Postmenopausal endometriosis, where are we now?

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Purpose of review
Postmenopausal endometriosis is a gynecologic disease, affecting 2–5% of postmenopausal woman. Current literature assessing the prevalence, pathogenesis, and treatment of this uncommon condition is limited, stressing the necessity for future research. This review examines the current literature on postmenopausal endometriosis to help inform clinical decision-making and point to novel approaches for treatment and management.

Recent findings
Although one unifying theory to explain the pathogenesis of endometriotic lesions has not been elucidated, estrogen dependence is central to the pathophysiological process. The total quantity of estrogen production is mediated by multiple enzymes in complex pathways. Recent studies have confirmed the presence of these necessary enzymes in endometriotic lesions thereby suggesting a local source of estrogen and a likely pathogenic contributor. More research is needed to fully elucidate the mechanism of local estrogen biosynthesis; however, the current data provide possible explanations for the presence of postmenopausal endometriosis in an otherwise systemically hypoestrogenic environment.

Summary
All suspected endometriosis lesions should be surgically excised for optimization of treatment and prevention of malignant transformation. If hormone replacement therapy is initiated, combined estrogen and progestin is recommended, even in the setting of previous hysterectomy, given the risk of disease reactivation and malignant transformation of endometriotic lesions. Further research is needed to understand the true prevalence, cause, and progression in this patient demographic. Histologic studies evaluating tissue lesions and peritoneal fluid for estrogen receptors, estrogen metabolizing enzymes, immune cells, and nerve fibers will aide in clinical management and treatment planning.

Keyword
endometriosis, estrogen dependence, postmenopausal

INTRODUCTION

Endometriosis is one of the most common benign gynecological conditions affecting an estimated 5–15% of reproductive aged women and up to 35–40% among those with chronic pelvic pain [1–3] It has typically been characterized as a disorder of reproductive aged women with regression of lesions after menopause. This progressive condition is characterized by chronic inflammation with the presence and proliferation of functional glandular epithelium and stroma outside of the uterine cavity [1,4]. Although controversial, the most widely accepted cause of endometriosis, as outlined in Sampson's implantation theory, is via retrograde menstruation [1,5▪] Once spread into the pelvic cavity, the endometrial cells attach, invade, and differentiate with cyclic growth and breakdown in response to hormonal stimulation. It has been further postulated that a permissive peritoneal environment favoring this implantation and growth is required [5▪,6▪] This is accomplished via a dynamic interactive process dependent on the presence of hormones, cytokines, enzymes, immune cells, and growth factors [5▪]. The pathophysiologic process involves various signaling pathways, peritoneal fluid interactions, immune dysfunction, genetic alterations, and environmental variants [4,5▪,7–8,9▪▪,10].

Although the disorder is associated mostly with reproductive aged women, there is no correlation between age and extent of disease [11].

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KEY POINTS

- Estrogen dependence is central to the pathophysiological process of endometriosis and while estrogen levels are decreased from premenopausal values, some estrogen may still be present from either endogenous or exogenous sources in postmenopausal woman.
- The biosynthesis of estrogen, in postmenopausal woman, likely results from impaired estrogen metabolism in the microenvironment of endometriotic lesions with the total quantity of estrogen production regulated by aromatase, 17β-hydroxysteroid (HSD17B), and the steroidogenic acute regulatory protein (StAR) all of which have been demonstrated in endometriotic stromal cells.
- Once synthesized, estrogen promotes endometriosis through multiple molecular pathways involving dysregulation of immune function, aberrant neuronal growth, neovascularization, and degradation of extracellular-matrix proteins and basement membranes.
- Given the potential for underlying malignancy and malignant transformation of endometriotic lesions swift assessment of postmenopausal patients with pain and abnormal bleeding is essential to ensure all suspected endometriosis lesions are surgically excised for optimization of treatment and prevention of malignant transformation.
- If hormone replacement therapy is initiated, combined estrogen and progestin is recommended, even in the setting of previous hysterectomy given the risk of disease reactivation and malignant transformation of endometriotic lesions.

Interestingly, the proportions of epithelium, stroma, or immunohistochemical staining of receptor densities are equivalent in premenopausal and postmenopausal woman [11]. In addition, the presence of both epithelial and stromal components with immunoreactivity of estrogen receptors in postmenopausal woman has been confirmed histologically [12]. These findings suggest the presence of biologically active endometriotic lesions, with sustained hormonal responsiveness, in postmenopausal patients, in the absence of reproductive estrogen levels. The presence of endometriosis in postmenopausal women presents an especially challenging issue. This review examines the current literature on both premenopausal and postmenopausal endometriosis to compare, contrast, and identify common pathways for the development of endometriosis. The assimilation of this knowledge can inform clinical decision-making and point to new and novel ways for treatment and clinical management.

PREVALENCE AND PATHOGENESIS

Although few studies exist, the available literature demonstrates a prevalence of 2–5% of endometriosis in postmenopausal women [3,13,14]. Table 1 summarizes the current literature on the presentation of women with postmenopausal endometriosis [12,14–72,73▪–77▪]. As shown, most of the literature is in the form of case reports and case studies with a large proportion of patients never having received hormonal replacement therapy (HRT). It is impossible to ascertain whether endometriosis was present prior to menopause with later development of symptoms or whether de novo lesions have occurred. If Sampson's theory of implantation is correct, then endometriotic lesions would have been present prior to menopause. Multiple studies have evaluated pain severity in relation to nerve fibers in the pelvic region. Increased neuronal growth over time may help explain why postmenopausal women develop symptoms years after initial implantation of endometrial cells. Studies have found that the peritoneal fluid of women with endometriosis has neurotropic properties with an overexpression of nerve growth factor with neurite outgrowth of dorsal root ganglia [78].

The pathways by which endometriotic lesions persist and become painful in a systemically hypoestrogenic environment remain unclear. Although estrogen levels are decreased from premenopausal values, some estrogen may still be present from either endogenous or exogenous sources [7,48,79▪▪]. In postmenopausal woman, local production of estrogen may be the driving source for continuation of disease. A continuous predominance of estradiol tissue levels well above the corresponding serum levels in patients with endometriosis has been demonstrated [80]. This aberrant biosynthesis of estrogen likely results from impaired estrogen metabolism in the microenvironment of endometriotic lesions [80–83]. The total quantity of estrogen production is a balance between synthesis and inactivation regulated by aromatase, 17β-hydroxysteroid (HSD17B), and the steroidogenic acute regulatory protein (StAR) [81,82]. By facilitating the entry of cholesterol into the mitochondrion, StAR coordinates the first step in steroidogenesis, which later results in a significant concentration of progesterone. Through a series of molecular steps progesterone is converted to androstenedione, which acts as the primary substrate for aromatase thereby catalyzing the production of estrone, which is further converted to the biologically active estradiol by the hydroxysteroid dehydrogenases. Aromatase, is then, thought to be involved in a feedback loop wherein estrogen stimulates cyclooxygenase type 2 enzyme resulting in

elevated levels of prostaglandin E2, which stimulates aromatase activity, thereby ensuring a continuous production of estrogen [84,85]. Although controversial, many authors report expression of aromatase by endometriotic lesions as well as the eutopic endometrium of women with endometriosis [86,87,88▪▪]. These steroidogenic gene products, including; StAR, aromatase, and HSD17B were demonstrated in endometriotic stromal cells in early studies [81,89].

Once synthesized, estrogen promotes endometriosis through multiple molecular pathways. One such pathway, wherein estradiol stimulates dorsal root ganglion neurons to produce chemokines, which promote macrophage recruitment has been outlined [10]. In this model, a reciprocal relationship exists, wherein estrogen also acts directly on macrophages to potentiate neurogenesis into lesions [10]. These activated macrophages may incorrectly recognize ectopic tissue as injured and activate survival and angiogenesis pathways [90]. Estrogen further promotes survival of endometriotic lesions by stimulating neovascularization, increasing the vascular endothelial growth factor via the Wnt/B-catenin pathway, degradation of the extracellular matrix, and basement membranes of intact peritoneum via dysregulated stimulation of matrix metalproteinases, and by altering immune function through increased release of tumor necrosis factor-α via activated macrophages [4,91,92▪,93].

More research is needed to fully elucidate the mechanisms of local estrogen biosynthesis and action on target molecules, however, the current data provide possible explanations for the presence of postmenopausal endometriosis in an otherwise systemically hypoestrogenic environment.

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) remains a concern in postmenopausal women with a history of endometriosis [3,94,95▪▪]. Treatment for endometriosis, when initiated at a young age, may involve inducing a medical or surgical hypoestrogenic state. The impact of decreased estrogen levels should not be overlooked as the symptoms often negatively impact quality of life. Patients report climacteric symptoms, such as vaginal dryness, hot flushes, and night sweats as well as painful intercourse, sleep deprivation, cognitive decline, and mood changes [96]. These patients are also at increased risk for osteoporosis and cardiovascular disease with declining estrogen levels. Given these factors, the benefits of estrogen replacement often outweigh the risks in young women who have undergone surgical menopause for the treatment of endometriosis [97]. Although obvious benefits for estrogen replacement exist in patients with decreased estrogen levels, its use is controversial, given the potential reactivation of residual endometriotic implants and recurrence of pain. Finally, there is speculation that increased estrogen levels will promote malignant transformation [95▪▪,97].

In their review, Gemmell *et al.* [95▪▪] presented 13 case reports and case series identifying endometriosis recurrence in postmenopausal women treated with HRT for treatment or prevention of menopausal symptoms. Seventeen women aged 30–65 who received exogenous estrogens were included in this review. In most cases, women received unopposed estrogens with only a few studies reporting recurrence when combined hormonal preparations were implemented. Patient's with recurrence presented with pain, abnormal bleeding including vaginal bleeding, hematuria, rectal bleeding, and hemoptysis with sites of recurrence including the bladder, ureter, ovary, cervix, vagina, gastrointestinal organs, and the pulmonary system.

MALIGNANT TRANSFORMATION

Like invasive cancer, endometriosis lesions display dysregulated cell growth, invasion of adjacent tissues, distant metastasis, angiogenesis, defective apoptosis, and cell adhesion [4,98–101]. Malignant transformation of endometriosis has been estimated to occur in 0.7–1% of cases [72,102▪]. Women are at increased risk of developing epithelial ovarian cancer [98,103]. Two cell types, clear cell and endometrioid, are highly associated with endometriosis and the risk associated with malignant transformation of endometriosis is likely dependent upon the histologic sub-type [98]. HRT, administered as unopposed estrogen, has also been implicated in the cause of malignant transformation [104–106]. Many other causes have been proposed including; oxidative stress, chronic inflammation, hyperestrogenism, and genetic defects. No studies to date have been able to definitively outline the carcinogenic pathway from endometriosis to invasive carcinoma. Molecular pathways and genetic defects permissive to malignant transformation, however, are likely contributing. Genetic alterations with mutations in PTEN, TP53, and ARIDIA have been outlined as a potential part in this molecular transition from benign endometriosis to carcinoma [107].

In the above-mentioned review, Gemmell *et al.* further identified 25 postmenopausal patients, taking HRT, between the ages of 38 and 75 years, who demonstrated malignant transformation of endometriotic lesions. Of these 25 women, 22 had undergone surgical menopause. As previously noted, most

women were on unopposed estrogens for a median duration of 6.7 years with endometrioid adenocarcinoma being the most commonly diagnosed malignancy in this cohort [95▪▪]. Similarly, we reported a case of a 61-year-old women, with a history of endometriosis who had been receiving estrogen and testosterone for 8–10 years via implantable hormone pellets, who presented with pelvic pain and was found to have a left lower quadrant mass. After final pathologic review, she was diagnosed with endometrioid endometrial adenocarcinoma arising in a colonic diverticulum within a background of endometriosis [72].

It is challenging to ascertain the true risk of disease reactivation and malignant transformation given that most of the available literature is presented as case reports and case series. The only randomized controlled trial included 172 patients with participants randomly assigned to treatment with combined HRT or no treatment. In the treatment group, HRT was initiated 4 weeks following surgery. The recurrence rate was 3.5% with all recurrences of endometriosis in the HRT treatment arm [40]. The greatest contributing risk factor was a history of incomplete surgical excision with 22.2% of these women experiencing recurrence while on HRT. A recurrence rate of 2%, has been demonstrated after estrogen-only HRT, in patients who underwent definitive surgery because of endometriosis [94]. In a more recent study, no recurrence of endometriosis was identified in 11 women who underwent surgical menopause and subsequent combined HRT for 1–2 years followed by a low-dose estrogen indefinitely [108]. Endometriosis phenotype, incomplete resection because of deeply infiltrating disease, and the presence or absence of the uterus and ovaries are factors which may affect responses after HRT. There is limited high-quality evidence to guide clinical decisions about which hormonal regimen and timing of administration. Trending evidence, however, would suggest that combined HRT for women with a history of endometriosis may be preferable, even in the absence of a uterus, and that a frank conversation with patients reviewing all risks and benefits is in order.

DIAGNOSIS AND TREATMENT

As noted in Table 1 and in the review by Gemmell *et al.*, most patients present with pain in the abdomen, pelvis, iliac fossae, and genitals. Patients may present without pain or dyspareunia, however, making the diagnosis more challenging. Abnormal bleeding is a common complaint including vaginal bleeding, hematuria, rectal bleeding, and hemoptysis. Evaluation should begin with noninvasive diagnostic modalities, such as a transvaginal ultrasound and CA-125, if malignancy is suspected. If high-risk cystic features, such as mural nodules, solid components, thickened wall, size greater than 7–8 cm, rapid growth over time, or septations are noted during ultrasonographic evaluation, surgical evaluation is warranted. Noninvasive imaging modalities including electronic absorption spectroscopy, near infrared approach, and magnetic resonance transverse relaxometry may be used in combination with traditional imaging modalities to aid in the diagnosis of malignant transformation [102▪]. Given the risk of malignant transformation of endometriotic lesions, it is imperative that clinicians have a high degree of suspicion with a low threshold to perform a diagnostic procedure.

The primary treatment modality for symptomatic postmenopausal endometriosis is surgical excision and includes removal of the uterus, fallopian tubes and ovaries, and all endometriotic lesions [109,110]. Surgery serves as both a diagnostic and therapeutic intervention, important for these patients with an elevated risk of underlying malignancy. Not all patients are good surgical candidates, however. aromatase inhibitors were first used for the treatment of postmenopausal, estrogen receptor positive, breast cancer [96]. Aromatase inhibitors can decrease estrogen production through inhibition of Aromatase P450, a key enzyme that catalyzes the conversion of andostenendione and testosterone to estrone and estradiol. Letrozole and anastrozole are reversible aromatase inhibitors, which may decrease estrogen levels by 97% to more than 99% [96]. With increased production of estrogen within endometriotic lesions aromatase inhibitors may exert a direct positive effect by blocking a key pathway of pathogenesis thereby providing a treatment modality for women who are unable to undergo surgical excision. Promising results have been reported with the use of aromatase inhibitors in menopausal women aged 47–61 years, most of whom had been previously treated with progestins, GnRH agonists, or surgery [35,48,53,55,63]. Anastrazole or letrozole reduced lesion size, pain, and other symptoms, such as urinary tract and bowel complaints, in these women. Patients may experience symptoms related to decreased estrogen levels including vaginal dryness, hot flushes, arthralgias, and decreased bone mineral density. Co-administration with micronized estradiol has been shown to help improve hot flushes [96]. Due to the risk of osteoporosis with increased fracture rates in this population, bisphosphonates may be considered in high-risk patients. The American Society of Clinical Oncologists recommends annual bone mineral density screening while receiving aromatase

Table 1. Current literature describing biopsy proven endometriosis in postmenopausal women

Ref. No.	Author (publication year)	Study design	Study purpose	Type of menopause	Age (years)	Presenting symptoms	Primary vs. recurrent endometriosis	Hormone replacement therapy	Site of endometriosis	Malignant transformation?
[15]	Henriksen (1955)	Retrospective review	Description of endometriosis diagnosis, features, and symptoms	Not reported	44–73	Not reported	Not documented	Not documented	Bowel, ovary	''Questionable' endometrial origin of malignancy in 1 case
[16]	Roger *et al.* (1960)	Retrospective review	To discuss clinical and histological aspects of endometriosis in postmenopausal women	Surgical and physiologic	>45	Pelvic pain, asymptomatic	Not documented	Not documented	Ovaries, intestines, vagina, diffuse	No
[17]	Stewart and Ireland (1977)	Case report	First report of postmenopausal endometriosis found in the bladder	Surgical	65	Painless hematuria	Primary	Yes (estrogen 2.5 mg qday x3 years)	Bladder, invading into the small bowel	No
[18]	Venter *et al.* (1979)	Case report	Describe a case of PM endometriosis treated with radiation therapy	Surgical	59	Vaginal bleeding	Recurrent	Yes (tablet then estrogen implant)	Vaginal vault, right USL	No
[19]	Punnonen *et al.* (1980)	Retrospective review	To show increased estrogen activity is often associted with PM adenomyosis and ovarian endomtriosis	Not reported	51–75	Metrorrhagia, abdominal pain	Not documented	Not documented	11 patients – ovarian, 8 patiens – adenomyosis, 1 patient – both	No
[20]	Djursing *et al.* (1981)	Case report	To describe a case of PM endometriosis not related to exogenous estrogen	Physiologic	66	Vaginal bleeding, abdominal pain	Primary	No	Large cyst within the pelvis, obliterating puch of douglas	No
[21]	Vorstman *et al.* (1983)	Case report	To describe a case of PM genitourinary endometriosis	Physiologic	64	Painless hematuria, suprapubic discomfort, stress incontinence	Primary	No	Upper right posterior bladder wall, bilateral ovaries	No
[22]	Kapadia *et al.* (1984)	Case report	Discuss treatment of PM ureteral endometriosis in addition to PM adenomyosis	Surgical	56	Hematuria	Recurrent	Yes (Premarin)	Left ureter, atypical adenomyosis	No
[23]	Nikkanen *et al.* (1984)	retrospective review	Discuss pattens associated with surgically diagnosed endometriosis, showing a 2.5% incidence of PM endometriosis	Both	18–69	Abdominal pain (most common)	Both	N/A	Ovaries, retrocervix, bladder, rectum, abdominal coverings, elsewhere	No
[24]	Ray *et al.* (1985)	Case report	Describe a report of PM endometriosis causing ureteral obstruction	Surgical	64	Painless hematuria	Recurrent	Yes (Premarin 2.5 mg qday x13 years)	Right ureter	No
[25]	Manyonda *et al.* (1989)	Case report (two cases)	Describe two cases of recurrent PM endometriosis at the level of the ureters	Surgical	47, 39	Vomiting, pelvic pain	Recurrent	Yes x2	Ureters	No
[26]	Henderson *et al.* (1990)	Retrospective review	Compare outcomes of women with endometriosis who had hysterectomy alone with implanted hormones versus hysterectomy with oophorectomy and implanted hormone therapy	Surgical	32–68	Pain	Not documented	Yes	Not documented	No
[27]	Goh and Hall (1992)	Case report	To report that postmenopausal endometriosis is usually associated with exogenous estrogen use	Physiologic	54	Left iliac fossa pain	Primary	Yes (Premarin 0.625 mg qday, cyclic provera 10 mg x12 months)	Left ovarian endometrioma adherant to the sigmoid colon	No
[28]	Duun *et al.* (1993)	Case report	Describing endometrioid carcinoma arising from endometriosis of the sigmoid colon	Physiologic	62	Pelvic mass	Recurrent	Yes, IM estrogen x20 years	Rectosigmoid, closely adherent to the bladder	Yes – endometrioid

Table 1 (*Continued*)

Ref. No.	Author (publication year)	Study design	Study purpose	Type of menopause	Age (years)	Presenting symptoms	Primary vs. recurrent endometriosis	Hormone replacement therapy	Site of endometriosis	Malignant transformation?
[29]	Hajjar *et al.* (1993)	Case report	Highlight the complications of tamoxifen	Physiologic	50	Crampy lower abdominal pain	Primary	Tamoxifen x2 year	Vaginl apex, perirectal mass	No
[30]	Bardi *et al.* (1994)	Case report	Describe occurrence of endometriosis in the setting of tamoxifen exposure	Physiologic	55	Symptomatic fibroids	Primary	Tamoxifen x2 year	Right adnexa, adenomyomatous hyperplasia	No
[31]	Cohen *et al.* (1994)	Case report, literature review	Describe PM endometriosis and endometrioid carcinoma in a breast cancer survivor on tamoxifen	Physiologic	71	Rapidly expanding ovarian cyst noted on TVUS	Primary (did have primary infertility, surgical treatment for b/l tubal occlusion)	Tamoxifen x1 year	Left ovary	Yes – endometrioid
[32]	Joseph *et al.* (1994)	Case report	Description of recurrent thoracic endometriosis after 2 months of HRT following TAH, BSO	Surgical	30	Chest pain, hemoptysis, pleural effusion	Recurrent	Yes (unknown regimen)	Left thorax	No
[33]	Redwine (1994)	Prospective longitudinal study	Describe characteristics of PM endometriosis in surgically menopausal patients and response to subsequent surgical management	Surgical	23-74	Pain	Recurrent and primary	Yes (70 out of 75 patients)	Cul de sac, USL, broad ligament, interstinal, rectal, ovary, fallopian tubes	No
[12]	Toki *et al.* (1996)	Retrospective review	To describe histopathologial and immunohistochemical features of PM endometriosis	Physiologic	44-71	Not reported	Primary	No	Not reported	Yes – 5 clear cell, 1 endometrioid, 1 serous + clear cell
[34]	Ismail *et al.* (1997)	Case report	To describe a case of PM endometriosis including unusual pathologic features	Physiologic	53	Heavy vaginal bleeding	Primary	No	Serosal uterine surface, right fallopian tube, ovarian mass, right ovary	No
[35]	Takayama *et al.* (1998)	Case report	Recurrent PM endometriosis causing severe pelvic pain relieved with anastrozole	Surgical	57	Pelvic pain	Recurrent	Yes (0.625 mg conjugated estrogen daily)	vaginal apex	No
[36]	Choi *et al.* (1999)	Case report	Describe a report of primary cutaneous endometriosis in a PM patient undergoing HRT	Physiologic	58	Erythematous plaques and papules on lower back	Primary	Yes (0.625 mg estrogen daily)	Cutaneous – lower back	No
[37]	Kurioka *et al.* (1999)	Case report	Describe a case of PM endometriosis unrelated to neoplasm	Physiologic	55	Asymptomatic	Primary	No	Right ovary	No
[38]	Schlesinger *et al.* (1999)	Case report, literature review	Describe a case of tamoxifen induced endometriosis	Physiologic	62	Postmenopausal bleeding	Primary	Tamoxifen x2 years	Endometriotic foci within cervix and bilaterla ovaries	No
[39]	Deval *et al.* (2002)	Case report	Description of a case of PM endometriosis mimicking colorectal malignancy	Physiologic	69	Pelvic pain, vaginal discharge, constipation, weight loss	Primary	No	Pelvic mass attached to the bladder, uterus, and sigmoid colon	No
[40]	Matorras *et al.* (2002)	Prospective randomized trial	Compare recurrent rates in women who underwent bilateral oopherectomy and were given HRT vs. no HRT	Surgical	42-54	Recurrence complaints: anal pain, pelvic pain, hypogastric pain, hematuria	Recurrent	No in control group, yes in study group	Recurrence at bladder, pelvis, paracervical endometrioma, sigmoid colon	No
[41]	Okugawa *et al.* (2002)	Case report	Description of malignant transformation of endometriosis in the setting of tamoxifen	Physiologic	67	Genital discharge, left adnexal mass	Primary	Tamoxifen x4 years	Left adnexa	Yes – endometrioid adenocarcinoma

Table 1 (*Continued*)

Ref. No.	Author (publication year)	Study design	Study purpose	Type of menopause	Age (years)	Presenting symptoms	Primary vs. recurrent endometriosis	Hormone replacement therapy	Site of endometriosis	Malignant transformation?
[42]	Bese *et al.* (2003)	Case report	Describe a case of primary PM endometriosis with recurrence of endometriosis and endocervical adenocarcinoma after tamoxifen therapy in a patient with a history of breast carcinoma	Physiologic	74	PMB	Primary, then recurred	Yes- tamoxifen x2 years	Primary occurrence – pelvis, recurrence- cervix uteri and rectal muscular wall	Yes – endocervical adenocarcinoma
[43]	Goumenou *et al.* (2003)	Case report	Possible relation between estrogen replacement and primary PM endometriosis	Physiologic	67	Ovarian mass, pelvic pain, dyspareunia	Primary	Yes, estrogen patch, testosterone implant	Left adnexa, pelvic peritoneum	No
[44]	Areia *et al.* (2004)	Case report	Description of endometrioid adenocarcinoma in the setting of HRT	Surgical	53	AUB	Primary	Yes (estradiol 1.5 mg 2x/week x6 years)	Vagina/bladder/ rectum	Yes – endometrioid
[45]	Jelovsek *et al.* (2004)	Case report	Describe a case of recurrent endometriosis of the liver containing Mullerian adenocarcinoma	Surgical	52	Flu-like symptoms	Recurrent	Yes (exogenous estrogen, then leuprolide)	liver	Yes – Mullerian adenocarcinoma
[46]	Razzi *et al.* (2004)	Case report	Description of a case of treatment of postmenopausal endometriosis with aromatase inhibitor in a 31-year-old woman	Surgical	31	Pelvic pain, dyspareunia	Recurrent	Yes (conjugated estrogen 0.625 mg daily with medroxyprogesterone acetate 5 mg, then 10 mg norethistrone x6 months, then 0.625 conj estrogen with danazol x2 months)	Rectovaginal septum	No
[47]	Strang *et al.* (2004)	Case report	Present a case of PM ureteral endometriosis with coexistant urethral leiomyoma	Not reported	65	Painless, gross hematuria	Not documented	Yes (conjugated estrogen)	Left ureter	No
[48]	Fatemi *et al.* (2005)	Case report	Treatment of recurrent PM endometriosis with aromatase inhibitor	Surgical	55	Abdominal pain (primary symptom), sciatic pain (recurrence symptom)	Primary, then recurred	Yes (0.625 mg estrogen daily x6 years)	Rectovaginal septum	No
[49]	Sesti *et al.* (2005)	Case report	Description of recurrent endometriosis involving the bladder in a PM woman	Surgical	56	Vaginal bleeding hematuria	Recurrent	Yes (conjugated equine 0.625 mg)	Posterior bladder wall, vaginal cuff	No
[50]	Taylor (2005)	Retrospective case series	Discuss the malignant potential of PM endometriosis	Surgical ×2, physiologic ×2	46, 54–56	Hematuria, rectal bleeding, abdominal pain, dyschezia, abdominal pain, abdominal mass	Primary	Yes x3, No x1	Bladder, sigmoid colon, bilateral USL,	Yes x2 – endometrioid adenocarcinoma
[51]	Nomura *et al.* (2006)	Case report	Description of case of endometrioid adenocarcinoma 22 months after primary endometriosis diagnosis	Surgical	40	Suprapubic pain, vaginal bleeding	Recurrent	Yes	Pelvic and ovarian endometriosis	Yes – endometrioid
[52]	Pugliese *et al.* (2006)	Case series (three cases)	Describe recurrent PM endometriosis causing ureteral obstruction in two cases, one case of primary endometriosis in a premenopausal woman causing ureteral obstruction	Surgical	51,49	Left flank pain x2	Recurrent	Yes (unopposed estrogen x2)	Left ureter	No

Table 1 (*Continued*)

Ref. No.	Author (publication year)	Study design	Study purpose	Type of menopause	Age (years)	Presenting symptoms	Primary vs. recurrent endometriosis	Hormone replacement therapy	Site of endometriosis	Malignant transformation?
[53]	Mousa *et al.* (2007)	Case report	Description of a case where letrozole was superior to exemestane in treating endometriosis pain in a PM woman	Surgical	Middle aged	Pelvic pain, bladder/ bowel symptoms	Recurrent	No	Terminal ileum, vaginal vault, posterior bladder wall	No
[54]	Sundar *et al.* (2007)	Case report	Document recurrence of endometriosis at vaginal vault following Tibolone HRT	Physiologic	52	Right groin pain	Recurrent	Yes – tibolone	Vaginal vault	No
[55]	Bohrer *et al.* (2008)	Case report	Present a case of PM endometriosis causing ureteral obstruction unrelieved with aromatase inhibitor	Surgical	47	Right sided pelvic pain, rectal bleeding	Primary	Oral megestrol acetate (240 mg daily)	Implants and adhesions between small bowel, sigmoid colon, vaginal cuff, anterior abdominal sidewall, pelvic sidewalls, ureters, iliac vessels	No
[56]	Mattar *et al.* (2008)	Case report	Unique presentation of PM endometriosis described as a parasitic mass	Physiologic	49	Asymptomatic, found on routine exam, increasing in size	Recurrent	Yes (0.625 mg conjugated estrogen daily, 0.15 norethisterone cyclically)	Vascular pedicle to the small bowel	No
[57]	Popoutchi *et al.* (2008)	Case report, literature review	Description of PM endometriosis mimicking colorectal cancer	Physiologic	74	Hematochezia, tenesmus, pelvic pain	Recurrent	No	Rectum	No
[58]	Rosa-e-Silva *et al.* (2008)	Case series (three cases)	Descriptive study of presentation to support celomic metaplasia as theory for disease genesis	Physiologic	54-78	Abdominopelvic pain	Primary	No	Ovary, recovaginal septum, abdominal wall	No
[59]	Efthymiou (2009)	Case report	Describe an endometriosis recurrence as endometrioid adenocarcinoma in a postmenopausal woman	Surgical	59	Constipation, tenesmus, weight loss	Recurrent	Yes (estradiol and testosterone implants)	Rectum	Yes – endometrioid
[60]	Giarenis *et al.* (2009)	Case report	Describe a case of endometriosis mimicking malignancy in the setting of HRT	Surgical	44	Painless vaginal bleeding	Recurrent	Yes (1.5 mg qday x10 years)	Vaginal vault, abutting the colon	No
[61]	Maeda *et al.* (2009)	Case report	Report of vesical endometriosis in a PM patient with HRT	Physiologic	65	Painless hematuria	Primary	No	Bladder	No
[62]	Manero *et al.* (2009)	Case report	Unique presentation of endometriosis in a postmenopausal woman	Physiologic	62	Acyclic pelvic pain	Primary	No	Left ovary	No
[63]	Sasson and Taylor (2009)	Case report	Management of recurrent postmenopausal endometriosis with aromatase inhibitor, progestin, and cyst aspiration	Physiologic	61	Left lower quadrant pain	Recurrent (primary event occurred after menopause)	No	Abdominal wall	No
[64]	Bailey *et al.* (2010)	Case report	Description of widespread endometriosis in postmenopausal woman	Surgical	53	Gross hematuria	Recurrent	not documented	Retroperitoneal mass, right kidney, small bowel, common iliac, mesentery, appendix	No
[65]	Flick *et al.* (2011)	Case report	Descriptive study of endometriosis invading into the IVC	Surgical	59	Left lower quadrant pain	Recurrent	Yes (conjugated equine estrogen x15 years)	Retro peritoneum surrounding the aorta invading into the IVC	No

Table 1 (*Continued*)

Ref. No.	Author (publication year)	Study design	Study purpose	Type of menopause	Age (years)	Presenting symptoms	Primary vs. recurrent endometriosis	Hormone replacement therapy	Site of endometriosis	Malignant transformation?
[14]	Morotti *et al.* (2012)	Retrospective review	72 women diagnosed with PM endometriosis who underwent surgery at one institution	Both	Median age- 58.5	AUB, abdominal pain, rectal bleeding	14 - recurrence	9/72 (3 on HRT at time of surgery, 4 with hx of HRT, 2 with hx of tamoxifen)	Ovary, peritoneum, right parametria, vagina, uterosacral ligament, rectum	No
[66]	Bhat *et al.* (2014)	Case report	Document a case of endometriosis mimicking a pelvic malignancy	Surgical	50	Acute abdomen, hemoperitoneum, vaginal bleeding	Recurrent	No	Pelvis, adhering to rectosigmoid, bilateral uterers, and invading into vagina	No
[67]	Kim *et al.* (2015)	Case report	Describe the first report of decidualized intranodal endometriosis in a postmenopausal woman undergoing HRT	Physiologic	52	Abominal pain, dyspnea	Primary	Yes (combined HRT x6 years)	Pelvic lymph nodes	No
[68]	Klenov *et al.* (2015)	Case report	PM endometriosis requiring supralevator exenteration	Surgical	65	Vaginal bleeding, hematuria, pelvic mass	Recurrent	Yes (estrogen replacement x20 years)	Left pelvic sidewall invading the ileum, rectum, vagina, bladder and suspected endometriosis pulmonary embolis	No
[69]	Agarwal Sharma *et al.* (2016)	Case report	PM endometriosis mimicking metastatic ovarian malignancy	Not reported	69	Abdominal distention, leg swelling	Primary	No	Peritoneum, bilateral ovaries	No
[70]	Jakhmola *et al.* (2016)	Case report	Description of bowel endometriosis mimicking colorectal cancer	Physiologic	50	Abdominal pain, altered bowel habits	Unknown	Unknown	Rectosigmoid, ovary adjoining lymph nodes	No
[71]	Matsushima and Asakura (2016)	Case report	Descriptive report of a 44 cm postmenopausal endometrioma	Physiologic	56	Abdominal fullness	Primary	No	Abdomen, pelvis, bilateral ovaries	No
[72]	Mohling *et al.* (2016)	Case report	Describe a case of malignant transformation of endometriosis within a colonic diverticulum	Surgical	61	LLQ pain, dyspareunia, hematuria	Recurrent	Yes (estrogen and testosterone pellets x8–10 years)	Mid-sigmoid colonic diverticulum	Yes – endometrioid
[73▪]	Cameron *et al.* (2017)	Case report	Endometriosis mimicking breast metastasis	Surgical	66	Palpable umbilical lesion	Recurrent	Anastrozole	Umbilicus	No
[74▪]	Ianieri *et al.* (2017)	Case report, literature review	Descriptive study of endometrioma causing DVT via compression of iliac vein	Physiologic	63	Abdominal pain	Primary	No	Retroperitoneum causing compression of left iliac vein	No
[75▪]	Threadcraft *et al.* (2017)	Case report	Description of endometriosis presenting as an erythematous vaginal plaque	Surgical	59	Chronic vaginal discharge	Recurrent	Yes (for >25 years)	Vaginal apex	No
[76▪]	Singh *et al.* (2018)	Case report	Endometriosis causing acquired diaphragmatic hernia	Not reported	57	Hypogastric pain	Recurrent	Not documented	Centrum tendineum	No
[77▪]	Solima *et al.* (2018)	Case report	Descriptive study PM endometriosis involving uterus, posterior bladder wall, rectum, posterior vaginal fornix	Physiologic	60	Asymptomatic, found on routine exam	Primary	No	Bilateral ovaries, fallopian tubes, bladder trigone, posterior rectal wall, posterior vaginal fornix	No

BSO, Bilateral salpingo-oophorectomy; HRT, hormonal replacement therapy; PM, post menopausal; TAH, total abdominal hysterectomy; USL, Uterosacral ligament.

inhibitor therapy with the administration of bisphosphonates when the bone mineral density measurement is −2.5 or lower [111].

CONCLUSION

Postmenopausal endometriosis is an uncommon occurrence. Given the potential for underlying malignancy and malignant transformation of endometriotic lesions, swift assessment of postmenopausal patients with pain and abnormal bleeding is essential. All suspected endometriosis lesions should be surgically excised for optimization of treatment and prevention of malignant transformation. Given the elevated risk of malignancy, HRT should include estrogen and progestin whenever initiated in postmenopausal women with endometriosis, including those who have undergone hysterectomy. Further research is needed to understand the true prevalence, cause, and progression in this patient demographic.

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