

Effects of Menopausal Hormone Therapy on Uterine Myoma in Menopausal Women

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Objectives: The aim of the present study is to evaluate the long term effects of estrogen-progestogen therapy (EPT) on uterine myomas volume in postmenopausal women.

Methods: We performed a retrospective analysis on postmenopausal women with asymptomatic uterine myoma during the period between April, 2008 and September, 2012. Postmenopause was defined as amenorrhea for longer than a year or serum follicle stimulating hormone levels higher than 40 IU/L. The volume of the myoma was assessed by transvaginal ultrasonography for every 6 months after administration of EPT.

Results: Thirty-eight women were included in the study, with 32 in the EPT group and 6 in the control group. Overall, uterine myoma volume (mean \pm standard deviation, cm³) in the EPT group was 19.5 \pm 24.6 at baseline, and those at 6 and 12 months were 24.7 \pm 35.1 and 28.5 \pm 56.4, respectively. Myoma volume did not change significantly with EPT, and these changes were not significantly different from the control group. Myoma volume changes were not significantly different in the subgroups according to the route of estrogen administrations and the method of progestogen administrations. Clinically significant volume increases during one year of EPT was noted in 28.1% (9/32), however, only one showed transient increases.

Conclusion: Our results suggest that treating postmenopausal woman with EPT on a long-term basis does not increase the volume of uterine myomas. (**J Menopausal Med 2013;19:123-129**)

Key Words: Estrogens, Myoma, Postmenopause, Progesterone, Uterus

Uterine myoma is the most common pelvic tumor in women, and its prevalence rate is 40–50% in women of childbearing age.^{1,2} The prevalence rate in the general population in South Korea has not been reported. The prevalence rate of uterine myoma in hospitalized patients

was found to be around 20%.^{3,4} However, its prevalence rate in general population is assumed to be higher.

The favorable effects of hormone replacement therapy (HRT) on hot flashes, phosphorus and calcium metabolism, and involution of the urogenital and cardiovascular systems

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during postmenopause are well known. In addition, HRT has an outstanding effect on the prevention and treatment of osteoporosis. However, the clinical trial of the Women's Health Initiative (WHI) in 2002 reported that the combination of conjugate equine estrogen and medroxyprogesterone acetate increased the risk of cardiovascular disorders and breast cancer.⁵ Thus, the debate over the advantages and risks of HRT continues. However, a great number of menopausal women still undergo HRT to reduce menopausal symptoms and prevent osteoporosis. The increasing knowledge of the effects of HRT has progressively reduced some traditional contraindications, diabetes mellitus, arterial hypertension, diseases of lipometabolism, and previous cardiovascular diseases. In fact some of them are today considered as clear indications able to modify the approach to HRT in postmenopause and to extend its applications. However, the administration of HRT in women with uterine myoma is still debated since hormone-dependent pathologies represent relative contraindication to HRT. Uterine myoma growth is known to be promoted by estrogen.^{5–7} Thus, doctors and menopausal patients with uterine myoma have been concerned about HRT as a risk factor for the increase in size of uterine myoma, worsening of symptoms, and the fear of cancer. However, studies about the effects of HRT on uterine myoma in menopausal women have been insufficient and remain inconclusive^{8–15} this study investigated the effects of estrogen–progestogen therapy (EPT) on the volume of uterine myomas in a year period of administration in postmenopausal women.

Materials and Methods

A retrospective study was performed among the women who visited the menopausal clinic in a university hospital from April 2008 to September 2012; subjects were menopausal women in whom an asymptomatic uterine myoma had been identified by ultrasound before starting HRT. Postmenopause was defined as amenorrhea for longer than a year or serum follicle stimulating hormone level higher than 40 IU/L. The location of uterine myoma in this study was not limited, but the maximum diameter of uterine myoma was over 2 cm, and the number of uterine myoma was less than 3 by ultrasonography. Women who had

contraindications for HRT and those with a past or currently taking oral contraceptives or HRT were excluded. The control group included menopausal women who had uterine myoma without HRT.

The size of the uterine myoma was measured by transvaginal ultrasound (5 MHz probe, Aloka SSD–1700; Toshiba, Tokyo, Japan) at baseline, 6 and 12 months after treatment. The volume of uterine myoma was calculated by the formula $0.521 \times D_1 \times D_2 \times D_3$, which used the diameters of 3 dimensions. A clinically significant change in volume was defined as a greater than 30% increase compared with baseline data.

All data are shown as mean \pm standard deviation and then A Mann–Whitney U test was used to analyze baseline data. The size change of uterine myoma was compared by a Wilcoxon two–sample test because the number of subjects was small, distribution of the data was wide, and the data did not follow normal distribution. A chi–square test was used to compare clinically significant changes in the size of uterine myoma. $P < 0.05$ was considered statistically significance.

Results

The study included 38 menopausal women. The number of members of the case with HRT was 32, and the control group without HRT was 6. All 32 cases took an EPT. The case was compared by estrogen taking methods.

The numbers in the case with oral estrogen was 22, transdermal estrogen was 10. As an oral estrogen, 12 patients has conjugate equine estrogen 0.625 mg and 8 patients has estradiol–17–valerate. As a transdermal estrogen, A 50– μ g 17 β –estradiol patch a day was prescribed to 5 patients, and 1.5 mg 17 β –estradiol gel a day was prescribed to 5 other patients. The continuous combined method was administered to 16 patients, and the sequential cyclic method, which adds medications for 12 days a month, was used in 16 patients. In the use of progestogen, 2 patients took medroxyprogesterone acetate 5 mg and 20 patients micronized progesterone 200 mg.

There were no significant differences among groups. The mean age was 55.5 ± 4.9 , the age for menarche was 15.6 ± 1.7 , the age for menopause was 51.8 ± 3.4 , and

the postmenopausal period was 3.9 ± 3.6 years. There were also no differences between the oral estrogen and the transdermal estrogen groups (Table 1).

The volume increase was not statistically significant compared to the baseline value between the case with hormone therapy and the control groups. And also there were no differences in the size of uterine myoma on baseline to 6 months, 6 months to 12 months, or baseline to 12 months. In addition, there were no differences in the change of the size of uterine myoma according to the prescription method of estrogen, or the progestogen protocol (Table 2).

However, there was a significant difference in the change of size of uterine myoma between baseline and 6 months in the oral estrogen and the transdermal estrogen groups (Table 3).

The number of cases with a significant change in the size of uterine myoma between baseline and 12 months was 9 (28.1%) (Table 4A). In 11 cases, the size of uterine myoma had significantly increased at 6 months; however, the size was unchanged or decreased after 6 months in 10 patients. Oral estrogen group in which the size of uterine myoma had increased after 6 months, was no change or decrease in size after 12 months (Table 4B, 4C, 4D). The size of uterine myoma continued to increase in the 1 remaining patient who

Table 1. Baseline characteristics of the study patients

| | Control (n = 6) | Estrogen-progestogen therapy (n = 26) | | | P value* |
|-------------------------|-----------------|---------------------------------------|------------------------------|----------------|----------|
| | | Oral estrogen (n = 22) | Parenteral estrogen (n = 10) | Total (n = 32) | |
| Age (year) | 60.5 ± 8.6 | 56.2 ± 4.3 | 53.9 ± 6.1 | 55.5 ± 4.9 | NS |
| Weight (kg) | 58.4 ± 7.3 | 61.7 ± 6.9 | 61.6 ± 11.8 | 61.7 ± 8.1 | NS |
| Height (cm) | 157.3 ± 4.6 | 156.3 ± 5.4 | 159.4 ± 3.9 | 157.9 ± 4.8 | NS |
| Age of menarche (year) | 15.7 ± 1.2 | 15.4 ± 1.9 | 16.0 ± 1.4 | 15.6 ± 1.7 | NS |
| Gravida | 3.7 ± 2.2 | 4.7 ± 2.1 | 6.1 ± 3.7 | 5.1 ± 2.7 | NS |
| Age of menopause (year) | 52.5 ± 4.6 | 51.1 ± 3.3 | 50.1 ± 3.5 | 51.8 ± 3.4 | NS |
| Years since menopause | 8.1 ± 9.9 | 4.4 ± 3.5 | 3.1 ± 3.5 | 3.9 ± 3.6 | NS |

Data are expressed as mean ± standard deviation.

*Mann-Whitney U test

NS: not significant (control vs. hormone replacement therapy group and oral vs. parenteral estrogen group)

Table 2. Changes in the volume of uterine myoma with estrogen-progestogen therapy

| | Baseline | 6 months | 12 months | P value* |
|---------------------------------------|--------------|-------------|---------------|----------|
| Control (n = 6) | 17.6 ± 26.8 | 16.5 ± 23.2 | 21.1 ± 34.6 | NS |
| Estrogen-progestogen therapy (n = 32) | 19.5 ± 24.6 | 24.7 ± 35.1 | 28.5 ± 56.4 | NS |
| Oral estrogen (n = 22) | 17.1 ± 26.1 | 18.2 ± 30.1 | 15.7 ± 24.4 | NS |
| Continuous combined (n = 11) | 20.1 ± 36.7 | 24.8 ± 41.7 | 20.5 ± 32.0 | NS |
| Sequential cyclic (n = 11) | 12.1 ± 11.0 | 12.7 ± 10.5 | 12.0 ± 13.6 | NS |
| Parenteral estrogen (n = 10) | 28.1 ± 21.5 | 36.2 ± 44.9 | 58.4 ± 91.8 | NS |
| Continuous combined (n = 5) | 8.7 ± 3.7 | 12.9 ± 7.2 | 9.5 ± 6.2 | NS |
| Sequential cyclic (n = 5) | 45.8 ± 6.7** | 60.3 ± 55.8 | 106.4 ± 115.1 | |

Data are expressed as mean ± standard deviation, cm³.

*Wilcoxon two-sample test, **P = 0.029, Wilcoxon two-sample test, sequential vs. continuous combined in parenteral estrogen group

NS: not significant between each time-interval

Table 3. Distribution of myoma volume change according to the route of estrogen administration

| Time intervals | Group | Decrease | No change | Increase | P value* |
|-----------------------|----------------------|-----------|------------|-----------|----------|
| Baseline to 6 months | Oral (n = 22) | 5 (22.7%) | 10 (45.5%) | 7 (31.7%) | 0.022 |
| | Transdermal (n = 10) | 4 (40.0%) | 1 (10.0%) | 5 (50.0%) | |
| 6 months to 12 months | Oral (n = 22) | 7 (31.8%) | 10 (45.5%) | 5 (22.7%) | 1.00 |
| | Transdermal (n = 10) | 3 (30.0%) | 4 (40.0%) | 3 (30.0%) | |
| Baseline to 12 months | Oral (n = 22) | 7 (31.8%) | 9 (40.9%) | 6 (27.3%) | 0.454 |
| | Transdermal (n = 10) | 3 (30.0%) | 3 (30.0%) | 4 (40.0%) | |

* χ^2 test

Table 4. Pattern of myoma volume changes with estrogen-progestogen therapy (EPT)

4A. Changes with one-year EPT for those from 6 to 12 months

| One-year change | Change from 6 to 12 months | | | |
|-----------------|----------------------------|------------|-----------|------------|
| | Decrease | No change | Increase | Total |
| Decrease | 6 | 3 | 1 | 10 (31.3%) |
| No change | 3 | 7 | 3 | 13 (40.6%) |
| Increase | 1 | 6 | 2 | 9 (28.1%) |
| Total | 10 (31.3%) | 16 (50.0%) | 6 (18.7%) | 26 (100%) |

P = 0.2078, χ^2 test

4B. Changes during initial 6 months and subsequent 6 months in the total EPT group

| Change to 6 months | Change from 6 to 12 months | | | |
|--------------------|----------------------------|------------|-----------|------------|
| | Decrease | No change | Increase | Total |
| Decrease | 2 | 4 | 3 | 9 (28.1%) |
| No change | 3 | 6 | 3 | 12 (59.0%) |
| Increase | 4 | 6 | 1 | 11 (18.3%) |
| Total | 9 (28.1%) | 16 (50.6%) | 7 (21.9%) | 32 (100%) |

P = 0.8698, χ^2 test

4C. Changes during initial 6 months and subsequent 6 months in the oral estrogen group

| Change to 6 months | Change from 6 to 12 months | | | |
|--------------------|----------------------------|------------|-----------|------------|
| | Decrease | No change | Increase | Total |
| Decrease | 1 | 2 | 2 | 5 (22.7%) |
| No change | 4 | 3 | 3 | 13 (59.0%) |
| Increase | 2 | 2 | 0 | 4 (18.3%) |
| Total | 7 (31.8%) | 10 (45.5%) | 5 (22.7%) | 22 (100%) |

P = 0.8993, χ^2 test

4D. Changes during initial 6 months and subsequent 6 months in the parenteral estrogen group

| Change to 6 months | Change from 6 to 12 months | | | Total |
|--------------------|----------------------------|-----------|-----------|-----------|
| | Decrease | No change | Increase | |
| Decrease | 0 | 2 | 1 | 3 (30.0%) |
| No change | 1 | 0 | 1 | 2 (20.0%) |
| Increase | 2 | 2 | 1 | 5 (50.0%) |
| Total | 3 (30.0%) | 4 (40.0%) | 3 (30.0%) | 10 (100%) |

$P = 0.7154$, χ^2 test

was prescribed transdermal estrogen. A hysterectomy was performed at patient's request, and a benign uterine myoma was confirmed by pathological study.

Discussion

Little has been published referring to the effect of HRT on uterine myomas in postmenopausal women. However, it is assumed that uterine myoma is strongly related with the physiological changes of ovarian hormone in the blood because uterine myoma has not been reported in women who have not started menarche, and the size of uterine myoma decreases after menopause.⁵ The presence of oestrogen and progesterone receptors in fibromatous tissue has now been confirmed by several studies. It is well known that uterine myoma occurrence and growth is dependent on estrogen.¹⁶ Furthermore, the role of progesterone in the proliferation of uterine myoma has been proposed. The effect of estrogen and progesterone on the occurrence and growth of uterine myoma has been reported to be strongly related with the increase of hormone receptors on uterine myoma tissue.^{17~19} The size of uterine myoma decreases after menopause, which is thought to be associated with decreasing levels of estrogen and progesterone in the blood. However, the effect of exogenous hormone on uterine myoma in menopausal women has not been definitively concluded. In this study, there was no significant change in the size on uterine myoma by HRT in menopausal women. In addition, there were no differences according to the prescription methods of estrogen and progestogen protocols.

The use of HRT in women with myomas has so far received scant attention in the literature, although the high

prevalence of this disease. Various studies have reported effects of HRT on uterine myoma after menopause.^{8~15} It is thought that the size of uterine myoma can be affected by various prescription methods of estrogen, doses of estrogen, and the types and doses of combined progestogen. The size of uterine myoma is not affected by oral estrogen type in most studies.^{9,12,13,20} However, the effects of transdermal estrogen is debated.^{8,11~13} Some reported that the size of uterine myoma is not increased by using the transdermal 17 β -estradiol patch.^{8,11} On the other hand, there are other agreement that the size of uterine myoma did increase in the transdermal estrogen group relative to the oral estrogen group.^{12,13} However, in this studies, it is not clear that the increase of the size of uterine myoma is caused by the prescription method of estrogen or the progestogen protocol because different protocols of progestogen were used in the oral estrogen and the transdermal estrogen groups. However, Sener et al.¹³ argued that the increase in the size of uterine myoma was caused by the different progestogen doses (5 mg medroxyprogesterone acetate vs. 2.5 mg) rather than the different methods of estrogen because there was no difference in estrogen level in the blood. Based on the results of a randomized study in 30 menopausal women, the size of uterine myoma had been significantly increased in the group prescribed 5 mg medroxyprogesterone acetate when 2 mg micronized estradiols were combined with 2.5 mg and 5 mg medroxyprogesterone acetate in each group.²¹

In this study, similar protocols of progestogen were used in the oral estrogen and the transdermal estrogen groups; nevertheless, there was a significant difference in the size of uterine myoma between baseline and 6 months. Remarkably, the results of the present study are uneven and inconsistent,

including increases, maintenance, and decreases in the size of uterine myoma. Thus, it is suggested that the direct effect of HRT on uterine myoma is not minimal in menopausal women. HRT should be discontinued if an increase in the size of uterine myoma occurs during HRT. Attentive size follow-up are important in case with uterine myoma during HRT. Colacurci et al.⁸ reported that follow-up ultrasounds performed once every 3 months are helpful to evaluate changes in the size of uterine myoma. And also, the decrease in the resistance of the uterine artery by the Doppler test is related to an increase in the size of uterine myoma after HRT.

Continuous growing uterine myoma causes doctors and patients anxious during HRT because it is difficult to diagnose uterine myoma and uterine sarcoma differently with only diagnostic radiologic studies including ultrasound. Uterine sarcoma is a rare malignant tumor which occurs as less than 1% of all malignant tumors, and has poor prognosis.²² Less than 0.5% patients who were diagnosed with uterine myoma before surgery are found as the sarcoma after surgery.²³ In addition, it is unknown whether uterine sarcoma originates from uterine myoma or uterine muscle cells. Besides, there is no evidence that exogenous estrogen increases the incidence rate of uterine sarcoma. If the size of uterine myoma increases continuously, medications should be changed, or medications should be discontinued temporarily and then check up the change of size.

This study has some limitations. It is a retrospective study that depends on medical records, and the number of the subjects is small. Another limitation is that the ultrasounds were performed by different radiologists. In addition, various hormone medications could have interactions with one another. Therefore, various prospective randomized studies are needed with a sufficient number of subjects.

In conclusion, HRT did not affect the size of uterine myoma significantly in menopausal women. There were no differences by used methods of estrogen or progestogen protocols. Our results appear to encourage the use of HRT in menopausal women with uterine myomas. However, attentive follow-up is needed in case of a continuous increase in the size of uterine myoma.

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