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European Menopause and Andropause Society (EMAS) and International Gynecologic Cancer Society (IGCS) position statement on managing the menopause after gynecological cancer: focus on menopausal symptoms and osteoporosis

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ABSTRACT

Introduction: Worldwide, it is estimated that about 1.3 million new gynecological cancer cases are diagnosed each year. For 2018, the predicted annual totals were cervix uteri 569,847, corpus uteri 382,069, ovary 295,414, vulva 44,235 and vagina 17,600. Treatments include hysterectomy with or without bilateral salpingo-oophorectomy, radiotherapy and chemotherapy. These can result in loss of ovarian function and, in women under the age of 45, early menopause.

Aim: The aim of this position statement is to set out an individualized approach to the management, with or without menopausal hormone therapy, of menopausal symptoms and the prevention and treatment of osteoporosis in women with gynecological cancer.

Materials and methods: Literature review and consensus of expert opinion.

Summary recommendations: The limited data suggest that women with low-grade, early-stage endometrial cancer may consider systemic or topical estrogens. However, menopausal hormone therapy may stimulate tumor growth in patients with more advanced disease, and non-hormonal approaches are recommended. Uterine sarcomas may be hormone dependent, and therefore estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-hormonal strategies should be used. The limited evidence available suggests that menopausal hormone therapy, either systemic or topical, does not appear to be associated with harm and does not decrease overall or disease-free survival in women with non-serous epithelial ovarian cancer and germ cell tumors. Caution is required with both systemic and topical menopausal hormone therapy in women with serous and granulosa cell tumors because of their hormone dependence, and non-hormonal options are recommended as initial therapy. There is no evidence to contraindicate the use of systemic or topical menopausal hormone therapy by women with cervical, vaginal or vulvar cancer, as these tumors are not considered to be hormone dependent.

1. Introduction

Worldwide, it is estimated about 1.3 million new gynecological cancer cases are diagnosed each year. For 2018 the predicted annual totals were cervix uteri 569,847, corpus uteri 382,069, ovary 295,414, vulva 44,235 and vagina 17,600 [1].

Depending on tumor type and stage, treatments include hysterectomy with or without bilateral salpingo-oophorectomy, radiotherapy and chemotherapy. These can result in loss of ovarian function and, in women under the age of 45, early menopause, which increases the risk not only of osteoporosis but also of cardiovascular disease and cognitive decline [2,3]. Surgically induced menopause often leads to the immediate onset of vasomotor symptoms, which may be more severe than after natural menopause [4]. Vasomotor symptoms may last

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for many years after natural or surgical menopause [5–7]. Other symptoms, such as those related to vulvovaginal atrophy, are lifelong [8,9].

The management of menopausal symptoms in gynecological cancer survivors depends on their age, tumor type and stage, as well as the use of anti-estrogen therapies (for cancers considered to be hormone dependent) and concomitant morbidities. The aim of this position statement is to provide an individualized approach to the management of menopausal symptoms and the prevention and treatment of osteoporosis [10].

2. Hormonal and non-hormonal management strategies

In women without cancer, administration of systemic estrogen-based menopausal hormone therapy for menopausal symptoms and osteoporosis has a favorable risk–benefit profile for those under the age of 60 years or up to 10 years after menopause [8,11–14]. Systemic menopausal hormone therapy can be administered orally or transdermally. Estrogen alone is given to women who have undergone hysterectomy. Progestogens and the selective estrogen receptor modulator bazedoxifene are added in regimens for women with an intact uterus to limit the increase in risk of endometrial hyperplasia and carcinoma which occurs with unopposed estrogen [8,15]. Tibolone is a synthetic steroid compound that is, in itself, inert, but whose metabolites have estrogenic, progestogenic and androgenic actions. It is classified as menopausal hormone therapy [16]. Availability of different menopausal hormone therapy preparations varies worldwide.

In women with early or premature menopause, systemic estrogen-based menopausal hormone therapy is recommended at least until the average age of natural menopause. Anecdotally, young women may need higher doses of estrogen initially to alleviate menopausal symptoms than their older counterparts [12]. Some young women may find taking combined oral contraception more acceptable. Menopausal hormone therapy at very low doses or non-estrogen-based therapies should be considered for older women [12]. Symptoms due to vulvovaginal atrophy can be managed with low-dose topical estrogen. There are no data on the use of ospemifene or prasterone in this context [17,18].

The efficacy and safety of different regimens have not been examined in many studies of the use of systemic menopausal hormone therapy after gynecological cancer. While the data regarding the use of topical vaginal estrogen after gynecological cancer are sparse, it must be remembered that with current low-dose options, for example estradiol (10 μg twice weekly), absorption is very low and estrogen levels remain in the postmenopausal range [19]. The total administered vaginal dose per year is similar to one daily dose of systemic oral therapy, that is 1 mg.

In women who are taking anti-estrogenic therapies such as aromatase inhibitors, estrogen-based therapies are contraindicated [20]. Here, non-hormonal options are recommended as initial therapy. For vasomotor symptoms the pharmacological options include selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, clonidine and gabapentin. Clinicians should be aware of potential drug interactions with anticancer and adjuvant therapies [see for example 21 and 22]. Cognitive behavioral therapy may also improve menopause symptoms [23]. For problems related to vulvovaginal atrophy, a variety of lubricants and bioadhesive moisturizers are available. Laser therapy for vulvovaginal atrophy is a new approach, but larger, long-term studies are required to explore its efficacy and safety before definite conclusions can be drawn [12].

The main pharmacological options to consider for the prevention and treatment of osteoporosis are bisphosphonates, denosumab and parathyroid hormone [12]. As calcium and vitamin D play a key role in bone metabolism, correction of nutritional deficiencies is advised as part of osteoporosis management [24]. Strategies need to be holistic and include maintaining a healthy weight, diet, exercise and lifestyle [25,26]. This statement will not consider herbal supplements and botanicals as there is a lack of data regarding safety and efficacy [27]. In addition, some products may contain compounds with estrogenic activity or may interact with anticancer therapies.

3. Management options by tumor type

3.1. Endometrial cancer

While most cases of endometrial cancer are diagnosed after the menopause it can occur in younger women, such as those with Lynch syndrome or polycystic ovary syndrome or who are obese. The majority of endometrial cancers are diagnosed at an early stage (Federation of Gynecology and Obstetrics (FIGO) stage I–II) and so have a good overall prognosis, with a 5-year survival rate of over 85 %. Treatment usually involves hysterectomy and bilateral oophorectomy. Studies of menopausal hormone therapy after endometrial cancer are limited to one randomized trial undertaken in 1236 women recruited between 1997 and 2003 with a mean follow-up of 35.7 months [28] and small observational retrospective cohort or case-control studies [29–35]. All studies were undertaken in women with early-stage disease. The randomized trial did not specify which type of menopausal hormone therapy was used (estrogen alone or estrogen plus progestogen). The observational studies documented a variety of preparations: systemic menopausal hormone therapy with estrogen alone or combined with progestogen delivered orally or transdermally, as well as topical vaginal estrogens. No studies are available for women with Lynch syndrome, who are also at increased risk of other cancers [36].

In 2018 a Cochrane systematic review concluded that there is insufficient high-quality evidence to inform women considering menopausal hormone therapy after treatment of endometrial cancer. However, the evidence does not suggest significant harm after surgical treatment for early-stage disease based on FIGO classification [37]. There is no information available regarding the use of menopausal hormone therapy in higher-stage endometrial cancer. The National Comprehensive Cancer Network Panel states that estrogen replacement is a reasonable option for patients who are at low risk of tumor recurrence, but that initiating such therapy should be individualized and discussed in detail with the patient [38]. Furthermore, if adjuvant treatment is carried out, there should be a 6–12-month waiting period before starting menopausal hormone therapy.

3.1.1. Summary recommendation

Thus, the limited data suggest that women with low-grade, early-stage endometrial cancer may consider systemic or topical estrogens. However, menopausal hormone therapy may stimulate tumor growth in patients with more advanced disease or high-risk early-stage tumors, and non-hormonal approaches to management of menopausal symptoms are recommended. In addition, there are no long-term data regarding the safety of menopausal hormone therapy in women with Lynch syndrome, who are also at increased risk of other cancers whose treatment may lead to premature or early menopause. With regard to atypical endometrial hyperplasia, it would not be unreasonable to consider menopausal hormone therapy in women who have undergone hysterectomy, despite the paucity of data.

3.2. Uterine sarcoma

Stromal or mesenchymal sarcomas are rare tumors, accounting for less than 5 % of all uterine cancers. While most cases are diagnosed after the menopause, these tumors can occur in younger women. The most common types are low-grade endometrial sarcomas, high-grade endometrial sarcomas, undifferentiated uterine sarcomas and uterine leiomyosarcomas [38]. As these tumors may be hormone dependent, estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-

hormonal strategies should be used for the management of menopausal symptoms and the prevention and treatment of osteoporosis. Low-grade stromal sarcomas may be sensitive to aromatase inhibitors or progestogens (such as megestrol acetate or medroxyprogesterone acetate). Gonadotropin-releasing hormone analogues are also an option. Randomized controlled trials have shown that progestogens are effective in treating hot flushes [39,40]. There are no data regarding the use of menopausal hormone therapy in non-hormone-dependent tumors. In addition, there are no studies regarding the use of menopausal hormone therapy in smooth muscle tumors of uncertain malignant potential [41].

3.2.1. Summary recommendation

Uterine sarcomas may be hormone dependent, and therefore estrogen and progesterone receptor testing should be undertaken to guide decisions as to whether menopausal hormone therapy or non-hormonal strategies should be used. No clinical trial data are available to inform practice in women whose tumors are steroid receptor negative or who have smooth muscle tumors of uncertain malignant potential.

3.3. Ovarian, fallopian tube and peritoneal cancers

The three major types of ovarian cancer are epithelial, accounting for 90 % of cases, germ cell (3 %), and sex cord-stromal (2 %) [42]. As fallopian tube cancer, primary peritoneal cancer and epithelial ovarian cancer are indistinguishable and share the same genomic signature, the three are considered together.

Epithelial, fallopian tube and peritoneal cancer. While these cancers often occur after the menopause, they also affect a significant number of premenopausal women [43–45].

Epithelial cancers are subdivided into five histotypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, and mucinous carcinoma [46,47]. The different histotypes are now considered to be different diseases. While serous tumors are mostly high grade, which are characterized by involvement of both ovaries, aggressive behavior, late-stage diagnosis, and low survival rates, the other subtypes tend to affect only one ovary. It is thought that serous tumors originate in the epithelial cells of the fallopian tube as microscopic preliminary lesions that subsequently migrate to the ovaries and/or peritoneum. However, endometrioid and clear cell tumors are thought to originate in the endometrium, and mucinous tumors in the ovaries or fallopian tube peritoneal junction. One of the risk factors for ovarian cancer is prior use of menopausal hormone therapy but the association appears to be confined to serous and endometrioid histotypes [48].

Two randomized trials as well as prospective and retrospective cohort and case-control studies have shown no adverse effect menopausal hormone therapy on survival in women who have been treated for ovarian cancer [49–55]. They used a variety of regimens: estrogen alone or combined with a progestogen or testosterone. The randomized trial by Guidozzi and Daponte, in which 130 women with invasive epithelial ovarian carcinoma were followed up for 48 months, used oral continuous conjugated equine estrogen. It did not distinguish between sub-types [49]. The authors reported median overall survival of 44 months (95 % CI, 10–112 months) and 34 months (95 % CI, 8–111 months) in the menopausal hormone therapy and control groups respectively. The differences in disease-free interval (P = 0.785) and overall survival (P = 0.354) between the two groups were not statistically significant. Eeles et al. [50] studied 150 premenopausal and postmenopausal women who had been diagnosed with epithelial ovarian cancer (any FIGO stage) nine or fewer months previously. They were randomized to either menopausal hormone therapy or not for 5 years. The choice of menopausal hormone therapy for individual patients was pragmatic and was determined according to consultant preference, with guidelines to recommend that premenopausal women receive higher doses than perimenopausal/postmenopausal women. The median follow-up of patients still alive was 19.1 years: overall and relapse-free survival was greater in the menopausal hormone therapy than in the control group.

A retrospective cohort study using the Manitoba Cancer Registry and Drug Programs Information Network of 357 women found that use of menopausal hormone therapy (n = 94) for non-serous epithelial ovarian cancer was not associated with harm and did not decrease overall or disease-free survival [55]. It found that in menopausal hormone therapy users under 55 years of age, disease-free survival was longer but there was no statistical difference in overall survival for this age group. No associations between menopausal hormone therapy use and overall survival or disease-free survival were found among women aged 55 years or more.

With regard to **endometrioid ovarian cancers**, which are potentially estrogen sensitive, menopausal hormone therapy does not appear to have adverse effects. However, while menopausal hormone therapy appears to be safe in early-stage disease, this may not be the case in women with more advanced cancers, who commonly have residual, potentially hormone-responsive disease after surgery [54,55]. As there is no clear evidence of benefit of aromatase inhibitors in the treatment of **clear cell and mucinous carcinomas**, estrogen replacement is a reasonable option for patients who are at low risk of tumor recurrence, but initiating such therapy should be individualized. Given the benefits seen with maintenance hormone therapy with letrozole, anastrozole, tamoxifen and leuprolide acetate after primary cytoreductive surgery and platinum-based chemotherapy in women with stage II to IV **low-grade serous carcinoma** of the ovary or peritoneum, estrogen-based therapies are currently not recommended in advanced disease of these types [56]. There is a paucity of evidence to inform practice for **high-grade serous carcinoma.**

Borderline malignant tumors or tumors of low malignant potential most often affect younger women. Histological types include serous, mucinous, endometrioid, clear cell and transitional cell (or Brenner) tumor [57]. Five-year survival rates are greater than 98 %. There is a paucity of data regarding the use of menopausal hormone therapy, but it would not be unreasonable to consider it for women with completely resected disease (i.e. without invasive implants). As always, the benefits of menopausal hormone therapy for women who have undergone premature menopause through cancer treatment need to be balanced against the risks.

The ***BRCA1* and *BRCA2* gene mutations** are associated with increased risk of developing invasive epithelial ovarian cancer. Risk-reducing salpingo-oophorectomy is therefore recommended. However, this will lead to early/premature menopause. Data on menopausal hormone therapy after prophylactic oophorectomy are sparse, but short-term use seems to be safe [58]

Ovarian germ cell tumors commonly affect girls and young women between 10 and 30 years of age. In most cases, fertility-preserving staging surgery is followed by platinum-based combination chemotherapy, which may lead to ovarian failure. The prognosis is excellent and 5-year survival is more than 85 % [59]. There is currently no evidence to suggest that these young women should not take menopausal hormone therapy.

Granulosa cell tumors are the most common ovarian sex cord stromal tumors. They secrete steroid hormones and commonly present with symptoms of hyperestrogenism, as they secrete estrogens as well as other hormones. They may have an indolent course and can recur up to 20 years after initial diagnosis. It is generally believed that estrogens should not be used, as these tumors are estrogen-dependent. Hormone recurrence therapy includes aromatase inhibitors, leuprolide and tamoxifen [59]. No study, however, has demonstrated a deleterious effect of menopausal hormone therapy.

3.3.1. Summary recommendation

Menopausal hormone therapy, either systemic or topical, does not appear to be associated with harm and does not appear to decrease

overall or disease-free survival in women with non-serous epithelial ovarian cancer and germ cell tumors, although the evidence is limited. The regimen (estrogen or estrogen combined with progestogen) will depend on whether hysterectomy has been undertaken. Duration of therapy will depend on the age of the woman. Caution is required for both systemic and topical menopausal hormone therapy in women with serous and granulosa cell tumors because of their hormone dependence [60].

3.4. Cervical, vaginal and vulvar cancers

Given that none of these cancers are considered to be hormone dependent, there is no evidence to contraindicate the use of systemic or topical menopausal hormone therapy. However, estrogen receptors are frequently (39 %) expressed in cervical adenocarcinomas, even though their expression does not correlate with clinicopathological parameters and does not influence overall and disease-free survival [10,61,62]. In the limited studies available, no significant difference in recurrence rate or survival [63–66] has been linked with menopausal hormone therapy use after treatment for cervical squamous cell carcinomas. In women who have been treated with radiotherapy, rather than hysterectomy, for cervical cancer, opposed estrogen therapy to prevent stimulation of residual endometrium should be used [67].

With regard to previous use of menopausal hormone therapy, a case-control study found that exogenous estrogens, especially unopposed estrogens, increased the risk of adenocarcinomas but not squamous cell carcinomas [68]. The study involved 124 women with adenocarcinomas, 139 women with squamous cell carcinomas and 307 healthy community controls matched on age, ethnicity, and residence. Only 13 women with adenocarcinoma (10.5 %), 7 with squamous carcinoma (5 %), and 20 controls (6.5 %) had used non-contraceptive hormones; most use was short-term former use. Ever-use was associated with adenocarcinomas (OR = 2.1, 95 % CI 0.95–4.6) but not squamous carcinomas (OR = 0.85, 95 % CI 0.34–2.1). Unopposed estrogens were positively associated with adenocarcinomas (OR = 2.7, 95 % CI 1.1–6.8). However, the authors of a Women's Health Initiative study concluded that its randomized trial data on cervical cancer were too limited to suggest there was any association with estrogen plus progestin therapy use in 8506 women compared with 8102 women taking placebo [69].

As women exposed *in utero* in the 1950s to 1960s to diethylstilbestrol are aging, the issue of the safety of menopausal hormone therapy in this group is becoming more important [70]. Diethylstilbestrol is associated with an increased risk of clear cell cancers of the vagina and cervix. Currently no safety data are available about the use of systemic or topical estrogens in these women.

3.4.1. Summary recommendation

Menopausal hormone therapy is not contraindicated and the regimen (unopposed or opposed estrogen) depends on whether or not hysterectomy has been undertaken.

4. Conclusion

An individualized approach to the management of menopausal symptoms and prevention and treatment of osteoporosis after gynecological cancer is required. It should take into account age, tumor type and stage, and concomitant therapies and morbidities. It is best undertaken by a multidisciplinary team of health and allied health professionals. It is of concern that there is a paucity of data. Therefore, there is a need for randomized trials and analysis of data registries to provide a stronger evidence base to inform practice.

Contributors

Margaret Rees prepared the initial draft, which was circulated to all other named authors for comments and approval before review and endorsement by the EMAS board and IGCS council members. Production was coordinated by Margaret Rees.

Conflict of interest

Margaret Rees reports personal fees from Sojournix, Inc, outside the remit of the submitted work.

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