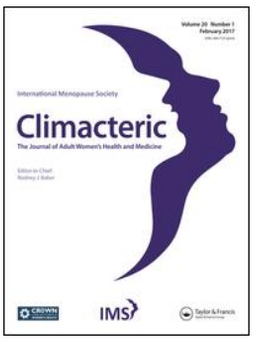

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REVIEW

Endometriosis after menopause: physiopathology and management of an uncommon condition

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ABSTRACT

Endometriosis is a hormone-dependent inflammatory disease that is usually characterized by infertility and pain symptoms. This disease mainly occurs during the reproductive years and is rarely diagnosed after menopause. We discuss the physiopathology of this condition after menopause as well as treatment options and the risk of malignant transformation. Occurrence or progression of postmenopausal endometriosis lesions could be related to extra-ovarian production of estrogen by endometriosis lesions and adipose tissue, which becomes the major estrogen-producing tissue after menopause. Postmenopausal women with symptomatic endometriosis should be managed surgically because of the risk of malignancy; medical treatments can be used in cases of pain recurrence after surgery. Aromatase inhibitors act by decreasing extra-ovarian estrogen production and by blocking the feed-forward stimulation loop between inflammation and aromatase within endometriosis lesions. The evidence is currently insufficient to support a conclusion about the optimal hormone replacement therapy for women with endometriosis. The question of malignant transformation of endometriosis in response to hormone replacement therapy in women with a history of endometriosis remains unanswered and needs a long-term follow-up study to evaluate the risk of an adverse outcome. Further studies should be performed to determine the optimal management of menopausal women with endometriosis.

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Introduction

Endometriosis is a hormone-dependent condition of women in their reproductive years that usually begins at menarche or early in adulthood. In the majority of cases, hypo-estrogenism induced by the cessation of follicular growth and ovulation at menopause leads to regression of endometriosis lesions and to alleviation of pain symptoms. Some ectopic endometrial islets can, however, remain active after menopause, causing persistence of disabling pain and other endometriosis-based symptoms. Occurrence of *de novo* lesions after menopause has also been reported; however, it is difficult to ascertain the true *de novo* nature of these lesions and to distinguish them from pre-existent lesions that become symptomatic only after menopause[1,2]. Asymptomatic endometriosis lesions can be discovered incidentally during pelvic imaging or surgical interventions performed on menopausal women for other conditions.

Pathogenesis of endometriosis after menopause

Data on the physiopathological mechanisms implicated in postmenopausal endometriosis are limited. Around 2–4% of postmenopausal women are estimated to suffer from endometriosis. The fact that endometriosis lesions are able to develop or persist in menopausal women in the absence of menstrual cycles and in a hypo-estrogenic environment sheds doubt on Sampson's physiopathological theory of retrograde bleeding and implicates other mechanisms[3–5].

Endometriosis is a well-known estrogen-dependent condition. During the reproductive years, estrogenic stimulation mainly results from ovarian secretion. After menopause, endometriosis lesions can be stimulated by estrogen from extra-ovarian sources including adipose tissue, the adrenal glands, or an exogenous source (e.g. hormone replacement therapy, HRT)[3,6]. Another mechanism has been suggested by the work of Bulun and colleagues[6,7]. This team describes estrogen production by endometriosis lesions themselves, whereas other authors have not confirmed the presence of aromatase expression in ectopic lesions[7,8]. According to Bulun and colleagues, aromatase is expressed in endometriosis implants and in the eutopic endometrium of women with endometriosis; autocrine and paracrine effects result in local production of estrogen. Estrogens stimulate COX-2 in a positive feedback loop, which increases the formation of prostaglandin E2 and, thereby, increases aromatase activity (Figure 1). This theory could explain how endometriosis lesions may persist and become symptomatic in the hypo-estrogenic environment after menopause[6]. Aromatase inhibitors (AIs), which act by interrupting this local feed-forward loop, thus reducing intralesional estrogen production, could

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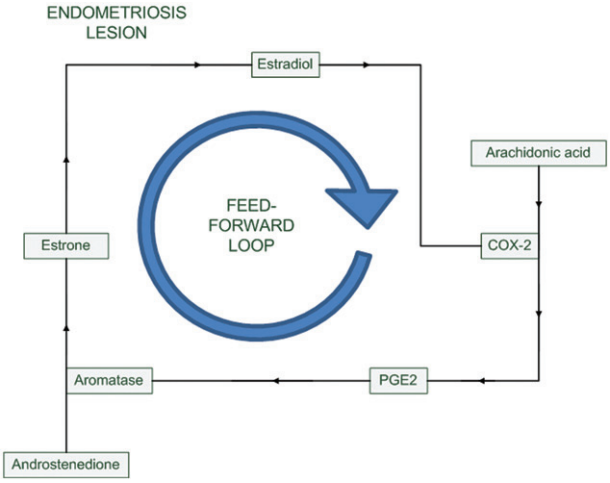

Figure 1. Feed-forward stimulation loop in endometriosis lesions. Adapted from Attar and colleagues[37]. Estrogen stimulates cyclo-oxygenase-2 (COX-2), which elevates prostaglandin E2 (PGE2) concentrations. PGE2, in turn, stimulates aromatase, allowing the androgen to convert to estrogen. This loop supports the growth of the lesion and local inflammation.

be an alternative treatment for women with postmenopausal endometriosis.

Management of endometriosis after menopause

The first-line treatment for new-onset symptomatic postmenopausal endometriosis should be surgical because of diagnosis uncertainty, the risk of associated malignancy, and the potential risk of subsequent malignant transformation. Several cases of neoplasia in postmenopausal endometriosis lesions have been reported in the literature and are summarized in a review article by Soliman and colleagues[9]. Imaging techniques, such as transvaginal ultrasound and pelvic magnetic resonance imagery, are generally not sufficiently accurate to distinguish between endometriosis lesions and cancer. The diagnosis must therefore be made after surgery and histological analysis.

Surgical treatment of postmenopausal endometriosis has a dual role of providing diagnostic confirmation and relieving pain symptoms. However, recurrences are common after surgical treatment and second-line drug treatment may be necessary (see Figure 2).

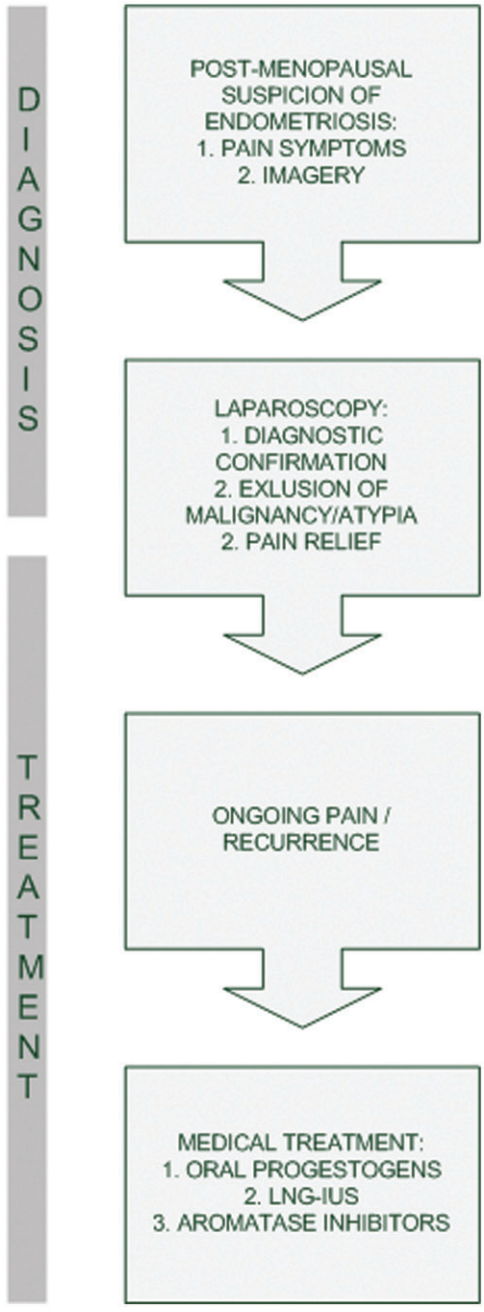

Figure 2. Algorithm of endometriosis management in postmenopausal women.

Aromatase inhibitors

Aromatase is the enzyme that catalyzes the conversion of androstenedione and testosterone to estrone and estradiol, respectively. This enzyme is expressed by growing ovarian follicles and other cell types including adipocytes. Its expression by endometriosis implants and eutopic endometrium of women with endometriosis is controversial; some studies report its expression, whereas others do not confirm this finding[7,8].

Third-generation AIs (exemestane, letrozole, and anastrozole) that selectively block the action of aromatase have been developed and validated for the adjuvant treatment of postmenopausal breast cancers expressing sex steroid hormone receptors. In premenopausal women, AIs have been studied in combination with treatments that block the hypothalamic–pituitary–ovarian axis. This combination treatment is needed because the isolated use of AIs leads to central hypo-estrogenism, which results in elevation of follicle stimulating hormone levels and ovarian stimulation. During the reproductive years, estrogen is mainly produced by the ovaries with a minimal contribution by extra-ovarian secretion. Therefore, first-line therapy for endometriosis is to block ovarian function with gonadotropin releasing hormone (GnRH) analogs, progestogens, or a combined estrogen/progestogen pill. AIs can be considered in addition to other treatments in patients with persistent pain. A randomized, controlled trial showed that combining AI with GnRH agonists increases the pain-free interval and decreases the recurrence of symptoms after surgery in women

before menopause[10]. Endometriosis after menopause is a rare condition and data on the use of AIs in symptomatic women are scarce. AIs could be an interesting option because of their action on extra-ovarian and intralesional estrogen production (Figure 1). Only five clinical cases have been reported and they have been summarized in a review article by Polyzos and colleagues[11].

Those five clinical cases involved women with recurrent symptomatic endometriosis lesions. Two women were taking HRT. One patient had a nodule at the vaginal apex, two had large masses, one a nodule in the bladder wall and the last one gastrointestinal and urethral lesions. Prolonged AI treatment was effective at alleviating pain, including urinary and digestive symptoms. In one patient, short-term treatment with exemestane was ineffective; her symptoms improved after a change of treatment to letrozole. AI use also reduced the size of her lesions, as observed on imaging.

The use of AIs for the treatment of postmenopausal endometriosis, although attractive from a physiopathological point of view, has been studied in few women with heterogeneous characteristics. Larger studies should be performed before making conclusions about its use after menopause. AI can cause many side-effects, including hot flushes, vaginal dryness, joint pain, and a risk of decreased bone mineral density because of its profound suppression of extra-ovarian estrogen secretion. An assessment of osteoporosis risk factors and a bone mineral density test should be performed before prescribing an AI[12]. Low-dose estrogen add-back therapy can be considered, as described for one patient in the case series by Polyzos and colleagues[13–15]. The risk of treatment failure and endometriosis lesion progression during AI therapy is unknown.

Progestogens

Progestogens, synthetic molecules that are derived from progesterone or from 19-nortestosterone, have been widely used and are effective in treating endometriosis pain in women before menopause. They act on two levels: (1) through negative feedback on the hypothalamic–pituitary–ovarian axis inducing anovulation; and (2) by inducing decidualization and atrophy in endometriosis lesions through direct action on the progesterone receptor[16,17]. Hypothetically, progestogens could be used as a treatment alternative in postmenopausal endometriosis for their direct action on lesions through the progesterone receptor. However, there have been no reports on their use in that population. Another alternative is the levonorgestrel intrauterine system (LNG-IUS). The LNG-IUS is indicated for contraception and for the treatment of abnormal uterine bleeding in premenopausal women. The LNG-IUS can be continued after menopause and can be used in conjunction with a systemic estrogen for HRT[18]. Several small, randomized, controlled trials have compared the LNG-IUS with postoperative expectant management or other hormonal treatments for endometriosis-related pain symptoms. Studies have shown a reduction in the severity of endometriosis lesions at laparoscopy and a reduction in the size of rectovaginal lesions on ultrasound in response to LNG-IUS treatment[19–21]. The mechanism by which the LNG-IUS decreases endometriosis-related symptoms is not fully understood. Because plasma levonorgestrel levels are too low to exert a strong feedback effect on the hypothalamic–pituitary–ovarian axis, a direct action on endometriosis lesions can only be hypothesized. Endometrial levels of levonorgestrel achieved with the LNG-IUS have been shown to be much higher than those obtained with oral administration. Continuous exposure to levonorgestrel exerts a local effect on the endometrium, inducing atrophy. This direct local effect could also be of interest for treating endometriosis symptoms in postmenopausal women, but there have been no reports on the use of the LNG-IUS in that population.

Oncological risk and postmenopausal endometriosis

Endometriosis is a benign proliferative condition; however, malignant transformation may occur in almost 1% of cases, occurring most commonly in ovarian lesions[22,23].

Endometriosis cells share common features with malignant cells; they are able to proliferate and survive in an ectopic environment and to metastasize to distant locations[24].

Ovarian clear-cell carcinomas are commonly associated with gene mutations of the AT-rich interactive domain 1A (ARID1A), coding for the tumor-suppressor protein BAF250, and the mutation of phosphatidyl inositol 3-kinase catalytic subunit alpha (PIK3CA). These mutations frequently co-exist and have been shown in endometriotic epithelial cells adjacent to clear-cell carcinomas. These findings suggest that they may be implicated in the benign course of endometriosis and its malignant transformation[25–27]. The risk of malignant transformation increases after menopause and after introduction of HRT, especially in case of unopposed estrogen substitution[9,28,29]. Stern and colleagues reviewed 1000 consecutive cases of surgically removed endometriosis and reported that the most common malignancies associated with endometriosis were endometrioid and clear-cell ovarian cancers[22]. In an analysis of 13 case–control studies (23 000 women, 7911 cancer diagnoses), Pearce and colleagues reported an increased risk of clear cell (odds ratio (OR) 3.05; 95% confidence interval (CI) 2.43–3.84), endometrioid (OR 2.04; 95% CI 1.67–2.48) and low-grade serous (OR 2.11; 95% CI 1.39–3.20) histology in patients with a self-reported history of endometriosis. The risk of high-grade serous and mucinous tumors was not increased[30]. The results of that study might have been limited by the fact that endometriosis was self-reported and the type of endometriosis (endometrioma, superficial, or deep endometriosis) was not reported[31].

Morotti and colleagues retrospectively analyzed 72 cases in postmenopausal women who underwent surgery for various indications (ovarian cysts in 43% of cases, ovarian cancer in 13.9%, endometrial cancer in 13.9%, and atypical endometrial hyperplasia in 6.9%) in whom endometriosis was diagnosed during surgery and confirmed histologically[2]. Only

Table 1. Studies assessing the effects of estrogen exposure on endometriosis recurrence and risk of malignant transformation.

Author (year)	*Study type*	*Sample size and subjects*	*Estrogen exposure*	*Objective and method*	*Results*
Zanetta *et al.* (2000)	Retrospective study	31 women with tumors and endometriosis	15 with obesity, 15 without HRT; 9 with estrogen only, 2 with estrogen–-progestin combination, 1 with progesterone only, 4 unknown	To compare clinical and epidemiologic variables and identify risk factors for the development of cancer	Cancer mainly arose in the ovary (15 patients) and the most common histological types were endometrioid and clear cell tumors. When compared with controls, no significantly higher risk for developing cancer was found except in obese patients with the use of unopposed estrogens ($p = 0.05$) *Hyperestrogenism stimulated the development of cancer endometriosis foci*
Rattanachaiyanont *et al*. (2003)	Observational retrospective study	123 women who underwent a total hysterectomy for endometriosis (surgical menopause)	17 without HRT; 50 with estrogen only, 16 with cyclic combined estrogen/progestin, 24 with continuous combined estrogen/progestin	To evaluate the effect of HRT regimens in surgical menopause patients with underlying endometriosis	There was 1 (2%) case of recurrent endometriosis overall and 3 (6%) cases of recurrent symptoms in the estrogen-only group; none required additional surgical treatment. No malignant transformation was found *HRT seems to be safe for postmenopausal women with underlyingendometriosis with rare recurrence, especially in those who received estrogen and progestin combination regimens*
Matorras *et al.* (2002)	Randomized trial	172 women who underwent a bilateral oophorectomy (BSO) with/without a hysterectomy for endometriosis (surgical menopause)	115 sequential combined HR; 57 without HRT, no placebo	To estimate the risk of endometriosis recurrence after HRT in women who underwent BSO with/without a hysterectomy	3.5% of recurrence (4/115), in women who received HRT. Risk factors for recurrence with HRT were detected: peritoneal involvement >3 cm (2.4% recurrence per year vs. 0.3%) and incomplete surgery (22.2% per patient vs. 1.9%) *HRT is a reasonable treatment option for women with BSO. However, in cases of peritoneal involvement >3 cm, the recurrence rate makes HRT a controversial option; if HRT is indicated, the patient should be monitored closely*
Namnoum *et al.* (1995)	Historical prospective study	138 women who underwent a hysterectomy for endometriosis	109 with oophorectomy, 29 without oophorectomy	To determine the relative risk of symptom recurrence and/or secondary intervention after a hysterectomy without oophorectomy to treat endometriosis	Ovary conservation was associated with a relative risk for pain recurrence of 6.1 (95% confidence interval [CI] 2.5–14.6) compared with patients with oophorectomy The relative risk for a second intervention in patients with ovary conservation was 8.1 (95% CI 2.1–31.3). *Patients with ovary conservation seem to develop recurrent pain more often and be at greater risk of needing a second intervention*
Fedele *et al.* (1999)	Randomized trial	21 postmenopausal women with residual endometriosis	10 with transdermal estradiol, 11 with tibolone	To compare the effect of transdermal estradiol with tibolone in postmenopausal women with residual endometriosis after 12 months	No patient suspended therapy because of side-effects. Four patients in the estradiol group experienced moderate pelvic pain during treatment compared with only 1 patient in the tibolone group. One patient in the estradiol group reported severe dyspareunia *Tibolone may be a safe hormonal treatment for postmenopausal women with residual endometriosis*

16.7% of women had a history of endometriosis. The most common localization of endometriosis was the ovary (79.2%). Among patients with ovarian endometriosis cysts, 64.9% had no hyperplastic lesions, whereas 35.1% had varying degrees of metaplasia (5.3%), hyperplasia (12.3%), atypical hyperplasia (10.5%), or endometrioid carcinoma (7%). That study showed that endometriosis can be an incidental finding during pelvic surgery for various indications such as ovarian or endometrial cancer.

HRT, recurrence of endometriosis, and malignant transformation risk

Endometriosis lesions – the growth and expansion of which are stimulated by estrogen[29] – can have malignant transformation potential. This risk is minimal in young women but it becomes more severe in women after menopause[28]. Therefore, the effect of HRT for menopause on the recurrence and malignant transformation risk in women with endometriosis should be considered. This issue is particularly important because some women suffering from severe symptomatic endometriosis undergo hysterectomy and bilateral salpingoophorectomy for pain relief. In those cases, a combined HRT is usually prescribed.

In Table 1, we review studies assessing the effect of estrogen exposure on endometriosis recurrence and the risk of malignant transformation[29,32–34]. The studies published by Matorras and Fedele are the only randomized trials published on the subject of HRT in women with endometriosis[33,35]. The results of these two studies were subsequently summarized in a Cochrane review in which the authors concluded that HRT may increase the risk of endometriosis symptoms and disease recurrence after surgically induced menopause[36]. Current data are, however, insufficient to justify not administering HRT for symptomatic women after surgically induced menopause.

Conclusion

Endometriosis in postmenopausal women is a rare condition. Surgical treatment is the first-line therapy to exclude malignancy, but drug treatment may be an option in case of pain recurrence after surgery. The evidence is currently insufficient to support any conclusions about the optimal HRT regimen for women with endometriosis. Postmenopausal women should be conscientiously evaluated before initiating HRT. Patients with endometriosis receiving HRT should be monitored regularly for pain recurrence.

The question of malignant transformation of endometriosis with HRT remains unanswered. Few data suggest a higher malignancy risk with estrogen-only HRT compared with combined HRT. The hypothesis that progesterone or progestogens could have an antiproliferative effect on endometriosis lesions and reduce the risk of malignant transformation remains unexplored. Further studies should be performed to determine the optimal management of postmenopausal women with endometriosis. However, the low prevalence of this disease in that age group will likely limit future studies.

Conflict of interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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