

Endometriosis in Postmenopausal Women

ABSTRACT

There is functional endometrial tissue anywhere other than the uterine cavity and uterine mucosa with a penchant for infiltration and invasion. It is labeled as endometriosis. It is a chronic inflammatory condition. It can occur anywhere, but the most common site is the ovary. It is also labeled as endometrioma or Chocolate cyst. Other common sites for endometriosis are the pouch of Douglas (POD), posterior leaf of the broad ligament, uterosacral ligament, fallopian tube. Barin is the least common site for Endometriosis. Endometriosis is never seen in the spleen. This condition, which impacts 10–15 percent of women of childbearing age, is characterized by pelvic pain and infertility. Dysmenorrhoea, adnexal mass, and infertility are the classical triad of clinical features. This classical triad is mainly seen in the women of childbearing age but can also be seen in the women after menopause. Endometriosis is an estrogen-dependent condition that tends to go away on its own or after surgery. It tends to regress after menopause because it is an estrogen-dependent condition. Endometriosis is associated with cellular and humoral immunity also. Impaired immune function may contribute to the development of endometriosis. Despite this, up to 2.2 percent of women after menopause are affected. Endometriosis in postmenopausal women is seen mainly after elevated systemic estrogen concentrations or excess exogenous estrogen intake. In most women, symptomatic endometriosis after menopause begins more than ten years after menopause in the absence of elevated systemic estrogen concentrations or exogenous estrogen intake. This is necessary to understand the pathophysiology and management of endometriosis after menopause.

KEYWORDS - endometriosis, menopause, estrogen.

INTRODUCTION

Endometriosis is ectopic functional endometrial glands and stroma in sites other than the uterine mucosa. Endometriosis is a disorder of contrast. It is a chronic inflammatory condition. Endometriosis is benign but locally invasive and disseminates widely. Endometriosis is now being seen in both premenarchal and postmenopausal women, thanks to paradigm change from the idea that it solely affects women of reproductive age. Higher circulating estrogen levels may exacerbate postmenopausal disease, especially in phytoestrogen and hormone therapy.

OBJECTIVES

- To provide basic information about endometriosis in postmenopausal women.
- Identification of causes contributing to postmenopausal endometriosis.

- Providing accurate information for the prevention and management of postmenopausal endometriosis.

ETIOPATHOGENESIS

In most women, symptomatic endometriosis in postmenopausal women begins more than ten years after menopause without elevated endogenous estrogen concentrations or excess estrogen intake. In postmenopausal women, this is required to understand the pathophysiology of endometriosis in women after menopause. Although there have been hypotheses made about the etiology and pathophysiology of endometriosis, no definitive explanation of the pathophysiological mechanism involved has yet been identified. The theory of cell transplantation, the theory of metaplasia, and the theory of the endometrial-sub endometrial unit or "archimetra" are all being debated. Other theories like Sampson's implantation theory explain why the ovary and Pouch of Douglas (POD) are the most common and second most common sites, respectively. Immunological, endocrinological, genetic, and inflammatory conditions have significant roles in the pathogenesis of endometriosis. Endometriosis is associated with cellular and humoral immunity. Impaired immune function may contribute to the development of Endometriosis in women after menopause. Endometriosis is like a chronic inflammatory condition. Progesterone acts as an anti-inflammatory agent. So the level of progesterone decreases during endometriosis. The hormonal theory also suggests an increase in prostaglandins, which is associated with symptoms of endometriosis. An increase in PGE2 causes inflammation, and an increase in the level of PGF-2 alpha leads to vasoconstriction and myometrium contraction, which is associated with dysmenorrhoea. The results suggest interleukins (IL1), Interleukin 2, Interleukin 6, Interleukin 8, and other inflammatory mediators (tumor necrosis factor-alpha, interferon-gamma, monocyte chemoattractant protein 1) may play a vital role in the pathophysiology of endometriosis since they allow the growth of ectopic endometrial cells. And develop or induce an etiopathogenic mechanism of coelomic metaplasia. We believe that many post-menopausal women may have an immunosuppression state that causes lesions to form and progress.¹ Estrogen dependency is thought to have a vital role in the pathophysiology and duration of the lesions. There is still a scarcity of information in the literature about endometriosis after menopause, with the prevalence in postmenopausal women is the most studied and described. Endometriosis after menopause is thought to have more complicated pathogenesis than premenopausal endometriosis. It is still unestablished if this is a recurrent condition, continues from past illness, or is a new ailment. Endometriosis is promoted by excess estrogen in general. It's a common adverse effect of Hormone Replacement Therapy (HRT). After menopause, there is a cessation of estrogen production at the ovarian level, but this estrogen deficit is balanced by estrogen production in peripheral tissues from the conversion of androgen to estrogen. Estrone is the most common estrogen discovered in these patients. "Estrogen threshold" means, when a particular systemic estrogen level is achieved and exceeded in women after menopause, it triggers undiscovered or transient foci for the pathogenesis of endometriosis, and it owes proper explanation about the pathogenesis of endometriosis in postmenopausal women. Although the immunochemical profile of endometriosis is the same before and after menopause and can reactivate when estrogen is stimulated, the lesions of endometriosis after menopause appear less frequently, are rarely widespread and have low activity levels in the majority of patients. Endometriosis in menopausal women manifests itself in various ways, including pelvic discomfort, ovarian cysts, and digestive problems. Patients are

frequently suspected of having a neoplastic condition due to their age. If any abnormal mass is observed on ultrasonography, especially after menopause, malignancy should be ruled out. After menopause, the decline in estrogen levels reduces endometriosis-related symptoms in women who had endometriosis during their reproductive years. ⁱⁱ

DIAGNOSIS

Endometriosis after menopause carries the danger of recurrence and malignant change. Clear cell and endometrioid ovarian cancer are associated with endometriosis lesions. Ovarian endometriosis with a diameter of 9cm or significant is a significant predictor of ovary cancer in women after menopause and 45 years or older. It is still a disease with a long latency period, particularly in older people. It is still a disease with a long latency period, particularly in older people. This is due to a scarcity of noninvasive technologies during the initial diagnosis phase. There is a persistent myth that endometriosis solely affects women in the childbearing age group. However, in the past few years, attention has been diverted to diagnosing endometriosis cases in women after menopause, as that pain can begin beyond menopause, and endometriosis has been reported in patients as old as 80. After menopause, endometriotic lesions are most commonly found in the ovaries. Regardless of age, laparoscopy and histopathological examination by biopsy of suspected lesions is currently the gold standard for diagnosing endometriosis. Laparoscopy is the primary method for investigating any abnormality in the pelvis and diagnosing and treating abnormalities simultaneously. Magnetic resonance imaging(MRI) and Ultrasonography are essential imaging techniques; however, it is tough to conclude and interpret in women after menopause than in women of reproductive age group patients because of heightened concern for malignancy and the unpredictable nature of endometriosis.

CLINICAL EXAMINATION

There is no direct relationship between symptoms and signs and the skeletal-surgical features of endometrial foci. The patient's treatment history, diagnostic examination, or symptoms before operation play a restricted role in identifying the length of endometrial foci. Endometriotic areas have more pain-sensitive nerve endings. Pain is related to the depth of the lesion. Severe pain is seen in deep infiltrating Endometriosis (DIE). Per vaginal examination shows retroverted flexed uterus, which can't be corrected manually. Hormone replacement therapy (HRT) is routinely used to alleviate climacteric symptoms and prevent bone loss in postmenopausal women; however, in women with a history of endometriosis, Hormone replacement therapy (HRT) may reactivate endometriosis and induce malignant transformation. In extreme situations, however, first-line pharmacological therapy (including the oral contraceptive pill or progestogens) or laparoscopic excision of endometriotic lesions may be insufficient, and menopause induction via GnRH analogs oophorectomy may be necessary.ⁱⁱⁱ Many patients with severe lesions who are asymptomatic have a gap between the intensity of their symptoms and the degree of their lesions. This plays a significant role in the 6 to 8-year delay between the development of symptoms and diagnosis in both premenopausal and postmenopausal women. Endometriosis nodules found in the posterior compartment in the lower part of the pelvic can be identified with the pelvic, vaginal, and rectal examination; however, clinical examination findings can be expected in a significant number of patients who have endometriosis infiltrates deeply.

Imaging

Transvaginal sonography is the first investigation done in suspicion of endometriosis. "Diagnostic laparoscopy" is the gold standard, but it's no longer the 1st choice of clinical diagnosis, as non-invasive tests are becoming increasingly popular for early detection and progression of endometriosis. On ultrasound, endometriomas appear as unilocular cysts, which are usually homogeneous in appearance and seem like ground glass. An endometrioma should be aware the doctor to the likelihood of an average to progressive disorder. Ovary cysts with a "ground glass" appearance corresponded with the incidence of cancer in 44% of postmenopausal women.^{iv} TVS can also be used to assess bladder and rectum diseases. Magnetic resonance imaging (MRI) is not a routine investigation. It is done when not sure about the nature of adnexal mass. It helps in the diagnosis of deep infiltrating Endometriosis (DIE) and rectovaginal disease. "rectal endoscopic USG," "Transvaginal sonography," "computed tomography," "magnetic resonance imaging," and "three-dimensional ultrasonography" are all imaging modalities that can be used to diagnose deep infiltrating endometriosis (DIE). Because it allows through pelvic exploration and is widely available, cost-effective, and well-tolerated. Transvaginal ultrasound has become popular in past years and is now suggested as the 1st treatment approach for endometriosis. Magnetic resonance Imaging and Ultrasonography are essential imaging techniques; however, it is tough to come to a conclusion and interpret in women after menopause than in women of reproductive age group patients because of heightened concern for malignancy and unpredictable nature endometriosis. Magnetic Resonance Imaging is a noninvasive Deep Infiltrating Endometriosis diagnostic technology that allows for a thorough examination of the pelvic cavity with reasonable accuracy but at a higher cost. A new diagnostic approach in Deep Infiltrating Endometriosis (DIE) is sonovaginography with a saline solution "saline contrast sonovaginography" or "gel infusion sonovaginography." Dessole et al. were the first to describe it, and it comprises TVS mixed with the infusion of saline solution or gel into the vagina, which allows for a more detailed view of the vaginal walls and fornix pouch Douglas, uterosacral ligaments, and rectovaginal septum.^v

Biomarkers

To so far, no exact markers for endometriosis diagnosis have been discovered. Compared to ordinary women, endometriosis patients have altered CA-125, cytokines, angiogenic, and growth factor ranges; however, all of these biomarkers are found in various other illnesses and are not specific enough to diagnose endometriosis. When compared to single biomarker readings, a mixture of biomarkers may improve sensitivity and specificity.^{vi} The results suggest that interleukins (IL1), Interleukins2, Interleukins 6, Interleukins 8 "and other inflammatory mediators (tumor -necrosis factor-alpha, interferon-gamma, monocyte -chemotactic protein1) may play an essential character in the pathology of endometriosis since they allow the growth of ectopic endometrial cells and develop or induce an etiopathogenic mechanism of coelomic metaplasia. We believe that some females after menopause may have a state of immune suppression that causes lesions to form and advance.

Treatment

Surgery:-As, the diagnosis and the threat of malignancy are unpredictable; exploration by surgery should be a primary therapy option for women after menopause who have symptoms suggestive of endometriosis. The surgical method, preferably laparoscopy or minimal access surgery, should be used to get histological confirmation of the illness and alleviate uncomfortable symptoms. Histology may be required in some cases to diagnose endometriosis

and rule out malignancy. Histological confirmation is necessary in ovary endometriomas (> 4 cm in diameter) and deep infiltration diseases to rule out a rare case of malignancy. Laparoscopy is used to diagnose and treat Deep infiltrating endometriosis and remove any visible endometriosis implants, which is particularly important in women after menopause because of the potential of malignant transformation. After complete resection of all visible lesions, several studies have reported significant reductions in clinical symptoms and a lower danger of cancer in females after menopause. Accurate preoperative images can help guide surgical therapy methods and achieve the best postoperative results.

Medical Therapy:- When surgery is unsuitable, and there is a recurrence of disease following surgery, a medicinal treatment should be used.

There is a lack of treatment options in women after menopause than with women who had endometriosis in the reproductive age group. The best plan for hormone replacement therapy (HRT) for menopausal women with a history of endometriosis is essential. Combined “hormone replacement therapy” (estrogens plus gestagens) and tamoxifen\ tibolone (which especially have an estrogenic result on symptoms of menopause and bone density, but has a gestagen result on tissues) have been studied as treatment options in postmenopausal women with endometriosis and women with endometriosis in the reproductive age group. Administration of a lower-dose levonorgestrel intrauterine system along with estrogen given systemically may be an alternative for women who cannot tolerate oral progestins. New combinations of hormone replacement therapy (HRT) containing estrogens and dienogest are proposed; The confirmation in the literature is still limited, but this method and the levonorgestrel intrauterine system plus oral estrogens may be effective in regulating menopausal symptoms and preventing endometriosis from recurring.

The isoflavone, given orally as a dietary additive, has been linked to a lower incidence of endometriosis recurrence. The Aromatase Inhibitors’ action on extra-ovarian estrogen production is the reason for their use. Treatment with the aromatase inhibitor reduced pain and, in some cases, reduced the proportion of the lesion. Due to reducing extra-ovarian estrogen secretion, Aromatase inhibitors can cause secondary climacteric symptoms such as hot flashes, vaginal dryness, and decreased bone density. Add-back therapy with low-dose estrogen could be an alternative. Neurotransmitter modulators such as serotonin reuptake inhibitors and gabapentin are often non-hormonal treatments for climacteric symptoms. These are just moderately better than placebo for the treatment of menopausal symptoms and are only half as effective as estrogen.

Risk for malignant transformation

Endometriosis lesions have been reported to transform from benign into malignant lesions and spread to the ovary on both sides, intestines, and even to the lungs. The incidence of malignant conversion from endometriosis to ovarian cancer is estimated to be 2% to 3%. The incidence is a little higher in patients receiving estrogen therapy. It's tough to distinguish between benign and malignant tumors in postmenopausal women. It's important to remember that some endometrial lesions resemble cancerous lesions and can induce local and distant metastases and invade neighboring tissues and organs. It is difficult to distinguish a benign tumor from a malignant one after menopause in clinical practice as the danger factors for endometriosis and malignancy of the ovary are similar such as lower parity, late first pregnancy, infertility, and use of oral contraceptive pills for a short period. Endometrial cancer risk is enhanced when estrogen is

stimulated without being resisted. Specific investigations have shown Exogenous estrogens increase the likelihood of endometriosis lesions' malignancy transformation. 7-11

Clinical Implications

This article suggests that endometriosis in postmenopausal women is a disease whose bulk part has not yet been discovered. After considering the studies that have been taken to date, it is suggestive that Hormone replacement therapy should be avoided in women with a history of endometriosis as it increases the risk of malignant transformation. The article mentioned above will be helpful in the early evaluation of endometriosis in females after menopause. Even if the patient does not have a history of endometriosis lesions, clinicians should evaluate the risk of endometriosis in situations of unexplained pain in the pelvic region in females after menopause, although it rarely occurs.

Conclusion

Endometriosis in postmenopausal women is seen mainly after elevated systemic estrogen concentrations or excess exogenous estrogen intake. Endometriosis is an estrogen-dependent condition that tends to go away on its own or after surgery. In most women, symptomatic endometriosis after menopause begins more than ten years after menopause in the absence of elevated systemic estrogen concentrations or exogenous estrogen intake. Understanding the pathogenesis and treatment of endometriosis after menopause is critical.

References

1. Manero MG, Royo P, Olartecochea B, Alcázar JL. Endometriosis in a postmenopausal woman without previous hormonal therapy: a case report. *J Med Case Rep.* 2009 Nov 18;3:135. doi: 10.1186/1752-1947-3-135. PMID: 20062773; PMCID: PMC2803807.
2. 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 Jul 1;23(4):481-500. doi: 10.1093/humupd/dmx011. PMID: 28498913; PMCID: PMC5850813.
3. L.C. Gemmell, K.E. Webster, S. Kirtley, K. Vincent, K.T. Zondervan, C.M. Becker, The management of menopause in women with a history of endometriosis: a systematic review, *Human Reproduction Update*, Volume 23, Issue 4, July-August 2017, Pages 481–500, <https://doi.org/10.1093/humupd/dmx011>
4. Schipper E., Nezhat C. Video-assisted laparoscopy for the detection and diagnosis of endometriosis: Safety, reliability, and invasiveness. *Int. J. Womens Health.* 2012;4:383–393. [PMC free article] [PubMed] [Google Scholar] [Ref list]
5. Saccardi C., Cosmi E., Borghero A., Tregnaghi A., Dessole S., Litta P. Comparison between transvaginal sonography, saline contrast sonovaginography and magnetic resonance imaging in the diagnosis of posterior deep infiltrating endometriosis. *Ultrasound Obstet. Gynecol.* 2012;40:464–469. doi: 10.1002/uog.11102. [PubMed] [CrossRef] [Google Scholar] [Ref list]
6. Secosan C, Balulescu L, Brasoveanu S, Balint O, Pirtea P, Dorin G, Pirtea L. Endometriosis in Menopause-Renewed Attention on a Controversial Disease. *Diagnostics (Basel).* 2020 Feb 29;10(3):134. doi: 10.3390/diagnostics10030134. PMID: 32121424; PMCID: PMC7151055.