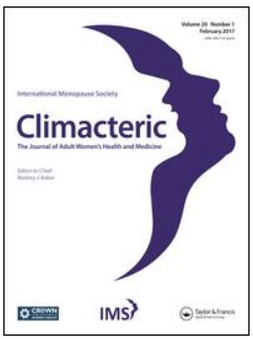

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REVIEW

Postmenopausal endometriosis: drawing a clearer clinical picture

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ABSTRACT

This review aims to draw a clearer clinical picture of postmenopausal endometriosis. Based on limited literature, postmenopausal endometriosis emerges as an infrequent entity but with a clinical picture significantly unlike that of premenopausal endometriosis. In contrast to the premenopausal disease, postmenopausal endometriosis occurs in a state of ovarian estrogen deficiency, appears to have a greater predisposition to malignant change, may have a greater tendency to spread to extragonadal organs and develop into constrictive and/or obstructive lesions, and is preferably treated surgically. The need to use hormone therapy for the management of menopausal symptoms that may concomitantly affect women with postmenopausal endometriosis is an unresolved therapeutic dilemma. This is mainly because the relationships of menopausal hormone therapy to recurrence of endometriosis and, more importantly, to increased risk of malignant degeneration, remain unclear.

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Postmenopausal endometriosis; menopausal hormone therapy; malignant transformation; surgical approach; aromatase inhibitors

Introduction

Pelvic endometriosis is an estrogen-dependent disease that predominantly affects reproductive-age women and is generally expected to become less active or even regress with the onset of natural or surgical menopause[1]. Still, endometriosis may occur and has been increasingly reported after the menopause.

The clinical picture of postmenopausal endometriosis has not yet been clearly defined. There is a dearth of information on the subject; whatever data are available consist of case series and case reports.

Defining the clinical picture of postmenopausal endometriosis requires answers to a number of questions. How frequent is postmenopausal endometriosis? Considering that estrogen is essential to the development and growth of endometriosis, how can endometriosis exist in a state of ovarian estrogen deficiency? Is postmenopausal endometriosis a persistence or recurrence of the premenopausal disease or is it a new lesion? Is the risk of malignant change higher with advancing age? With longer duration of premenopausal disease, is there more extragonadal involvement, particularly of the adjacent intestinal and urinary organs? Will the use of menopausal hormone therapy affect the course of postmenopausal endometriosis? Is surgery rather than medical the better management option?

The objective of this review is to draw a clearer clinical picture of postmenopausal endometriosis based on analysis of the data, admittedly still inadequate, available to date. Such a characterization of postmenopausal endometriosis should be essential to understanding the disease and to providing appropriate clinical care to this subset of women with an uncommon but plausibly serious type or consequence of endometriosis. A total of 89 published studies were reviewed which consisted of 15 case series and 74 case reports.

Prevalence

The prevalence of postmenopausal endometriosis, based on published cohorts of women with endometriosis, is less than 3%. An early (1980) case series[2] showed that endometriosis, all ovarian in location, was present in 2.2% of symptomatic postmenopausal women. The mean of the menopausal ages in the 11 patients with endometriosis was 50.3 years and the average time elapsed since menopause was 7.3 years. A more recent (2012) retrospective study[3] of the age pattern of 42 079 German women with histologically confirmed endometriosis demonstrated that 2.55% of the women were postmenopausal (age 55–95 years), 17.09% were perimenopausal (age 45–55 years), while 80.36% were premenopausal (0–45 years).

Pathogenesis

Dependence on estrogen is considered a central mechanism for the development and progression of premenopausal endometriosis. The pathogenesis of postmenopausal endometriosis poses an intellectual challenge as it occurs in the absence of menstruation and during a state of ovarian inactivity. For this reason, postmenopausal endometriosis

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does not seem at first glance explainable by currently suggested theories for the premenopausal disease, particularly by Sampson's theory of retrograde menstruation[4].

Based on recent reviews[4–7], the prevailing opinion is that postmenopausal endometriosis is likely a persistence or recurrence of pre-existing premenopausal disease. It is possible for endometriosis to develop *de novo* in the postmenopausal woman but its plausibility has been difficult to establish[4].

Persistence or recurrence of premenopausal endometriosis

If postmenopausal endometriosis is to arise from premenopausal disease, it is necessary for the endometriotic lesions to retain the capacity to persist and/or progress in the absence of ovarian estrogen production.

Retained hormonal responsivess

Two studies went into detailed analyses of the morphologic and immunohistochemical profiles of postmenopausal endometriosis. Compared to the corresponding eutopic endometrium, the endometriotic lesions retained hormonal responsiveness (greater positive progesterone receptor staining and higher positivity of KI-67 antigen)[8]. Compared to women with premenopausal endometriosis, women with postmenopausal endometriosis had statistically less disease but retained the same immunohistochemical profile (staining for estrogen receptor, progesterone receptor, and CD10 antigen)[9]. Given these findings, it was inferred that endometriotic tissue remains biologically active and retains the potential to reactivate given the appropriate stimulation, even in the low-estrogen milieu of the postmenopausal age.

Local estrogen production

Recent studies have demonstrated that the endometriotic implant itself is capable of producing estradiol despite the relatively low circulating estradiol levels during the menopause[10–12]. Aromatase p450 (p450arom) is the key enzyme for biosynthesis of estrogen essential for the establishment and growth of endometriosis. Endometriosis tissue, in contrast to normal endometrium, contains very high levels of aromatase enzyme, which leads to production of significant quantities of estrogen. Moreover, one of the best-known mediators of inflammation and pain, prostaglandin E_2, strikingly induces aromatase enzyme activity and formation of local estrogen in this tissue[13]. Additionally, estrogen itself stimulates cyclo-oxygenase-2 and therefore increases the formation of prostaglandin E_2 in endometriosis. This establishes a positive feedback loop in favor of continuous estrogen production in endometriotic lesions.

It is therefore possible that, once established, endometriosis becomes a self-perpetuating condition, the lesions themselves driving local estrogen production and disease progression, even in postmenopausal women[11,12].

Table 1. Women with postmenopausal endometriosis ($n = 108$) classified according to body mass index (BMI). Subjects collated from six case series and 19 case reports with BMI data.

Body mass index (kg/m^2)	*n (%)*
<25	56 (51.9%)
<30	22 (20.3%)
≥30	30 (27.8%)

Extraovarian sources of estrogens

A number of studies have looked at possible sources of estrogens in postmenopausal women that may serve as risk factors for postmenopausal endometriosis. These include obesity, consumption of phytoestrogens, and the use of menopausal hormone therapy (MHT) and tamoxifen.

Obesity

In the postmenopausal woman, the skin and adipose tissue become the main sites of estrogen production through aromatization of adrenal androstenedione. This endogenous postmenopausal production is enhanced in obese individuals and may result in elevated estradiol levels.

It is still not clear whether overweight/obesity is a risk factor for the development of postmenopausal endometriosis. In a study which looked into the experience of a single institution[14], among 72 postmenopausal women with endometriosis, the median body mass index (BMI) was 25.0 kg/m^2 with 26.4% of the women with BMI ≥25 kg/m^2 and 15.3% with BMI ≥30 kg/m^2. Our analysis of 108 cases of postmenopausal endometriosis collated from six case series and 19 case reports (Table 1) with available BMI data showed that 56 (51.9%) of the subjects had a BMI <25 kg/m^2, 22 (20.3%) had a BMI <30 kg/m^2, and 30 (27.8%) had a BMI ≥30 kg/m^2.

Phytoestrogens

The consumption of phytoestrogens has been postulated as a source of exogenous estrogen and as a risk factor for endometriosis. A possible link between phytoestrogens and postmenopausal endometriosis was seen in a report of a 75-year-old woman who developed a ureteral malignant Müllerian carcinosarcoma associated with endometriosis after 5 years of phytoestrogen supplementation consisting of 72 mg/day of superconcentrated soy isoflavones[15].

Menopausal hormone therapy

A 2009 Cochrane review which included only two trials[16] concluded that MHT for women with endometriosis in post-surgical menopause could result in pain and disease recurrence. Both trials, however, demonstrated no statistically significant differences between MHT users and non-users. The first trial compared tibolone (2.5 mg/day) with transdermal 17β-estradiol (0.05 mg/day) plus cyclic medroxyprogesterone acetate (MPA, 10 mg per day) for 12 days per month. Recurrence of pain and dyspareunia was reported in 1/11 patients in the tibolone arm and in 4/10 patients in the transdermal 17β-estradiol + MPA arm compared with 0/57 in patients in the no-treatment arm. The second trial compared

Table 2. Postmenopausal endometriosis ($n = 202$) and use of menopausal hormone therapy (MHT) (collated from 10 case series and 33 cases reports with MHT data).

Number of patients who used MHT	64 (31.7%)
Mean duration of MHT use	8.1 years (range 3 months to 30 years)
Type of MHT	
Estrogen alone	40 (62.5%)
CEE	17
estradiol implant	8
estradiol patch	1
estradiol implant, patch	1
estrogen injection	1
unspecified	12
Combined estrogen–progestin therapy	10 (15.6%)
estrogen + testosterone implant	4
ethinylestradiol + levonorgestrel	2
CEE + MPA	2
estradiol + MPA	1
transdermal estradiol + MPA	1
Concentrated phytoestrogens	1 (1.6%)
Unspecified	13 (20.3%)

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

no treatment against sequential administration of estrogens and progesterone patches applied weekly (controlled release of 0.05 mg/day) plus micronized progesterone administered orally (200 mg/day) for 14 days. No recurrence nor re-operation was reported in the no-treatment group. In the treatment group, 2/115 developed recurrence of endometriosis and 2/115 had a re-operation.

A breakdown of 202 cases of postmenopausal endometriosis collated from ten case series and 33 case reports (Table 2) showed that 64 (31.7%) of the subjects had used MHT. Whether they were past or current MHT users cannot be determined from the available data. The mean duration of use was 8.1 years (range 3 months to 30 years). Regarding the type of MHT regimen used, 40 subjects (62.5%) had used estrogen alone, ten (15.6%) had used combined estrogen–progestin therapy, one (1.6%) had consumed concentrated phytoestrogens, and 13 (20.3%) had used unspecified regimens.

The effect of oophorectomy

Patients with a history of endometriosis in whom total hysterectomy and bilateral salpingo-oophorectomy have been performed have a low risk of recurrence when MHT is administered. In a randomized trial involving 115 subjects vs. 57 controls, the recurrence rate was 3.5% vs. 0%, equivalent to 0.9% per year in women who received MHT[17]. The prominent risk factors for recurrence among women receiving MHT were peritoneal involvement >3 cm (2.4% recurrence per year vs. 0.3%) and especially incomplete surgery (22.2% per patient vs. 1.9%). The risk of recurrence with hormone therapy is probably increased in women with residual disease after surgery.

De novo development

If endometriosis is to arise for the first time during the postmenopause, it must be assumed that endometriosis was not present before the menopause. The absence of premenopausal endometriosis cannot be implied historically from the lack of symptoms consistent with endometriosis; it should have been excluded by laparoscopic inspection of the pelvic cavity. On the other hand, the exclusion of pelvic disease by laparoscopic visualization at any given time, however, does not preclude the later development of endometriotic lesions prior to the menopause[4].

Celomic metaplasia

The possibility that postmenopausal endometriosis may arise from metaplastic transformation of peritoneal mesothelial cells into endometrial glandular cells[18] was invoked in a report of three cases of postmenopausal endometriosis who had no history of hormone therapy and no previous history of endometriosis or infertility[19]. These women, aged 54, 62, and 78 years old, had a rectovaginal nodule, ovarian cystic mass, and abdominal wall mass, respectively, that were confirmed as endometriosis histologically after excision and biopsy.

Malignant transformation

Both ovarian and extraovarian endometriosis have the potential for malignant change. A 2001 review of 1000 consecutive cases of surgically proven endometriosis demonstrated that cancers were more commonly found in ovaries when endometriosis was present in that ovary (5%) compared to when endometriosis was present at other sites (1%)[20]. Clear cell and endometrioid carcinomas were the malignancies most commonly seen in ovaries containing endometriosis, while clear cell adenocarcinoma and adenosarcoma were most commonly seen in conjunction with extraovarian endometriosis.

A similar predisposition of ovarian endometriosis to transformation to clear cell and endometrioid carcinomas was shown in a later (2005) study[21]. Significant increases in risk occurred for clear cell carcinoma (relative risk (RR) 3.37, 95% confidence interval (CI) 1.24–9.14) and endometrioid cancer (RR 2.53, 95% CI 1.19–5.38) after 5 or more years from the initial diagnosis of endometriosis.

Risk of malignant change

A recent review[6] cited the risk of malignant change of ovarian endometriosis at ~1%, but this was based on the first report of malignancy arising from ovarian endometriotic tissue made by Sampson in 1925[22]. In a Japanese case series of 147 cases of ovarian endometriosis, malignant change occurred in 0.7% of cases of the disease[23]. However, a prospective study of 6398 Japanese women with ovarian endometrioma showed a higher risk of malignancy. During a follow-up of up to 17 years (median 12.8 years), the risk of ovarian cancer was significantly elevated (standardized incidence ratio [SIR] 8.95, 95% CI 4.12–15.3)[24].

Several studies have shown that the transformation of ovarian endometriosis into malignancy occurred during the perimenopause[24–26]. On the other hand, women with

Table 3. Analysis of 62 cases of postmenopausal endometriosis with malignant degeneration (collated from eight case series and 18 case reports).

Mean age at time of diagnosis of malignant change (years)	58.2 (range 38–81)
Mean duration since menopause at time of diagnosis (years)	9.3 (range 3–34)
Number of patients who used menopausal hormone therapy	31 (50.0%)
Mean duration of MHT use (years)	10.1 (range 3–30)
Type of MHT	
Estrogen alone	22 (71.0%)
CEE	7
estradiol implant	3
estrogen injection	1
unspecified	11
Combined therapy	7 (22.6%)
estrogen + testosterone implant	4
ethinylestradiol + levonorgestrel	1
CEE + MPA	1
estradiol + MPA	1
MHT not specified	1 (3.2%)
Concentrated phytoestrogens	1 (3.2%)
Histologic type of malignancy	
endometrioid	42 (67.7%)
clear cell	6 (9.7%)
sarcoma	2 (3.2%)
adenosquamous	4 (6.4%)
papillary	1 (1.6%)
serous (ovary), carcinosarcoma (colon)	1 (1.6%)
unspecified	6 (9.7%)

MHT, menopausal hormone therapy; CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

extraovarian cancers arising in endometriosis were more likely to be postmenopausal ($p < 0.001$)[25].

In a retrospective survey of 18 Japanese women with a history of ovarian endometrioma, the mean age at the time of malignant transformation on the basis of imaging findings was 45.2 years (range 36–66 years)[27]. Among 49 Chinese women with ovarian endometriosis with malignant transformation, the median age was 49 years (range 29–70 years)[28]. The investigators concluded that ovarian endometrioma should be viewed as a neoplastic process, particularly in perimenopausal women.

However, our analysis of 62 women with postmenopausal endometriosis with malignant change collated from eight case series and 18 case reports (Table 3) showed a mean age of 58.2 years (range 38–81 years) when they were diagnosed. The mean duration since onset of menopause was 9.3 years (range 3–34 years).

Other cancers

Women with endometriosis have an increased risk of some other malignancies aside from ovarian cancer. A study of 20 686 Swedish women who were hospitalized with endometriosis during the period 1969–1983 showed an increased overall risk for cancer (SIR 1.2, 95% CI 1.1–1.3) during a mean follow-up of 11.4 years[29]. Significant increases were observed, not only for ovarian cancer (SIR 1.9, 95% CI 1.3–2.8), but also for breast cancer (SIR 1.3, 95% CI 1.1–1.4) and hematopoietic malignancies (SIR 1.4, 95% CI 1.0–1.8); this latter excess was largely driven by an excess risk of non-Hodgkin's lymphoma (SIR 1.8, 95% CI 1.2–2.6). In an extended follow-up study involving 64 492 women hospitalized for endometriosis from 1969 to 2000, the overall cancer risk became statistically insignificant (SIR 1.04, 95% CI 1.00–1.07)[30]. There were, however, continued elevated risks for ovarian cancer (SIR 1.43, 95% CI 1.19–1.71), endocrine tumors (SIR 1.36, 95% CI 1.15–1.61), non-Hodgkin's lymphoma (SIR 1.24, 95% CI 1.02–1.49) and brain tumors (SIR 1.22, 95% CI 1.04–1.41). These findings suggest that further attention be given to the risk of cancers other than ovarian cancer in women with endometriosis in their advanced ages.

Menopausal hormone therapy and malignant change

There is evidence to suggest that the risk of malignancy associated with endometriosis could be enhanced in women with postmenopausal disease who have been exposed to MHT[24,31,32]. The risk of malignant transformation of endometriosis seems to be higher with estrogen-alone therapy than with combined estrogen–progestin therapy although solid evidence is lacking.

In a retrospective analysis of 31 patients with cancer developing from endometriosis, 15 were classified as obese, indicating a trend toward a higher risk of malignancy compared to controls. When obesity was combined with the use of unopposed estrogen which was present in nine patients, the difference became statistically significant ($p = 0.05$)[31].

In a small case series, long-standing menopausal hormone therapy resulted in malignant transformation of residual endometriosis after hysterectomy in three women many years after the initial surgery[33].

Analysis of 62 cases of postmenopausal endometriosis with malignant degeneration (Table 3) showed 31 (50.0%) of the women had a history of MHT use; of these, 22 (71.0%) used estrogen-alone therapies, seven (22.6%) used combined therapies, and one (3.2%) took concentrated phytoestrogens. The mean duration of MHT use was 10.1 years (range 3–30 years). The most common histologic type of malignancy was endometrioid carcinoma (42 cases, 67.7%), followed by clear cell carcinoma (six cases, 9.7%).

Tamoxifen

A possible association between tamoxifen therapy and malignant transformation of concomitant endometriosis was shown in four case reports[34–37]. All patients were on adjuvant tamoxifen therapy for breast carcinoma from 2 to 4 years. The association with prolonged unopposed estrogen-like stimulation with tamoxifen was proposed as a possible factor in the development of ovarian endometrioid carcinoma[33].

Favorable prognosis

Endometriosis-related malignancies appear to have a favorable prognosis. In a 2003 study of 27 patients with a mean age of 51.4 years, after surgery and postoperative chemotherapy or regional radiation therapy, 19 (70.4%) of patients were without evidence of recurrence after a mean follow-up of 31 months[38].

Table 4. Postmenopausal endometriosis with extragonadal spread ($n = 103$) and the presence of constrictive and/or obstructive lesions (compiled from 14 case series and 66 cases reports).

Number of patients with constrictive and/or obstructive lesions	54 (52.4%)
Sites of constrictive and/or obstructive lesions	
ureteral	20 (37.0%)
intestinal (small intestines, rectosigmoid)	18 (33.4%)
rectovaginal	5 (9.3%)
vesical	4 (7.4%)
vaginal	3 (5.5%)
multiple	4 (7.4%)

Extragonadal spread and constrictive and/or obstructive lesions

Postmenopausal endometriosis may spread extragonadally, involving a variety of organs and structures and causing constrictive and/or obstructive lesions[6].

Analysis of 103 cases of postmenopausal endometriosis with extragonadal spread gathered from 66 case reports and 14 case series (Table 4) demonstrated the presence of constrictive and/or obstructive lesions in 54 (52.4%) cases. These lesions frequently and directly involved the ureters in 20 cases (37.0%) and the intestines (small intestines and rectosigmoid) in 18 cases (33.4%).

The tendency of postmenopausal endometriosis to spread extragonadally and develop into constrictive and/or obstructive lesions may complicate the differential diagnosis and may require a more aggressive, even multidisciplinary, approach to surgical management[39,40].

Management of postmenopausal endometriosis

Surgical therapy

Surgical therapy should be the first-line option for postmenopausal women with symptomatic endometriosis because of the risk of, and the need to exclude, malignancy[5,41]. Thus, the surgical approach may have to be aggressive and, because of frequent involvement of extragonadal organs, multidisciplinary. Additional risks that may complicate surgery include co-morbidities because of advancing age and pelvic adhesions from previous surgeries[41].

Medical therapy

Medical therapy may be an option in case of pain recurrence after surgery or if surgery is contraindicated[5].

Aromatase inhibitors

Aromatase inhibitors (AIs) represent one of the most recently used drugs for postmenopausal endometriosis. AIs inhibit mainly extra-ovarian synthesis of estrogens which make them particularly relevant in older patients, as most of the body's estrogen is produced outside the ovaries after menopause. Up to 2011, only five case reports are available regarding the use of these agents in postmenopausal women[42]. Treatment with letrozole and anastrozole for 4–15 months reduced pain in all patients with endometriosis.

Progestogens

Hypothetically, progestogens could be used as a treatment alternative in postmenopausal endometriosis for their direct action on lesions through the progesterone receptor. Another alternative is the levonorgestrel-releasing intrauterine system. However, there have been no reports on its use in women with postmenopausal endometriosis[5].

Management of menopausal symptoms

Although the use of MHT in women previously treated for endometriosis appears to increase the risk of recurrence and the risk of malignant transformation, the available evidence is not strong enough to recommend depriving severely symptomatic patients of hormone therapy[16].

The observation that disease recurrence was not substantially increased among women with endometriosis who had hysterectomy and bilateral oophorectomy and subsequently receive low-dose hormone therapy for bone protection and symptom relief after surgical menopause[17] would imply that various tissues differ in their sensitivity to estrogen. A dose of estrogen sufficient to provide bone protection would not necessarily be high enough to reactivate endometriosis. This concept forms the basis of the 'estrogen threshold theory'[43]. It is possible that a threshold dose of estrogen exists, above which endometriotic lesions might be stimulated and potentially re-activated in postmenopausal women receiving MHT.

Nevertheless, MHT should generally be reserved for patients with severe climacteric complaints, and, if indicated, combined therapy should be used[44]. A 1999 study of 21 women with residual pelvic endometriosis after bilateral oophorectomy with or without hysterectomy showed that moderate pelvic pain was experienced by only one of 11 (9.1%) patients who used tibolone 2.5 mg daily and by four of ten (40%) patients who used a combination of transdermal estradiol 50 mg twice weekly and cyclic medroxyprogesterone acetate 10 mg daily for 12 months[45].

Both the 2010 European Menopause and Andropause Society position statement[46] and the 2014 European Society of Human Reproduction and Embryology guideline[47] recommend avoiding unopposed estrogen treatment. The theoretical benefit of avoiding disease reactivation and malignant transformation of residual disease with estrogen/progestogen therapy should be balanced against the increased systemic risks associated with its use. A 2017 systematic review on the management of the menopause in women with a history of endometriosis[48] concludes that, due to the lack of high-quality studies, it remains unclear how to advise women with a history of endometriosis regarding the management of menopausal symptoms.

Recently published national and international guidelines (2016, 2017) on menopause management[49–51] have no statements on the treatment of menopausal symptoms in women with postmenopausal endometriosis.

Conclusion

From this review, postmenopausal endometriosis, although infrequent, emerges as a clinical entity with features not

commonly associated with endometriosis in younger women. A major limitation in drawing a clearer clinical picture of postmenopausal endometriosis is the dearth of relevant data. This made the review process difficult and the conclusions must be considered tentative.

First, although postmenopausal endometriosis is often a recurrence of premenopausal disease, it arises when ovarian estrogen production is deficient. Aside from local estrogen production by the endometriotic lesion itself, a higher prevalence of overweight/obesity and the use of menopausal hormone therapy and tamoxifen among postmenopausal women are considered potential sources of estrogen that may reactivate a latent premenopausal disease.

Second, women with postmenopausal endometriosis may have a higher risk of malignant transformation. Other forms of cancer unrelated to endometriosis may also increase.

Third, postmenopausal endometriosis may have a greater tendency to spread and involve extragonadal organs and structures that may develop into constrictive and/or obstructive lesions.

Fourth, the need to use menopausal hormone therapy poses an unresolved therapeutic dilemma as it may increase the risk of disease and/or pain recurrence and especially the risk of malignant change.

Last, surgical management is recommended as first-line choice in postmenopausal women with endometriosis. Postmenopausal endometriosis may be an indication for an aggressive and even multidisciplinary approach to surgery.

Need for further research

The optimal management of postmenopausal endometriosis is still undetermined. Guidelines on the surgical approach to management need to be established. The use of aromatase inhibitors and other medical options needs clinical evaluation. The hypothesis that progesterone or progestogens could have an antiproliferative effect on endometriosis lesions and reduce the risk of malignant transformation should be explored.

The association between menopausal hormone therapy and malignant transformation of endometriosis remains uncertain and needs a long-term follow-up study to evaluate actual risk.

Likewise, the optimal management of menopause, both natural and surgical, in women with postmenopausal endometriosis is undetermined.

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References

1. Fagervold B, Jenssen M, Hummelshoj L, Moen MH. Life after a diagnosis with endometriosis–a 15 years follow-up study. *Acta Obstet Gynecol Scand* 2009;88:914–19
2. Punnonen R, Klemi PJ, Nikkanen V. Postmenopausal endometriosis. *Eur J Obstet Gynecol Reprod Biol* 1980;11:195–200
3. Haas D, Chvatal R, Reichert B, *et al*. Endometriosis: a premenopausal disease? Age pattern in 42,079 patients with endometriosis. *Arch Gynecol Obstet* 2012;286:667–70
4. Bendon CL, Becker CM. Potential mechanisms of postmenopausal endometriosis. *Maturitas* 2012;72:214–19
5. Streuli I, Gaitzsch H, Wenger JM, Petignat P. Endometriosis after menopause: physiopathology and management of an uncommon condition. *Climacteric* 2017;20:138–43
6. Brosens I, Puttemans P, Benagiano G. Endometriosis: a life cycle approach?. *Am J Obstet Gynecol* 2013;209:307–16
7. Shah D. Postmenopausal endometriosis: an enigma revisited. *J Midlife Health* 2014;5:163–4
8. Toki T, Horiuchi A, Li SF, Nakayama K, Silverberg SG, Fujii S. Proliferative activity of postmenopausal endometriosis: a histopathologic and immunocytochemical study. *Int J Gynecol Pathol* 1996;15:45–53
9. Cumiskey J, Whyte P, Kelehan P, Gibbons D. A detailed morphologic and immunohistochemical comparison of pre- and postmenopausal endometriosis. *J Clin Pathol* 2008;61:455–59
10. Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Sebastian S. Estrogen production and metabolism in endometriosis. *Ann N Y Acad Sci* 2002;955:75–85
11. Bulun SE, Fang Z, Imir G, *et al*. Aromatase and endometriosis. *Semin Reprod Med* 2004;22:45–50
12. Bulun SE. Endometriosis. *N Engl J Med* 2009;360:268–79
13. Noble LS, Takayama K, Zeitoun KM, *et al*. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. *J Clin Endocrinol Metab* 1997;82:600–6
14. Morotti M, Remorgida V, Venturini PL, Ferrero S. Endometriosis in menopause: a single institution experience. *Arch Gynecol Obstet* 2012;286:1571–5
15. Noel JC, Anaf V, Fayt I, Wespes E. Ureteral mullerian carcinosarcoma (mixed mullerian tumor) associated with endometriosis occurring in a patient with a concentrated soy isoflavones supplementation. *Arch Gynecol Obstet* 2006;274:389–92
16. Al Kadri H, Hassan S, Al-Fozan HM, Hajeer A. Hormone therapy for endometriosis and surgical menopause. *Cochrane Database Syst Rev* 2009;(1):CD005997
17. Matorras R, Elorriaga MA, Pijoan JI, Ramón O, Rodríguez-Escudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertil Steril* 2002;77:303–8
18. Matsuura K, Ohtake H, Katabuchi H, Okamura H. Coelomic metaplasia theory of endometriosis: evidence from in vivo studies and an in vitro experimental model. *Gynecol Obstet Invest* 1999;47(Suppl 1):18–20
19. Rosa-e-Silva JC, Carvalho BR, Barbosa Hde F, *et al*. Endometriosis in postmenopausal women without previous hormonal therapy: report of three cases. *Climacteric* 2008;11:525–8
20. Stern RC, Dash R, Bentley RC, Snyder MJ, Haney AF, Robboy SJ. Malignancy in endometriosis: frequency and comparison of ovarian and extraovarian types. *Int J Gynecol Pathol* 2001;20:133–9
21. Brinton LA, Sakoda LC, Sherman ME, *et al*. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. *Cancer Epidemiol Biomarkers Prev* 2005;14:2929–35
22. Sampson JA. Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Arch Surg* 1925;10:1–72
23. Nishida M, Watanabe K, Sato N, Ichikawa Y. Malignant transformation of ovarian endometriosis. *Gynecol Obstet Invest* 2000;50(Suppl 1):18–25
24. Kobayashi H. Ovarian cancer in endometriosis: epidemiology, natural history, and clinical diagnosis. *Int J Clin Oncol* 2009;14:378–82
25. Modesitt SC, Tortolero-Luna G, Robinson JB, Gershenson DM, Wolf JK. Ovarian and extraovarian endometriosis-associated cancer. *Obstet Gynecol* 2002;100:788–95
26. Kobayashi H, Sumimoto K, Kitanaka T, *et al*. Ovarian endometrioma–risks factors of ovarian cancer development. *Eur J Obstet Gynecol Reprod Biol* 2008;138:187–93

27. Kawaguchi R, Tsuji Y, Haruta S, *et al*. Clinicopathologic features of ovarian cancer in patients with ovarian endometrioma. *J Obstet Gynaecol Res* 2008;34:872–7
28. Shen YM, Wu XL, Xu L, *et al*. Malignant transformation of ovarian endometriosis: a clinicopathologic analysis of 49 cases. *Ai Zheng* 2008;27:1106–10
29. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;176:572–9
30. Melin A, Sparén P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Hum Reprod* 2006;21:1237–42
31. Zanetta GM, Webb MJ, Li H, Keeney GL. Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis. *Gynecol Oncol* 2000;79:18–22
32. Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006;9:325–35
33. Karanjgaokar VC, Murphy DJ, Samra JS, Mann CH. Malignant transformation of residual endometriosis after hysterectomy: a case series. *Fertil Steril* 2009;92:2037.e19–2021
34. Cohen I, Altaras MM, Lew S, Tepper R, Beyth Y, Ben-Baruch G. Ovarian endometrioid carcinoma and endometriosis developing in a postmenopausal breast cancer patient during tamoxifen therapy: a case report and review of the literature. *Gynecol Oncol* 1994;55:443–7
35. McCluggage WG, Bryson C, Lamki H, Boyle DD. Benign, borderline, and malignant endometrioid neoplasia arising in endometriosis in association with tamoxifen therapy. *Int J Gynecol Pathol* 2000;19:276–9
36. Okugawa K, Hirakawa T, Ogawa S, Kaku T, Nakano H. Ovarian endometrioid adenocarcinoma arising from an endometriotic cyst in a postmenopausal woman under tamoxifen therapy for breast cancer: a case report. *Gynecol Oncol* 2002;87:231–4
37. Bese T, Simsek Y, Bese N, Ilvan S, Arvas M. Extensive pelvic endometriosis with malignant change in tamoxifen-treated postmenopausal women. *Int J Gynecol Cancer* 2003;13:376–80
38. Leiserowitz GS, Gumbs JL, Oi R, *et al*. Endometriosis-related malignancies. *Int J Gynecol Cancer* 2003;13:466–71
39. Popoutchi P, dos Reis Lemos CR, Silva JC, Nogueira AA, Feres O, Ribeiro da Rocha JJ. Postmenopausal intestinal obstructive endometriosis: case report and review of the literature. *Sao Paulo Med J* 2008;126:190–3
40. Wolthuis AM, Meuleman C, Tomassetti C, D'Hooghe T, de Buck van Overstraeten A, D'Hoore A. Bowel endometriosis: colorectal surgeon's perspective in a multidisciplinary surgical team. *World J Gastroenterol* 2014;20:15616–23
41. Inceboz U. Endometriosis after menopause. *Womens Health (Lond)* 2015;11:711–15
42. Polyzos NP, Fatemi HM, Zavos A, *et al*. Aromatase inhibitors in post-menopausal endometriosis. *Reprod Biol Endocrinol* 2011;9:90
43. Barbieri RL. Endometriosis and the estrogen threshold theory. Relation to surgical and medical treatment. *J Reprod Med* 1998;43(3 Suppl):287–92
44. Oxholm D, Knudsen UB, Kryger-Baggesen N, Ravn P. Postmenopausal endometriosis. *Acta Obstet Gynecol Scand* 2007;86:1158–64
45. Fedele L, Bianchi S, Raffaelli R, Zanconato G. Comparison of transdermal estradiol and tibolone for the treatment of oophorectomized women with deep residual endometriosis. *Maturitas* 1999;32:189–93
46. Moen MH, Rees M, Brincat M, European Menopause and Andropause Society, *et al*. EMAS position statement: Managing the menopause in women with a past history of endometriosis. *Maturitas* 2010;67:94–7
47. Dunselman GA, Vermeulen N, Becker C, European Society of Human Reproduction and Embryology, *et al*. ESHRE guideline: management of women with endometriosis. *Maturitas* 2014;29:400–12
48. Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT, Becker CM. The management of menopause in women with a history of endometriosis: a systematic review. *Hum Reprod Update* 2017;23:481–500
49. Baber RJ, Panay N, Fenton A. IMS Writing Group. 2016 IMS recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016;19:109–50
50. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American menopause society. *Menopause* 2017;24:728–53
51. Cobin RH, Goodman NF. AACE Reproductive Endocrinology Scientific Committee. American Association of clinical endocrinologists and American college of endocrinology position statement on menopause – 2017 update. *Endocr Pract* 2017;23:869–80