Endometriosis in Menopause

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Contributor: Cristina Secosan

Endometriosis, an estrogen-dependent inflammatory disease characterized by the ectopic presence of endometrial tissue, has been the topic of renewed research and debate in recent years. The paradigm shift from the belief that endometriosis only affects women of reproductive age has drawn attention to endometriosis in both premenarchal and postmenopausal patients. There is still scarce information in literature regarding postmenopausal endometriosis, the mostly studied and reported being the prevalence in postmenopausal women. Yet, other important issues also need to be addressed concerning diagnosis, pathophysiology, and management.

Keywords: endometriosis ; menopause ; diagnosis ; management ; malignancy

1. Introduction

The concept that endometriosis is a disease that only affects women of reproductive age has prevailed since 1942, when the first case of endometriosis in a postmenopausal patient was reported by Edgar Haydon [1].

In spite of this early report, endometriosis has also been described in premenarchal patients and is a common occurrence in adolescents [2][3][4].

The recurrence of endometriosis lesions in patients with a prior diagnosis of endometriosis during the premenopausal period or the de novo appearance of endometriosis in postmenopausal patients with no prior history of endometriosis-related complaints has been however well documented in numerous case series, case reports, and retrospective studies [5][6][7][8][9].

The management of endometriosis in postmenopause and hormone replacement therapy (HRT) in patients with a history of endometriosis remains controversial.

2. Pathophysiology

Endometriosis is an estrogen-dependent inflammatory disease characterized by the presence of ectopic endometrial tissue. The pathogenesis of endometriosis remains enigmatic [10].

Postmenopausal endometriosis is considered to have an even more complex pathophysiology than premenopausal endometriosis. It is still unclear whether this represents a recurrence or continuation of a previous disease or a de novo condition. Excess estrogen, in general, represents a promoting factor for endometriosis. The arrest of estrogen production at the level of the ovaries at the time of menopause is counterbalanced by peripheral estrogen production from conversion of androgens (especially in the adipose tissue and skin). The leading estrogen found in these patients is estrone.

An attractive theory regarding the pathogenic mechanism of postmenopausal endometriosis involves the “estrogen threshold”, i.e., when a certain estrogen level is reached or surpassed in postmenopausal patients it activates undetected or “transient” foci of endometriosis.

In addition to the peripheral estrogen production, a high circulating level of estrogen may be of external source, especially in the form of phytoestrogens and HRT. Phytoestrogens appear to exert estrogenic effects on the uterus, breast, and pituitary and could also support the growth of endometriotic lesions [11][12][13].

Despite the fact that postmenopausal endometriosis has the same immunochemical profile as premenopausal endometriosis and has the potential to reactivate under estrogen stimulation, endometriosis lesions in the postmenopausal period seem to be less common, less extensive, and less active in most cases [14].

3. Diagnosis

Despite intensive research conducted in the last decades, endometriosis remains a disease with a delayed diagnosis, especially in older patients. This results from the lack of noninvasive tools available for early stage diagnosis. For many years, there has been a long-standing myth that endometriosis is a disease that affects only adult women of reproductive age. However, in recent years, focus has turned to the diagnosis of endometriosis in postmenopausal patients, given that the onset of pain can start after the onset of menopause, with reports of endometriosis occurring even in 80-year-old patients [1][5].

The ovaries are the most common location of endometriotic lesions in postmenopausal patients (79.2% of cases) [15].

Distinction between endometriosis lesions and cancer is complicated by the fact that some of the risk factors are similar, such as low parity rate, infertility, late childbearing age, and a short duration of oral contraceptive use [16].

Currently, laparoscopy and biopsy for histological confirmation of suspicious lesions is the gold standard for diagnosis of endometriosis, irrespective of age. Laparoscopy, the standard technique for inspecting the pelvis, can provide simultaneous diagnosis and treatment of lesions. Additional tools are needed for a noninvasive diagnostic and classification. To this date, no serum marker or test is available for reliably diagnosing endometriosis [17][18]. Regarding imaging investigations, MRI and ultrasound are important, but findings are more difficult to interpret in menopausal patients than in younger patients due to the higher suspicion for neoplastic lesions and the polymorphic aspect of endometriosis.

3.1. Clinical Examination

The patient's medical history, clinical examination, or preoperative symptoms have a limited role in determining the extent of endometriosis lesions as there is no direct relationship between symptoms and the anatomic-surgical characteristics of endometriotic lesions [19]. Also, there is usually a discrepancy between the severity of symptoms and the extent of lesions with many patients whose severe lesions remain asymptomatic. This is an important factor contributing to a delay of approximately 6 to 8 years from onset of symptoms to diagnosis in premenopausal and postmenopausal patients alike [20].

Pelvic vaginal and rectal examination is useful in identifying endometriosis nodules in the lower posterior compartment, but clinical examination may be normal in many patients with deep infiltrating endometriosis [20].

3.2. Imaging

While diagnostic laparoscopy remains the gold standard, it is often not the first line of diagnosis any more, as noninvasive testing for early diagnosis and progression of endometriosis is being preferred [21]. Yet, no imaging method can definitively confirm the diagnosis of endometriosis, being notably inconclusive in case of peritoneal implants [22].

Deep infiltrating endometriosis (DIE) can be investigated through several imaging techniques, including transvaginal sonography (TVS), magnetic resonance imaging (MRI), computerized tomography, rectal endoscopic sonography, and three-dimensional (3D) ultrasound [20].

TVS has gained interest in recent years and is starting to be recommended as the first-line investigation technique in endometriosis because it allows extensive exploration of the pelvis, is widely available, cost efficient, and well tolerated [23][24][25].

TVS has the benefit of a lack of exposure to radiation and is the main method for the evaluation of adnexal masses, but remains limited for the diagnosis of other kinds of endometriosis. Endometriomas have distinct characteristics on ultrasound: unilocular cysts, most often of homogenous "ground glass" appearance. The identification of an endometrioma should alert the clinician to the possibility of moderate-to-advanced stage disease. An important exception is postmenopausal women, in whom ovarian cysts with a "ground glass" appearance are associated with a 44% risk of malignancy. In addition, TVS may have a role in assessing disease involving the bladder and rectum [26].

Computed tomography (CT) plays a major role in the diagnosis of bowel endometriosis in the presence of colon distension. Genitourinary tract involvement should be taken into consideration in case of hydronephrosis or hydroureter diagnosed on CT scan, especially in patients with a history of chronic pelvic pain or in patients with a history of endometriosis. Radiation exposure should be taken into consideration [26].

MRI is a noninvasive diagnostic method of DIE that offers the possibility to fully investigate the pelvic cavity with a high accuracy, but increased costs [27]. Nevertheless, MRI has limited indication in the diagnosis of endometriosis. It can confirm the diagnosis of endometrioma in the presence of an adnexal mass when TVS is uncertain. MRI can also be used as an investigation method when involvement of the ureter is suspected, and may be beneficial in the evaluation of anatomy when expanded pelvic adhesions are suspected [26].

Sonovaginography using saline solution (saline contrast sonovaginography (SCSV)) or gel infusion sonovaginography is a new diagnostic method in DIE. First described by Dessole et al., it consists of TVS combined with the introduction of saline solution or gel infusion into the vagina, which offers the benefit of a more complete view of the vaginal walls and fornix, pouch Douglas, uterosacral ligaments, and rectovaginal septum [19]. The data available in literature is limited, with only a few reports from Brazil, Italy, Romania, and Australia, but the methods seems beneficial in the diagnosis of posterior deep infiltrating endometriosis. Up to date, no studies have reported its use in postmenopausal patients [19][28][29][30].

The role of double-contrast barium enema (DCBE) in the evaluation of rectovaginal endometriosis is controversial. Some studies have reported high accuracy in predicting the need for intestinal surgery in endometriosis cases. The superiority of DCBE over rectal ultrasound or MRI is not well established, the results reported in literature being scarce and contradictory. However, certain studies have demonstrated a lower sensitivity of DCBE for rectovaginal disease. DCBE does not allow the examination of the entire intestinal wall thickness and does not provide information regarding the depth of infiltration, but may provide useful information for preoperative planning when severe disease is suspected [26].

3.3. Biomarkers

To this date, no specific markers for the diagnosis of endometriosis have been identified. A change in levels of proteins, microRNAs, and other markers corresponding to a disease state could be the basis for identifying novel biomarkers. Endometriosis patients often show modified ranges of CA-125 (Cancer Antigen 125), cytokines, angiogenic and growth factors compared with normal women, but all of these biomarkers are frequently encountered in various other pathologies and are not specific enough for diagnosing endometriosis. A combination of biomarkers may improve the sensitivity and specificity over single biomarker measurements. Moreover, stem cell, proteomic, and genomic studies could contribute to the development of new high-sensitivity biomarkers in the diagnosis of endometriosis in the future [21].

Many authors have studied the role of biomarkers for diagnosis of endometriosis and concluded that, to date, endometrial tissue, menstrual or uterine fluids, and immunologic markers in blood or urine are not recommended for clinical use for diagnosis of endometriosis [21].

Regarding the differential diagnosis between endometriomas and malignant ovarian tumors in postmenopausal patients, we have not found any information in the literature that supports the use of any novel tests, such as OVA1 (Ovarian Malignancy Algorithm), ROMA (risk of ovarian malignancy algorithm), circulating miRs, etc. Despite the potential clinical utility of these biomarkers in the diagnosis of malignant ovarian tumors in premenopausal patients, the costs implied, the lack of easy availability, and the decreased incidence of endometriomas in older patients make the usefulness of novel biomarkers difficult to assess [31][32][33].

3.4. Minimally Invasive Surgery: Laparoscopy and Robot Assistance

Because of the lack of specific and efficient noninvasive tests for endometriosis, there is often a significant delay in diagnosis of this disease, especially in older patients. The gold standard for the diagnosis of endometriosis remains visual inspection by laparoscopy, preferably with histological confirmation. A positive histological examination confirms the diagnosis, but negative histology does not exclude it, in the presence of pathognomonic lesions [20].

Whether histology should be obtained if peritoneal disease alone is present is controversial: a visual inspection of the pelvis should be enough, but histological confirmation of at least one lesion is ideal. In some cases, histology should be obtained to identify endometriosis and to exclude malignant disease. For example, in ovarian endometriomas (>3 cm in diameter) and in deeply infiltrating disease, a histological confirmation to exclude a rare instance of malignancy is necessary [34].

Laparoscopy is used for the diagnosis and treatment of DIE and serves to eradicate all visible endometriosis implants, especially in postmenopausal patients due to the risk of malignant transformation. Several studies have shown a significant improvement of symptoms and a decreased risk of malignancy in postmenopausal women after complete resection of all visible lesions. Precise preoperative imaging may help guide surgical therapeutic approaches and aid to obtain the best postoperative results [20]. In the last years, the da Vinci surgical system started to be used in the diagnosis

and treatment of endometriosis. Three-dimensional (3D) vision offers the advantage of improved depth perception and accuracy in the performance of robotic surgery, particularly for complex surgical tasks such as identifying suspected implants. However, the robotic platform has the distinct disadvantage of offering only a unidirectional view within the abdominal cavity. Authors recommend for the first instance to undertake a diagnostic laparoscopy to exclude a suspected lesion of endometriosis in the upper abdomen, liver, diaphragm, and appendix before using the da Vinci robotic system in the pelvis. Another disadvantage is the loss of haptic feedback to identify fibrotic lesions which are characteristic of deeply infiltrating disease. However, the da Vinci robot may offer improved ease by avoiding hand and more instinctual movement of the wristed instruments in the treatment of endometriosis. The cost related to the procedure also make it unavailable at a large scale [26].

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