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EMAS position statement: Managing the menopause in women with a past history of endometriosis

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ABSTRACT

Introduction: Endometriosis is a common disease in women of reproductive age. The symptoms usually disappear after a natural or a surgical menopause. Estrogen-based hormone therapy is required in women with premature or early menopause until the average age of the natural menopause and should be considered in older women with severe climacteric symptoms. However use of hormone therapy raises concerns about disease recurrence with pain symptoms, need for surgery and possibly malignant transformation of residual endometriosis.
Aim: To formulate a position statement on the management of the menopause in women with a past history of endometriosis.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: The data regarding hormone therapy regimens are limited. However it may be safer to give either continuous combined estrogen–progestogen therapies or tibolone in both hysterectomised and nonhysterectomised women as the risk of recurrence may be reduced. The risk of recurrence with hormone therapy is probably increased in women with residual disease after surgery. Management of potential recurrence is best monitored by responding to recurrence of symptoms. Women not wanting estrogen or those who are advised against should be offered alternative pharmacological treatment for climacteric symptoms or skeletal protection if indicated. Herbal preparations should be avoided as their efficacy is uncertain and some may contain estrogenic compounds.

1. Introduction

Endometriosis is a common gynecological disease affecting about 6–10% of all women [1]. It is considered to be a chronic inflammatory condition with great impact on a woman's life. It may cause pain, infertility, reduced quality of life, repeated surgery and medical treatments with considerable side effects. As endometriosis is an estrogen-dependent condition it is therefore generally limited to the fertile period of a woman's life. In most cases symptoms will improve after the menopause [2].

Hormone therapy (HT) in climacteric women with a history of endometriosis is debated as it may reactivate residual endometriosis or even produce new implants [3]. In addition, the potential of malignant transformation of endometriosis after the menopause, spontaneously or in association with HT, must be considered.

On the other hand, women with a history of endometriosis may be at particular risk of the long term consequences of estrogen deficiency as a consequence of repeated courses of gonadotropin-releasing hormone analogues (GnRH-a) or depot progestogens or surgery [4]. Premature menopause (before age 40 years) or early

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menopause (between ages 40 and 45 years) is identified as risks for excess overall mortality, cardiovascular disease, osteoporosis, dementia, cognitive decline and Parkinsonism [5].

In official endometriosis guidelines on endometriosis, there are no established recommendations about of the treatment of menopausal women with a history of the disease [6,7]. The aim of this position statement is to provide evidence-based advice.

2. Clinical issues

The purpose of medical and conservative surgical treatment of endometriosis is often to relieve symptoms in anticipation of a naturally occurring menopause. Occasionally it is necessary to perform radical surgery with hysterectomy and bilateral oophorectomy to control symptoms and to avoid further surgery. An early menopause or severe menopausal complaints raise a new problem concerning HT in this group of patients. Is it prudent to offer HT? What are the risks? What type of HT should be given and when should treatment be initiated? What alternatives to HT should be proposed? How should these women be followed up?

3. Surgical and natural menopause

Menopause can result from surgery and be premature. Repeated ovarian surgery can lead to tissue loss or damage. The ultimate treatment of endometriosis is hysterectomy and bilateral oophorectomy, an option that is considered when there is no wish (or hope) of childbearing and where other treatments have failed. Prior to this radical intervention, the woman might have undergone treatment with GnRH-a to test the effect of ovarian suppression on pain and as a predictor of the effects of estrogen deficiency. In a comparative study oophorectomy has been found to have a considerably greater negative impact on quality of life than medically induced menopause with GnRH-a, especially with regard to psychological symptoms [8]. On the other hand, compared with women who have oophorectomy for endometriosis, patients who undergo hysterectomy with ovarian conservation have a 6.1 times greater risk of developing recurrent pain and an 8.1 times greater risk of reoperation [9].

There are no data on the average age of the natural menopause in women with endometriosis. In a case–control study, levels of antimuellerian hormone were significantly decreased in women with stages III–IV endometriosis [10], reflecting a reduced ovarian follicle pool, but this could be partly explained by more ovarian surgery in severe disease. Once premature ovarian failure has occurred the mainstay of treatment is estrogen-based therapy at least until the average age of natural menopause [11]. Thus for a number of menopausal women with endometriosis, HT is indicated and should be considered.

4. Reactivation of endometriosis

A major concern about the use of HT is the risk of reactivation of residual endometriosis causing pain and a potential need for surgery. There are numerous case reports about postmenopausal endometriosis, especially located at the ovaries or at extragenital sites (bowel, intestines, bladder, ureter, lung, liver and skin). Postmenopausal endometriosis has been associated with obesity [12]. A review article [13] of 32 case reports of postmenopausal endometriosis finds that the disease can occur in both HT (estrogen alone and combined with progestogen) and non-HT users. In the review, a study from 1955 [14] is referred to where estimates of the risk of recurrence of endometriosis were 2.9% after castration and 3.7% after natural menopause, but HT use was not detailed. A retrospective 41.2 months study of 123 women with endometriosis after hysterectomy with bilateral salpingo-oophorectomy given no HT ($n = 17$), estrogen alone ($n = 50$), cyclic estrogen/progestogen ($n = 16$), and continuous combined estrogen/progestogen ($n = 24$) found evidence of recurrence only in those given estrogen alone. There was 1 case of recurrent endometriosis and 3 with further symptoms, but none required surgery [15].

A recent Cochrane review on HT for endometriosis after surgical menopause found only two randomized controlled trials (RCT) aimed to look at pain and disease recurrence in women with endometriosis who used HT for post-surgical menopause [16]. Fedele et al. [17] studied 21 women with residual pelvic endometriosis after bilateral oophorectomy with or without hysterectomy followed up for 12 months. The women were randomized to transdermal estradiol 50 mcg patches twice weekly ($n = 10$) combined with cyclic medroxy progesterone acetate (10 mg per day) for 12 days per month in women with a conserved uterus ($n = 3$) or with continuous tibolone (2.5 mg/day) ($n = 11$ of whom one had a conserved uterus). After 12 months, four patients (40%) in the estradiol group and one (9%) in the tibolone group experienced moderate pelvic pain. In the other RCT [18], 172 patients with bilateral oophorectomy were randomized to either 50 mcg transdermal estradiol daily combined with 14 days out of 30 of 200 mg micronized progesterone ($n = 115$) or no HT ($n = 57$). After a mean follow up time of 45 months, four (3.5%) patients in the HT-group experienced recurrence and none in the untreated group. Neither RCT showed statistical significance, probably due to the limited number of patients. It is noteworthy that progestogen was administered cyclically in both studies.

There was a remarkable high rate of return of symptoms in the first RCT [17] but this could be explained by the presence of residual endometriosis in areas such as the rectovaginal septum, the bladder and sigmoid. The second study [18] found that peritoneal involvement of more than 3 cm and incomplete surgery in HT users were risk factors for recurrence. In women with severe or residual endometriosis after surgery, the use of HT should be critically assessed.

5. Malignant transformation of endometriosis

Of great concern is the risk of malignant transformation in residual endometriosis. In a study of one thousand cases of endometriosis, malignancy occurred in 0.9% [19]. After the menopause HT could increase the risk of malignant transformation. A review of 33 case reports found that all patients had been treated with unopposed estrogen [20]. In a case–control study comparing patients with cancer and endometriosis to patients with endometriosis only, unopposed estrogen use in women with body mass index greater than 27 was the only significant risk factor for malignancy [21]. Malignant transformation in association with tamoxifen use has been described [22–24]. Of note, malignant transformation can also occur in non-HT users [21].

Although data are limited it appears that malignant transformation is more likely to occur in unopposed estrogen users.

6. Selecting hormone therapy regimes

As most of the literature is limited to case reports rather than randomized prospective studies, recommendations should be given with caution. While not using HT is safer with regard to disease recurrence it is not suitable for all, especially those with a premature or early menopause or those who have marked climacteric symptoms. In young menopausal women the benefits of HT probably outweighs the risks. As the risk of recurrence and malignant transformation seems to be associated with the use of unopposed estrogen, progestogen addition should be considered

despite the increase in breast cancer risk found in the Women's Health Initiative study [25].

In the absence of data comparing cyclical versus continuous combined regimes in endometriosis, one may wish to extrapolate from results of these regimens on normally sited eutopic endometrium. Continuous combined regimens lead to endometrial atrophy and may even revert hyperplasia in the absence of cytological atypia [26]. Although eutopic and ectopic endometrium (endometriosis) may not respond similarly to sex steroids [27], it would seem advisable to use continuous combined estrogen–progestogen regimes.

Barbieri introduced the 'estrogen threshold theory' in relation to 'add-back' treatment with estrogen in women given GnRH-a [28]. The basis of this theory is that individual tissues have different sensitivities to estradiol so that levels sufficient to prevent bone loss or relieve menopausal symptoms may not stimulate endometriotic tissue. This has been found with eutopic endometrium [29]. This is in accordance with the current trend of offering ultra-low dosage HT, with as little as 0.5 mg estradiol and 0.1 mg norethisterone acetate which may both provide symptom relief [30] and give bone protection [31].

A combination of low dose estrogen and progestogen should thus, at least theoretically, be preferable in women with a history of endometriosis, even after hysterectomy despite the increased risk of breast cancer with progestogen addition compared with estrogen alone as found in both the Women's Health Initiative and Million Women Studies [25,32]. In women aged less than 50, there is probably no increased risk of breast cancer in HT users compared to premenopausal women of corresponding age [33,34].

Tibolone has frequently been used as an add-back regimen with GnRH-a and is considered to be an effective and safe option for relieving symptoms [35]. A large RCT has showed that tibolone does not induce endometrial hyperplasia or carcinoma in postmenopausal women [36]. This suggests that tibolone is comparable to continuous combined estrogen–progestogen therapy in eutopic endometrium and possibly also in endometriosis. Again, the potential endometrial benefits of tibolone need to be balanced against potential adverse effects on the breast which have been found in some but not all studies [32,37].

Data regarding testosterone addition are lacking in women with endometriosis. Testosterone patches (300 μg) for women are now available in some but not all countries. They are currently licensed for hysterectomised and oophorectomised women taking concomitant estradiol-based hormone replacement therapy [38,39].

7. Timing of hormone therapy after oophorectomy

A commonly used strategy is to delay starting HT for a few months after surgery. However this is not supported by the available evidence. In a retrospective cohort study [40] of 95 women who underwent hysterectomy and bilateral oophorectomy, 60 received HT within 6 weeks of operation and 35 delayed HT for more than 6 weeks, timing did not significantly affect pain recurrence. Pain was experienced by 4 (7%) and 7 (20%) in the early and late start groups respectively. Therefore, unless there are other considerations, HT can be started immediately after surgery.

8. Non-estrogen based treatments

Non-estrogen based treatments are used to treat hot flushes [41] and symptoms of urogenital atrophy. These include clonidine, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin and vaginal lubricants and moisturizers. Herbal preparations should be used with caution as their efficacy is uncertain and some may contain estrogenic compounds [42]. While bisphosphonates will conserve bone mass, there are little data in young women and there are concerns about the safety of long term use [43].

9. Follow up

Regular follow up is recommended to ascertain recurrence of symptoms and adjust HT regimens. This is especially important in women with residual disease. If symptoms recur, HT should be stopped and the pain investigated. Active postmenopausal endometriosis after the menopause may be treated surgically or pharmacologically, and aromatase inhibitors are emerging as a promising treatment option [44].

There are concerns that endometriosis may be associated with an increased risk of developing certain cancers, though endometriosis is not associated with an increased risk of cancer in general. Data from large cohort and case–control studies indicate an increased risk of ovarian cancers in women with endometriosis [45]. The observed effect sizes are modest varying between 1.3 and 1.9. Evidence from clinical series consistently demonstrates that the association is confined to the endometrioid/clear-cell histotypes. Also breast cancer has been associated with endometriosis, and relative risks of 1.1–3.2 have been reported [45]. Available studies are characterized by several limitations, some of which potentially bias results towards the null hypothesis whereas others overestimate the association. Evidence for an association with melanoma and non-Hodgkin's lymphoma is increasing but needs to be confirmed, whereas an increased risk for other gynecological cancer types is not supported [45]. While health professionals need to be aware of these concerns there is currently insufficient evidence to investigate asymptomatic women.

10. Summary recommendations

- Estrogen-based hormone therapy is required in women with premature or early menopause until the average age of the natural menopause and should be considered in older women with severe climacteric symptoms.
- The data regarding hormone therapy regimens are limited. However it may be safer to give either continuous combined estrogen–progestogen therapies or tibolone in both hysterectomised and nonhysterectomised women as the risk of recurrence and malignant transformation of residual endometriosis may be reduced.
- Alternative pharmacological treatment for climacteric symptoms or skeletal protection if indicated should be considered in women not taking hormone therapy.
- Herbal preparations are not recommended as their efficacy is uncertain and some may contain estrogenic compounds.

Contributors

MHM and MR prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by MR.

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