



# Management of menopause in women with a history of endometriosis

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## Abstract

Due to increasing life expectancy, women spend a significant part of their lives in menopause. Women with a history of endometriosis are more likely to become menopausal at an early age due to bilateral oophorectomy or repeated ovarian surgery. In addition, some medical therapies used for endometriosis, such as gonadotropin releasing hormone agonists or progestins reduce bone mineral density. Furthermore, women with endometriosis have a higher background risk of cardiovascular disorders and hypercholesterolemia. Hence, it is important to recommend the use of hormone replacement therapy (HRT) to these women when they become menopausal, at least until the age of natural menopause. Although based on limited data, there is a possibility of reactivation of symptoms of endometriosis or its lesions, and a theoretical possibility of malignant transformation, although this remains unproven. Therefore, women should be advised in the light of this information before starting HRT after the age of natural menopause and are asked to seek help if they experience symptoms that may indicate these changes. Estrogen only HRT should be avoided and combined HRT preparations should be recommended, even after a hysterectomy. (J Turk Ger Gynecol Assoc 2024; 25: 107-11)

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## Introduction

Endometriosis is estimated to be present in 5-10% of women in the general population, while postmenopausal women form 2-5% of cases in the published series (1-5). As in reproductive age women, the correct prevalence of endometriosis in menopausal women is not clearly known due to some women being asymptomatic (6). Endometriosis is a hormone dependent condition; it is rare or absent before menarche, it commonly affects reproductive age women, its prevalence reaching a peak in the late reproductive years and it regresses after menopause (7,8). Although many women become asymptomatic after menopause, some will continue to have symptoms. Persistent/recurrent symptoms may be due to hormone replacement therapy (HRT) but some women are still

symptomatic despite not being on HRT (9). It is postulated that extra-ovarian (conversion of androgens in the adipose tissue depending on body weight) or locally produced estrogens (due to increased aromatase activity in endometriotic tissue) continue to stimulate endometriotic lesions in symptomatic women (10-13).

In clinical practice, menopausal women may present either following natural menopause or following surgery to remove ovaries with or without removal of the uterus/endometriosis as part of their treatment for endometriosis. Endometriotic tissue may still be present in some menopausal women even after prior surgical treatment, as there may be residual or recurrent lesions of endometriosis in a significant proportion.

Adverse health outcomes of early surgical menopause, such as dementia, cardiovascular disease and osteoporosis, are



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well known and this applies to women with a history of endometriosis (14). These women may even be at higher risk due to the possible use of medical therapies that may have caused reduced bone mineral density (BMD), such as gonadotrophin releasing hormone (GnRH) analogues or progestins. In addition, women with endometriosis are known to have a higher background risk for hypercholesterolemia and cardiovascular diseases, or conditions predisposing to cardiovascular disease such as hypertension (15,16). Therefore, use of HRT becomes an issue of discussion during consultations with these women (15,16).

In this article we will give a practical overview of management of postmenopausal endometriotic symptoms, use of HRT in postmenopausal women with a history of endometriosis and future risk of malignancy.

### **Management of symptomatic postmenopausal women with endometriosis**

There are few data in the literature on treatment modalities for symptomatic post-menopausal endometriosis. Pelvic pain tends to be the most common presenting symptom, mostly caused by endometriotic lesions, as in reproductive age women (13). Others may present with a pelvic mass or some form of bleeding, such as vaginal bleeding, hematuria, rectal bleeding, and hemoptysis (9). Since the risk of malignant disease is naturally higher in women with endometriosis than in other groups, a careful examination of the genital, gastrointestinal and urinary tracts with appropriate imaging should be performed, depending on the nature of the symptom(s) (3,17).

If the symptoms are triggered by initiation of postmenopausal HRT, consideration can be given to discontinuation of HRT, following discussion with the woman. This may be more acceptable if the woman has become menopausal naturally. However, in early menopause, particularly following surgical menopause, concern over the detrimental impact of hypoestrogenism may make this approach less viable (10). Other approaches include reducing the dose of estrogen, switching from sequential to continuous combined HRT and changing the type of progesterone.

Medical treatment options for symptomatic endometriosis are limited in postmenopausal women. Limited data published in the literature suggest aromatase inhibitors (AI), including anastrozole, letrozole or exemestane, can be administered orally at doses of 1-5 mg/day, especially when surgery is not feasible. The main mechanism of action of AI is the inhibition of cytochrome P450, which catalyzes the conversion of androgens to estrogens. They not only inhibit estrogen production in the ovaries, adrenal glands, brain, and peripheral adipose tissue but also regulate local estrogen formation in endometriotic lesions as well (11). These drugs have been reported to be

effective in treating postmenopausal recurrence, reducing mass and decreasing pressure, as well as having a good safety record in the development of postmenopausal breast cancer (12). However, AI increase the possibility of osteoporosis in the long term (18). Besides, BMD may have already diminished due to prior use of GnRH agonists or progestins in patients with endometriosis (19). Additional bone loss due to the menopausal process requires special attention due to the possible low background BMD in these patients (20). It should be remembered that BMD decreases significantly after treatment with AI, even with concomitant use of calcium and vitamin D (21). Hot flashes, vaginal dryness, and arthralgic symptoms are the other possible side effects (21).

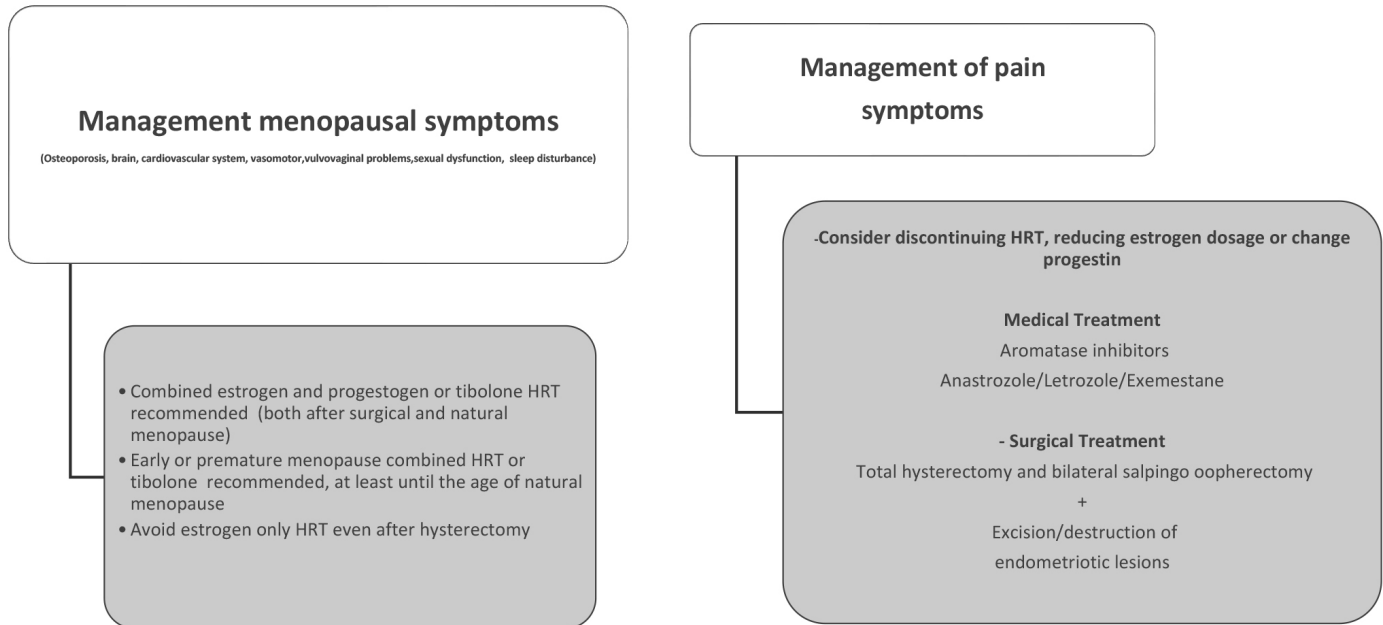
Surgery remains a viable option for symptomatic postmenopausal women, especially if there are visible endometriotic lesions on imaging, particularly when new ovarian cysts develop. The presence of suspicious appearances within endometriotic lesions, either within or outside the ovaries in women after the age of natural menopause should prompt appropriate investigations and treatment following local guidelines. Even in the absence of any suspicious lesions, surgery would usually involve removal of the ovaries, uterus and endometriotic lesions, if surgical treatment is chosen (Figure 1).

### **Use of HRT in women with a history of endometriosis**

HRT is effective in relieving menopausal symptoms, but its use in postmenopausal endometriosis patients may lead to reactivation of symptoms or endometriotic lesions and malignant transformation (22). Currently, there is limited published information on the efficacy of HRT in relieving menopausal symptoms, specifically in women with a history of endometriosis (13). Most published data come from studies which report on the efficacy of HRT following surgical menopause, hence there is no data on the use of HRT in women with endometriosis who have reached menopause naturally (13). Patients who undergo surgical menopause for endometriosis at a younger age report sudden onset of more severe menopausal symptoms (23).

Considering the aforementioned health risks in women with a history of endometriosis who become menopausal earlier than the natural age of menopause, HRT is strongly recommended, at least until the age of natural menopause (13,24). It has been reported that 40% of endometriosis patients do not take HRT after hysterectomy and oophorectomy, including those who enter surgical menopause prematurely (25). Therefore, it is suggested that consideration could also be given to ovarian preservation in hysterectomy for endometriosis (25).

Due to the risk of recurrence of endometriosis or its symptoms, and the theoretical risk of malignant transformation, use of



**Figure 1. Management of postmenopausal endometriosis**

combined HRT with estrogen and progesterone or tibolone has been recommended, even after hysterectomy, in international guidelines such as the European Society of Human Reproduction and Embryology and European Menopause and Andropause Society for women with a history of endometriosis (13,24). A potential disadvantage of using progesterone in all women with a history of endometriosis is a slight increase in risk of breast cancer, compared to estrogen only HRT (26).

A survey conducted among a total of 216 physicians in the United Kingdom revealed that only two-thirds of the gynecologists/menopausal physicians prescribe combined HRT, 11.1% use tibolone, 13.0% only estrogen HRT and 7.8% prescribe variable HRT (27). The underlying reason for this was that some physicians stated they would not prescribe HRT because there was insufficient evidence to support this, while others argued that HRT was only necessary for severe symptoms, especially if the lesions had not been effectively removed. In addition, some doctors were concerned about progestogen-associated increased risk of breast cancer (28).

Matorras et al. (29) compared women who received HRT (n=115) following bilateral salpingo-oophorectomy (BSO) ± hysterectomy with a control group (n=57) who did not receive HRT following surgery. In the group of patients who started treatment four weeks after BSO surgery, 3.5% had recurrent symptoms after approximately four years, whereas there were no recurrences in the group who did not receive HRT. The risk of recurrence was higher, especially in cases in which hysterectomy was not performed, or a subtotal hysterectomy was performed (as opposed to total hysterectomy) and in

those with endometriotic lesion >3 cm. These differences were not statistically different but the numbers were too small to reach statistical significance (29). Another non-randomised retrospective study from Thailand showed recurrence of endometriosis symptoms in 6% of 50 (n=3) women who used estrogen only HRT compared to those who did not use HRT (n=17) or used combined HRT (n=40) following surgical menopause (30).

Based on this limited information there is overall agreement that HRT can be used in women with a history of endometriosis for the treatment of menopausal symptoms and to protect bone health in the long term. Combined HRT is recommended and use of estrogen only HRT should be avoided (13,31).

#### **HRT in women with a history of menopause and risk of malignant transformation**

Malignant transformation whilst using HRT is uncommon and has only been published in case reports. Some studies have shown that the prevalence of ovarian cancer in women with endometriosis is higher than that of sporadic ovarian cancer in the general population (32). A systematic review and meta-analysis of published studies showed that, whilst there is no overall increase in risk of cancer in women with a history of endometriosis, the lifetime risk of ovarian cancer increased from 1.3% in the general population to 2.5%, breast cancer from 12.8% to 13.4% and thyroid cancer from 1.3% to 1.8%, whereas the risk of colorectal cancer did not change and the risk of cervical cancer was lower (33). In another systematic review, Gemmel et al. (22) found malignant transformation

in 25 patients between the ages of 38 and 75 years. The most common complaints in these patients were vaginal bleeding, pain, a mass in the pelvis, weight loss, constipation and flank pain. Histologically, the most common malignancies were endometrioid adenocarcinoma and the other histological types included adenosarcoma, clear cell cancer, Mullerian carcinosarcoma and endometrial stromal sarcoma. Of these, 76% had received unopposed estrogen therapy and three of these 25 women died from cancer.

The impact of HRT on malignant transformation of endometriosis remains uncertain. A recent study from South Korea examined 20,608 postmenopausal women with de novo endometriosis or a history of endometriosis and compared the impact of HRT on the risk of ovarian cancer. These authors showed that HRT did not increase the risk of ovarian cancer (34).

## Conclusion

Women with a history of endometriosis are more likely to undergo repeated surgery with decreasing ovarian reserve and early menopause due to removal of ovaries. In addition, some medical therapies used for endometriosis, such as GnRH agonists or progestins reduce BMD. Furthermore, women with endometriosis have a higher risk of cardiovascular disorders and hypercholesterolemia. Hence, it is important to recommend use of HRT to these women when they become menopausal at an early age, at least until the age of natural menopause. Although based on limited data, there is a possibility of reactivation of symptoms of endometriosis or its lesions, and a theoretical possibility of malignant transformation, although this remains unproven. Women should be advised to consider these before starting HRT and are asked to seek help if they experience symptoms, which may indicate these changes. Estrogen only HRT should be avoided and combined HRT preparations should be recommended even after a hysterectomy.

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