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Leading Article

Postmenopausal Endometriosis

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Abstract

Endometriosis is a disease of reproductive age group is no longer true. Postmenopausal endometriosis accounts for 2-5% of postmenopausal women. It should be considered as a differential diagnosis if the symptoms are suggestive of endometriosis, though majority of them present with nonspecific symptoms. It is unclear that postmenopausal endometriosis is due to recurrence/reactivation of pre-existing endometriosis or as a de novo condition. Retained hormonal responsiveness and local estrogen productive mechanisms with positive feedback cycle emerged as potential mechanisms. Obesity, phytoestrogens, menopausal hormonal therapy and tamoxifen therapy are considered as risk factors. There is a potential malignant transformation of 1%. Gold standard of diagnosis of postmenopausal endometriosis is laparoscopic visualization and biopsy. Histological diagnosis is mandatory due to risk of malignant transformation and coexisting malignancies at this age group. Hysterectomy, bilateral salpingo-oophorectomy and complete excision of endometriotic lesions are considered as the first line treatment modality in postmenopausal endometriosis due to risk of malignancy. Aromatase inhibitors, progestogens and GnRH analogues are considered as second line treatment if surgery is contraindicated or if there is a recurrence following surgery. Follow up MRI scan in 6 months needs to be considered and further follow up should be planned individual basis. There are no evidenced based management guidelines for postmenopausal endometriosis due to scarcity of good quality data and multicentre randomized trials or large observational studies are required for further evaluation of postmenopausal endometriosis.

Keywords – postmenopausal endometriosis, menopausal hormone therapy, recurrence/reactivation

What is Endometriosis?

Endometriosis is defined as presence of functional endometrial glands and tissues outside the endometrium. It is also considered as a estrogen-dependent inflamamtory condition. Endometriosis only affect women in reproductive age gorup is no longer valid since there are number of reported cases of endometriosis in both premenarchial and postmenpousal women.

Postmenospausal endometriosis

Postmenopausal endometriosis is defined as diagnosis of endometriosis during postmenopausal period in the absence of previous history of clinically or histologically proven endometriosis during premenopausal or perimenopausal period. First case report of postmenopausal endometriosis was reported in 1942, in 78-year-old women, by Edgar Haydon[1]. Following that, number of case reports and case series have been reported. However, there is no clear evidence that postmenopausal endometriosis is due to either recurrence/reactivation of pre-existing nonclinical endometriosis or as de-novo endometriosis.

In contrast to the peri and premenopausal endometriosis, postmenopausal endometriosis occurs in relatively deficient estrogen status. However, it appears to have a greater predisposition to malignant

transformation and preferebly treated with complete surgical excision[2].

Incidance

The incidence of postmenopausal endometriosis is approximately 2–5%. A study done in year 2012, involving 42,079 confirmed endometriosis patients, to evaluate the age pattern of endometriosis, by Haas et al, found 2.55% of patients were in postmenopausal group[4]. Another study done by Henriksens in 1955, involving 1000 cases of endometriosis over 20 years of age, found 3.7% had postmenopausal endometriosis[3].

Pathophysiology

Endometriosis is considered as estrogen-dependent inflammatory condition; however, definitive pathophysiology of postmenopausal endometriosis is not clear since ovarian estrogen production is minimal during postmenopausal period. Main estrogen source during postmenopausal period is peripheral conversion of androgens. Further, it is unclear that postmenopausal endometriosis is due to either recurrence/reactivation of pre-existing endometriosis or de novo condition. Retained hormonal responsiveness and local estrogen production with positive feedback cycle are two main concepts described to explain the pathophysiology of postmenopausal endometriosis. However, current evidence is more suggestive of recurrence/reactivation of pre-existing endometriotic disease.

a. Retained hormonal responsiveness

There is evidence suggestive of recurrence/reactivation of preexisting nonclinical endometriotic lesions due to retained hormonal responsiveness. A study was done by Cumiskey et al in 2007, to compare the morphological and immunohistochemical features of premenopausal and postmenopausal endometriosis[5]. This study included 100 cases of confirmed pre and postmenopausal endometriosis. It concluded that postmenopausal endometriosis has same immunohistochemical features with presence of active estrogen and progestogen receptors as in premenopausal period, suggestive of recurrence/reactivation of preexisting disease due to retained hormonal responsiveness. The study also found that endometriosis does occur in postmenopausal women but is less common, smaller volumes, and less active.

Another study was done by Toki et al in 1996, involving 21 cases of postmenopausal endometriosis. This study found that endometriotic lesions are remained biologically active, with preserved proliferative activity and hormonal responsiveness, despite low estrogen levels during postmenopausal period[6].

b. Local estrogen production and positive feed back cycle

There is evidence that endometrial tissue has aberrant Aromatase activity[7]. In contrast, normal endometrium does not contain aromatase activity. Both Aromatase expression and activity are mediated by prostaglandins (PGE2), resulting in local production of estrogen. Estrogen induces PGE2 formation and therby establishes a positive feedback cycle within endometrial tissues. Further, hydroxysteroid 17-beta dehydrogenase 2 (HSD17B2) expression is deficient in

endometriotic tissues and this reduces the conversion of estradiol to estrone[7]. These molecular changes collectively favor accumulation of high levels of estradiol and PGE2, enhancing the positive feed back cycle. The relevance of these findings are proven by the improvement of the endometriosis with the treatment of Aromatase inhibitors.

Risk factors

Excessive endogenous and exogenous estrogen activity are considered as risk factors for postmenopausal endometriosis. Risks of obesity, phytoestrogens, tamoxifen therapy, and menopausal hormone therapy are discussed in this review.

a. Obesity

Skin and adipose tissue become the main sites of estrogen production during postmenopausal period via peripheral conversion of androgens. More adipose tissue causes more estrogen production and endogenous postmenopausal estrogen production is high in obese women. Obesity may cause stimulation of endometriotic lesions and subsequent symptoms in postmenopausal endometriosis[10].

b. Phytoestrogens

Phytoestrogens are a source of exogenous estrogen. There are no conclusive evidence of phytoestrogen causing postmenopausal endometriosis. However, there is a case report of 75-year-old lady, who had a history of hysterectomy with bilateral salpingo-oophorectomy 30 years ago due to severe endometriosis. She developed a ureteral malignant carcinosarcoma associated with endometriosis following 5 years of continuous postsurgical phytoestrogen therapy[9].

c. Menopausal hormone therapy (MHT)

The role of menopausal hormonal therapy in recurrence/reactivation of postmenopausal endometriosis is not proven. However, ther are evidance which show an association with postmenopausal endometriosis secondary to activation of endometrial lesions by exogenous estrogen[10]. A study done by Tan and Almaria in 2018, involving 202 cases of postmenopausal endometriosis (collected from 10 case series and 33 case reports), to assess the effects of MHT in postmenopausal endometriosis found that 31.7% of the subjects who had postmenopausal endometriosis had MHT[11]. Mean duration of MHT use was 8.1 years (range 3 months to 30 years). Among them 62.5% had used estrogen alone, 15.6% had used combined therapy.

A Medline search of 32 case reports of postmenopausal endometriosis done by Oxholm et al, found that there is a risk of recurrence/reactivation or de novo occurrence of endometriosis after the menopause in women who received menopausal hormone therapy (MHT) and the risk is lower with combined hormonal therapy and higher with estrogen only therapy (ET)[2].

d. MHT following surgical menopause

A randomised control trial (RCT) was done in 2002, to estimate the risk of recurrence of endometriosis after MHT among women who had bilateral salpingo-oophorectomy[12]. 172 women with histologically confirmed endometriosis were participated and among them 115 women were receiving HRT and 57 were

not receiving HRT. Mean follow up time of the trial was 45 months. Trail found that patients who had total hysterectomy, bilateral salpingo-oophorectomy with complete removal of endometriotic tissue had a low risk of recurrence with MHT. Patients who had peritoneal involvement of more than 3 cm and incomplete surgical evacuation had increased recurrence rate.

e. Tamoxifen

Tamoxifen is a nonsteroidal triphenylethylene derivative and it has anti-estrogenic effect on breast tissue and estrogenic effect on endometrium. It is widely used in breast cancer patients to traet the contralateral breast and to decrease the risk of recurrence. There are copule of case reports to discuss the relationship between postmenopausal endometriosis and tamoxifen use. A case report in 1993, reported a 50-year-od lady who had 2 year adjuvant tamoxifen therapy for breast carcinoma, developed severe postmenopausal pelvic endometriosis and warrented surgical treatment[8].

The risk of malignant transformation

The risk of malignant transformation of postmenopausal endometriosis is around 1%[2]. The risk of malignant transformation of postmenopausal endometriosis appears to be higher in patients who take estrogen only hormonal therapy[2]. There are some evidance showing postmenopausal endometriosis is also asoicted with high risk for ovaraian malignancy[2].

Symptomatology

Postmenopausal endometriosis may present with typical symptoms like dyspareunia, dyschezia, chronic pelvic pain, ovarian cysts, and genitourinary symptoms depending on the location. However, most of the time clinical presentation is nonspecific and may present with abdominal or pelvic discomfort. During postmenopausal period, decreased estrogen levels may result in minimal endometriosis related symptoms, however, severity of the disease is not necessarily reflected in the severity of symptoms. It may also mimic malignancy or may have associated malignancy.

Clinical Examination

Clinical examination has a limited role in the diagnosis of postmenopausal endometriosis since there is no direct relationship of clinical signs with severity and extent of endometriotic lesions. Sometimes severe lesions remain asymptomatic even with deeply infiltrating endometriosis (DIE), and clinical examination may be normal. Per vaginal and per rectal examinational may be helpful in palpating nodules in vaginal wall, rectovaginal septum and rectal wall in certain patients. However, clinical examination is important to identify palpable lesions and to exclude other differential diagnoses.

Diagnosis

Postmenopausal endometriosis remains a disease with a delayed diagnosis due to lack of specific and efficient diagnostic tests. Laparoscopic visualization with biopsy for histological confirmation is considered as the gold standard for the diagnosis. It also provides the benefit of simultaneous diagnosis and treatment of the lesions. Imaging modalities can be used effectively in the management of suspected cases and for pre-surgical evaluation. However, no

serum marker or test is available for reliable diagnosis.

a. Imaging

Transvaginal ultrasound scan (TVS), magnet resonance imaging (MRI) and computerised tomography (CT) are useful in management of postmenopausal endometriosis. However, findings are more difficult to interpret since polymorphic aspects of endometriosis and suspicion of neoplastic/malignant lesions. Imaging modalities are more useful in deeply infiltrated endometriosis. It also important in preoperative assessment of the extent of the disease and thereby to achieve the best postoperative outcome.

1. TVS

TVS is recommended as the first-line choice of investigation modality in postmenopausal endometriosis. It has gained more interest in recent years due to cost effectiveness, widely availability, easy use, lack of radiation exposure and well tolerability. However, it remains limited for the diagnosis of extra pelvic endometriosis.

2. MRI

MRI is considered as the investigation of choice for deeply infiltrated endometriosis, since deeply infiltrated endometriotic lesions may not be seen in laparoscopic visualization. It also allows to assess whole pelvic cavity more accurately. Pre-surgical assessment of the location, extent and severity of the lesions with MRI scan can be recommended to achieve the best postoperative disease control. However, its use can be limited due to increased cost and availability.

b. Laparoscopy

Laparoscopy is considered as the gold standard investigation for the diagnosis of postmenopausal endometriosis, since it allows the direct visual inspection of the lesions and collection of biopsies from suspected lesions. A positive histology report confirms the diagnosis of postmenopausal endometriosis. However, negative histology report does not exclude postmenopausal endometriosis, since deeply infiltrated endometriotic lesions may not be seen in laparoscopic visualization.

c. Biomarkers

Currently, there are no effective biomarker is identified though many researchers have studied the role of biomarkers for diagnosis of postmenopausal endometriosis.

Management

Management of postmenopausal endometriosis includes surgical treatment and pharmacological options. Primary treatment modality is surgical and pharmacological options are considered as secondary options if surgery is contraindicated, not applicable or if there is a recurrence following surgery. Pharmacological options include Aromatase inhibitors such as Letrozole / Anastrozole, Progestogens, and GNRH agonists.

a. Surgical treatment

Surgical treatment is considered as the recommended first-line option for management of postmenopausal endometriosis due to diagnosis uncertainty, the risk of associated malignancy, and the potential risk of subsequent malignant transformation. It has a triple benefit of

removal of the lesions, providing diagnostic confirmation and relieving of symptoms. Complete excision of all endometriotic tissue is important to minimise possible recurrences.

b. Aromatase Inhibitors

Aromatase inhibitors act by inhibiting the peripheral conversion of androgens to estrogens, by decreasing extra-ovarian estrogen production, and by blocking the positive feedback loop within endometriotic lesions[13]. Third generation Aromatase inhibitors like Letrozole and Anastrozole are considered as more selective Aromatase inhibitors.

There is some evidence of Aromatase inhibitors improving the symptoms of postmenopausal endometriosis and reducing the size of the lesions probably via lowering estrogen levels. In 2011, a review article was published by Polyzos et al, to discuss the prolonged use of Aromatase inhibitors in postmenopausal endometriosis. The study found that Aromatase inhibitors were effective in improving the symptoms of postmenopausal endometriosis, including pelvic pain genito-urinary and gastro-intestinal symptoms[14]. It has also reduced the size of the lesions. However, convincing data on Aromatase inhibitors use is still scarce.

It is advised to consider the side effects profile when prescribing Aromatase inhibitors. Side effects include hot flushes, osteoporosis, vaginal dryness, etc. Further research regarding long-term effects and side-effects of Aromatase inhibitors is important for more wider use in postmenopausal endometriosis.

Currently, Aromatase inhibitors are considered as second line treatment of postmenopausal endometriosis if surgery is contraindicated or if there is a recurrence following surgery.

c. Progestogens

Progestogens are widely used in the management of peri and premenopausal endometriosis. Progestogens act on two levels, negative feedback on hypothalamic-pituitary-ovarian (HPO) axis and direct action on progestogen receptors. However, no proven data is available on progestogen's use in the management of postmenopausal endometriosis, and further studies are needed

d. GnRH agonist

The role of GnRH agonist in management of postmenopausal endometriosis is not clear. It can be considred as a second line treatment if surgery is contraindicated or if ther is a recurrence following surgical treatment.

Followup

Ther are no current recommendations available for follow up of postmenopausal endometriosis. Considering the potential risk of mailgnant transformation, it can be considered an initial follow up MRI scan in 6 months time. Further follow up should be planned on individual basis based on extent of the suregry, extent of the excision, extent of the residual disease, and histological characteristics. Further research is required to determine the optimal follow up imaging modality, follow up interval and duration of followup.

Postmenopausal Endometriosis	
Clinical Symptoms	○ **Typical** - dyspareunia, dyschezia, chronic pelvic pain, ovarian cysts, and genitourinary symptoms
	○ **Atypical** - abdominal or pelvic discomfort
Investigations	○ **Gold standard** – Laparoscopic visualization and biopsy for histological confirmation
	○ **Imaging** – Transvaginal ultrasound scan (TVS), magnet resonance imaging (MRI) and computerised tomography (CT)
Treatment	○ **First line** - Surgical treatment - hysterectomy + bilateral salpingo-oophorectomy + complete excision of lesions
	○ **Other** – Aromatase inhibitors (Letrozole / Anastrozole), Progestogens, and GNRH agonists
Follow up	○ **Initial follow up** - MRI scan in 6 months
	○ **Subsequent follow up** - Planned on individual basis

Figure 1 - Outline or Postmenopausal Endometriosis

Conclusion

Endometriosis is a disease of reproductive age group is no longer true. Postmenopausal endometriosis accounts for 2-5% of postmenopausal women. It should be considered as a differential diagnosis if the symptoms are suggestive of endometriosis, though majority of them present with atypical symptoms. There is a potential malignant transformation as well. Gold standard of diagnosis of postmenopausal endometriosis is laparoscopic visualization and biopsy. Histological diagnosis is mandatory due to risk of malignant transformation and coexisting malignancies at this age group. Hysterectomy, bilateral salpingo-oophorectomy and complete excision of endometriotic lesions are considered as the first line treatment in postmenopausal women. Aromatase inhibitors and other pharmacological options are considered as second line treatment if surgery is contraindicated or if there is a recurrence following surgery. Follow up MRI scan in 6 months needs to be considered and further follow up should be planned individual basis.

Due to the lack of high-quality studies and scarcity of proven data, it remains unclear to give defenitive recommendations on investiagtions and management of postmenopausal endometriosis. Therfore, multicentred randomized control trials or large scale observational studies are required for further evaluation of postmenopausal endometriosis.

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