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Review Article

Menopausal replacement therapy following the treatment of gynaecological malignancies including the breast

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Abstract

Gynaecological malignancies have been known to be prevalent among the postmenopausal category of women, although a considerable fraction is being increasingly diagnosed in the premenopausal age group as well. Owing to the improvement in survival rates among women who are being diagnosed with gynaecological malignancies in recent times, the need to improve the quality of life among these women has become imperative. Standard treatment regimens for gynaecological malignancies include surgery, chemotherapy and radiotherapy and these are known to cause a prolonged oestrogen deficiency which inevitably leads to menopause in younger women. Therefore, it is essential to formulate an appropriate strategy to overcome this concern. This article focuses on the benefits of MRT in women following menopause after having been subjected to standard therapeutic methods for gynaecological malignancies. It also scrutinizes whether the benefits outweigh the risk of recurrence in women suffering from ovarian, endometrial, cervical, vaginal and vulval malignancies.

In addition, this article also focuses on the use of MRT before (the at-risk population), and after breast cancer. Estrogen alone MRT is considered safe carrying no or similar risks among the population. Among those whose symptoms are refractory, MRT can be considered, but it should only be prescribed following a careful discussion between the patient and a breast specialist.

Introduction

A significant proportion of cancers arise in the postmenopausal category of women.

However, 30-40% of women diagnosed with these cancers are premenopausal. The management strategy of a gynaecological malignancy typically involves surgery, chemotherapy and/or radiotherapy. In younger women, this may induce menopause, and other debilitating symptoms of oestrogen deficiency.

Prolonged oestrogen deficiency prior to the age of natural menopause is associated with a reduced quality of life.

Owing to the improvement of survival rates amongst women who are being diagnosed with gynaecological malignancies in recent times, the significance of improving the quality of life among these women has become imperative.

Hence, it is of utmost importance for medical professionals involved in the care of these women to take into consideration additional cancer-related risks that would advocate against the use of menopausal replacement therapy (MRT) where it may otherwise be recommended. MRT has a minimal

risk for most of the women and very few absolute contraindications[1].

Many would receive conflicting information regarding the use of MRT[2].This article analyses data regarding cancer-related risks of HRT in patients who have undergone treatment for ovarian, endometrial, cervical, vaginal, vulval and breast malignancies.

Endometrial cancer

Endometrial cancer is the commonest malignancy involving the female genital tract and the fourth commonest cancer among those affecting females in the UK.

It usually affects women in their sixth decade, while 5% of those affected are under the age of 40 years and 20–25% are premenopausal. The mainstay of treatment also involves BSO[3].

Type 1 endometrial cancer is oestrogen dependent and account for majority of cases[4]. Unopposed effect of oestrogen in women with an intact uterus significantly increases the risk of endometrial cancer (odds ratio [OR] 6.2, 95% confidence interval [CI] 3.1–12.6), and this can essentially be overcome if progestogens are incorporated as well[5]. Consequently, MRT is not widely used in patients with a history of endometrial cancer due to the mutagenic effect that the oestrogen component has on endometrial tissue, and the likely stimulatory effect on occult foci resulting in recurrence of the disease.

Various retrospective studies analysing the effects of HRT on women following treatment for endometrial cancer were conducted. All of them reported no rise in the incidence of recurrence or decrease in survival. Following this, two large prospective studies concluded that the rate of recurrence in those subjected to MRT was 2.3% and those receiving placebo was 1.9% ($P > 0.05$)[6]. The inclusion criteria for one of these studies, constituted of women who had undergone total hysterectomy and BSO (pelvic and para-aortic lymphadenectomy) for stage I or II, grade 1, 2 or 3 endometrial adenocarcinomas. Although this study could not irrefutably confirm the safety of using exogenous oestrogen, the absolute recurrence rate in this population was significantly low. The second study looked into 100 women who had undergone total hysterectomy, BSO, peritoneal cytology, infracolic omentectomy and complete pelvic and para-aortic lymphadenectomy for histologically confirmed stage I or II endometrioid endometrial cancer[7]. The mean duration of HRT use was 49.1 months (range 13–96 months). None of the case individuals and only one control individual developed a recurrence of the disease. The authors therefore came to the conclusion that MRT in women who had undergone treatment for endometrial cancer does not increase the risk of recurrence.

However, these studies have their limitations. Most women in this study had stage I disease (only six had stage II disease) and all of them had an endometrioid type of endometrial cancer. Although this histopathology is known to be typical among most women diagnosed with endometrial cancer, the conclusions derived from this study cannot be effectively extrapolated to women with stage III or IV disease or endometrial malignancy of non-endometrioid histology. However, there is increasing evidence to suggest that the use of MRT is not associated with increased recurrence or decreased survival in patients with early stage, low-grade, endometrioid adenocarcinoma of the endometrium.

Ayhan and colleagues were given continuous combined HRT, in contrast to an oestrogen-only regimen which is the standard practice for women without a uterus. Although this reduces undesirable effects of unopposed oestrogen, the progestogenic component of MRT can increase the risk of breast cancer [8].

If women have been adequately staged, an oestrogen-only preparation of MRT should be sufficient. More radical surgery with the purpose of staging is not the standard practice, where women with grade 1 or 2 endometrioid endometrial cancer confined to the uterus typically undergo hysterectomy and BSO.

A 2008 study reported that, in women with presumed stage I endometrioid endometrial cancer, there were no positive lymph nodes[9]. 10.4% (19/182) of women with grade 2 disease were found to have positive nodes (and were therefore actually stage iiic). There is therefore the possibility that, in standard practice, a small proportion of women with presumed early-stage endometrioid endometrial cancer actually have more advanced disease, and it is these women who might suffer if oestrogen-only preparations of MRT were used instead of continuous combined preparations.

It has also been concluded that a minor proportion of women treated for endometrial cancer will develop recurrent disease in the long run. Most of these recurrences occur within 3 years of treatment and are located at the vault[10]. Certain studies have revealed that the use of unopposed topical vaginal oestrogen is not associated with an increased risk of endometrial hyperplasia or cancer, but it needs further evaluation to be validated[11].

Ovarian cancer

Ovarian cancer is the sixth commonest type of cancer in women. Epithelial ovarian cancer (EOC) accounts for more than 90% of ovarian malignancies, while germ call tumours and sex cord stromal tumours account for 5% and 1.2% respectively[12].

Although most ovarian malignancies develop in postmenopausal women, 20–25% occur in the younger age group as well. Although the median age for diagnosis of EOC is 63 years, it can affect women as young as 40 years of age. Germ cell tumours commonly affect those aged between 10 and 30 years. Nearly 60% of women with sex cord stromal tumours present between the ages of 30 and 59 and 12% are below the age of 30[13].

Treatment of EOC constitutes cytoreductive surgery and platinum-based chemotherapy. For a wide proportion of women with germ cell tumours, fertility preserving surgery is followed by platinum-based combination chemotherapy. TAH and BSO is recommended for most women with sex cord stromal tumours.

The overall 5-year survival rate for ovarian cancer is approximately 46.2%. In the meantime, the five-year survival rates for women under the age of 40, those with stage I disease or those with a germ cell or sex cord stromal tumour exceed 90%[12].

Epithelial ovarian cancers, especially serous and endometrioid subtypes, have been shown to express both oestrogen and progesterone receptors. Clinically, the oral contraceptive pill protects against development of ovarian cancer, but data for MRT have been shown to be inconclusive[14].

A meta-analysis incorporating 52 studies and 21,488 postmenopausal women shows that taking MRT, even if just for a few years, is associated with an increased risk of serous (relative risk [RR] 1.53, 95% CI 1.40– 1.66; $P < 0.0001$) and endometrioid (RR 1.42, 95% CI 1.20– 1.67; $P < 0.0001$) ovarian cancer. The absolute risk, however, is subsidiary[15]. Conversely, randomised data from a post-hoc analysis of the Women's Health Initiative failed to demonstrate any association between MRT and an increased recurrence of ovarian carcinomas[16].

A randomised, non-blinded, phase III study, incorporated 150 women with EOC from across UK, Spain and Hungary[17]. It was concluded that both overall survival (HR 0.63; 95% CI 0.44–0.90; $P = 0.011$) and progression-free survival (HR 0.67; 95% CI 0.47–0.97; $P = 0.032$) were significantly improved in the women who received MRT. This study, however, failed to be standardised as clinicians were allowed to use their choice of MRT.

As a result of variations in stage, histology and MRT regimes, the decision to use MRT in patients with EOC following surgery remains controversial based on current evidence. Prior to promoting MRT for women with ovarian cancer to alleviate menopausal symptoms, more data will be needed to support its use with safety. Although all the studies that have been carried out advocate

the safety of MRT in patients with EOC, most of these have reservations in terms of methodology. At the moment, there is no conclusive evidence to promote the safety of MRT after treatment for ovarian germ cell tumours or sex cord stromal tumours of the ovary.

As granulosa cell tumours are endocrinologically active and hormone dependent, it is not advisable to use MRT in these women. There is insufficient data to suggest the use of MRT in women with borderline ovarian tumours[18].

Cervical cancer

Cervical cancer is the 13th commonest cancer in women in the UK. The incidence of cervical cancer is highest in the age category of 25–29, and most cases in the UK are diagnosed in women under the age of 45[19].

The overall 5-year survival rate is 67%, but this depends on the stage: women with stage I disease have a 5-year survival rate of 95.9%, whereas women with stage IV cervical cancer have a 5 year survival rate of 5.3%[19].

The treatment modality for women with cervical cancer depends on the stage of the disease. Surgery is usually reserved for early stage disease, and this ranges from conisation to radical hysterectomy. On the other hand, primary chemo-radiotherapy is recommended for disease more advanced than FIGO (International Federation of Gynaecology and Obstetrics) 2018 stage IB3. Women with intermediate or high risk for recurrence after surgery are identified based on various pathological factors, and will receive adjuvant radiotherapy, with or without chemotherapy.

Among the types of cervical carcinoma, squamous cell carcinoma (SCC) accounts for more than 70% of cases, while adenocarcinoma accounts for approximately 25% of cases. Ovarian metastasis for SCC and adenocarcinoma are 0.2% and 4% respectively. Therefore, if surgery is indicated in these patients, most gynaecological oncologists opt for BSO as well[20].

Young women who have undergo BSO will inevitably become menopausal due to the treatment. Those who receive chemotherapy and/or radiotherapy are also at risk of an induced menopause. In order to overcome this, the ovaries can be preserved by transposing them out of the pelvis to avoid direct radiation. This may be rendered ineffective, as scatter alone may cause ovarian failure[21].

Several studies have demonstrated the presence of estrogen and progesterone receptors in the cervix. These receptors are overexpressed in approximately one-third of adenocarcinomas. The recurrence rate of cervical cancer has been shown to increase with the increased duration of use of the combined oral contraceptive pill.

There is insufficient data evaluating the safety of MRT in patients following treatment for cervical cancer. The use of MRT in women who have undergone treatment for SCC of the cervix is found to be safe. However, due to evidence that suggests that oestrogen plays a role in the pathogenesis of adenocarcinoma of the cervix, the use of MRT in women who have undergone surgery for adenocarcinomas of the cervix is controversial[22]. Therefore, MRT should be used with extreme caution in this category of women.

Patients who have undergone hysterectomy and BSO only require oestrogen.

Patients are generally treated with radiation doses that ablate the endometrium entirely, but several studies have demonstrated that some endometrial tissue may persist following ablation[23]. Hence, if MRT is being considered for these women, a continuous combined preparation should be prescribed to oppose the effects of oestrogen.

Brachytherapy is associated with significant radiation toxicity to the vagina, causing partial stenosis in approximately 27%[24]. This inevitably contributes to the development of dyspareunia and sexual dysfunction, for which local oestrogens may be beneficial. There is no evidence to suggest that the use of vaginal oestrogens has an adverse effect on the course of a cervical cancer.

Vaginal cancer

Vaginal cancer accounts for approximately 3% of gynaecological malignancies. Most occur in postmenopausal women and are of squamous histology, occurring mainly as a consequence of HPV-related vaginal intraepithelial neoplasia. These tumours are not oestrogen-dependent, and the use of MRT appears to be safe[18]. However, research on the safety of hormone therapy in female patients exposed to diethylstilboestrol in utero which result in clear-cell vaginal cancer is limited[18]. MRT should therefore be used cautiously, if at all, in these women.

Vulval cancer

Vulval cancer accounts for approximately 5% of gynaecological malignancies. The incidence is highest in women over the age of 90 years. HPV-related vulval intraepithelial neoplasia is, however, becoming more prevalent in young women and this may lead to more vulval cancers being diagnosed at a younger age in the future. The most common type of vulval cancer, accounting for 90% are SCC which is not oestrogen dependent. In addition, oestrogen is not associated with VIN. There is no evidence that MRT increases the risk of recurrence after treatment for vulval cancer[25]. Systemic and topical oestrogens can therefore be used safely after treatment for Squamous cell carcinoma of the vulva.

Breast cancer

The risk involved in using MRT is of a similar degree to other postmenopausal lifestyle risk factors for breast cancer (e.g. obesity, alcohol), irrespective of phenotype[26]. Media reporting accompanying the publication of some clinical trials has often over emphasised the risks of MRT, whilst studies not showing the adverse risks get little attention.

Following the Women's Health Initiative Study (WHI) and observational Million Women's Study (MWS) in 2002 and 2003, a collaborative group reanalysis established a duration-dependent association between MRT and the risk of diagnosis and emergence after five years' exposure (an over-all risk ratio of 1.35). This appeared greater with combined rather than unopposed MRT and fell following cessation[27,28].

This controversial observation led to the fall in the world-wide prescription of MRT, despite subsequent studies which revealed a similar or lower risk[29]. Taken as a whole, clinical studies to date have shown that where the risk is increased, it is limited to lean women, there does not appear to be a dosage effect and there is no additive effect in women at elevated personal risk due to a family history or high-risk benign breast condition[30].

For combined MRT, a duration-dependent increase in risk is associated with sequential and continuous preparations and appears elevated, regardless of route of administration, including delivery of progestogen via LNG-IUS. There is some evidence suggesting that the risk may not be elevated if dydrogesterone or micronized progesterone are used in preference to synthetic progestogens in combined preparations[29].

In women with premature ovarian insufficiency (POI), MRT is effective for the management of vasomotor symptoms and is likely to lower the long-term risk of cardiovascular disease, prevent osteoporosis and have a beneficial effect on cognitive function. It is recommended that years of MRT exposure should be counted from the age of 50 and not at the age of MRT commencement. (when POI is diagnosed)[31].

However, the risk of diagnosis is not higher in past users of MRT. Any increase in risk is related to treatment duration and falls after stopping MRT and no significant increase in breast cancer mortality was found. This has been confirmed subsequently with long-term follow-up of the WHI study and a large meta-analysis, where use of unopposed or combined MRT was not associated with any adverse effect on all-cause mortality, total cancer or breast cancer mortality[32].

Finally, in the population of women at risk of breast cancer, the overall risk:benefit ratio for both unopposed and combined MRT is favourable with overall reductions in all-cause mortality.

In women with a familial risk or a high-risk benign breast condition (i.e. biopsy-proven epithelial atypia or lobular carcinoma in situ), MRT exposure has not been shown to have an additive effect on the risk of diagnosis. Although it is recommended that lifestyle and non-hormonal alternatives should be used as the first line of management of vasomotor symptoms in high-risk women, MRT may be needed for severe, refractory symptoms and should be considered on an individual basis following specialist and patient discussion[29].

For patients who have BRCA1 & 2 mutations and others who had prophylactic BSO, add-back MRT is used until the age of an expected natural menopause, after which non-hormonal alternatives are used as first-line management for symptom control and the prevention of chronic, estrogen-deficiency related health problems[33].

Women treated for breast cancer may experience multiple symptoms including hot flushes and vulvo-vaginal atrophy as a consequence of a natural menopause or as a side effect of treatment aimed at reducing the activity or synthesis of estrogen. Systemic MRT and vaginal estrogen are the most efficacious treatments but contraindicated in women with ER positive disease. MRT, however, may not be risk free for those with an ER negative primary. An ER negative primary may present with an ER positive contralateral cancer (up to 30%) and approximately 8% may present with ER positive metastatic disease[34]. NICE has taken a pragmatic approach, recommending lifestyle and non-hormonal alternatives for first-line management of vasomotor symptoms, recognising that MRT could be considered if symptoms are refractory. Among them, topical oestrogen therapy can be considered in the treatment of vulvo-vaginal atrophy if treatment with vaginal moisturisers fails to alleviate symptoms[35]. Neither systemic MRT nor topical estrogen are recommended in women taking an aromatase inhibitor and with both, prescription should only take place after discussion between the patient and a breast specialist.

Conclusion

Improving the quality of life in women being treated for gynaecological malignancies is becoming increasingly important, since their life expectancies have been increasing in the recent past owing to extensive improvements in oncological care.

In the general population of women having undergone standard therapeutic regimes for gynaecological malignancies, the benefits of MRT for the treatment of the immediate symptoms of oestrogen deficiency cannot be disputed. Nevertheless, there are cancer recurrence related risks that must also be considered. A multi-disciplinary, individualised, patient-centred, evidence-based approach to management is essential for women to make an informed decision when considering the use of MRT for the treatment of menopausal symptoms following treatment of gynaecological malignancies.

With regard to breast cancer, oestrogen alone MRT is considered safe, but for some it can be only be used after a careful discussion between the patient and a breast specialist.

Disclosure of interest - None

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