

Opinion Paper

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Endometriosis and the menopause: why the question merits our full attention

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Abstract:

As an estrogen-dependent disease, endometriosis was thought to become less active or regress with the onset of the menopause. However, based on some new data, we are discovering that this pathology can emerge or reappear at this period of life. Clinicians must consider it as a possible cause for cases of pelvic pain, and heavy bleeding. Authors have described a possibility of transformation of the intraperitoneal proliferation into a malignant type with ovarian, bowel and even lung metastasis. The risk of transformation into an ovarian cancer is around 2 or 3%. The role of menopausal hormonal therapy will be discussed as in recurrence in the case of residue existence, especially after incomplete surgery. Is it possible to prescribe hormonal therapy to a menopausal women suffering climacteric symptoms as it could trigger a recurrence of endometriosis and even an increased risk of malignant degeneration? This remains unclear. It is an unresolved therapeutic dilemma; the choice between surgery or medical treatment?

Keywords: carcinoma, clear cell carcinoma, endometrioma, endometriosis, HRT, levonorgestrel, menopause

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Introduction

Endometriosis is an estrogen-dependent disease that predominantly affects reproductive-age women, which becomes less active or regresses with the onset of the menopause; nevertheless, certain data, essentially case series and case reports, are demonstrating that this pathology is, in fact, described even after the decrease of ovarian hormonal secretion. Therefore, clinicians must take this into account in the case of pelvic pain (dysmenorrhea, dyspareunia, chronic pelvic pain) and heavy bleeding during this period.

Endometriosis can be considered as an intra peritoneal benign proliferation but of a malignant type, which can metastasize to the ovaries, bowel and even the lung. Endometriosis is strongly associated with the increased risk of ovarian cancer; this risk is around 2 or 3%.

Definition

Endometriosis is an enigmatic disease characterized by the development of functional endometrial tissue outside the uterine cavity [1]. Endometriosis is a well-known estrogen-dependent disease and is heterogeneous in nature with lesions having three distinct phenotypes: superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA) and deeply infiltrating endometriosis (DIE) (Figure 1). Moreover, endometriosis is frequently associated with adenomyosis. The pathogenesis of endometriosis is unclear and it is unknown why different patients present with SUP, OMA or DIE lesions, and sometimes all the types present in the same patient. The fact that endometriosis phenotype pathogenesis remains unclear suggests that multifactorial mechanisms are involved [2] including hormonal [3], inflammatory [4], [5], immunologic [6], [7], genetic [8], [9], [10], epigenetic [11], environmental [12] and other influences.

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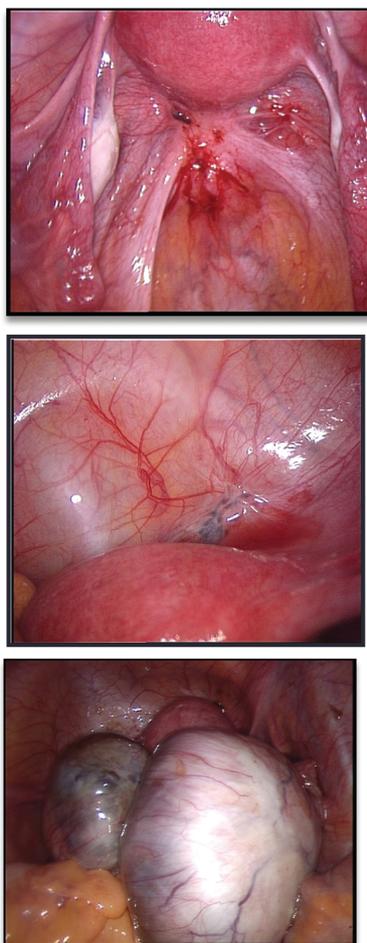


Figure 1: DIE, deep infiltrating endometriosis; SUP, peritoneal superficial endometriosis; OMA, Ovarian endometrioma. DIE: left utero sacral ligament and vagina; SUP: vesico uterine peritoneum; OMA: kissing ovarian cysts.

Physiopathology

Data on the physiopathological mechanisms implicated in postmenopausal endometriosis are limited. Around 2–4% of postmenopausal women are estimated to suffer from endometriosis. The fact that endometriosis lesions are able to develop or persist in menopausal women in the absence of menstrual cycles and in a hypo-estrogenic environment sheds doubt on Sampson's physiopathological theory of retrograde bleeding and implicates other mechanisms [13], [14].

During the reproductive years, estrogenic stimulation mainly results from ovarian secretion. At menopause, there is a cessation of menstruation related to a state of ovarian inactivity.

However, many issues remain: is it a persistence or a recurrence of a pre-existing disease? A de-novo development? A local estrogen production such as is found in the case of obesity; phyto-estrogens, hormone replacement therapy (HRT) or tamoxifen intake? What is the possible role of stress, what is the relationship with a variant polymorphism (genetic-epigenetic), with hypothyroidism or even the role of fatty acids (unsaturated omega 3)? That was one of the main topics discussed in the last society of endometriosis and uterine disorders (SEUD) Conference (Firenze 2018).

Bulun et al. studied estrogen production by endometriosis lesions themselves [14]. According their work, aromatase is expressed in endometriosis implants and in the eutopic endometrium of women with endometriosis; autocrine and paracrine effects result in the local production of estrogen. Estrogens stimulate Cox-2 which increases the formation of prostaglandin E₂, and therefore increases aromatase activity. Thus, there is a positive feedback loop in favor of continuous estrogen production in endometriotic lesions.

This theory developed by Bulan et al. could explain how endometriosis lesions may persist and become symptomatic in the hypo-estrogenic environment after menopause [15].

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. There is a possibility that exogenous estrogen will reactivate growth of endometriotic deposits and cause symptomatic recurrence [16], [17].

Does endometriosis persist after menopause?

Endometriosis is a disease that affects an estimated 6–10% of reproductive aged women, totaling approximately 176 million women worldwide [14]. Even if endometriosis is more frequent between the years of 25 and 45, it does not disappear after the onset of the menopause. Around 2–4% of postmenopausal women are estimated to suffer from endometriosis [15], [18]. This statement raises three important issues: thinking about the diagnosis, being aware of the role of HRT on recurrence, not forgetting the risk of malignant change with or without HRT, especially in the case of ovarian disease. The case of pain and bleeding should raise our suspicions; imagery will confirm: ultrasound and magnetic resonance imaging (MRI) are both necessary. The first-line treatment for new-onset symptomatic post-menopausal endometriosis should be surgical because of diagnosis uncertainty, the risk of associated malignancy, and the potential risk of subsequent malignant transformation [19]. A laparoscopy will be carried out to fully confirm the diagnosis, to exclude a malignant tumor and, sometimes, to treat the pain surgically. Imaging techniques (transvaginal ultrasound, MRI), are generally not sufficiently accurate to distinguish between endometriosis lesions and cancer. Medical treatment is sometimes prescribed using a levonorgestrel intrauterine contraceptive device (IUD), gestodene or aromatase inhibitors.

Role of HRT

The effect of HRT for menopause on the recurrence and malignant transformation risk in women with endometriosis should be considered. In women suffering from severe symptomatic endometriosis undergoing hysterectomy and bilateral salpingoophorectomy for pain relief, combined HRT is usually prescribed. If there are residues before the treatment, increased risk exists, especially in the case of significant endometriosis and incomplete surgery without hysterectomy, HRT must be avoided in these cases. In a 2009 Cochrane Review, Al Kadri et al. concluded that HRT may increase the risk of endometriosis symptoms and disease recurrence after surgically induced menopause [20]. According to the literature, HRT can be prescribed to women after menopause in the case of significant climacteric symptoms. Authors recommend continuous estrogen-progestin. Tibolone is sometimes better [21]. This treatment can be prescribed immediately after surgery in the case of bilateral ovariectomy and early menopause. Patients must be informed of the possibility of recurrence. If pain returns, treatment must be stopped. The European Menopause and Andropause Society (EMAS) statement agrees with these conclusions [22].

Malignant transformation

Endometriosis is a benign proliferative condition; however, malignant transformation may occur in almost 1% of cases, occurring most commonly in ovarian lesions [23], [24]. In a meta-analysis done on this subject and published in 2014, Audebert et al. concluded : *“Endometriosis is strongly associated with the increased risk of ovarian cancer, and Endometriosis Associated Ovarian Cancer (EAOC) shows favourable characteristics including early-stage disease, low-grade disease and a specific histology such as endometrioid or clear cell carcinoma”* [25]. In 2016, Chene put forward that endometriosis could be a pre-cancerous lesion, which may evolve into atypic hyperplasia and finally into EAOC [26]. Clear cell and endometrioid carcinomas were the malignancies most commonly seen in ovaries containing endometriosis (Figure 2).

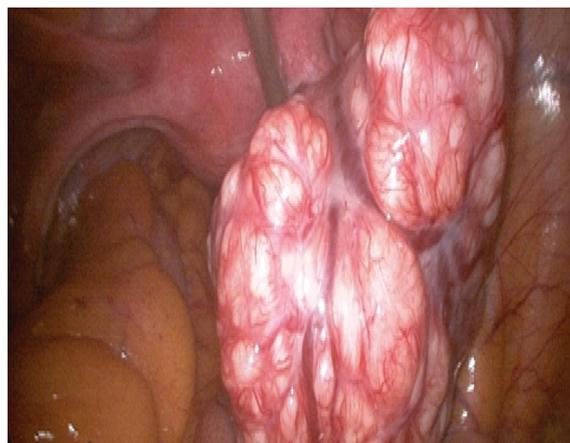


Figure 2: Ovarian malignant tumor.

How to deal with it

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 [27]. In the case of postmenopausal pelvic mass, surgery will be proposed to confirm the diagnosis and to eliminate malignancy or atypia. In the case of pain, it can be used to treat.

Medical therapy may be an option in the case of pain recurrence after surgery or if surgery is contraindicated [28]; a levonorgestrel IUD or progestins such as gestodene have been tried out. Also, some data consider using aromatase inhibitors; this kind of medical therapy would block the extra ovarian production of estrogens thus decreasing pain and lesion size [29].

Conclusion

Post-menopausal endometriosis is a rare condition but is a reality. Diagnosis will be carried out through collecting patient history, doing a clinical examination and using imagery. As a first-line treatment, surgery will be used to treat the pain, and to eliminate the malignancy. The risk of malignant evolution should not be underestimated: endometrioid, or clear cell carcinoma. Medical therapy comes in the second line: aromatase inhibitors, levonorgestrel IUD, gestodene. HRT increases recurrence risk. Nevertheless, it is imperative, before prescribing, to weigh the risks and benefits.

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