

# Hormonal Replacement Therapy in Surgical Menopause with Underlying Endometriosis

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## Abstract

**Objective :** To evaluate the effect of hormonal replacement therapy (HRT) regimens in surgical menopause patients with underlying endometriosis.

**Design :** Observational retrospective study.

**Material and Method :** 123 women with endometriosis after definite surgery (total abdominal hysterectomy with bilateral salpingo-oophorectomy) were followed in the Gynecologic Endocrinology and Menopause clinics. Patients were classified into 4 groups according to HRT regimens, i.e. control (no HRT, n = 17), estrogen only (ERT, n = 50), cyclic estrogen/progestin regimen (cyclic E/P, n = 16), and continuous combined estrogen/progestin (ccE/P, n = 24). 12 patients who received more than one regimen and 4 patients who received less than 6 months of HRT were excluded from the study. The information was obtained from the medical records.

**Results :** Mean age at surgery of all patients was 38.9 years old. Mean duration of HRT was 41.2 months. There was no difference in age at surgery or duration of follow-up in each group. There was 1 (2%) case of recurrent endometriosis and 3 (6%) cases of recurrent symptoms in the estrogen only group; none of them required additional surgical treatment. Malignant transformation was not found.

**Conclusions :** Although the present series is small, it seems that HRT is safe for postmenopausal women with underlying endometriosis. Recurrence of endometriosis has rarely been a problem with HRT, especially in those who received the combination of estrogen and progestin regimens.

**Key word :** Surgical Menopause, Endometriosis, HRT

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The favorable effects of hormonal replacement therapy (HRT) in estrogen deficient women are well established. However, in women with intact uterus, treatment with unopposed estrogen is associated with an increased risk in endometrial hyperplasia and neoplasia. The risk can be reduced with the addition of a progestational agent to the regimen<sup>(1,2)</sup>.

In hysterectomized women, there are some special conditions that warrant the use of a combined estrogen/progestin regimen. One of them is a patient with a past history of endometriosis<sup>(1,2)</sup>. Endometriosis is a common gynecologic disorder, affecting 5 per cent to 15 per cent of premenopausal women<sup>(3)</sup>. It has been implicated as the cause of symptoms in up to 30 per cent of patients undergoing laparoscopy for chronic pelvic pain<sup>(4)</sup>. When conservative treatments fail to relieve the symptoms associated with endometriosis and when child bearing has been completed, definite surgery is often indicated.

A number of patients with endometriosis are encountered with premature surgically induced menopause. Therefore, HRT is exclusively indicated for these particular patients. Nevertheless, studies concerning HRT in this condition are inadequate. Most of them are retrospective, and some reported with out-dated HRT regimens<sup>(5,6)</sup>. Estrogen replacement therapy (ERT) in patients with underlying endometriosis raises concerns that it may reactivate residual endometriosis implants or may induce malignant transformation in such implants<sup>(7,8)</sup>. Owing to these concerns, the addition of progestin to the HRT regimen is recommended<sup>(1)</sup>, although there is no outcome-based evidence to support this recommendation.

In Siriraj Hospital, there are 3 regimens of HRT used in these patients i.e. estrogen only (ERT), continuous combined estrogen and progestin (ccE/P), and cyclic estrogen and progestin (cyclic E/P) regimens. The objective of this study was to evaluate the effect of HRT regimens on the recurrence of symptoms and disease in hysterectomized patients with underlying endometriosis.

## MATERIAL AND METHOD

This observational study took place in the Gynecologic Endocrinology and Menopause Clinics, Division of Gynecologic Endocrinology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University. Medical records of 123 patients with underlying endometriosis after definite surgery (hysterectomy and bilateral salpingo-

oophorectomy) who were followed until December 2001 were reviewed. The patients were grouped according to the HRT regimens, i.e. ERT ( $n = 50$ ), cyclic E/P ( $n = 16$ ), and ccE/P ( $n = 24$ ). There were 17 patients who did not receive HRT and were used as the control group. Patients receiving more than one regimen without identifiable reason ( $n = 12$ ) and those receiving HRT for less than 6 months ( $n = 4$ ) were excluded.

The ERT comprised daily oral estrogen. The cyclic E/P comprised 21 to 28 days of oral estrogen and 10-12 days oral progestin per month. The ccE/P comprised daily oral estrogen and progestin. The estrogen may be conjugated equine estrogen (CEE) or 17- $\beta$  estradiol (E2). The progestin may be medroxyprogesterone acetate (MPA) or norethisterone (NET). All patients were started with standard postmenopausal HRT dosage, i.e. estrogen in an equivalent dose of 0.625 mg CEE and progestin in an equivalent dose of 2.5 mg MPA in ccE/P regimen or 10 mg MPA in cyclic E/P regimen. The dosage was later adjusted according to the patients' symptoms.

All the patients underwent a periodic clinical examination every 6 months. Recurrence was diagnosed based on either histological study of vaginal nodules or clinical findings i.e. pelvic pain and/or pelvic mass.

## Statistical analysis

Descriptive statistics were used to describe the patients' characteristics. Chi-square, Fisher's Exact test, and ANOVA test were used to compare the characteristics of the patients, duration of follow-up and recurrence. Statistically significant results were taken at the conventional level of the p-value being less than 0.05.

## RESULT

A total of 107 women were included in the study. Mean age at surgery of all patients was 38.9 (range 29-50) years old; mean duration from surgery to last follow-up was 3.5 (0.5-18) years; mean duration of HRT was 41.2 (range 6-90) months. These parameters were not different among the groups (Table 1).

Recurrent endometriosis was found in 1 case (2%) of the ERT group. The patient had a hemorrhagic nodule at the vaginal stump 7 years after surgery and 69 months after starting HRT; the diagnosis was confirmed by the pathological section of the biopsy specimen. Recurrent pain was also found in 3 cases (6%) of the ERT group. The pain recurred

**Table 1. HRT regimen and recurrent endometriosis and pain.**

	HRT regimens				P-value
	No HRT	ERT	Cyclic E/P*	ccE/P*	
Number	17	50	16	24	
Age at surgery (yr)	38.0 ± 6.0	38.7 ± 4.8	38.9 ± 5.0	39.4 ± 4.4	0.856**
Duration from surgery to last follow-up (yr)	3.4 ± 3.4 (0.5-11)	5.0 ± 3.9 (0.5-18)	3.8 ± 1.9 (1-8)	4.5 ± 3.6 (1-18)	0.323**
Duration of HRT (mo)	35.9 ± 22.2 (6-71)	44.8 ± 24.8 (8-88)	46.7 ± 21.9 (6-76)	52.9 ± 25.4 (6-90)	0.183**
Recurrent disease (no)	0	1 (2%)	0	0	0.765*** 1.000****
Recurrent pain (no)	0	3 (6%)	0	0	0.318*** 1.000****

Note : ERT = estrogen replacement therapy; Cyclic E/P = cyclic estrogen progestin, ccE/P = continuous combined estrogen progestin.

\* Estrogen/progestin

\*\* ANOVA

\*\*\* Chi square

\*\*\*\* Fisher's Exact test (Comparison between HRT and no HRT groups)

at 36 (Premarin 0.625 mg), 41 (Premarin 0.625 mg x 24 months then Premarin 1.25 mg x 17 months) and 46 (Premarin 0.625 mg) months after starting HRT. The symptom disappeared after changing HRT to the ccE/P regimen in one case. The others continued ERT despite the pain. None required reoperation. The recurrence was not found in the control group and in the groups receiving the progestin-containing HRT, either continuous or cyclic regimen. The overall recurrent rate was 3.7 per cent (4 in 107 cases) in the mean duration of 3.5 years.

## DISCUSSION

In the present study, the majority of endometriosis patients necessitating definite surgery were the in reproductive age (38.9 years old). The incidence of recurrent symptoms was minimal following definite surgery (TAH BSO). The overall recurrent rate of 3.7 per cent in a mean duration of 3.5 years was not higher than other studies<sup>(5,9-11)</sup>. Based on the results of a retrospective analysis of women monitored for a mean duration of 58 months after hysterectomy, those with bilateral adnexectomy had a 10 per cent risk of symptom recurrence and a 4 per cent likelihood of additional surgery, whereas those with ovarian preservation had a 62 per cent and 31 per cent chance respectively<sup>(9)</sup>.

After definite surgery, HRT was indicated either for the treatment of menopausal symptoms or the prevention of long-term consequence of hypo-estrogenic stage. The HRT was even more necessary

in younger patients. Although the incidence of recurrent symptoms is minimal following definite surgery, the potential for estrogen replacement therapy (ERT) to reactivate microscopic or residual endometriotic implants remains unclear. Endometriosis may recur in up to 15 per cent of such patients whether or not they are treated with estrogen replacement therapy (ERT) following bilateral oophorectomy<sup>(12)</sup>. Some authors suggested that ERT did not stimulate recurrence of the symptoms related to endometriosis<sup>(13)</sup> but others advocated delaying the initiation of ERT after surgery<sup>(2)</sup>. So far, it appears that there is no advantage in delaying HRT as a means of avoiding symptom recurrence<sup>(14)</sup>.

In the present study, 3 regimens of HRT were compared, using the group of patients who did not receive HRT as the control group. Recurrence was found only in the ERT group. Neither the control group nor the groups receiving progestin-containing HRT had evidence of recurrence. It seemed that progestin might protect the patients from recurrence during HRT use. However, a recent randomized controlled trial demonstrated that patients on cyclic E/P had a recurrent rate of 0.9 per cent per year, whereas no recurrence was found in the control group during the 4-year follow-up period<sup>(11)</sup>. In the present study, recurrence was not found in the cyclic E/P group. However, there were only 16 patients in this group. If the recurrent rate in this regimen was really 0.9 per cent per year, it would take 7 years before 1 case of recurrence was found.

It is possible that cyclic E/P regimen may have a higher recurrent rate than ccE/P regimen. In the cyclic E/P, cyclical change of E/P may stimulate the growth of residual endometrial tissue in a similar pattern to that found in the natural cycle, on the other hand a constant level of E/P in the ccE/P may suppress the growth. Unfortunately, until now there is no study that has enough evidence to prove this hypothesis. Neither did the result from the present study. Nevertheless, there is indirect evidence from tibolone, a steroid with combined actions of estrogen, progesterone, and testosterone, that tibolone was associated with a lower recurrent rate compared to cyclic E/P(15).

Malignant transformation was found in none of the 107 patients in the present study. Although the incidence of malignant transformation is estimated to be up to 1 per cent of all patients with endometriosis(16), those after ERT are rare and unable to be estimated. In 1998, there were at least 20 reported cases of malignant transformation in patients with underlying endometriosis and using ERT(7). Since malignant transformation took many years before its manifestation, it should be noted that a few of the presented patients were followed for more than 5 years

and the average length of follow-up was approximately 3.5 years.

Although the number of patients in the present study was too small to reach statistical significance, the results suggested that the recurrence tended to occur in patients who received only estrogen. Therefore, the authors recommend using the progestin-containing HRT in this group of patients. However, there is increasing evidence that long-term use of HRT increases the risk of breast cancer, especially with the ccE/P regimen(17,18). Since surgical menopause patients need long-term HRT, the risk and benefit of ERT and progestin-containing HRT should be periodically discussed with the patients.

## SUMMARY

Although the present series is small, it seems that HRT is safe for postmenopausal women with underlying endometriosis. Recurrence of endometriosis has rarely been a problem with HRT, especially in those who received the progestin-containing HRT regimens. The authors recommend using the combination of estrogen and progestin either the continuous or cyclic regimen in surgical menopausal women with underlying endometriosis.

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## การใช้ฮอร์โมนทดแทนในสตรีที่หมดประจำเดือนจากการผ่าตัดมดลูกและรังไข่เนื่องจากโรคเยื่อบุมดลูกงอกผิดปกติ

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เพื่อศึกษาลักษณะของการใช้ฮอร์โมนทดแทนชนิดต่าง ๆ ในสตรีที่หมดประจำเดือนภายหลังการตัดมดลูกและรังไข่เนื่องจากโรคเยื่อบุมดลูกงอกผิดปกติ คณะผู้ทำการวิจัยได้ทำการศึกษาแบบย้อนหลังโดยการทบทวนแฟ้มประวัติของสตรีจำนวน 123 รายที่ได้รับการติดตามผลการรักษาหลังผ่าตัดในคลินิกต่อมไร้ท่อทางนรีเวช โดยแบ่งผู้ป่วยออกเป็น 4 กลุ่มตามชนิดของฮอร์โมนทดแทน คือกลุ่มควบคุมที่ไม่ได้รับฮอร์โมนทดแทน 17 ราย กลุ่มที่ได้รับเอสโตรเจนเพียงอย่างเดียว 50 ราย กลุ่มที่ได้รับเอสโตรเจนและโปรเจสเตอโรนแบบเป็นรอบ ๆ 16 ราย และกลุ่มที่ได้รับเอสโตรเจนและโปรเจสเตอโรนทุกวัน 24 ราย ผู้ป่วยจำนวน 16 รายถูกตัดออกจากการศึกษาเนื่องจากมีการเปลี่ยนชนิดของฮอร์โมนโดยไม่ทราบสาเหตุที่แน่ชัด หรือใช้ฮอร์โมนน้อยกว่า 6 เดือน ผลการวิจัยพบว่าสตรีที่ทำการศึกษามีอายุเฉลี่ยขณะที่ได้รับการผ่าตัดคือ 38.9 ปี ได้รับฮอร์โมนทดแทนเฉลี่ย 41.2 เดือน พบว่าในกลุ่มที่ได้รับเอสโตรเจนอย่างเดียวมีการกลับเป็นซ้ำของโรค 1 ราย (คิดเป็นร้อยละ 2) และมีการกลับเป็นซ้ำของอาการ 3 ราย (คิดเป็นร้อยละ 6) ในขณะที่ไม่พบการกลับเป็นซ้ำในกลุ่มอื่น สรุปได้ว่าการให้ฮอร์โมนทดแทนในสตรีที่หมดประจำเดือนภายหลังการตัดมดลูกและรังไข่เนื่องจากโรคเยื่อบุมดลูกงอกผิดปกติอาจจะทำให้มีการกลับเป็นซ้ำของโรคได้ โดยมีแนวโน้มที่จะพบการกลับเป็นซ้ำในสตรีที่ได้รับเอสโตรเจนเพียงอย่างเดียว จึงแนะนำให้ฮอร์โมนทดแทนที่มีโปรเจสเตอโรนเป็นส่วนผสมในผู้ป่วยกลุ่มนี้

**คำสำคัญ :** สตรีที่หมดประจำเดือนจากการผ่าตัด, การให้ฮอร์โมนทดแทน, โรคเยื่อบุมดลูกงอกผิดปกติ

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