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Clinical Practice Statement

Hormone therapy (HT) in women with gynecologic cancers and in women at high risk for developing a gynecologic cancer: A Society of Gynecologic Oncology (SGO) clinical practice statement☆,☆☆
This practice statement has been endorsed by The North American Menopause Society

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HIGHLIGHTS

- Treatment or prevention of gynecologic cancer often results in induced menopause significantly impacting quality of life.
- Hormone therapy is underutilized in in these settings despite more severe symptoms with induced menopause.
- The risk/benefit profile of HT is favorable in most EOC, early stage endometrial, and cervical cancer.
- HT is not recommended in women with advanced EC, uterine sarcoma, endometrioid or low grade serous ovarian cancer.
- Lynch syndrome patients and *BRCA* mutation carriers without history of breast cancer may also use HT to improve QOL.

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1. Introduction

Approximately 40% of women with gynecologic malignancies are pre- or perimenopausal at the time of diagnosis [1,2]. Combined multimodality therapy including surgery, chemotherapy and/or radiation often results in induced menopause. The Society of Gynecologic Oncology and NCCN recommend prophylactic risk reducing surgery between ages 35–45, or at the completion of child bearing, depending on the specific germline mutation for women with Lynch syndrome, *BRCA*1 or *BRCA*2 mutations [3–5]. Induced menopause is defined by The North American Menopause Society as the cessation of menstruation following bilateral oophorectomy or iatrogenic ablation of ovarian function due to chemotherapy or pelvic radiation [6]. Compared with natural menopause, acute induced menopause results in a more rapid onset of the hypoestrogenic state and is associated with more severe menopause symptoms and a higher negative impact on quality of life [7,8]. These include vasomotor symptoms [9], genitourinary syndrome of menopause (GSM) with associated sexual and urinary dysfunction [10], premature bone loss, and increased cardiovascular risk [11,12]. Systemic and local hormone therapies (HT) are the most effective treatments for menopause symptoms [6,13–16] but are persistently underutilized in this patient population. The aim of this practice statement is to clarify the use of hormone therapy in women affected by uterine, ovarian (including fallopian tube and primary peritoneal cancer), and cervical cancer and in patients who are at an increased genetic risk of these cancers (Table 1). The use of HT in women with a history of breast cancer is beyond the scope of this paper, except as it pertains to women with a *BRCA1* or *BRCA2* mutation.

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Table 1
Recommendations for hormone therapy in gynecologic cancer survivors.

	Recommendation	Selected articles	Notes
Uterine cancer			
Early stage endometrial cancer	HT acceptable	1. (18) Barakat et al. JCO 2006 2. (19) Shim et al. Eur J Cancer 2014	1. 1236 patients, stage I–II EC randomized to HT vs placebo. Closed early due to WHI results. No difference in recurrence rate (2.3% vs1.9% NS) 2. Meta-analysis - no increased risk of recurrence in EC survivors who receive HT
Advanced stage endometrial cancer	HT not recommended		
Uterine sarcoma	HT not recommended		
Ovarian cancer			
High grade serous ovarian cancer	HT acceptable	1. (26) Guidozzi et al. Cancer 1999 2. (28) Eels et al. JCO 2015	1. RCT; 130 patients < 59 years old randomized to HT or placebo, no difference in PFS or OS. 2. RCT; 150 patients randomized to HT vs placebo OS improved in patients HT arm (hazard ratio, 0.63; 95% CI, 0.44 to 0.90; P = .011)
Low grade serous and endometrioid ovarian cancer	HT not recommended		
Cervical cancer			
	HT acceptable	(36) Polch et al. Gynecol Oncol 1987	Prospective study, 120 patients, no difference in recurrence rate with use of HT

2. Hormone therapy in uterine cancer survivors

Endometrial cancer (EC) is often diagnosed at an early-stage, with 25% of patients being premenopausal at the time of diagnosis [2]. EC is commonly estrogen receptor positive and providers have been reluctant to prescribe HT to EC survivors due to the theoretical risk of promoting recurrence [17]. In a prospective, randomized, controlled, double blind clinical trial [18], 1236 patients with stage I-II EC were followed for a median of 35.7 months after being treated with a hysterectomy and bilateral oophorectomy. Of the 618 assigned to systemic estrogen therapy (ET), 14 (2.3%) developed disease recurrence, compared to 12 of 618 (1.9%) in the placebo group (HR 1.27; 80% CI, 0.916 to 1.77). This study closed prematurely without meeting its target accrual following the results of the Women's Health Initiative Trial; however, authors concluded that the overall absolute cancer recurrence rate was low (2.1%) in this low-risk population followed for a median of three years. A meta-analysis that included this trial in addition to 5 observational studies, demonstrated no significant increase in risk of EC recurrence among survivors who received ET [19]. A Cochrane review concluded that there was insufficient high-quality evidence to inform decisions on HT in EC survivors, but existing limited data do not appear to suggest significant harm in early-stage, low-risk patients [20]. Based on available evidence, use of ET in patients with early-stage EC (I-II) is reasonable and should be individualized in patients experiencing significant menopause symptoms following appropriate counseling regarding risks and benefits of HT. This is particularly true in women who have undergone early bilateral oophorectomy and are at higher risk of adverse health consequences related to estrogen loss. Of note, ovarian preservation at the time of hysterectomy for stage I endometrial cancer had no effect on cancer-specific (hazard ratio [HR] = 0.58; 95% CI, 0.14 to 2.44) or overall (HR = 0.68; 95% CI, 0.34 to 1.35) survival in an analysis of Surveillance, Epidemiology, and End Results Database [21]. Furthermore, the 2019 NCCN guidelines state that "ovarian conservation may be safe in select women with early stage endometrioid cancer" [22]. There are no data supporting hormone use in late stage EC (Stage III-IV), and therefore, ET is not recommended. In this group of patients, tested and effective non-hormone therapies are available for vasomotor symptoms and prevention of bone loss. On the other hand, some uterine sarcomas including both leiomyosarcomas and endometrial stromal sarcomas express estrogen and progesterone receptors and are known to respond to anti-estrogen therapy [23,24]. Given the lack of data regarding the safety of HT in this setting and potential response to antiestrogen therapy, systemic HT for uterine sarcomas, particularly those which express hormone receptors is not recommended.

3. Hormone therapy in ovarian, fallopian tube, and primary peritoneal cancer survivors

A significant proportion of women diagnosed with ovarian cancer will be pre-or perimenopausal and will develop bothersome menopausal symptoms after cytoreductive surgery. Multiple randomized and observational studies dispel the concerns regarding the oncologic safety of oral, systemic HT in this patient population [25–27]. In a randomized, non-blinded, controlled clinical trial, Eeles et al. demonstrated an improved overall and relapse free survival in ovarian cancer patients randomized to ET versus those randomized to routine care [28]. The patients included in this trial included all histologies (39% serous, 15% mucinous, 11% clear cell, and 10% endometrioid) and were followed for a median of 19 years. A subsequent meta-analysis did not demonstrate an association between estrogen use and an increased risk of death in patients with ovarian cancer [29]. Based on these data, ET can be prescribed for women with epithelial ovarian cancer. There is lack of data as it pertains to specific subsets of epithelial ovarian cancer, however given that low grade serous and endometrioid ovarian cancer may respond to treatment with anti-estrogen therapies [30,31], HT is not recommended. There is insufficient data to make a recommendation regarding HT in women with a history of borderline tumors of the ovary. In a prospective study that included 150 women with borderline ovarian tumors, HT (estrogen alone or estrogen and progesterone (EPT)) did not significantly impact 5 year overall survival [25].

4. Hormone therapy in cervical cancer survivors

HT is underutilized in cervical cancer patients despite 40% of newly diagnosed women being under the age of 45 [32,33]. Cervical cancer is not considered a hormonally responsive cancer and estrogen/progesterone receptor positivity has no prognostic significance in this population [34]. Ovarian conservation is recommended in premenopausal women with squamous cell carcinoma of the cervix to prevent induced menopause, as the incidence of ovarian metastasis is <2% [35]. In a prospective study of 120 women with stage I–II cervical cancer treated surgically or with radiation, no difference in recurrence rates or overall survival was identified in patients receiving HT (ET or EPT) vs placebo after follow up of 5 of more years [36]. Combination estrogen and progestogen (progestin or progesterone) therapy, or the combination of conjugated estrogen

Table 2
Recommendations for hormone therapy in women at high risk for developing gynecologic cancer.

	Recommendation	Selected articles	Notes
BRCA mutation with no personal history of breast cancer	HT acceptable	(44) Kotsopolus et at. JAMA Oncol 2018	Prospective cohort 872 *BRCA* mutation carriers post prophylactic oophorectomy. No increased risk of breast cancer with HT use: HR 0.97 (95% CI, 0.62–1.52; P = .89). Patients treated with progesterone containing HT had a significantly higher rate of breast cancer versus estrogen only regimens (12% vs 22% p = .04)
BRCA mutation with personal history of breast cancer	HT not recommended	(49) Holmbert et al. JNCI 2008	RCT; 221 women with a personal history of breast cancer. Patients treated with HT had a significantly increased risk of a new breast cancer event: HR 2.4 (95% CI 1.3–4.2)
Lynch syndrome	HT acceptable	1. (52) Symer et al. Clin Colorectal Cancer, 2018 2. (53) Dashati et al. JAMA 2015	1. Prospective cohort of the PLC Reduction in colon cancer risk in general population with HT (0.81; 95% confidence interval [CI], 0.69–0.94; P = .005) 2. Women with Lynch syndrome can be counseled similar to the general population regarding the use of HT

with the selective estrogen reuptake inhibitor bazedoxifene (a progestogen free combination therapy) [37] should be used for women treated by primary chemotherapy and radiation without hysterectomy as endometrial tissue has been shown to persist despite radiation [38]. HT is safe in women with cervical cancer and should be offered to cervical cancer patients with induced menopause. HT can also be considered as an alternative to ovarian transposition if the latter is considered for hormonal preservation only.

5. Hormone therapy in women at an increased genetic risk of gynecologic cancer

For women with known pathogenic *BRCA* mutations, risk reducing bilateral salpingo-oophorectomy between ages 35–45 or upon completion of childbearing, is recommended for cancer risk reduction [3–5]. The ensuing surgical menopause often has a negative impact on long-term health, survival, and quality of life [39–42]. Although HT is effective at alleviating menopausal side effects, patients and physicians are often wary of its use due to perceived risks of cancer promotion. For *BRCA* mutation carriers without a personal breast cancer history who have undergone a bilateral prophylactic oophorectomy, short term HT may improve quality of life and increase life expectancy without negating the protective effects of the oophorectomy on subsequent breast cancer risk [43–47]. In a prospective, longitudinal cohort study, including 872 *BRCA*1 mutation carriers followed for a mean of 7.6 years ever use of any HT (ET or EPT) was not associated with an increase in the incidence of breast cancers compared to never users (10.3% versus 10.7%, P = .89). ET use in women with a previous hysterectomy resulted in a notable, but not statistically significant, 8% reduction in breast cancer per year of use [44]. This reduction is consistent with findings reported in the general population within the estrogen alone trial of the WHI [48]. Duration and optimal treatment combination for women with an intact uterus remain unanswered questions. Patients must be counseled on the need for protection of the intact uterus with progesterone when systemic estrogen therapy is used, and consider the role of hysterectomy at the time of RRSO to simplify hormonal therapy.

HT should be avoided in *BRCA* mutation carriers with a history of hormone dependent breast cancer due to the increased risk of recurrence [43–47,49]. In a randomized, open-label noninferiority trial that enrolled women with a personal history of breast cancer, the hazard ratio for recurrence in patients randomized to HT (ET or EPT) for menopause symptom management was 2.4 (95% CI 1.3–4.2) [49]. Caution is recommended even in those with triple negative breast cancer due to theoretical increased risk of recurrent or new breast cancers. A recent review by Gorhandas et al. provides a comprehensive, systematic review of risk and benefits of HT including quality of life, sexual function, bone health, cardiovascular health and cognitive risk, as well as breast cancer risk [50].

For women with mismatch repair mutations who have undergone a prophylactic hysterectomy and bilateral salpingo-oophorectomy, estrogen alone therapy can be considered for relief of menopause symptoms given the associated risk reduction in colon cancer incidence demonstrated in the Women's Health initiative [51,52]. A secondary analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial which included average risk individuals, found a reduced risk of colorectal cancer incidence and improved colorectal cancer-specific survival, as well as a reduction in all-cause mortality, in current HT users when compared with never users (the specific type of HT estrogen alone vs combination therapy was not specified) [53]. Of note, 47.1% of the current user group in this study had undergone a hysterectomy. For women with an intact uterus, there are no compelling data to guide clinical practice for the use of hormone therapy however, these patients should not receive unopposed estrogen therapy due to known increased risk of endometrial cancer with unopposed estrogen therapy [44,54] (Table 2). There is a lack of mature data on the role of HT in women with genetic mutations identified via newer expanded panels.

6. Summary statement

Despite being the most effective treatment modalities for menopause symptoms, systemic and local hormone therapy are consistently underutilized in women with personal history or at high risk for developing a gynecologic cancer. Despite a lack of Level I evidence, the risk/benefit profile of HT appears to be favorable in many women with a personal history of high grade serous ovarian cancer (Level II evidence), early stage endometrial cancer (Level II evidence), and cervical cancer (Level III evidence). *BRCA* mutation carriers who do not have a personal history of breast cancer and women with Lynch syndrome may also use HT to alleviate symptoms of early menopause (Level III evidence). HT is not recommended in women with advanced endometrial cancer, uterine sarcoma, endometrioid ovarian cancer or low grade serous ovarian carcinoma. Furthermore, *BRCA* carriers with a personal history of hormone receptor positive breast cancer should avoid use of HT.

Declaration of competing interest

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Drs. Sinno, Febbraro, Jones, Khanna, Temkin, Iglesias and Pothuri report no conflict of interest.

All authors contributed equally to this practice statement.

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