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British Gynaecological Cancer Society and British Menopause Society guidelines: Management of menopausal symptoms following treatment of gynaecological cancer

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Abstract

These guidelines have been developed jointly by the British Gynaecological Cancer Society and British Menopause Society to provide information for all healthcare professionals managing women treated for gynaecological cancer. Menopausal symptoms can have a significant impact on quality of life for women. Cancer therapies, including surgery, pelvic radiotherapy, chemotherapy and endocrine therapy, can all affect ovarian function. The benefits and risks of using hormone replacement therapy are considered by cancer type with guidance on the type of HRT and optimal time of commencement after cancer treatment. Vaginal estrogens can be very effective for improving urogenital symptoms and are safe for the majority of women, including those for whom systemic HRT is contraindicated with rare exceptions. Alternative options to HRT are reviewed including pharmacological and non-pharmacological approaches.

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Introduction

Menopausal symptoms can have a significant impact on quality of life for women following treatment for gynaecological cancer. Cancer therapies, including surgery, pelvic radiotherapy, chemotherapy and endocrine therapy, can all cause premature ovarian insufficiency (POI) or iatrogenic menopause. With continued advances in oncology, there are increasing numbers of long-term survivors, and it is therefore essential to consider and manage the consequences of treatment.

Menopause can cause a variety of symptoms including vasomotor symptoms, sleep disturbance, variable mood, sexual dysfunction, musculoskeletal symptoms, fatigue and cognitive symptoms. The health risks from premature ovarian insufficiency include loss of fertility, increased incidence of osteoporosis, mortality from heart disease, bladder dysfunction and dementia or neurocognitive impairment. This impact may be more significant in the context of menopause due to the diagnosis and treatment of gynaecological cancer. Many of the treatments, such as pelvic radiotherapy, can exacerbate and mimic menopausal symptoms including bladder dysfunction, sexual dysfunction and pelvic bone thinning.

Hormone replacement therapy (HRT) is an effective treatment for menopausal symptoms, for primary prevention of the health risks associated with early menopause, and is an effective therapy for osteoporosis prevention in women under 60 years. For the majority of women with premature ovarian insufficiency, the benefits of HRT outweigh the risks. When deciding on management options, consideration of whether the patient had a hormone-sensitive tumour, such as endometrial stromal sarcoma, is required to fully inform decisions. When quality of life is being impacted by menopausal symptoms, women should be counselled regarding the known risks and benefits of HRT and about the alternative options to enable them to make an informed decision about their treatment.

The aim of this guideline is to provide information for healthcare professionals managing women treated for gynaecological cancer who are reporting menopausal symptoms when other causes have been excluded.

For more comprehensive information on general management of the menopause, we refer the reader to British Menopause Society (BMS) guidance and National Institute for Health and Care Excellence (NICE) guidelines:

⇒ The British Menopause Society and Women's Health Concern 2020 recommendations on Hormone Replacement Therapy in menopausal women;[1]
⇒ The National Institute for Health and Care Excellence Guideline [NG23]. Menopause: diagnosis and management.[2]

Methods

An expert panel of clinicians, nurses and charity partners was nominated by the British Gynaecological Cancer Society (BGCS) and the British Menopause Society (BMS). The group included healthcare professionals with expertise in management of women with gynaecological cancer and menopause. For each topic, focused literature review was undertaken to develop evidence-led recommendations. The guidance statements were determined by consensus within the group and have been approved by the BMS and BGCS councils.

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines (Table 1).

These guidelines refer to the treatment of all people with, or at risk from, gynaecological malignancies. The majority will define themselves as women and, in line with other RCOG guidelines where the term women is used, this also includes those who have other gender identities.

General recommendations

- **All women who are likely to go through menopause as a result of surgery, systemic therapy and/or radiotherapy treatment should have a pre-treatment discussion of possible menopausal symptoms and potential management options (Grade D).**
- **Women should have access to evidence-based information about menopausal symptoms, HRT and alternative treatment options (Grade D).**
- **Evaluation of symptoms and individual needs should be reassessed on a regular basis, with annual review once stable (Grade D).**
- **All clinicians and clinical nurse specialists managing gynaecological cancer should have appropriate training to support women with menopausal symptoms. Referral to or discussion with a menopause specialist is recommended for complex situations (Grade D).**
- **High-quality research studies are required on management of menopausal symptoms in women treated for gynaecological cancers (Grade D).**

Throughout these recommendations, the term hormone replacement therapy (HRT) refers tosystemic HRT and this

Table 1. Classification and strength of evidence.

Classification of evidence levels	
1 ++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1−	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2 ++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, for example, case reports and case series
4	Expert opinion
Strength	
A	At least one meta-analysis, systematic reviews or RCTs rated as 1++ and directly applicable to the patient population or A systematic review of RCTs or a body of studies rated as 1+ directly applicable to the patient population and demonstrating consistency of results.
B	Evidence from Level 2++ studies directly applicable to the patient population or extrapolated from Level 1 studies.
C	Evidence from Level 2+ studies directly applicable to the patient population or extrapolated evidence from studies rated at 2++.
D	Evidence from Level 3 or 4 studies or extrapolated evidence from studies rated as 2+.

does not include vaginal estrogen which is considered separately.

Many of the recommendations are based on expert opinion. There is a paucity of evidence in many areas and individual patient decision-making is necessary, balancing uncertainties and individual risks and benefits, with input from specialist services for complex patients.

Hormone replacement therapy after treatment for specific gynaecological tumour types

The following sections consider the evidence for HRT after treatment for gynaecological cancer and the recommendations are summarised in Table 2. However, for women with a life-limiting illness, consideration of quality of life is essential and there may be benefits from HRT even with hormone-sensitive tumours on an individualised basis. In addition, vaginal estrogens can have significant benefits for many women and can be considered even when systemic HRT is contraindicated or not required. Where recommendations for HRT are made, the options of estrogen-only HRT versus combined continuous HRT, optimal time of commencement after cancer treatment, recommended dose and duration of use are discussed in later sections of this guidance.

Ovarian cancer (includes ovarian, fallopian tube and primary peritoneal cancer)

- **HRT is not usually contraindicated following treatment for epithelial ovarian cancer and potential risks and benefits should be discussed with women (Grade B).**
- **Although the majority of high-grade serous and endometrioid ovarian cancers express estrogen receptors, the limited randomised controlled trial data do not suggest an increased risk of disease recurrence with systemic HRT. It may be appropriate to offer non-hormonal options in the first instance, particularly for women who do not have the health impacts of an early menopause (Grade B).**
- **Non-hormonal options should be offered in the first instance to women with FIGO Stage I low-grade serous ovarian cancers, but HRT is not contraindicated (Grade D).**
- **HRT is not recommended for women with FIGO stages II–IV or recurrent low-grade serous ovarian cancers, as the disease is hormone-sensitive and there is an advantage to estrogen-suppressing treatment (Grade D).**

Table 2. Summary of recommendations for use of systemic HRT and vaginal estrogen following treatment of gynaecological cancer.

Primary Cancer	Subtype/Risk Group	Systemic HRT	Vaginal Estrogen
Ovarian Fallopian tube Primary peritoneal	High grade serous		
	Low grade serous stage 1		
	Low grade serous stage 2+		
	Endometrioid stage 1		
	Endometrioid stage 2+		
	Clear cell		
	Mucinous		
	Granulosa cell stage 1		
	Granulosa cell stage 2+		
	Germ Cell		
	Borderline tumour: No residual disease		
	Borderline tumour: Peritoneal implants, microinvasive disease, residual disease, recurrence		
Endometrial	Low and intermediate risk		
	High-intermediate risk		
	High risk: ER/PR negative		
	High risk: ER/PR positive		
	Advanced and metastatic		
Cervical	All		
Vulval	All		
Vaginal	All		
Uterine sarcoma	Leiomyosarcoma		
	Endometrial stromal sarcoma		

	Benefits usually outweigh risks. Suitable for non-specialist use.
	Refer to text of BGCS BMS guidelines. Discuss benefits and risks for the individual patient. Consider specialist advice.
	Not recommended. Refer for specialist advice if non-hormonal approaches are not effective.

Type of HRT	**Evidence is only with use of low/standard doses of estrogen*
Estrogen only HRT	Following hysterectomy. NB: combined continuous HRT is indicated when history of endometriosis
Continuous combined HRT	Uterus still in situ, including after radiotherapy or endometrial ablation Progestogen dose must be proportionate to estrogen dose.

- **HRT should be offered to women who have menopausal symptoms following treatment for borderline ovarian tumours and actively recommended for those with surgical menopause as a result of treatment for early-stage disease (Grade C).**
- **HRT should be offered to women who have premature ovarian insufficiency following treatment for germ cell tumours (Grade D).**
- **Limited evidence does not demonstrate harm with HRT following treatment for stage I granulosa cell**

tumours, but these tumours are hormone-sensitive and women should be counselled regarding the uncertainties (Grade D).

High-grade serous epithelial ovarian carcinoma. The majority of women with epithelial ovarian cancer (EOC) are diagnosed at a late stage and with high-grade serous carcinoma. There is a need to balance quality and quantity of life, and the risk/benefit profiles need to be individualised based on symptoms and cancer risks.[3] Furthermore, many women with early-stage cancer are younger, have a good prognosis and treatment potentially leads to surgical menopause or premature ovarian insufficiency, and so the impact of early menopause in long-term survivors needs to be balanced with the risks of cancer recurrence.[4] HRT may therefore be an important consideration for women with both early- and late-stage disease.

There is a theoretical risk of estrogen use for women with high-grade serous or endometrioid EOC since up to 85% of these tumours express estrogen receptors.[5] Endocrine (anti-estrogen) therapy with aromatase inhibitors is a treatment option for recurrent, late-stage disease although to date small, non-randomised studies have demonstrated a very limited response.[6] Clinical trials are ongoing for women with newly diagnosed early and late-stage, and recurrent heavily pre-treated disease.[7,8]

In contrast, there are specific data that support the use of HRT in women with EOC. In a Swedish observational study of 649 patients previously treated for high-grade epithelial ovarian cancer, there was improved survival in the cohort that received HRT after diagnosis (HR = 0.57, 95% CI 0.42 to 0.78). This was particularly for serous EOC, but it must be noted that this subgroup consisted of only 42 of the 649 patients.[9] A randomised trial of 150 patients receiving systemic HRT after an ovarian cancer diagnosis demonstrated improved overall and relapse-free survival, with a hazard ratio (HR) of 0.63 (p = .011) and 0.67 (p = .032), respectively, although this was a small trial, with a short follow-up and in varying tumour types.[10]

A Cochrane review assessing HRT after treatment for EOC identified three studies involving 350 women.[11] Two studies included pre- and postmenopausal women and one only included premenopausal women. The age range of the women included in the studies was 20 to 89.6 years old. Median follow-up ranged from 31.4 months to 19.1 years. They reported that HRT may slightly improve overall survival (OS) after surgical treatment for EOC (HR 0.71, 95% CI 0.54 to 0.93; 350 participants, 3 studies; low-certainty evidence) and little or no effect of HRT use on progression-free survival (PFS) (HR 0.76, 95% CI 0.57 to 1.01; 275 participants, 2 studies; low-certainty evidence). With regard to non-survival outcomes, they found that HRT makes little or no symptomatic difference as certainty of evidence was very low for quality of life (QoL) (MD 13.67 points higher, 95% CI 9.26 higher to 18.08 higher; 1 study; 75 participants); incidence of breast cancer (relative risk [RR] 2.00, 95% CI 0.19 to 21.59; 225 participants, 2 studies); transient ischaemic attacks (RR 5.00, 95% CI 0.24 to 102.42; 150 participants, 1 study); cerebrovascular accident (RR 0.67, 95% CI 0.11 to 3.88; 150 participants, 1 study); myocardial infarct (RR 0.20, 95% CI 0.01 to 4.10; 150 participants, 1 study).

A recent systematic review and meta-analysis identified eight publications including 3578 patients of whom 912 received systemic HRT and this did report an impact of HRT on survival. This highlighted a slight benefit in OS and PFS in favour of HRT (HR 0.66 and 0.73) and no difference based on age or stage and grade of tumour.[12]

Non-serous epithelial ovarian cancer (clear cell, mucinous, endometrioid). The impact of HRT in non-serous tumours is less clear. A retrospective cohort study of 357 women with non-serous cancers demonstrated no harmful effects and no impact on OS or PFS.[13]

In those with endometrioid ovarian cancer, HRT did not appear to worsen outcomes despite these being potentially estrogen-sensitive tumours.[9] Following treatment for FIGO Stage I disease, non-hormonal options should be considered in the first instance, but HRT is not contraindicated. However, in those with more advanced or residual disease, HRT should be used with caution as the presence of residual disease may promote tumour growth.

For women with clear cell and mucinous cancer, where endocrine treatments are not routinely used, HRT can be considered. However, treatment should be individualised and the uncertainties discussed, especially for patients with advanced disease.

Low-grade serous ovarian cancer (LGSOC). Low-grade serous ovarian tumours are generally ER-positive and commonly hormone-sensitive, with anti-estrogen treatment frequently used in the recurrent setting.[14,15] There is a lack of data on the safety of HRT in women treated for low-grade serous carcinoma and so a precautionary principle is advisable. Non-hormonal options should be offered in the first instance to women with Stage I low-grade serous ovarian cancers, but HRT can be considered after a discussion of the individualised potential risks and health benefits. A joint position statement by the European Menopause and Andropause Society (EMAS) and the International Gynecological Society (IGCS) concluded that 'given the benefits seen with 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, [sic] estrogen-based therapies are currently not recommended in advanced disease of these types'.[16]

Borderline ovarian tumour (BOT). Borderline ovarian tumours (BOTs) more commonly occur in younger women compared to epithelial ovarian cancer. Treatment that involves bilateral salpingo-oophorectomy may therefore cause significant rates of premature menopause. Furthermore, in young women retention of fertility is a common consideration and fertility-sparing surgery is often appropriate. With high overall survival rates, women with surgically induced menopause are likely to live for many years associated with increasing consequences of estrogen deficiency, unless appropriate hormone replacement therapy is provided.

In the Swedish observational study, in addition to epithelial ovarian cancers discussed above, there were 150 women who had been treated for BOT.[9] With a 5-year follow-up, 93% of the patients with BOT were alive and 51% of the women used HRT after diagnosis. There were ten deaths from any cause occurring among women with BOT with only three deaths due to ovarian cancer and none of these women had used HRT before or after diagnosis.

After examination of the available evidence, the French national guidelines concluded that use of hormonal contraception after serous or mucinous BOT was not contraindicated.[17,18] Specifically for women aged under 45 years who had a surgical menopause as a result of treatment, given the benefit of HRT on cardiovascular and bone risks, and the lack of hormone-sensitivity of mucinous BOTs, they actively recommended the use of HRT, in the absence of other contraindications. For women over 45 years of age, they found no argument to contraindicate the use of HRT on the basis of the BOT diagnosis alone and recommended that HRT can be prescribed for menopausal symptoms, as part of an individual benefit to risk assessment. However, there should be caution if there is residual disease following surgery, advanced stage or recurrent disease.

Germ cell tumours. Germ cell tumours most commonly occur in young women and account for 70% of ovarian tumours in the under 20s, and a third of these are malignant.[19] Since most dysgerminomas present at an early stage in girls and young women, conservative surgery is optimal; unilateral oophorectomy is appropriate to preserve fertility and ovarian function, even in the presence of metastatic disease. Dysgerminomas are very chemo-sensitive with cure rates of 90–100% achieved for advanced disease. Combination chemotherapy regimens typically include bleomycin, etoposide and cisplatin with which ovarian function is normally preserved.

Treatment should therefore be aimed at preserving ovarian function for the majority of patients. However, in those who either have bilateral oophorectomy or lose ovarian function due to chemotherapy, HRT use should be encouraged. Due to the rarity, there are no specific studies of HRT use in germ cell tumours, and recommendations are based on the theoretical lack of hormone response and significant non-cancer-related benefits of HRT.[16]

Granulosa cell tumours. Granulosa cell tumours can present at any age, although are most common in postmenopausal women. An important minority of granulosa cell tumours (5%) occur in pre-pubertal girls, who often present with precocious puberty, as these tumours commonly secrete estrogen.[20] Surgery is the first-line of treatment. In premenopausal women, unilateral oophorectomy is undertaken if disease is limited to one ovary, co-existing endometrial disease has been excluded and fertility is desired. In postmenopausal women, or in those where fertility is not desired, total hysterectomy, bilateral oophorectomy and omentectomy are recommended. In advanced disease, optimal debulking is associated with longer survival.[21]

A study of 454 patients, previously diagnosed with granulosa and theca cell tumours, reviewed the original histology and re-classified the cases based on current diagnostic criteria and methods.[22] Only 58% of granulosa cell tumours were stage I, compared with 80% of granulosa-theca or theca cell tumours. Median follow-up data was available for 6.6 years, and 5- and 10-year survival rates were 89.0% and 76.8%, respectively. Granulosa cell tumours were also more likely to recur (24.7% confirmed recurrence) than granulosa-theca cell tumours (1.0%). Recurrences may occur after some considerable time following the initial diagnosis. One of the longest intervals is 37 years,[23] with 33% of recurrences within 5 years, 50% between 5 and 9 years, and 17% more than 10 years from diagnosis.[22]

Granulosa cell tumours are potentially estrogen-dependent and commonly produce estrogens and inhibin. Treatment of advanced or recurrent disease usually involves endocrine approaches including aromatase inhibitors, leuprolide and tamoxifen. There are no data on the safety of HRT with early-stage disease. HRT use, especially in advanced disease, would depend on treatment regimens, individual symptoms and risk/benefit discussions, but non-hormonal treatment options should be strongly considered initially in advanced and recurrent disease and women counselled about the uncertainties and minimal evidence-base.[16]

Cervical and vaginal cancer

- **HRT is not contraindicated after treatment for cervical or vaginal cancer, with the recommended HRT options dependent on the received treatment (Grade B).**
- **Estrogen-only HRT should be offered after hysterectomy and bilateral salpingo-oophorectomy for cervical cancer in premenopausal women (Grade B).**

- **Continuous combined estrogen–progestogen HRT or tibolone is recommended after chemoradiotherapy to the pelvis for premenopausal women (Grade B).**

Cervical and vaginal cancers are not hormone dependent, and there is no contraindication to the use of HRT or vaginal estrogens. Although adenocarcinomas of the cervix commonly express estrogen receptors, several studies have found that estrogen and progesterone receptor expression does not correlate with recurrence or survival outcomes, and no detrimental impact has been reported with the use of HRT following treatment.[24–27] Furthermore, there was no correlation of ER or PR expression and prognostic factors, such as stage, age, lymph node status or lymphovascular invasion.[25]

Treatment-induced menopause is a significant problem after cervical cancer treatment, especially in women diagnosed at a young age and with a good prognosis. A population-based study of 837 women aged under 45 years at the time of cervical cancer diagnosis demonstrated that almost a third had treatment-induced menopause due to surgery or radiotherapy.[28] Fewer than half of the women who had therapy-induced early menopause used HRT at the recommended dose. By 4.5–5 year follow-up, HRT use decreased further with only 21% receiving at least 75% of the recommended dose. Increased awareness of the significant health benefits of HRT for this patient group is needed among professionals and women.

In a randomised clinical trial of HRT use in 120 women aged under 45 at diagnosis (80 HRT; 40 controls) treated with surgery and/or radiotherapy for cervical cancer, there was no difference in disease-free or overall survival between those prescribed HRT and controls.[29] This study demonstrated better control of menopausal symptoms and relief of radiation-induced bladder, rectal, and vaginal symptoms in the HRT group. Narrative reviews of the literature have consistently concluded that there is no evidence that HRT-use after a diagnosis of cervical cancer is associated with an increased risk of cervical cancer recurrence or death.[30–32]

Following hysterectomy and bilateral salpingo-oophorectomy, estrogen-only HRT is recommended. Some clinicians would recommend combination HRT instead of estrogen-only HRT following treatment for adenocarcinoma of the cervix, but data are lacking for this approach.

After pelvic radiotherapy, for those who have not had a hysterectomy, continuous combined estrogen and progestogen HRT should be prescribed for premenopausal women. Functional endometrium can persist after pelvic radiotherapy for cervical cancer, and endometrial cancer has been reported in women previously treated with radiotherapy who have an intact uterus.[28,32,33] HRT reduces the incidence of vaginal toxicity, sexual dysfunction and pelvic insufficiency fractures following radiotherapy and should ideally be commenced during or within a few weeks of completing radiotherapy.

Endometrial Carcinoma

- **Premenopausal women with low-risk endometrial cancer can be considered for ovarian-sparing surgery to prevent surgical menopause (Grade D).**
- **Women with low-risk and intermediate-risk endometrial cancer, who are premenopausal or have menopausal symptoms, should have discussion about the advantages and disadvantages of HRT after hysterectomy. The limited evidence to date does not identify an increased risk of recurrence with HRT (Grade B).**
- **For women with high-intermediate risk, or high-risk endometrial cancer with estrogen- and progesterone-receptor negative tumours, treatment should be individualised following discussion of theoretical risks and benefits as the risk of HRT is unknown (Grade D).**
- **HRT is not recommended for women with high risk, advanced or metastatic disease that is expressing hormone receptors (Grade D).**
- **Women with advanced disease, where treatment is with palliative intent, should have careful consideration of all treatments to improve quality of life, which may include HRT depending on symptoms (Grade D).**
- **Women diagnosed with endometrial cancer whilst on tamoxifen for breast cancer should be discussed with their breast oncology team, with consideration being given to either switching to an aromatase inhibitor or discontinuation of endocrine therapy (Grade D).**

Endometrial cancer is the fourth most common cancer in females in the UK, and the numbers are escalating due to increasing rates of obesity. Risk groups have been identified based on tumour histology, stage and molecular profile which can guide management options and help to provide patients with informed advice.[34,35] In these recommendations, the risk groups are defined according to the ESGO-ESTRO-ESP 2021 guidelines and BGCS guidelines (Appendix 1).

There is limited evidence in the literature around HRT after treatment for endometrial cancer. A Cochrane review assessed the available evidence with data from one randomised controlled trial that closed early and two low-quality studies, and found no evidence of increased recurrence for use of HRT after endometrial cancer.[36] The randomised trial contained 1236 participants who had FIGO stage I–II endometrial cancer and the rate of tumour recurrence was not significantly different during the 36 month follow-up (2.3% in the estrogen arm vs 1.9% receiving placebo [RR 1.17]).[37] A meta-analysis by Shim *et al* based mainly on observational studies showed no significant increase in recurrence with HRT use following endometrial cancer, irrespective of tumour stage or type of HRT.[38]

Ovarian conservation is an option in premenopausal women with a low-grade endometrioid endometrial cancer with less than 50% myometrial invasion on MRI and no extrauterine disease on imaging.[35]

It is advisable to await final pathology and the potential need for adjuvant treatment before discussing menopausal symptoms and management with the patient. With low- and intermediate-risk endometrial cancer it is reasonable to discuss both systemic and vaginal estrogen.[1,39]

It should be discussed with women with high-intermediate and high-risk endometrioid endometrial cancer that there is no evidence on the harms and benefits of HRT use. There are also no data on the impact of HRT on tumours that do not express hormone receptors. Endocrine therapies are used for treatment of recurrent and metastatic disease, particularly for tumours with strong expression of estrogen and/or progesterone receptors, so there is a theoretical risk associated with HRT use in women at a higher risk of recurrence.

In the palliative situation, HRT can be discussed with women as part of managing symptoms and quality of life. It should be a priority to ensure that all women can access a specialised clinic to discuss the risks and benefits of HRT if they are struggling with menopausal symptoms.

There is evidence that combined HRT can reduce the risk of developing endometrial cancer in women with a uterus. The Women's Health Initiative (WHI) study published in 2016 showed a significant decrease in endometrial cancer from the background population of women with a uterus having continuous combined HRT compared to no HRT.[40] This data could be extrapolated to consider prescribing continuous combined HRT to women after treatment for endometrial cancer, particularly in women with high-intermediate or high-risk endometrial cancer whose quality of life is severely affected by menopausal symptoms. However, there are no data comparing continuous combined HRT with estrogen-only HRT in women with endometrial cancer and breast cancer risk needs to be taken into consideration.

Tamoxifen is one of a class of agents known as selective estrogen receptor modulators (SERMs). It is used as an adjuvant treatment for breast cancer but has a weakly positive effect on the estrogen receptors in the endometrium. It therefore increases the risk of endometrial cancer two- to three-fold.[41] Any woman who has developed endometrial cancer whilst on tamoxifen should be advised to stop the tamoxifen and be referred back to their breast oncology team for consideration of alternative endocrine options.

Uterine sarcomas

- **Uterine leiomyosarcomas can be hormone-sensitive, and therefore HRT should be avoided (Grade C).**
- **For women with significant menopausal symptoms following treatment for leiomyosarcoma, HRT should only be considered if alternative options have been ineffective (Grade D).**
- **Women should be advised to avoid HRT after treatment for endometrial stromal sarcoma, unless the individual benefits outweigh the risk (Grade C).**

Leiomyosarcoma. Leiomyosarcomas are rare tumours, making up 1–2% of all uterine malignancies. They are generally poor prognostic tumours, with 40% of patients developing lung metastases and with a 5-year overall survival between 15 and 25%. Published data shows that the hormone receptor status for leiomyosarcomas is 25–60% estrogen receptor positivity and 35–60% progesterone receptor positivity.[42,43] Aromatase inhibitors can have a positive therapeutic effect, and there have also been case reports describing a partial response when stopping HRT at the time of disease recurrence.[44–46] It is therefore recommended that HRT is avoided, unless quality of life benefits for an individual outweighs the risk. Referral to a healthcare professional with expertise in menopause is recommended if HRT is considered.

Endometrial stromal sarcoma. Endometrial stromal sarcomas are hormone-sensitive tumours which are usually treated with endocrine approaches for advanced and recurrent disease. These cancers often occur in premenopausal women. Oophorectomy as part of surgery improves progression-free survival compared to women with retained ovaries, but not overall survival, so this is an important area to counsel women about when planning surgery.[47] There is a paucity of evidence with regards to endometrial stromal sarcoma. There are only two retrospective studies in the literature looking at HRT after treatment for endometrial stromal sarcoma. In these studies, 12 out of 23 patients with recurrence were on HRT, and 6 of 23 were taking tamoxifen.[48,49] It is therefore recommended that HRT is avoided in this group, unless quality of life benefits for an individual outweighs the risk. Referral to a healthcare professional with expertise in menopause is recommended if HRT is considered.

Vulval cancer

- **Following treatment for squamous cell carcinoma of the vulva, there is no contraindication to HRT or local estrogens (Grade D).**
- **Evidence from cutaneous melanoma at all sites does not support or contradict HRT use following treatment for melanoma of the vulva (Grade C).**

The majority of vulval cancers are squamous cell cancers, adeno-squamous or adenocarcinomas which are not

hormonally driven and are not hormone-sensitive tumours. These cancers are either HPV-associated or related to inflammatory skin disorders such as lichen sclerosus. Adenocarcinomas can arise in the Bartholin's gland or in Paget's disease of the vulva. Since radical surgery does not affect the menopausal status of women, the quality-of-life discussions related to menopause are less affected by treatment unless pelvic radiotherapy is used. If a postmenopausal woman is on HRT when diagnosed with vulval cancer, there is no contraindication to continuing with this.

Local estrogen can be beneficial to aid healing of the vulva, and also as part of management of inflammatory vulval skin disorders. However, it can increase the risk of candidiasis, particularly in women also on topical steroids, and this should be discussed with women when prescribing.

Melanoma is the fourth most common histological type of vulval cancer. For melanomas at all sites, there have been several studies assessing the association between HRT and melanoma. A meta-analysis including five prospective studies in the literature looking at HRT use and likelihood of developing melanoma does not support or contraindicate the use of HRT in women following treatment for vulval melanoma.[50]

HRT for women with an increased risk or genetic predisposition to develop breast, ovarian and/or endometrial cancer

- **Premenopausal women need careful counselling with consideration of HRT options and access to evidence-based patient information prior to decision-making for risk-reducing surgery (Grade D).**
- **Access to a specialist service for women with a high risk of gynaecological cancer is strongly recommended (Grade D).**
- **Following premenopausal oophorectomy, HRT should be offered until the usual age of the natural menopause, unless there is a personal history of breast cancer (Grade C).**
- **Continuation beyond this age lacks an evidence base in women with a cancer susceptibility gene associated with an increased risk of breast cancer (such as BRCA carriers) and is not routinely recommended. However, continuation can be considered depending on the individual balance of risks and benefits in women who have had bilateral risk-reducing mastectomy for primary breast cancer prevention (Grade D).**
- **Hysterectomy is not indicated at the time of risk-reducing salpingo-oophorectomy (RRSO) if there is no increased genetic risk for endometrial cancer or other clinical indication for hysterectomy (Grade D).**
- **Women with Lynch syndrome or BRIP1 mutation are not at an increased risk of breast cancer. HRT use beyond the usual age of menopause for these women should be governed by the same principles as for population-based risk.**

Risk-reducing surgery

Risk-reducing surgery with bilateral salpingo-oophorectomy (RRSO) is the most effective method of preventing ovarian cancer for those with an increased risk due to inherited pathogenic variants and likely pathogenic variants (henceforth called pathogenic variants or PVs) in cancer susceptibility genes associated with an increased risk of ovarian cancer. This includes the breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*), as well as moderate penetrance genes *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*. Women with Lynch syndrome have PVs in mismatch repair genes (MMR) (*MLH-1*, *PMS-2*, *MSH-2 and MSH-6*) and are at an increased risk of ovarian cancer as well as endometrial cancer. RRSO is cost-effective for women at 4–5% or greater lifetime ovarian cancer risk, and at 4–5% lifetime risk level it can save 7–10 years of a woman's life.[51,52] Hysterectomy is not routinely indicated at the time of RRSO if there is no increased genetic risk for endometrial cancer (such as in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1* and *PALB2*) or other clinical indication for hysterectomy. For women with Lynch syndrome, both total hysterectomy and bilateral salpingo-oophorectomy are recommended for cancer prevention. Baseline investigations of an ultrasound scan and CA125 are recommended within 6–8 weeks of risk-reducing surgery to exclude asymptomatic visible disease. Women with Lynch syndrome should also have an endometrial biopsy prior to hysterectomy, as if disease is diagnosed pre-operatively, this may change the surgical approach and extent. Despite this, due to the natural history of the disease, and lack of an effective biomarker for occult disease, some occult tumours and/or serous tubal intraepithelial carcinomas (STICs) will be found on histology, requiring further staging and/or other treatment.

With increasing uptake of risk-reducing surgery, more women will be exposed to the long-term consequences of premature surgical menopause.[53,54] Risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) as a two-step alternative for ovarian cancer risk reduction should at present only be considered in a research study due to current paucity of long-term outcome data, particularly with respect to reduction in cancer incidence and endocrine function.[55–57]

Role of HRT

Women considering risk-reducing surgery should be provided with evidence-based information and multidisciplinary input, with advice on symptom management, use of HRT if appropriate, specialist counselling and sustained support to deal with various physical, emotional and long-

term health consequences of a surgical menopause.[58,59] Women at high-risk are best managed in multidisciplinary teams which should include a gynaecologist/ gynaecological oncologist with a special interest, a menopause specialist, a clinical nurse specialist and psychological support. It should be discussed that retaining the uterus impacts on HRT options, as estrogen must be combined with a progestogen (either cyclical or continuous) to protect against endometrial hyperplasia, whereas estrogen alone is required following hysterectomy.

HRT can ameliorate symptoms and reduces the adverse long-term consequences of premature menopause.[54,60,61] It should be routinely offered to all women having premenopausal RRSO unless there is a personal history of breast cancer which necessitates a more detailed consultation. Historically, use or compliance with HRT after RRSO has been limited (8–47%), although higher compliance rates of 74% and improved satisfaction have been reported in patients treated in multidisciplinary specialist high-risk centres.[62]

Short-term HRT use in *BRCA* mutation carriers below the age of natural menopause does not increase the risk of breast cancer.[53,63–66] The health benefit of HRT is greatest after RRSO at younger ages. One small retrospective cohort study has reported breast cancer risk may rise from use at 45–50 years.[66]

Some women at an increased risk of ovarian cancer may not be at an increased risk of breast cancer (e.g. those with *BRIP1* mutations or Lynch syndrome), and HRT use beyond the usual age of natural menopause in these women should be governed by the same principles as women at population-based risk. These principles should also be applied to cancer susceptibility gene carriers associated with an increased risk of breast cancer (such as *BRCA* or *PALB2*), but no personal history of breast cancer, following risk-reducing bilateral mastectomy for primary breast cancer prevention.

HRT is usually contraindicated in women with a personal history of breast cancer. It should not be routinely recommended to women with a history of estrogen receptor or progesterone receptor positive breast cancers, although it can be considered on an individualised basis after careful counselling for women with significant symptoms where non-hormonal alternatives are not effective or acceptable.[67] Short-term HRT may be considered on a case-by-case basis in women with triple-negative breast cancer. Any such decision should be individualised, and multidisciplinary team involvement is important including the woman, breast oncologist and menopause specialist/gynaecologist experienced in caring for women with a high risk of cancer. Even if HRT is contraindicated, vaginal estrogens can still be considered, especially in women taking tamoxifen.[68]

Options for hormone replacement therapy

- **Transdermal administration of estradiol is unlikely to increase the risk of venous thromboembolism (VTE) or stroke above that of non-users and is associated with a lower risk than oral administration of estradiol. The transdermal route should therefore be considered as the preferred choice for women with related risk factors (Grade A).**
- **Oral estradiol is effective and safe in most women unless there are concerns about gut malabsorption, drug interactions or there are risk factors for VTE (Grade A).**
- **The lowest effective dose of estrogen that relieves symptoms should be used (Grade B).**
- **Serum levels of estrogen should not be routinely measured to titrate HRT dosage, other than in situations to check absorption (Grade C).**
- **Continuous combined HRT should be offered to all non-hysterectomised women once clearly postmenopausal if HRT is indicated (Grade A).**
- **The dose of progestogen should be proportionate to the dose of estrogen. Women who require high doses of estrogen should consider having their progestogen dose increased to ensure adequate endometrial protection (Grade D).**
- **The use of compounded bioidentical hormone replacement therapies from 'Specialist Pharmacies' is not recommended. These products do not follow the same regulatory pathways as prescribed HRT, with potential issues related to their purity, safety and efficacy (Grade D).**
- **Due to the potential risk of stimulation or malignant conversion of endometriotic deposits with unopposed estrogens, continuous combined HRT should be prescribed following hysterectomy in women with a history of endometriosis (Grade D).**

In women with previous gynaecological cancer, HRT options depend on tumour factors, oncological treatment and the type of drug to be used, always balancing risk and benefit for the individual.[69] In addition to the oncology history, other risk factors to consider include history of VTE, cerebrovascular accident (CVA), myocardial infarctions (MI), liver dysfunction, gut malabsorption syndromes and high body mass index (BMI).

Further information is available in the following documents:

⇒ The British Menopause Society and Women's Health Concern 2020 recommendations on Hormone Replacement Therapy in menopausal women;[1]
⇒ International Menopause Society Recommendations on women's midlife health and menopause hormone therapy;[70]
⇒ The National Institute for Health and Care Excellence Guideline [NG23]. Menopause: diagnosis and management;[2]
⇒ 2022 Hormone Position Statement of the North American Menopause Society.[71]

Estrogen

Transdermal estradiol does not increase the risk of VTE or stroke above baseline risk.[72–74] Whilst transdermal estrogen is optimal for most women, oral estrogens are effective and safe in most women without risk factors for VTE or malabsorption. Oral conjugated equine estrogens (CEEs) do have a higher risk of VTE than oral estradiol.[72]

Women should use the dose of estrogen that relieves their symptoms. The long-term data for higher doses are unknown, and caution is advised for using higher doses when there is the possibility of estrogen stimulation of tumour. Women with premature ovarian insufficiency may need higher doses than women with menopause at an average age. However, high doses of estrogen which exceed the product licenses should not be regularly prescribed as these limits are informed by the results of clinical trials to ensure patient safety. If in exceptional circumstances a higher than licensed dose is deemed necessary for symptom control, informed consent should be obtained according to good medical practice guidance and patients must be made aware that treatment falls outside of currently available safety evidence. In addition, the dose of progestogen should be increased proportionately.[75]

Progestogens

Progestogen administration is required to protect against endometrial stimulation that can occur with unopposed estrogen. The dose of progestogen should be proportionate to the dose of estrogen.[75,76] Observational and case control data suggest that micronised progesterone may reduce the increased risk of VTE conferred by oral estrogen, compared to that noted with synthetic progestins.[75]

The type of progestogen can also impact on the risk of developing breast cancer. A meta-analysis by Asi *et al* found that micronised progesterone was associated with a lower risk of breast cancer compared with synthetic progestins although longer-term data are lacking.[77] Compared with HRT never-use, there was no increased risk of breast cancer with micronised progesterone (relative risk [RR] 1.00) for up to 5 years use, whereas women using estrogen plus progestins had an RR of 1.16–1.69.[78] Similarly, Cordina-Duverger *et al* reported no increased risk of breast cancer among users of estrogen with micronised progesterone for any duration (odds ratio [OR] 0.80), whereas among users of combined HRT containing a synthetic progestin, the OR was 1.57–3.35 (depending on the progestin used).[79]

Sequential combined HRT given for more than 5 years does slightly increase the risk of endometrial cancer, but there is no increased risk when estrogen is combined with continuous daily progestogen in postmenopausal women using standard dose estrogen.[80] Therefore, continuous combined HRT should be offered to all non-hysterectomised women once clearly postmenopausal, if HRT is indicated. Further detail about progestogens and endometrial protection is available in the BMS document 14-BMS-TfC-Progestogens-and-endometrial-protection-01H.pdf (thebms.org.uk).[81]

The BMS Consensus Statement on Bioidentical HRT highlights concerns related to the efficacy and safety of non-regulated compounded bioidentical products, and the lack of evidence that this route and dosage of progesterone provides sufficient endometrial protection. The use of such compounded products is therefore not recommended.[82]

Tibolone is an alternative option to estrogen–progestogen combination HRT. It produces metabolites that have estrogenic, progestogenic and androgenic effects, and it does not stimulate the endometrium. Cummings *et al* not only reported a reduction in risk of fractures and of breast and colon cancer with tibolone but also reported a small increase in the risk of stroke in older women with additional risk factors.[83]

In women with a history of endometriosis, there is a potential risk of stimulation of quiescent endometriosis or malignant conversion with unopposed estrogens.[84] ESHRE guidelines recommend continuous combined HRT at least up to the age of natural menopause following surgical menopause.[85] Further information is available in the BMS document: Induced menopause in women with endometriosis - British Menopause Society (thebms.org.uk).[86]

Vaginal estrogens (alone or in addition to HRT)

- **Always enquire specifically about symptoms of urogenital atrophy and sexual dysfunction. General advice about vaginal lubricants and moisturisers should be provided (Grade D).**
- **Vaginal estrogens are safe for the majority of women after treatment for a gynaecological malignancy, including those for whom systemic HRT is contraindicated with rare exceptions (Grade B).**
- **For those in whom HRT is not contraindicated, women may need vaginal estrogen in addition to systemic HRT for treatment of urogenital symptoms (Grade D).**

Urogenital symptoms including vaginal dryness, itching, discomfort and painful sexual intercourse can be very distressing. Alternative terminology used for these symptoms includes vulvovaginal atrophy (VVA), urogenital atrophy (UGA) and genitourinary syndrome of menopause (GSM). These symptoms are under-reported, often not recognised by healthcare professionals and under-treated. In addition, many of the treatments for cancer can exacerbate these symptoms. Sexual dysfunction is particularly

common in cancer survivors especially in younger women and in those who have had pelvic radiotherapy.

Vaginal estrogens are very effective at improving urogenital symptoms.[1,87] They have also been found to be superior to placebo for urinary symptoms including urgency, urge incontinence, frequency and nocturia. For some women taking HRT, vaginal estrogen may be required in addition to improve urogenital symptoms. Vaginal lubricants and moisturisers can be used as well as vaginal estrogen. Further information is available in the BMS consensus statement on Urogenital Atrophy and the North American Menopause 2020 position statement on genitourinary syndrome.[88,89]

While the data regarding the use of topical vaginal estrogen after gynaecological cancer are sparse, it should be highlighted that with current low-dose estrogen preparations, the total administered vaginal dose per year is equivalent to just a single dose of systemic oral therapy. Systemic absorption is minimal and vaginal estrogens are therefore not generally contraindicated, even when systemic HRT is not recommended.

Women with a history of breast cancer who have significant symptoms of urogenital atrophy may consider low-dose vaginal estrogens.[71,90,91] Although there is a theoretical increased risk of recurrence, this is not borne out in the available data.[92] While non-hormonal vulvo-vaginal preparations are preferable in the first instance, for women with severe symptoms there should be joint decision-making between the patient and her oncology team to consider a switch in adjuvant breast therapy and/or vaginal estrogens on an individualised basis.[93] Women on aromatase inhibitors who wish to use vaginal estrogen treatment could consider switching their adjuvant therapy to tamoxifen given that the mode of action of tamoxifen is through estrogen receptor antagonism while aromatase inhibitors exert their effect by lowering total estrogen levels.

Vaginal dehydroepiandrosterone (DHEA) is converted intra-cellularly within the vaginal mucosa to estradiol and testosterone and is contraindicated for breast cancer survivors.[1] Ospemifene is an oral selective estrogen receptor modulator (SERM) which can act similarly to estrogen on the vaginal epithelium, and it is licensed for treatment of moderate-to-severe VVA in postmenopausal women who are not candidates for vaginal estrogen therapy.[94] It is contraindicated in women undergoing active treatment for breast cancer, but it may be used once adjuvant therapy is complete although data are limited.

Testosterone

- **Sexual dysfunction is very common in women who have had treatment for a gynaecological cancer and is often multi-factorial. Access to psycho-sexual services is strongly recommended (Grade D).**
- **Testosterone replacement therapy can be considered, if indicated, for women in whom estrogen replacement has been optimised and other causes have been assessed (Grade D).**
- **Testosterone is only indicated for hypoactive sexual desire disorder, and all products currently available are off-label. There is insufficient evidence to recommend testosterone for other indications, including brain fog and lack of energy (Grade B).**
- **Testosterone should not be offered if estrogen replacement is contraindicated (Grade D).**

Testosterone levels in women decline gradually with age, and there is no sudden change at menopause unless oophorectomy is performed. Sexual dysfunction is very common following treatment for gynaecological cancer. Testosterone levels do not correlate with symptoms. Testosterone supplementation should only be considered in women who complain of low sexual desire after a biopsychosocial approach has excluded other causes, such as relationship, psychological and medication related issues. Testosterone is only indicated for hypoactive sexual desire disorder (HSSD). There is a lack of scientific evidence supporting its use for 'brain fog', cognitive function and tiredness and it should not be prescribed for this indication.[95]

Testosterone should only be considered after a trial of standard HRT and should be prescribed in conjunction with HRT. Whilst some studies have shown benefit on its own this is not recommended. Testosterone is metabolised to estrogen, so it should not be used if estrogen is contraindicated.

The most common side effects are excess hair growth and acne which are reversible with reduction in dosage. Alopecia, deepening of voice and clitoral enlargement are rare with physiological testosterone replacement. Levels should be monitored to ensure systemic levels stay within the physiological range. There are no licensed testosterone products available, so all prescribing is off label. More detail on prescribing and monitoring testosterone for menopausal women is available via the BMS tool for clinicians document on Testosterone Therapy in Menopause.[96]

When to start HRT and duration of usage?

- **When treatment for gynaecological cancer will result in surgical menopause and the tumour type is not hormone-sensitive, discussion regarding HRT should be made before surgery. If the woman wishes to start HRT and there are no contraindications, this should be commenced as soon as clinically appropriate (Grade D).**

- **When provision of HRT is complex and/or controversial, the decision to start HRT should wait until the histology is known, full staging has been achieved and a plan for any additional treatment has been made (Grade D).**
- **In the context of a potentially hormone-sensitive cancer, such as ER-positive endometrial cancer, the final pathology is required before considering HRT. There may also be an advantage to delaying further in peri-menopausal and older women, to evaluate the need for HRT to treat menopausal symptoms (Grade D).**
- **Women who are receiving chemotherapy or radiotherapy can be commenced on HRT during treatment, provided there are no contraindications (Grade D).**
- **Maintaining HRT compliance is necessary to minimise the detrimental consequences of premature ovarian insufficiency (Grade D).**
- **If HRT is prescribed, the medication should be used for as long as the benefits outweigh the risks for the individual woman (Grade A).**
- **HRT in younger women replaces ovarian hormones that would normally be produced at this age and should be continued at least until the age of natural menopause (Grade A).**
- **If vaginal estrogen therapy is appropriate, this therapy can be started once the vagina has healed from any surgical intervention and there is no time-limit on its use (Grade B).**

The decision whether to take HRT, the dose of HRT and the duration of its use should be made on an individualised basis after discussing the benefits and risks with each patient. NICE guidance recommends that women who are likely to go through menopause as a result of medical or surgical treatment (including women with cancer, at a high risk of hormone-sensitive cancer or having gynaecological surgery) should be offered support and information about menopause and fertility before they have their treatment, and referral to a healthcare professional with expertise in menopause.[2]

When bilateral oophorectomy results in surgical menopause, symptoms start very soon after surgery and commencing HRT will prevent symptoms from the outset. In cases where the tumour type is not hormone-sensitive, the decision regarding HRT can be made before surgery. If the woman wishes to start HRT and there are no contraindications, this can be started before discharge from hospital and/or a recommendation to the GP should accompany the discharge summary.

When the decision about commencing HRT is complex and/or controversial the decision to start HRT should wait until the histology is known, full staging has been achieved and a plan for any additional treatment has been made.

Duration of treatment

If HRT is prescribed, the medication should be used for as long as the benefits outweigh the risks for the individual women taking into account the tumour prognosis, symptom relief, beneficial long-term effects versus the potential for increased risk of recurrence or a new primary including breast cancer. Arbitrary limits should not be placed on the duration of usage of HRT.

HRT in younger women is thought to simply replace ovarian hormones that would normally be produced at this age, and years of HRT exposure should be counted from age of natural menopause with respect to breast cancer risk. The average age at natural menopause is around 51 years in Caucasian women but may be a bit earlier in women from other ethnic backgrounds.[97] The Collaborative Group on Hormonal Factors in Breast Cancer concluded that for women under the age of 40 there was no increased breast cancer risk. In a worldwide meta-analysis of worldwide epidemiological data, there was insufficient evidence in the 40–45 year group with a reported increase in risk in observational studies, and a slight rise in the age 45–50 year group, but these were not compared with the appropriate control group of age-matched premenopausal women.[98]

HRT in the form of estradiol and micronized progesterone or dydrogesterone used for 5 years or less in women aged 50 years old or older with no genetic predisposition to breast cancer appears to have a neutral effect on breast cancer risk.[78,99]

If vaginal estrogen therapy is appropriate, this can be started once the vagina has healed from any surgical intervention. There is no time-limit to use and no evidence of an increased risk of breast cancer with this treatment.

Non-hormonal options for management of menopausal symptoms

- **Non-hormonal treatment options should be discussed with women who choose not to use HRT, or for whom HRT is less desirable or is contraindicated. This should be revisited at intervals for women who were premenopausal at the time of treatment and in whom HRT would usually be recommended (Grade D).**
- **Women should be informed that several non-hormonal therapies are used to reduce the impact of menopausal symptoms yet none are as effective as estrogen-based therapies (Grade A).**
- **Cognitive behavioural therapy (CBT) should be considered to alleviate vasomotor symptoms, low mood, sleep difficulties or anxiety that arise as a result of the menopause (Grade B).**
- **Phyto-estrogens should be discouraged for women who had hormone-sensitive tumours if formal HRT is contraindicated (Grade D).**

- **St John's Wort should be discouraged due to its drug interactions, especially with chemotherapy or PARP inhibitors (Grade D).**
- **Selective serotonin re-uptake inhibitors, such as paroxetine and citalopram, and serotonin noradrenaline re-uptake inhibitor/selective serotonin re-uptake inhibitors (SSRI-SNRI), such as venlafaxine, can be considered to reduce vasomotor symptoms (Grade A).**
- **For women on tamoxifen, venlafaxine, escitalopram and citalopram can be offered but paroxetine, sertraline and fluoxetine are contraindicated due to cytochrome P450 interactions (Grade D).**
- **Pregabalin and gabapentin are effective alternatives to manage vasomotor symptoms as well as improving sleep and musculoskeletal issues but can be very sedative (Grade A).**
- **Oxybutynin may improve generalised sweating and vasomotor symptoms, but caution should be exercised in the older population due to toxicity profile including cognitive impairment (Grade C).**
- **Neurokinin 3 receptor antagonists can be considered for treatment of moderate-to-severe vasomotor symptoms (Grade A).**
- **Women should be referred to a healthcare professional with expertise in menopause if non-HRT treatments do not improve their symptoms or they have ongoing troublesome side effects (Grade D).**

Healthcare professionals within the oncology team should be encouraged to develop skills and knowledge in non-hormonal options to alleviate menopausal symptoms. This is required to help inform and guide women for whom HRT is contraindicated, or who choose not to use it, as to which options are most likely to be beneficial to them. Services for non-hormonal treatment options including cognitive behavioural therapy should be available, and women should be signposted to these.

Further information and guidance are available in:

⇒ The National Institute for Health and Care Excellence guideline. Menopause: diagnosis and management;[2]
⇒ British Menopause Society Consensus Statement: Non-hormonal-based treatments for menopausal symptoms;[100]
⇒ British Menopause Society Tool for clinicians. Prescribable alternatives to HRT;[101]
⇒ The North American Menopause Society Position Statement on nonhormone therapy.[102]

Lifestyle modifications

Cognitive behavioural therapy (CBT). Cognitive behavioural therapy (CBT) can improve both vasomotor symptom perception and control and reduce stress, sleep problems, low mood, insomnia or anxiety that arise as a result of the menopause (NICE 2019)[103]

Exercise. Randomised clinical trials have reported that exercise-based interventions including yoga and Pilates had limited impact on vasomotor and psychological symptoms. Whilst some international guidelines recommend exercise as part of lifestyle modification at menopause and there are additional health benefits, the evidence does not support exercise as an effective treatment for vasomotor symptoms.[102,104,105]

Weight loss. Observational data indicate that higher body mass index and increasing body fat are associated with more frequent and/or severe vasomotor symptoms. These observations have led to recommendations that weight loss may reduce vasomotor symptoms. This should also be encouraged in overweight postmenopausal women to reduce other adverse health outcomes including diabetes, cardiovascular disease, renal impairment and osteoarthritis.[104]

Avoiding triggers. It is also often recommended that women avoid 'triggers' such as alcohol, spicy foods and hot foods or liquids. No clinical trials have studied the effect of presumed triggers, and the Melbourne Women's Midlife Health Project found no significant association between alcohol intake and vasomotor symptoms.[102]

Acupuncture. Although acupuncture is superior to no treatment or a wait-list control in randomised clinical trials, systematic reviews concluded that acupuncture was not significantly superior to sham acupuncture.[102,106]

Herbal options

Many women seek herbal options to manage menopausal symptoms hoping these will be associated with less side effects. However, evidence for efficacy is very limited and no specific preparation can be recommended. Careful counselling regarding indication, side-effect profile and drug interaction is recommended. Patients who choose to take a herbal treatment should be advised to look for the Traditional Herbal Remedy (THR) stamp validating strength and quality.[100]

Phyto-estrogens should be discouraged for women with hormone-sensitive tumours. In some studies, Black Cohosh has been shown to reduce hot flushes but can be associated with adverse effects such as constipation, arrhythmia, weight gain and abdominal cramps. Additionally, it should be avoided by women taking tamoxifen because it interferes with drug action.[100]

Whilst St John's Wort may be of benefit to relief vasomotor symptoms, it should be discouraged due to its drug interactions, especially with chemotherapy and PARP inhibitors.[107] There are also uncertainties about dose, variation in the nature and potency of preparations and interactions with other drugs including tamoxifen, anticoagulants and anticonvulsants. Ginseng does not appear to be effective for vasomotor symptoms and therefore should not be recommended.[102]

Pharmacological alternatives to HRT

There are multiple prescribable non-hormonal therapies that have been tested in randomised placebo-controlled trials and shown benefits in alleviating vasomotor symptoms, although none are as effective as HRT. These can vary in side effect profiles and patient preference, and potential drug interactions should be considered.[101]

Selective serotonin re-uptake inhibitors (SSRIs) are antidepressants that include paroxetine, fluoxetine and citalopram. Women should be counselled about the negative impact these drugs can have on sexual function. Paroxetine 10 mg once daily is the SSRI with the best evidence for efficacy and is the choice for patients not taking tamoxifen. It is now a licensed treatment for menopausal hot flushes in the USA. Fluoxetine should similarly be avoided in women on tamoxifen. Venlafaxine is a serotonin noradrenaline re-uptake inhibitor/selective serotonin re-uptake inhibitor (SSRI-SNRI). At doses starting from 37.5 mg titrated up to 150 mg per day, it consistently is effective in recent studies with benefit in 20–66% patients. It is the safest option for patients on tamoxifen as it does not interact with cytochrome P450. Escitalopram is another option for those taking tamoxifen.

Pregabalin and gabapentin are effective alternatives to manage vasomotor symptoms as well as improving sleep and musculoskeletal issues. They can improve hot flushes by up to about 66%, and anecdotally women find pregabalin is better tolerated than gabapentin. They may be useful even at doses as low as pregabalin 25 mg twice daily and titrated up as needed. Pregabalin 75–150 mg twice daily showed statistically significant improvement in hot flushes compared with placebo. Gabapentin can be initiated at 300 mg daily increasing up to 300 mg three times daily if needed. In a randomised, cross-over study of venlafaxine versus gabapentin, the different side effect profile resulted in patient preference of 68% for venlafaxine versus 32% favouring gabapentin.[108]

Clonidine has a licenced indication for control of hot flushes in the UK. It has been shown to be modestly more beneficial than placebo but less beneficial than SSRIs, SNRIs, pregabalin and gabapentin, and it can cause significant side effects. It must be withdrawn gradually and is not suitable for patients with hypotension at baseline.

Emerging options. Oxybutynin is an anticholinergic, antimuscarinic medication traditionally used for urinary urge incontinence and overactive bladder. There is recent evidence that oxybutynin is effective at improving generalised sweating and vasomotor symptoms in postmenopausal women taking the medication for overactive bladder.[109] Doses of 2.5 mg or 5 mg twice daily are effective at improving hot flushes, sleep and quality of life and were safe in patients with breast cancer not on cytotoxic treatment.[110] The effect was estimated at 50–77% reduction in hot flush frequency.[111] The most common side effects are dry mouth and urinary difficulties, and these appear to be dose dependent.[110] Long-term use of oral preparations of anticholinergic medications may be associated with cognitive effects and contribute to medication interactions, especially in the elderly population, even in patients without baseline cognitive impairment.[112]

Neurokinin 3 receptor antagonists including fezolinetant and elinzanetant have shown benefit for improving vasomotor symptoms, quality of life and sleep quality.[94,113,114] This non-hormonal approach directly targets the neural mechanism underlying vasomotor symptoms. Two randomised clinical trials with fezolinetant have shown significant benefit compared to placebo, and a systematic review concluded that it compared favourably to other non-hormonal options, and it is now licensed in the UK.[115]

Who should manage menopause and HRT?

- **All healthcare professionals (HCPs) looking after women with gynaecological malignancies should have an understanding of the menopause and know where to signpost women for advice, support and treatment whenever appropriate (Grade D).**
- **Gynaecologists, oncologists and specialist nurses should initiate discussions about menopausal symptoms and management options including HRT in women who have treatment for gynaecological cancers, including chemotherapy or radiotherapy (Grade D).**
- **Assessment of menopausal symptoms should be conducted at each follow-up review or, if agreed via shared care, with ongoing primary care team (Grade D).**
- **Consider recording indications and/or contraindications for HRT within a treatment summary and recommendations for ongoing review or onward referral to specialist menopause services (Grade D).**
- **All HCPs should have access to specialists with expertise in menopause management for advice, support, onward referral and leadership of multidisciplinary education (Grade D).**
- **Although decisions about HRT are often straightforward and can be made in primary and secondary care, some patients have complex needs and access to specialist multi-disciplinary menopause clinics is necessary (Grade D).**

- **Healthcare professionals managing women with gynaecological cancer should demonstrate continuing professional development about management of menopause (Grade D).**

All women should be able to access advice regarding transition through menopause and can be seen in any area of healthcare. All medical and nursing healthcare professionals dealing with women of menopausal age should be familiar with recognising symptoms and signposting for women. A holistic and individualised approach is required, with an emphasis on the importance of accurate, evidence-based patient education.

NICE guidance recommends review at 3 months after commencing treatment to assess efficacy and tolerability and then annually unless there are clinical indications for earlier review including ineffectiveness, side effects or adverse events. There should be clarity about responsibility for ongoing assessment and management if care transitions between secondary and primary care. A treatment summary should include recommendations regarding menopause care which includes any indications or contraindications for HRT or specialist review.

Healthcare professionals managing women with gynaecological cancer should demonstrate continuing professional development about management of menopause.

Further information is available in the following documents:

⇒ BMS Menopause Practice Standards;[116]
⇒ Royal College of Nursing. Nurse Specialist in Menopause. Updated 2022.[117]

Levels of practice

The Royal College of Nurses has produced guidance on the levels of clinical practice that are required to manage women with menopausal symptoms.[117]

Level one: Every healthcare professional should have some understanding of the impact of menopause and know where to signpost women for support and advice.

Level two: Healthcare professionals with a special interest in menopause. National guidelines will be followed, and discussions will include symptoms, medication and non-prescribed therapies. Local pathways should be developed with routes to specialist-level menopause services for further advice or referral.

Level three: The menopause specialist will have additional knowledge and skills for assessing and treating women with complex needs. They are also responsible for provision of local education and engaging with multidisciplinary teams across specialities with development of local pathways and guidelines.

Indications for specialist menopause referral

Criteria for referral to (or seeking advice from) a specialist menopause service include the following:[116]

◊ premature ovarian insufficiency (POI);
◊ women with high-risk cancer gene variants;
◊ women with menopausal symptoms and contraindications to HRT;
◊ multiple treatment failure and poor symptom control;
◊ persistent side-effects;
◊ complex medical history;
◊ past hormone-dependent cancer;
◊ other related issues where it is felt specialist input is required.

Bone health and monitoring (whether on HRT or not)

- **Baseline bone mineral density testing with a DEXA scan, or FRAX scoring with DEXA scanning depending on the risks, should be considered for premenopausal women with treatment-induced menopause or women commenced on aromatase inhibitors (Grade B).**
- **Baseline 25-OH vitamin D level measurement or blanket vitamin D supplementation of 1000 IU/day should be considered for women at a higher risk of bone loss (Grade B).**
- **Weight-bearing exercise, smoking cessation, reduced alcohol intake and adequate dietary calcium intake should be encouraged (Grade C).**
- **For women under 50, HRT is recommended for prevention of bone loss, if not contraindicated (Grade D).**

Women with gynaecological cancer are at an increased risk of bone loss due to the combined effects of oophorectomy and adjuvant therapies.[118–121] Data on bone loss in women with gynaecological cancer is lacking compared to other cancer populations. Consequently, guidelines for osteoporosis screening in women with cancer are largely based on data generated from non-gynaecological cancer survivors.[122]

Estrogen deficiency is the major cause of accelerated bone loss. Studies showed that estrogen deprivation in women with breast cancer accelerates bone turnover leading to a decrease in bone mineral density (BMD) and a 40%–50% increase in fracture incidence.[123] A Cochrane review which included data from 19 trials ($n = 42{,}830$) showed a significant reduction in risk of any fracture with women taking estrogen-only HRT (RR 0.73, 95% CI 0.65 to 0.80) and combined HRT (RR 0.78, 95% CI 0.71 to 0.85).[124] Additionally, pelvic radiotherapy has a deleterious effect on bone mineral density and is associated with an increased incidence of insufficiency fractures.[119,120]

It is important to consider bone health at diagnosis of gynaecological cancer and during ongoing care. NICE clinical

guideline CG146 on assessing the risk of fragility fracture recommends measuring bone mineral density (BMD) with dual-energy X-ray absorptiometry (DEXA) before starting treatments that may have a rapid adverse effect on bone density.[125] Similarly, the European Society for Medical Oncology (ESMO) practice guidelines on bone health in cancer and the American Society of Clinical Oncology (ASCO) practice guideline on management of osteoporosis in survivors of adult cancers with nonmetastatic disease also suggest that the measurement of BMD should be considered for all premenopausal patients with treatment-induced menopause or ovarian suppression, and women commenced on aromatase inhibitors for cancer treatment, especially where there are additional risk factors.[123,126]

Bone mineral density assessment

Dual-Energy X-ray Absorptiometry (DEXA) is the most reliable assessment for BMD, and the amount of ionising radiation used is very small. While DEXA is considered the 'gold standard' method of BMD measurement, it has limitations, including large size of the equipment, high cost and limited availability. Also when repeat measurements are indicated, intervals of several years are required based on the limitations of DEXA for measuring small changes in BMD.[127] Therefore, clinicians may use a risk assessment tool such as the WHO Fracture Risk Assessment Tool (FRAX) to quantify the risk estimates for osteoporotic fracture in adult patients with cancer. To date, existing risk assessment tools have not been validated in patients with cancer, and clinical judgment is necessary for interpreting results from these tools.[126]

There is no clear consensus on how often the DEXA scan should be repeated.[127–129] The British Menopause Society recommendation on premature ovarian insufficiency and Scottish intercollegiate Guideline Network (SIGN) on managing osteoporosis and fragility fracture prevention suggest that the frequency of repeat bone density assessment should be guided by the woman's risk for developing osteoporosis, and consideration should be given to repeat bone mineral density assessment in women with osteoporosis within 2–3 years of the diagnosis.[130,131]

Women who are not on HRT and who are prescribed a drug that causes bone loss or whose baseline or subsequent BMD is near the threshold of treatment using FRAX should be offered BMD testing every 2 years, or more frequently if deemed medically necessary. Testing should generally not be conducted more than annually.[123,126]

Lifestyle modification

There are a number of modifiable risk factors associated with fracture risk that are of potential relevance to women with premature menopause. Cigarette smoking negatively affects bone quality and increases fracture risk.[132,133] Data from the Nurses' Health Study on alcohol consumption and health outcomes found that chronic alcohol use is associated with low bone density and a high risk of fracture.[134]

Data for exercise in survivors of cancer are conflicting as to the preservation of BMD.[135] A meta-analysis in women who were treated for breast cancer supports the findings of preserved bone health among premenopausal but not postmenopausal women.[136] Nonetheless, exercise is recommended by relevant guidelines because of its known benefits in the maintenance of overall health, including improved sleep, mood, fitness and a reduction in the risk of cancer recurrence and/or certain new cancers.[123,126,127,131]

Vitamin D and calcium

Vitamin D levels are typically low in patients with cancer. Measurement of plasma 25(OH)D is the best way of estimating vitamin D status, and a baseline level should be considered when starting any cancer therapy that is associated with bone loss including pelvic radiotherapy, premature ovarian insufficiency below 40 years old or when the first DEXA scan shows osteopenia or osteoporosis.[126] However, in most cases, routine vitamin D testing is unnecessary and women can be advised to take vitamin D supplementation with 1000 iu/day.[137]

Adequate calcium intake in the presence of adequate vitamin D status has been shown to reduce bone loss in peri- and postmenopausal women and reduce fractures in postmenopausal women older than age 60 with low calcium intakes.[138–140] Patients should be encouraged to consume a diet with adequate calcium and vitamin D. If intake of calcium (1,000 to 1,200 mg/d) and vitamin D (at least 800 to 1,000 IU/d) is not being consumed, then supplements to reach those levels are recommended.[123,126,138]

Key messages

Key messages for commissioners

- Women with complex menopausal symptoms or decision-making regarding HRT require ready access to specialist menopause services.
- All healthcare professionals should have access to specialists with expertise in menopause management for advice, support, onward referral and leadership of multidisciplinary education.
- Although decisions about HRT are often straightforward and can be made in primary and secondary care, some patients have complex needs and access to specialist MDT menopause clinics is necessary.

Key messages for primary care

- A gynaecological malignancy is not an automatic contraindication to HRT.

- Women with treatment-induced premature ovarian insufficiency are at an increased risk of osteoporosis and reduced overall survival from other causes; HRT should therefore be considered.
- Women with a uterus following treatment (e.g. chemoradiotherapy for cervical cancer) will need a continuous combined HRT preparation to reduce the risk of abnormal bleeding and later development of endometrial cancer.
- Vaginal estrogen is safe for the majority of women after treatment for a gynaecological malignancy.
- Women should be asked about menopausal symptoms at their follow-up appointments.

Key messages for secondary and tertiary care

- All healthcare professionals looking after women with gynaecological cancers should have an awareness of menopause management and the options for HRT, especially in women with premature ovarian insufficiency.
- Treatment-induced menopause should be discussed with pre- and peri-menopausal women prior to treatment and options for HRT considered, if recommended or required.
- Women should be asked about menopausal symptoms at hospital follow-up appointments. Health services should have access to specialist menopausal clinics for help with management of complex patients.

Key messages for patients

- A gynaecological malignancy is not an automatic contraindication to HRT, and there are potential benefits for many women.
- Premenopausal women should ask about treatment-induced menopause when oncological treatment options are being considered, and about the options for HRT or alternatives after treatment.

Suggested priority topics for research

- Safety of HRT following endometrial cancer treatment. Is there a survival advantage to continuous combined HRT versus estrogen only and what is the optimal timing to start treatment?
- Safety and efficacy of HRT following ovarian cancer treatment.
- Inclusion of HRT usage in databases of patients treated for rare tumours.

Further Resources

- British Menopause Society https://www.thebms.org.uk.
- National Institute of Care and Excellence https://www.NICE.org.uk.
- Daisy Network https://www.daisynetwork.org.uk.
- Rock my menopause https://rockmymenopause.com/.
- Menopause Matters https://www.menopausematters.co.uk.
- Women's Health Concern https://www.womens-health-concern.org.
- Primary Care Women's Health Forum https://pcwhf.co.uk/.
- Menopause education for nurses https://www.themenopausecourse.com.
- Faculty of Sexual and Reproductive Healthcare https://www.fsrh.org.

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Appendix

Appendix 1

Risk groups for endometrial cancer as defined in the ESGO-ESTRO-ESP 2021 guidelines based on FIGO 2009 staging.[34]

Risk group	Molecular classification unknown	Molecular classification known
Low	· Stage IA endometrioid + low-grade* + LVSI negative or focal	· Stage I-II POLEmut endometrial carcinoma, no residual disease · Stage IA MMRd/NSMP endometrioid
Intermediate	· Stage IB endometrioid + low-grade* + LVSI negative or focal · Stage IA endometrioid + high-grade* + LVSI negative or focal · Stage IA non-endometrioid** without myometrial invasion	· Stage IB MMRd/NSMP endometrioid carcinoma + low-grade* + LVSI negative or focal · Stage IA MMRd/NSMP endometrioid carcinoma + high-grade* + LVSI negative or focal · Stage IA p53abn and/or non-endometrioid** without myometrial invasion
High-intermediate	· Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion · Stage IB endometrioid high-grade*, regardless of LVSI status · Stage II	· Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion · Stage IB MMRd/NSMP endometrioid carcinoma high-grade*, regardless of LVSI status · Stage II MMRd/NSMP endometrioid carcinoma
High	· Stage III-IVA with no residual disease · Stage I-IVA non-endometrioid** with myometrial invasion, and with no residual disease	· Stage III-IVA MMRd/NSMP endometrioid carcinoma with no residual disease · Stage I-IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease · Stage I-IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced	· Stage III-IVA with residual disease	· Stage III-IVA with residual disease of any molecular type
Metastatic	· Stage IVB	· Stage IVB of any molecular type

*** As per binary FIGO classification (Grade 1/2 = low; Grade 3 = high)**

**** includes serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed**