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The Role of Hormone Replacement Therapy in the Treatment of Menopausal Symptoms in Patients Diagnosed with Gynecologic Cancer

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Abstract

The incidence of most cancers increases with age, especially from middle age onward, so today cancer can be considered an age-related disease. One of the keys to healthy and successful aging is reducing the advent of serious disabilities caused by diseases related to aging. One of the cornerstones of anti-aging is hormone replacement therapy to treat age-related diseases caused by sex hormone deficiency in women. However, there are many studies that question the relationship between hormone replacement therapies with cancer recurrence. Hormone replacement therapy (HRT) has the potential to affect both quality of life and survival in menopausal women. Although data in the literature is controversial, many clinicians remain reluctant to write HRT for gynecologic cancer patients due to fear of relapse but HRT does not appear to be associated with an increased risk of relapse in ovarian and endometrial cancer survivors, especially when used for a short period of time.

Keywords: endometrial cancer, gynecologic cancers, hormone replacement therapy, ovarian cancer, cervical cancer

1. Introduction

Menopause is defined by the World Health Organization (WHO) as the complete disappearance of cyclic menstruation over a period of 12 months due to a reduction in the production of estrogen and progesterone hormones from a woman's ovaries [1]. Menopause can be defined by more concrete values in laboratory tests. According to the findings of amenorrhea and hypestrogenemia studies, serum FSH levels above 40 IU/L were defined. Subjectively, menopause can also be diagnosed by vasomotor symptoms, such as hot flashes. The permanent cessation of menstrual periods can occur naturally or can be induced by surgery, chemotherapy or radiation, leading to estrogen deficiency and loss of reproductive function [2]. Symptoms are more pronounced with a sudden drop in circulating estrogen levels. These symptoms are severe in premature ovarian failure and surgical menopause. Natural menopause is often seen between the ages of 45 and

55, but its onset varies from woman to woman. The average age of natural menopause in our country (Turkey) is 47 [3].

A menopausal statement can disrupt a woman's personal and social life. Vasomotor symptoms (e.g., hot flashes and night sweats) are the most common symptoms and can be treated very effectively with estrogen-based hormone therapy. The decision to use estrogen (usually only hormone therapy or hormone replacement therapy or HT) treatment involves balancing potential benefits with potential risks. A woman who desires HRT and has an intact uterus must also receive progestogen with the estrogen to protect her uterus from endometrial hyperplasia or malignancy. It is assumed that if a woman has had a hysterectomy that she no longer needs a progestin. However, progesterone is different, as it can provide symptom relief from sleep disturbance and mood instability, and there is increasing evidence to support its offering protection to breast tissue [4].

The relationship between early surgical menopause and poor cognitive outcomes has been demonstrated. Increased risk of cognitive impairment especially in patients undergoing oophorectomy at a young age revealed that this relationship is age-related [5].

Furthermore, cancer treatment often accelerates menopause and then affects quality of life. Postmenopausal women are at increased risk for vaginal dryness, dyspareunia, urogenital atrophy and sexual dysfunction. Hormone replacement therapy (HRT) has been proven to be highly effective in alleviating menopausal symptoms, such as hot flashes, night sweats, dyspareunia, sexual disorders and insomnia, as well as preventing osteoporosis. Life satisfaction and social functioning can be improved by overcoming menopausal symptoms and increasing resistance to age-related pathologies.

The number of menopausal women will also increase as the population ages. Accurate estimation of the postmenopausal population is an important point for health care providers to consider, as the incidence of all cancers increases with aging. If life satisfaction, social functioning and psychological resources are enhanced by increasing resistance to against age-related pathologies, the experience of aging can be improved.

To clarify the possible effective management of menopausal symptoms, the main evidence in the literature was analyzed to investigate the role of hormone replacement therapy in patients affected by endometrial, ovarian or cervical cancer.

2. Endometrial cancer

A number of clinical trials have reported that HRT does not increase the risk of recurrence of endometrial cancer (EC) even after treatment [6, 7]. In contrast, studies' showing that estrogen exposure is associated with an increase in mitosis of endometrial cells, placing them in a specific molecular configuration sensitive to DNA damage [8].

The most common gynecological cancer, endometrial cancer is seen in the postmenopausal period, but 25% of diagnosed patients are premenopausal with approximately 2.5–14.4% of the patients less than 40 years old [9].

As a result, a large number of women will be exposed to the sudden iatrogenic onset of postmenopausal morbidity, consisting of standard abdominal hysterectomy and bilateral oophorectomy procedures. In addition, surgery-induced menopausal symptoms tend to be more severe than those caused by normal menopause, and in these patients, surgery is usually followed by chemotherapy or radiotherapy [10]. Since EC is typically diagnosed with a good prognosis in the early stage of the

disease, relieving these symptoms is an important issue in terms of quality of life after treatment [11].

The endometrioid EC type is associated with estrogen exposure and endometrial hyperplasia. The role of estrogens in providing relapse after hysterectomy for EC is less clear and controversial. Since it does not increase recurrence, there are a number of current clinical studies that report HRT should be considered even after EC therapy [12]. For relief of menopause-related vasomotor symptoms (VMS), systemic usage of HRT with either (1) conventional estrogens/progestogens or (2) conjugated estrogens/bazedoxifene is the most effective regime. Currently, method 2 conjugated estrogens, with a selective estrogen receptor modulator such as bazedoxifene, is a very popular replacement of progestin. This method is useful for protection of the endometrium.

Although these findings were based on retrospective or cohort controlled study results, HRT use does not seem to increase the risk of EC recurrence. Creasman et al. reported a retrospective study of 47 cases of stage I endometrial cancer patients treated with via the oral or vaginal route using conjugated estrogen (0.625 or 1.25 mg/dl). HRT was initiated within 15 months (range 0–81 months) of the median interval after cancer treatment and patients were followed up for 32 months (range 6–84 months) after the onset of HRT. In the control group, 174 patients who began treatment at the same time were compared. No difference was observed between the groups in terms of prognostic aspects. Only one recurrence (2.1%) was observed in the estrogen-treated group and 26 recurrences (14.9%) were observed in the control group. The recurrent patient in the HRT group had been treated with estrogen only for 3 months and had discontinued HRT use 18 months before relapse. Disease-free survival (DFS) and overall survival (OS) were significantly longer in the estrogen-treated group [13].

A retrospective paired cohort study was conducted with 75 women being treated for stages I–III EC who received an average of 83 months of HRT (conjugated equine estrogen-oral, 0.625 mg/dl with or without medroxyprogesterone acetate-oral, 2.5 mg/dl). These women were then compared with matched controls who received an average of 69 months of treatment. The study revealed lower recurrence rate (1 vs. 14% in the control group) and significantly longer DFS ($P = 0.006$) in the HRT group [14].

A total of 50 patients with stage I or stage II EC who had combined HRT (0.625 mg conjugated equine estrogen plus continuous oral daily regimen and 2.5 mg medroxyprogesterone acetate) of 4–8 weeks postoperatively were compared to 52 patients for control purposes. In the first prospective paired cohort study, no recurrence was observed in the HRT group but a relapse was observed in the control group [12].

A retrospective case-control study was conducted with 44 clinical stage I patients (defined as grade 1 or 2 tumors), using oral estrogens (0.625 or 1.25 mg/dl) with or without combined progesterone. The study revealed no metastases to lymph nodes or other organs [15].

Serous papillary and clear cell carcinomas, which are mostly seen in postmenopausal women and constitute approximately 8% of all ECs, have poor prognosis even if they are caught at an early stage. Since they do not have estrogen and progesterone receptors, it is not thought that they are not stimulated when HRT is used after surgical treatment. A safe recommendation cannot be raised because no study has addressed the use of HRT after treatment in all of the above histological subtypes of EC. As for uterine sarcomas, endometrial stromal sarcomas are considered estrogen-dependent because they express estrogen and progesterone receptors, and the application of HRT in these sarcomas should be avoided [16].

Although it is mainly based on retrospective, case or cohort controlled studies based on various biases, the use of HRT, in women with stage I and/or II EC, the risk of relapse was demonstrated with data that did not increase. Selecting healthier and younger women to explain the protective effect of HRT on recurrence in survivors of EC may eliminate this publication bias.

Although it is based on retrospective or cohort-controlled studies, nowadays, a number of clinical studies have reported that HRT should be considered even after treatment of endometrial cancer (EC) without increasing the risk of recurrence [17].

Although the results related to EC do not completely exclude the possibility of increasing the risk of recurrence, they argue that HRT does not matter the magnitude of such a risk. The positive effect of HRT on quality of life outweighs the unfounded risk of recurrence. Additional well-designed RCTs are needed for the definite recommendations including the factors that may be related to recurrence such as characteristics and treatment of cancer, different types of HRT, the disease-free interval before the onset of HRT, and the duration of HRT use. To determine the best therapeutic option between new hormones and non-hormonal regimens every EC survivor dealing with HRT must be informed of the available data and analyzed in a personalized way.

3. Ovarian cancer

Worldwide, among patients diagnosed with gynecological malignancies, ovarian cancer is the leading cause of death. Most women affected are postmenopausal, but some are younger. Menopausal symptoms in the iatrogenic group are generally more pronounced than those following naturally occurring menopause and affect quality of life and health outcomes [18, 19].

After the treatment of a serious disease such as ovarian cancer, more attention should be paid to the women's quality of life. Presently, the WHO, Europe, and the United States (US) have guidelines on hormone therapy that do not mention ovarian cancer and conclude that evidence for the increased risk of cancer due to HRT is insufficient to make a definite recommendation. According to the guidelines in the United Kingdom (UK), such risk is only increased by prolonged use. In the case of epithelial ovarian cancer, the World Health Organization, European and US guidelines on hormone therapy suggest, that evidence for increased risk of relapse due to HRT is insufficient to make a definite suggestion, but the rules in the UK indicate increased risk for long-term users [20].

There is insufficient data on the effect of HRT usage period on the onset and progression of ovarian cancer. The effect of some known prognostic factors, such as residual tumor and tumor differentiation during diagnosis, are more important than the duration of HRT use [21]. Despite these results, it is very likely that the heterogeneity of samples, including factors of age, stages and classifications, different treatment modalities (chemotherapy, surgery alone, radiotherapy or both) and different follow-up times, will reflect the selection bias [22].

As we know, estrogen replacement therapy (ERT) is safe in patients who have undergone surgically induced menopause by the removal of the uterus and bilateral ovaries. In order to prevent the stimulating effect of estrogen on normal and hyperplastic endometrium, several studies have added progesterone to HRT in patients with early stage EOC who protect their uterus after primary surgery [17].

With regard to duration, there is insufficient data on the effect of long or short term use of HRT on the onset or progression of ovarian cancer. A recent meta-analysis conducted by Li et al. on 1448 patients who investigated the effect of postoperative HRT on the clinical outcome of patients treated for EOC revealed

that post-operative HRT did not have an impact on surveillance and recurrence (HR = 0.68, 95% CI: 0.54–0.86) [23].

Among the HRT users diagnosed with invasive EOC (n = 649) and borderline ovarian tumors (BOT; n = 150), there was no difference in 5-year survival of invasive cancer patients among HRT users and non-users. However, survival was better for those with borderline tumors who used HRT after diagnosis [24]. In addition, tumor types classified as border type, including serous and mucinous tumors had a large heterogeneity. There have been recent studies showing that borderline serous tumors can progress to low-grade serous ovarian cancer. Low-grade serous cancers are considered hormone-sensitive tumors, and therefore, it is important to avoid using HRT in patients with borderline serous tumors, although there is no definitive evidence to indicate this [25].

Evaluation of HRT after radical treatment of germ cell and cord ovarian malignancies is very important, as most of the cases are in young, premenopausal women who may be subject to several reductions in estrogen levels. However, there are no trials evaluating the use of HRT in these patients. Although HRT can be used safely for many of the germ cell tumors, we believe that it should be used carefully in a small subgroup of germ cell tumors that may secrete hormones. In the cases, the treatment of menopausal symptoms with HRT should be avoided and alternatives should be investigated after diagnosis [26].

In the foreground affects postmenopausal women, the improvement of climacteric symptoms following ovarian cancer diagnosis is an important concern for young women. Meta-analysis of 6 studies comparing 451 ovarian cancer patients who were treated with HRT after the diagnosis compared with 1070 women treated with HRT for control; revealed that there was no statistically significant difference in survival results [27, 28].

Some observational studies in this patient population have shown a possible benefit, as there is no increase in the risk of recurrence with HRT [29].

When we look at the results of two studies, which are very valuable because being prospective and evaluate according to whether or not patients with ovarian cancer receive random HRT. One of these studies was conducted on 59 patients who were received HRT with only estrogen and 66 control patients who did not receive any treatment. All stages of ovarian cancer were included in the study and the mean follow-up period was 42 months. In the group receiving HRT, the disease-free interval and OS were 34 and 44 months respectively, while in the non-treatment group, these durations were 27 and 34 months respectively, but the difference between the groups was not statistically significant [30].

For ovarian cancer, the available evidence suggests either a neutral effect on survival or a possible benefit from HRT. In view of the limitations of available evidence, factors such as the age of the patient, the presence of menopausal symptoms, and the molecular and hormonal characteristics of the tumor affect the initiation of HRT in some histological types of ovarian cancer [31].

A number of problems could not be resolved. For example, what the best HRT regimens are for patients with ovarian cancer and how long patients should take HRT after surgery, as well as how the use of HRT affects the clinical outcomes of patients with previous EOC diagnoses, require further study. At present, we know that in ovarian cancer patients there is no published study confirming the growth of microscopic residues that are encouraged by the use of HRT.

4. Cervical cancer

The mean age of cervical cancer is 48 years, and when diagnosed 70% of patients are under 54 years of age. Depending on the patient's age, the stage and

histology of the tumor, such patients are usually treated with radical hysterectomies without preserving the ovarian or chemo-radiation treatment, in which patients begin to have sudden menopausal symptoms [32].

Approximately 80% of cervical cancers are composed of squamous cell carcinomas (SCC), 15% are adenocarcinoma and 5% are adenosquamous. The development of squamous cell carcinomas has never been associated with HRT. In contrast, there are studies that report the risk of adenocarcinoma of the cervix as notable in women receiving estrogen therapy (OR 2.7) [33].

In 80 patients under 45 years of age with early-stage disease treated with surgery or radiotherapy, HRT was used, while the remaining 40 cervical cancer patients were used as controls. No significant difference in survival or survival was observed between the groups [34].

5. Conclusions

According to preclinical data, estrogen and progesterone are thought to play a role in the induction and progression of endometrial cancers. When the data is examined, epithelial ovarian cancer (EOC) appears to be at least partially hormonally affected. Considering the literature, the use of HRT is controversial in gynecologic cancer survivors. Given the fear of recurrence and the risk of developing ovarian or endometrial cancer most clinicians are reluctant to write HRT prescriptions for these patients but HRT does not appear to be associated with an increased risk of relapse in ovarian and endometrial cancer survivors, especially when used for a short period of time. In order to make an inference in terms of cervical cancer, squamous cell cancer is not associated with estrogen as mentioned above, but the risk of cervical adenocarcinoma increased significantly in women receiving estrogen therapy. Prior to the decision to use HRT, it is imperative that a proper consultation is done to individualize treatment on the basis of potential risks and benefits, including close follow-ups. However, with strongly informed consent, we believe that physicians may consider writing a course of HRT treatment to minimize menopausal symptoms and illnesses related to hormonal reduction on an individual basis.

In conclusion, further studies are needed for the role of hormonal modulation in the development, treatment, and management of climacteric symptoms after diagnosis, despite the modern emphasis of precision medicine in cancer care. In the patient group diagnosed with gynecological cancer, it is necessary to better define the conditions in which HRT can provide benefit or harm. Although there are some pre-clinical and epidemiological evidence that contradicts individual experience, observational or small randomized studies, there are available data in the literature to advice women on general and specific risks and benefits of HRT. Given high discontinuation rates and low medical compliance, we still have much to do in terms of informing women about the advantages and disadvantages of HRT and encouraging the appropriate use of HRT. Finally, to the extent that we can get rid of progressive diseases such as cancer, we can achieve the expected successful healthy aging goal.

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Conflict of interest

The author of this manuscript declares that there is no conflict of interest.

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