthopedic diseases were excluded from the study. The body mass index (BMI) was calculated before the operation. During the laparotomy, the revised American Society for Reproductive Medicine (rASRM) classification of endometriosis[5] was used to stage the disease and any other pelvic pathology was noted, such as adenomyosis, chronic pelvic inflammatory disease, and myoma uteri. In addition, any gross residual endometriotic lesions left during an operation were recorded.

Patients were requested to return for follow-up one month after their surgery. Peripheral blood samples were obtained to measure follicle stimulating hormone (FSH). Screening mammography was performed in patients who were at least 40 years old. Any patient with an FSH level less than 40 mIU/mL or abnormal mammographic findings was excluded from the study. Eligible patients gave written informed consent to the study. Before and during the HT, deep dyspareunia was assessed by the VRS and pain not associated with sexual intercourse by asking whether the patients had pain of the same characteristics and severity as they had felt before their operations. Between July 2003 and October 2008, continuous oral conjugated equine estrogen (CEE) 0.625 mg per day was initiated one month after the operation in every patient who had no contraindications to oral estrogen. In November 2008 the regimen of HT for all patients in Songklanagarind Hospital changed to a daily combination of continuous oral CEE 0.625 mg and oral medroxyprogesterone acetate (MPA) 2.5 mg starting one month after the surgery unless there were contraindications. The subjects were advised to stop the HT whenever they felt that their pain recurred and to make immediate contact with the authors. At six-month intervals, patients were questioned to ascertain if they had any recurrent pain, side effects from the medication, or other health related concerns and, in addition, a pelvic examination was performed. After definitive surgery, recurrence of dysmenorrhea and/or non-menstrual pain was perceived as pain not associated with menstruation, so recurrent endometriosis-associated pain was defined as deep dyspareunia or pain of the same characteristics and severity experienced before the surgery. Patients with recurrent pain received transvaginal ultrasonography to rule out pelvic masses. Then, the HT was discontinued for three months and the improvement of pain was evaluated.

The time between the start of HT and pain recurrence was analyzed with the Kaplan-Meier technique. Subjects deciding to stop HT for personal reasons were censored. The difference in curves was evaluated using the log-rank test. Cox proportional hazards models were used to estimate the effects of several covariates, which included age at the time of definitive surgery, previous medical therapy for endometriosis, previous surgical therapy for endometriosis, severity of pain, BMI, rASRM score, stage of endometriosis, the presence of ovarian endometrioma(s), complete cul-de-sac obliteration, or residual disease, and the pathology report. In addition, Student's t-test, rank-sum test, Chi-squared test, and Fisher's exact test were used as appropriate. Probability values less than 0.05 were considered statistically significant.

Results

There were 68 patients in the EPT group and 93 patients in the ET group. The mean ± SD of

Table 1. Patient demographics and pretreatment characteristics

Characteristic	Estrogen plus progestin (n = 68)	Estrogen (n = 93)	Statistical test	p-value
Age at the time of definitive surgery (years)[a]	41 [38, 44]	41 [37, 43]	Rank-sum test	0.853
Previous medical therapy for endometriosis[b]			Chi-squared test	0.966
Yes	34 (50.0)	45 (48.4)		
No	34 (50.0)	48 (51.6)		
Previous conservative surgery for endometriosis[b]			Chi-squared test	0.741
Yes	17 (25.0)	20 (21.5)		
No	51 (75.0)	73 (78.5)		
Pain score[b]				
Dysmenorrhea			Fisher's exact test	0.718
0	4 (5.9)	3 (3.2)		
1	22 (32.4)	35 (37.6)		
2	12 (17.6)	13 (14.0)		
3	30 (44.1)	42 (45.2)		
Dyspareunia			Fisher's exact test	0.915
0	31 (50.8)	32 (44.4)		
1	21 (34.4)	27 (37.5)		
2	6 (9.8)	9 (12.5)		
3	3 (4.9)	4 (5.6)		
Non-menstrual pain			Chi-squared test	0.647
0	21 (30.9)	35 (37.6)		
1	19 (27.9)	27 (29.0)		
2	16 (23.5)	15 (16.1)		
3	12 (17.6)	16 (17.2)		
Body mass index (kg/m^2)[c]	24.3±3.5	23.1±3.2	Student's t-test	0.030
rASRM score[a]	80 [52.2, 104]	44 [20, 92]	Rank-sum test	0.005
Stage of endometriosis[b]			Fisher's exact test	0.008
Minimal	7 (10.3)	17 (18.3)		
Mild	1 (1.5)	4 (4.3)		
Moderate	4 (5.9)	18 (19.4)		
Severe	56 (82.4)	54 (58.1)		
Endometrioma(s)[b]			Chi-squared test	0.355
None	21 (30.9)	39 (41.9)		
Unilateral	22 (32.4)	26 (28.0)		
Bilateral	25 (36.8)	28 (30.1)		
Complete cul-de-sac obliteration[b]			Chi-squared test	0.007
Yes	51 (75.0)	49 (52.7)		
No	17 (25.0)	44 (47.3)		
Residual disease[b]			Chi-squared test	0.276
Yes	19 (27.9)	18 (19.4)		
No	49 (72.1)	75 (80.6)		
Pathology report[b]			Chi-squared test	0.237
Endometriosis only	18 (26.5)	34 (36.6)		
Endometriosis with other pathology (adenomyosis, chronic pelvic inflammatory disease, myoma uteri)	50 (73.5)	59 (63.4)		

[a] Values are medians [interquartile ranges], [b] Figures are numbers of patients (%), [c] Values are means ± SD
rASRM = revised American Society for Reproductive Medicine

follow-up time in the EPT group and the ET group was 20.9±9.4 months and 28.5±18.1 months, respectively. Table 1 shows the patient demographics and pretreatment characteristics. The BMI, rASRM score, stage of endometriosis and the presence of complete cul-de-sac obliteration in the two groups were significantly different (Table 1). Before starting the HT, no sexual intercourses and no recurrent pain were reported. Menopausal symptoms were well controlled in all of the patients. No women left the study because of side effects of the hormonal drugs. Twelve (17.6%) subjects in the EPT group and eight (8.6%) subjects in the ET group were lost to follow-up. One (1.4%) participant in the EPT group and nine (9.7%) participants in the ET group had recurrent endometriosis-associated pain not related to sexual intercourse. No recurrent deep dyspareunia was reported. The crude recurrence rate of endometriosis-associated pain at month 36 was 1.5% (1/68) in the EPT group and 6.5% (6/93) in the ET group. Fig. 1 shows the survival curve of pain-free patients. The numbers of patients who completed the evaluations at months 12, 24, and 36 were 53, 29, and six patients, respectively in the EPT group and 79, 54, and 38 patients, respectively in the ET group. The cumulative recurrence rates of pain at months 12, 24, and 36 were 0%, 2.9%, and 2.9%, respectively in the estrogen plus progestin group and 4.4%, 6.0%, and 8.2%, respectively in the estrogen group. No significant difference in cumulative recurrence rates of pain between the two groups was observed (Fig. 1). Focal tenderness in the pelvis was found in all of the patients who had pain recurrence. No pelvic masses were demonstrated and no re-operations were performed on patients with recurrent endometriosis-associated pain. All of the patients who experienced pain recurrence reported pain relief during the three months of hormone interruption. The most common side effect was breast tenderness. Three (4.4%) patients in the EPT group and two (2.2%) patients in the ET group had breast tenderness during HT. It could not be demonstrated that a regimen of HT was an independent risk factor

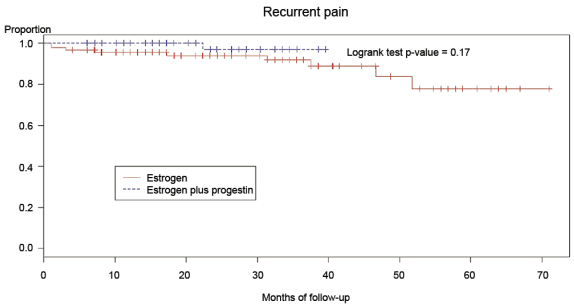

Fig. 1 Survival curve of pain-free patients.

of recurrence of endometriosis-associated pain by Cox proportional hazards models (Table 2). Malignant transformation of endometriosis was not observed in any of the patients.

Discussion

The authors observed lower cumulative recurrence rates of endometriosis-associated pain in the EPT group than in the ET group, but no statistically significant difference between the two groups was demonstrated. Histological diagnoses were not ascertained in patients with pain recurrence in the present study; however, our clinical diagnoses were confirmed by pain relief during the three months of hormone discontinuation. The major limitation of the present study includes the lack of randomization and the possibility of biases, especially self-selection bias. Statistical regression analysis can do some adjustment, but not entirely. The second drawback was our small sample size. Since the cumulative recurrence rate of endometriosis-associated pain at month 36 was 2.9% in the EPT group and 8.2% in the ET group, a sample size of 292 patients in each group would give the study an 80% chance to detect the difference of 5% between the two groups at an overall significance level of 5%. However, because of the risk of malignant transformation of residual endometriosis after prolonged unopposed estrogen the authors could not perform a randomized trial comparing EPT and ET in Songklanagarind Hospital. The third drawback of

Table 2. Factors associated with recurrent pain after treatments

Factor	Hazard ratio	95% confidence interval	p-value
Hormone (reference = estrogen)			
Estrogen plus progestin	0.24	0.03-2.11	0.20
Body mass index (BMI)	1.09	0.88-1.35	0.44
Complete cul-de-sac obliteration	0.49	0.06-4.12	0.51
rASRM score	0.99	0.96-1.01	0.38

the present study was the high rate (17.6%) of loss to follow-up in the EPT group. The loss to follow-up may be related to pain recurrence or side effects of the drugs.

The indication for definitive surgery was the same during the entire period of the study. However, in recent years many patients with minimal/mild/moderate endometriosis in Songklanagarind Hospital requested repetitive conservative surgery or more medical therapy. Accordingly, the percentage of patients with severe endometriosis was higher in the EPT group than in the ET group. Although the rASRM score, stage, and prevalence of complete cul-de-sac obliteration were significantly higher in the EPT group than in the ET group, the proportions of patients with large bowel endometriosis in the two groups were similar. Hence, the percentage of patients with residual disease was not different between the groups.

Studies evaluating HT after definitive surgery for endometriosis are scarce and most of them are retrospective[6-8]. To our knowledge, there are only two prospective clinical trials[9,10] in English determining the risk of recurrence of endometriosis after administration of HT. In a retrospective study, 11 (11.3%) of 97 patients who received ET had recurrent pain[7]. The Kaplan-Meier survival curve for the first 36 months of the ET group in our study (Fig. 1) was comparable with that in their study. Therefore, it is reasonable to assume that the cumulative recurrence rate of pain at month 36 in patients receiving ET after definitive surgery for endometriosis is approximately 8.2 to 10%. In a small study, 21 women with residual pelvic endometriosis after BSO were randomized into HT with transdermal estradiol and treatment with tibolone[9]. Four of the patients (40%) in the estradiol group experienced moderate pelvic pain compared with only one (9%) patient in the tibolone group. The high rate of recurrence of pain in the estradiol group in the study of Fedele et al[9] might be due to the inclusion of only patients who had residual endometriosis in their study.

In a randomized controlled trial, 172 women who had endometriosis and underwent BSO were randomized into sequential administration of estradiol patches and micronized progesterone or no HT[10]. Recurrence of endometriosis occurred in four (3.5%) out of 115 patients (0.9% per year) in the HT group. The cumulative recurrence rate of pain in the EPT in our study (2.9% at month 36) was in line with their rate of 0.9% per year[10]. Thus, the authors postulate that the cumulative recurrence rate of pain at month 36 in women having EPT following definitive surgery for endometriosis is around 2.7 to 2.9%.

In contrast to the other studies[7,10], no pelvic masses were demonstrated and no re-operations were performed on patients with recurrent pain in the present study. This was perhaps related to early diagnosis and immediate discontinuation of HT. Since all of our patients had had endometriosis-associated pain before definitive surgery, their recurrent disease was associated with recurrent pain.

Besides pain and disease recurrence, malignant transformation of residual endometriosis may occur during HT. EPT has been suggested to reduce the chance of malignant change of residual endometriosis. However, there is no evidence from clinical studies supporting that progestin is effective in reducing the risk of developing a malignancy in residual endometriosis[1]. In fact, there are cases that reported that a carcinoma arising in endometriosis was associated with the exclusive use of progestin[11,12]. Moreover, the addition of MPA 2.5 mg per day appears to increase the risks of invasive breast cancer, coronary heart disease, stroke and pulmonary embolism after a mean of 5.2 years of treatment among postmenopausal women aged 50 to 79 years[13]. These risks should be considered, especially in a subgroup of patients with endometriosis, who are young at the time of radical surgery, because they need HT to the age of 45 years[14,15].

In conclusion, the present study demonstrated a marginally lower recurrence rate of endometriosis-associated pain in patients receiving EPT than in those using ET, although the difference was not statistically significant.

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Potential conflicts of interest

None.

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เอสโทรเจนร่วมกับโพรเจสตินเปรียบเทียบกับเอสโทรเจนหลังการผ่าตัดรักษาเยื่อบุมดลูกต่างที่แบบตัดหมด: การศึกษาอาการปวดซ้ำ

โสภณ ชีวะธนรักษ์, ชัยณรงค์ โชคสุชาติ, ศรันญา วัฒนกำธรกุล

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการปวดซ้ำสะสมในผู้ป่วยเยื่อบุมดลูกต่างที่ หลังการผ่าตัดรักษาแบบตัดหมด ระหว่างกลุ่มที่ได้รับเอสโทรเจนร่วมกับโพรเจสตินกับกลุ่มที่ได้รับเอสโทรเจน*

วัสดุและวิธีการ: *ผู้นิพนธ์ศึกษาตามแผนวิธี cohort ในโรงพยาบาลมหาวิทยาลัย ผู้ป่วยเยื่อบุมดลูกต่างที่ซึ่งมีอาการปวดและอยู่ในวัยเจริญพันธุ์ได้รับฮอร์โมนหลังการผ่าตัดรักษาแบบตัดหมด ก่อนเดือนพฤศจิกายน พ.ศ. 2551 ผู้ป่วยทุกรายรับประทาน conjugated equine estrogen วันละ 0.625 มก. แต่หลังจากนั้นผู้ป่วยทุกรายรับประทาน conjugated equine estrogen วันละ 0.625 มก. ร่วมกับ medroxyprogesterone acetate วันละ 2.5 มก. ผู้ป่วยมาติดตามการรักษาทุก 6 เดือน เพื่อรับการประเมินอาการปวดซ้ำ*

ผลการศึกษา: *อัตราการปวดซ้ำสะสม ณ เดือนที่ 12, 24 และ 36 ของกลุ่มที่รับประทานเอสโทรเจนร่วมกับโพรเจสติน (n = 68) คิดเป็นร้อยละ 0, 2.9 และ 2.9 ตามลำดับ และของกลุ่มที่รับประทานเอสโทรเจน (n = 93) ร้อยละ 4.4, 6.0 และ 8.2 ตามลำดับ ผลการวิเคราะห์ทางสถิติไม่พบความแตกต่างของอัตราการปวดซ้ำระหว่างกลุ่ม และไม่พบว่าชนิดของฮอร์โมนเป็นปัจจัยเสี่ยงอิสระของการเกิดอาการปวดซ้ำ*

สรุป: *อัตราการปวดซ้ำของกลุ่มที่รับประทานเอสโทรเจนร่วมกับโพรเจสตินต่ำกว่ากลุ่มที่รับประทานเอสโทรเจนเล็กน้อย โดยไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*