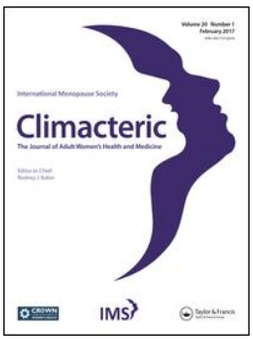

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REVIEW

Surgical challenges in the treatment of perimenopausal and postmenopausal endometriosis

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ABSTRACT

Endometriosis is classically defined as a chronic, recurrent and progressive disease. It is known to be estrogen-dependent, but can still be observed during the peri- and postmenopausal periods. Medical management of endometriosis is palliative symptomatic relief. Surgery when properly and timely performed for the right person may treat endometriosis. However, there is always a risk of possible major or minor surgical complications, as well as loss of some functions due to nerve damage. Management of endometriosis in the woman approaching the end of her reproductive life may require special attention both due to the potential for recurrence and transformation into various endometriosis-associated malignancies.

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Endometriosis; surgery; postmenopausal; recurrence; malignant transformation

Introduction

Endometriosis is defined as a chronic, recurrent and transiently progressive disease. It is known to be estrogen-dependent, but can still be sustained, revived or possibly generated during or after the menopause.

Endometriosis should regress in parallel with the regression of gonadal steroidogenesis during the menopausal transition. This has not been shown in longitudinal studies at the tissue level, but only 'presumed' due to alleviation of symptoms of disease[1]. According to Sampson's theory of the pathogenesis of endometriosis, during the menopausal transition the already present endometriosis foci should stop growing and regress due to the absence of retrograde menstruation and weakened estrogenic stimulation[2].

However, at least 2–5% of women have been found to be afflicted with endometriosis within 7 years of their menopause[3]. This may be due to metaplasia, induction of endometriotic implants through continued gonadal steroidogenesis, exogenous estrogen administration, peripheral aromatization by adipose tissue, and *in situ* aromatization within a cycle of estrogen stimulating cyclooxygenase activity and prostaglandins, which in turn stimulate aromatization[4].

Objectives of surgery for the peri-/postmenopausal endometriosis patient

The main indications for surgical treatment of endometriosis are pain which cannot be cured with drugs; infertility not curable with conventional treatment modalities; endometriomas and symptomatic deep infiltrating endometriosis[5].

The ESHRE 2014 guidelines recommend that, in order to treat pain associated with deep infiltrating endometriosis or endometriotic cysts, all endometriotic lesions should be resected. Medical therapy is not useful prior to or after surgery as an adjunctive measure to improve the surgical outcome, but only to delay recurrences and to treat cyclical pain. Of course, histological confirmation is mandatory[6].

Endometriosis in the postmenopausal period

Even though endometriosis is not always progressive, the patient's characteristics or epigenetic/environmental conditions may revive or maintain endometriosis until or even after menopause[7]. In the postmenopausal period, endometriosis is observed at a rate of 2–5% within a period of 7.3 years following menopause. Endometriosis at this stage of life displays different tissue characteristics, hormone sensitivity profiles and anatomic distribution (more commonly in extrapelvic locations) compared with endometriosis observed before menopause[8,9]. Moreover, in about 97% of these cases, endometriosis presentation after menopause is not associated with its premenopausal diagnosis[3].

Endometriotic implants in postmenopausal patients show less hemorrhagic foci and present strong positivity for estrogen and especially progesterone receptors (in contrast to their premenopausal counterparts) as well as the ki-67 antigens[10,11]. Extrapelvic involvement by endometriosis has been reported including vena cava, the liver parenchyma, the skin and the diaphragm, in addition to rectal and ureteral involvement[12–16].

Recurrence and incomplete resection

Approximately 12% of all endometriosis cases will finally require a hysterectomy with or without oophorectomy[17]. It is

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now recommended that surgical treatment of endometriosis requires as complete as possible resection of implants in order to alleviate pain and restore bowel, urinary and sexual function and to prevent recurrences[6,18–20].

Shakiba and colleagues[21] have shown that conservative endometriosis surgery would necessitate further surgery within the following 2, 5 and 7 years in 20.6, 46.7 and 55.4% of cases, respectively. However, when bilateral adnexectomy was performed together with hysterectomy, additional surgery was needed within the annotated time periods in 4, 8.3 and 8.3% of cases, respectively. The same group also showed that the preventive benefit of oophorectomy to obviate the need for additional surgery due to persistence or recurrence was especially significant for women older than 39 years of age. Preserving one of the ovaries was not associated with a lower risk of recurrence than preserving both. It was also concluded that the age when the operation was performed was an independent predictor of the need for additional surgery, being more probable for younger patients[21].

Vercellini and colleagues[22] found that, following conservative surgical intervention, there was a 20–40% chance of pain recurrence and a 15–20% need for additional surgery. Hysterectomy with bilateral salpingoophorectomy (BSO) significantly reduced but did not entirely eliminate these risks.

Limits of excision should include all endometriotic deposits and parametria[23]. A more radical surgical approach (e.g. modified radical hysterectomy) for recurrent deep infiltrating endometriosis has also been shown to drastically reduce recurrence rates[24]. Recurrence following incomplete resection may be increased by estrogen-only menopausal hormone therapy (MHT); however, the risk of recurrence seems marginal if combined estrogen and progestogen preparations or tibolone are used. Estrogen-only therapy should be avoided to minimize risk of adenocarcinoma arising from endometriotic remnants[25,26].

Postmenopausal recurrence commonly presents as low back or rectal pain, painful defecation, 'deep' dyspareunia, rectal/vaginal bleeding or hematuria/flank pain or even hydronephrosis and renal failure[27–29]. Specific biomarkers or imaging criteria to detect recurrences are still lacking[30].

Although the recurrence rate of endometriomas following ovarian cyst excision may be as high as 37.5% over 5 years, we must also be mindful of the effect of removal of endometrioma on ovarian reserve and this must be discussed with patients prior to surgery[31,32].

Is endometriosis associated with malignancy?

The risk of malignant transformation for endometriosis is at least 2.5%. The prevalence of endometriosis varies with different types of ovarian cancer (4.5%, 1.4%, 35.9% and 19% for serous, mucinous, clear cell and endometrioid types, respectively)[14]. Ovarian endometriosis is especially associated with clear cell, endometrioid types and low-grade seromucinous tumors. Endometriosis is usually not associated with high-grade serous tumors or mucinous tumors. Despite the rarity of endometrioid borderline ovarian tumors (3.5%), they are more likely to be transformed from atypical endometriotic foci and pose a better prognosis[33].

Results of epidemiologic studies on the association between endometriosis and malignancies are not in agreement[34–36]. Brinton and colleagues reported that the relative risk (RR) of cancer following a hospital discharge diagnosis of endometriosis was 1.2 (95% confidence interval (CI) 1.1–1.3) overall, for breast cancer 1.3 (95% CI 1.1–1.4), and for ovarian cancer 1.9 (95% CI 1.3–2.8). For women with a long-standing history of ovarian endometriosis, the RR was 4.2 (95% CI 2.0–7.7)[34]. In the Iowa Women's Health Study, women with a self-reported diagnosis of endometriosis followed for 13 years did not show any increased risk of breast or ovarian cancer, although the risk for non-Hodgkin lymphoma was increased (RR 1.8, 95% CI 1.0–3.0)[35]. In a retrospective study of 72 postmenopausal women operated on for endometriosis, 35% of the specimens contained atypia, different grades of metaplasia or endometrioid carcinoma arising from endometriosis[36].

There are three hypothetical explanations for the perceived link between endometriosis and malignancy:

(1) All or a certain proportion of cases of endometriosis may be premalignant lesions[37];
(2) The environmental, endocrinologic, epigenetic or genetic factors may be etiologic for both endometriosis and some malignancy types[38];
(3) Endometriosis may be a metaplastic component of the malignant transformation[39].

The criteria required to confirm concomitance of endometriosis with ovarian cancer were initially defined by Sampson and Scott[40,41]. Van Gorp and colleagues classified endometriosis and ovarian tumor concomitance into three stages: (A) endometriosis discovered in the same ovary with histologic proof of transition; (B) endometriosis discovered in the same ovary but without histologic proof of transition or without knowledge whether this transition was further investigated; (C) endometriosis discovered at any location in the pelvis. For each tumor type, this staging can be used to decide whether endometriosis and the tumor type studied are associated[15].

Somigliana and colleagues reported concurrence rates with clear cell carcinoma (39.2%)[11], whilst Sainz de la Cuesta and colleagues reported rates of an association with endometriosis in 31% of clear cell carcinoma, in 18% of mixed type, and in 9% of other types of malignancy[13].

Molecular and genetic studies provide evidence that endometriosis may be a premalignant condition. Clonality studies, allelotyping of endometriotic implants and synchronous ovarian tumors reveal that common allelic or focal losses of heterozygosity), especially of 4q, 5q, 6q, 9p, 11q and 22q, are observed in about 81.7% of Class B endometriosis-associated ovarian tumors. These variations were observed much less commonly in solitary endometriotic foci or non-endometriosis-associated ovarian cancers. Studies of tumor suppressor genes (*K-ras*, *ARID-1A*) both in humans and rodents suggested that endometriosis and the endometriosis-specific ovarian tumors may be interrelated and could be successive

stages of a sequence of malignant transformation rather than being merely coincidental[42]. Microsatellite analysis for 17p13.1 or p53 mutation analysis has shown that dysfunction of this tumor suppressor gene does *not* play a significant role in the malignant transformation of endometriosis[7].

Atypical endometriosis may occur in up to 35% of all cases. Czernobilsky and Morris defined mild atypical endometriosis as 'a single epithelial layer of slightly eosinophilic cuboidal or flattened cells with slightly enlarged hyperchromatic and pleomorphic nuclei', whilst severe atypical endometriosis was defined as the presence of large pleomorphic hyperchromatic or pale nuclei, eosinophilic cytoplasm, occasional squamoid features, tufting, crowding and stratification, and intraluminal projections and bridging in glandular structures[43]. This entity was associated with both epithelial and non-epithelial tumors[44].

Endometrioma: benign or malignant?

The decision to operate on endometriomas is critical in the menopausal transition. Differentiation of an endometrioma from a malignant adnexal mass must be made using the usual diagnostic modalities and clinical characteristics[45]. The postmenopausal status has a factorial contribution to risk. For instance, even in the presence of a unilateral benign-appearing cyst in a postmenopausal woman, a moderately elevated or rising levels of cancer antigen 125 (CA125) may point to a 'high-risk' status[33]. Hence, the threshold for surgery to treat ovarian cysts that are presumed to be endometriomas in the postmenopausal stage is set lower than when the situation is encountered in the reproductive stage of life.

CA125 is a non-specific tumor marker that is elevated in endometriosis and bowel disease and also varies according to the menstrual cycle status. Human epididymis protein 4 is a robust tumor marker that has a comparable sensitivity to CA125 but a significantly higher specificity in differentiating endometriosis cases from malignancies[46].

Using 3-Tesla magnetic resonance imaging (MRI) techniques in dynamic contrast-enhanced MRI, the time–intensity curves have been shown to be much more accurate than diffusion-weighted imaging or evaluation of the diffusion coefficient values. Malignant masses display early, steeply rising and short-lasting perfusion curves with MRI[47]. Endocystic papillary formations within endometriomas, especially on T1-weighted images, also increase the suspicion for a malignancy. The mere appearance of endocystic papillary formations has a very low sensitivity for a malignant transformation (39%)[48]. The disappearance of these 'papillary formation' images in the T2-weighted images (especially in successive MRIs) may be suggestive of malignant transformation[49]. However, the T2-weighted loss of intracystic shading should be differentiated from the phenomenon described above. This is often due to the presence of a hemorrhagic cyst instead of an endometrioma[50].

Surgery for recurrent endometriosis

The management of recurrent endometriosis with a conservative surgical approach has been shown to be ineffective. However, in the case of postmenopausal women, there are no data on the benefit or otherwise of a conservative approach in this low-estrogen environment[51,52]. In a report of 75 cases of recurrent endometriosis, bowel involvement was reported in 33% of the re-operated cases[53].

In a recent review, it was suggested that, for women with persistent or recurrent endometriosis following laparoscopic surgery, medical treatments might be preferred, providing endometriosis was histologically confirmed and malignancy/atypia was ruled out[54].

Prior to any surgery for supposed recurrence, irritable bowel syndrome, interstitial cystitis, myofascial and vertebral pathologies should be ruled out and the patient warned of potential complications of radical surgery[22,55–59]. Presacral neurectomy or lower uterine nerve ablation do not have any additional benefit in decreasing persistence rates of postoperative symptoms and may cause chronic constipation and bladder dysfunction[60].

Menopausal hormone therapy after definitive surgery to treat endometriosis

Women with endometriosis are reported to experience menopause at younger ages, most likely due to diminishing ovarian reserves because of endometriomas or surgical interventions[61,62]. These women are often in need of MHT. However, MHT may cause recurrence of endometriosis and may also be involved in the development of endometriosis-associated malignancy (EAM) even though not all of these malignancies express estrogen receptors[63–65].

The link between risk of recurrence or risk of EAM appears greater with unopposed estrogen therapy (RR 3.2, 95% CI 1.7–5.7)[66–68] and therefore, even in women who have undergone hysterectomy, MHT should comprise both estrogen and progestogen therapy or tibolone[69,70].

Recurrence of disease is a concern, with a prevalence of about 3.5% and annual incidence of 0.9% while using MHT. Risk factors include peritoneal involvement >3 cm and incomplete surgery[71]. For these reasons, it is recommended that patients operated on for residual endometriosis be followed every 6–12 months with transvaginal sonography and CA125 measurement[15]. Whether the MHT is initiated late or early appears to make no difference[70,72].

Quality of life considerations for the perimenopausal endometriosis patient

Recovery from endometriosis should not only be considered limited to excising the organic pathology, but also as a psychological and social process. Endometriosis-associated complaints are generally expected to improve during the menopausal transition due to reduced estrogenic stimulation[14].

Interestingly, physical and social restrictions due to endometriosis in the premenopausal period are very strongly correlated with postmenopausal sexual disturbances in postmenopause[73].

When considering whether surgery for endometriosis has any benefit for women within 6–8 years of their menopause transition, the only determining factor for predicting improvement in sexuality is whether a hysterectomy plus BSO is performed[74].

However, treating dyspareunia and improving sexual quality of life are different concepts and are not necessarily consequential[75]; improvement in sexual quality of life may follow recovery of dyspareunia after as long as 6–12 months[76].

Discussion

Clinical manifestations of endometriosis appear less commonly after the menopause. However, endometriotic implants may not disappear with menopause, but rather stay dormant and yet potentially responsive to hormones and other factors. Some premalignant subsets of endometriotic lesions may also be more prone to malignant transformation. Malignant transformation of endometriotic lesions may also be due to MHT, but there is no systematic evidence to support this concept, only case reports. Endometriotic lesions also have a propensity to recur long after menopause, especially surgical menopause and also in association with some types of MHT. Radical surgery to remove both ovaries, especially in women over age 39, will also reduce the risk of recurrence but this must be weighed against potential harm arising from a premature surgical menopause.

Measures of long-term quality of life suggest that bowel or urinary tract endometriosis should be treated with organ-preserving approaches (e.g. rectal nodule shaving and treating extrinsic ureteral involvement without ureteral resection). The evidence also shows that it may be best to start MHT early postoperatively with a continuous combined regimen or tibolone.

There is a pressing need for effective markers or predictors (e.g. atypical endometriosis, losses of heterozygosity, the *K-ras* gene, the *PTEN* gene or the *ARID-1A* gene in endometriomas) in order to define endometriosis cases more likely to recur and/or transform into malignancies.

Conclusion

Surgery for endometriosis in the peri- and postmenopausal periods may be for primary or recurrent disease and to eliminate concerns for malignant transformation. Both recurrences and malignant transformation may be due to estrogenic stimulation of endometriotic foci or remnants of previous surgeries. There is an urgent need for multicenter studies and re-evaluation of clinical and laboratory data to define those cases with a higher propensity to recur and/or transform to malignancies in order to limit, and accurately define the indication for, radical surgery in the perimenopause.

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