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Vaginal estrogen use for genitourinary symptoms in women with a history of uterine, cervical, or ovarian carcinoma

Laura M Chambers,[1] Alyssa Herrmann,[2] Chad M Michener,[1] Cecile A Ferrando,[3] Stephanie Ricci[4]

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[1]Division of Gynecologic Oncology, Cleveland Clinic Foundation, Cleveland, Ohio, USA
[2]Women's Health Institute and Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, Ohio, USA
[3]Department of Urogynecology, Cleveland Clinic, Cleveland, Ohio, USA
[4]Gynecologic Oncology Division, Ob/Gyn and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Dr Laura M Chambers, Division of Gynecologic Oncology, Cleveland Clinic Foundation, Cleveland, OH 44195-5243, USA; chambel2@ccf.org

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HIGHLIGHTS

- Genitourinary symptoms including dyspareunia and vaginal dryness are prevalent among gynecologic cancer survivors.
- Cancer recurrence following vaginal estrogen use is low.
- Vaginal estrogen may be considered safe in gynecologic cancer survivors.

ABSTRACT

Objective Menopausal symptoms may adversely affect quality of life and health in women diagnosed with a gynecologic malignancy. The aim of this study was to determine the incidence of adverse outcomes, including cancer recurrence, venous thromboembolism, and secondary malignancies, among patients with a history of endometrial, ovarian, or cervical cancer prescribed vaginal estrogen for genitourinary syndrome of menopause.

Methods A retrospective cohort study was performed including women who were diagnosed with endometrial, ovarian, or cervical cancer from January 1, 1991 to December 31, 2017 and subsequently treated with vaginal estrogen for genitourinary syndrome of menopause. Patients were included if not undergoing active cancer treatment and were disease-free based on most recent cancer surveillance visit with physical exam and/or imaging. Demographics, oncologic variables, estrogen use, and adverse outcomes were recorded. Descriptive statistics and univariate analysis were performed.

Results Of 244 women who received vaginal estrogen, 52% (n=127) had a history of endometrial, 25.4% (n=62) cervical, 18.9% (n=46) ovarian cancer, and 3.7% (n=9) low malignant potential tumors. The mean age and body mass index were 55.5±12.5 years and 29.2±8.6 mg/kg^2, respectively. With a median follow-up of 80.2 months, the incidence of recurrence for endometrial, ovarian, and cervical cancer was 7.1% (n=9), 18.2% (n=10), and 9.7% (n=6), respectively. In patients with endometrial cancer who recurred, the incidence was 2.4% (n=3) for stage I/II and 4.7% (n=6) for stage III/IV disease. Similarly, recurrence rates for ovarian cancer were 4.3% (n=2) for stage I/II and 17.4% (n=8) for stage III/IV disease. All cervical cancer recurrences were in patients with stage I/II disease. Adverse outcomes including breast cancer (1.6%, n=4), secondary malignancy (2.5%, n=6), and venous thromboembolism (2.5%, n=6) were rare.

Conclusion In women with a history of endometrial, ovarian, or cervical cancer prescribed vaginal estrogen use for genitourinary syndrome of menopause, adverse outcomes, including recurrence and thromboembolic events, are infrequent. Vaginal estrogen may be considered safe in gynecologic cancer survivors.

INTRODUCTION

Of the 100 000 women diagnosed annually with gynecologic cancer, up to 40% of diagnoses are made prior to menopause.[1 2] The treatment of gynecologic cancer utilizes a multimodal approach including surgery, chemotherapy, and/or radiation. Unfortunately, these therapies often lead to menopausal symptoms which can adversely affect quality of life and health.[3 4] Management of such symptoms, including genitourinary symptoms, is an important aspect of gynecologic cancer patient care. Among gynecologic cancer survivors, genitourinary syndrome of menopause, including dyspareunia and vaginal dryness, is prevalent.[5–11] In a study of endometrial cancer survivors by Onujiogu et al, the incidence of sexual dysfunction was 89%.[5] Similarly, compared with controls, patients with cervical cancer had higher reported levels of sexual dysfunction and worse quality of partner relationships following surgery.[8]

Evidence to guide systemic and local hormone therapy for the management of menopausal symptoms in women with a history of gynecologic cancer is limited. Evidence-based management can be challenging due to concerns for disease recurrence and side effects. To date, one randomized trial by the Gynecologic Oncology Group has investigated the safety of systemic estrogen in patients with a history of stage I or II endometrial cancer.[12] Despite early closure of the study following publication of Women's Health Initiative data, there were no differences in rate of recurrence between patients receiving hormone replacement therapy (n=618) compared with controls (n=618) (1.5% vs 1.3%).

Vaginal estrogen therapy is one of the most effective treatments for genitourinary syndrome of menopause.[13–17] In the general population, vaginal estrogen has been proven safe and efficacious.[15 17] Furthermore, in women with breast cancer, including estrogen receptor-positive tumors, vaginal estrogen use does not increase risk of recurrence.[18 19] To date,

use of vaginal estrogen in women with a history of gynecologic cancer has not been studied. Given the high incidence of genitourinary syndrome of menopause among gynecologic cancer survivors and concerns for safety of systemic therapy, further investigation is needed to determine the safety of vaginal estrogen therapy.

The objective of this study was to determine the incidence of adverse outcomes, including cancer recurrence, venous thromboembolism, and secondary malignancies, among women with a history of endometrial cancer, cervical cancer, or ovarian cancer survivors receiving vaginal estrogen for genitourinary syndrome of menopause.

METHODS

This was an Institutional Review Board approved, multicenter, single institution, retrospective cohort study of all women with a diagnosis of endometrial, cervical, or ovarian cancer from Jaanuary 1, 1991 to December 31, 2017 who received treatment with vaginal estrogen for genitourinary symptoms of menopause following their cancer diagnosis. Patients included in the study were not undergoing active cancer treatment and were considered disease-free based on their most recent cancer surveillance visit with physical exam and/or imaging by their gynecologic oncologist. Subjects were identified from the electronic medical record by International Classification of Diseases - 10 codes for uterine (C54, 55), ovarian (C56, 57), or cervical cancers (C53). Among women identified with ovarian neoplasms, those with ovarian tumors of low malignant potential or borderline tumors were grouped separately. Subsequently, pharmacy records were reviewed for patients who had been prescribed vaginal estrogen (conjugated estrogen cream, estradiol cream, estradiol tablet, estradiol ring insert) with at least 1 month's supply. Patients who received vaginal estrogen before diagnosis only were excluded. Patients with a history of gynecologic cancer who had received cancer-related treatment at an outside institution with incomplete records were excluded.

The medical records were reviewed for patient demographics, oncologic treatments including surgical procedures, chemotherapy, and radiation therapy, genitourinary symptoms and use patterns of vaginal estrogen and adverse outcomes. Outpatient clinic and inpatient encounter notes were reviewed for reported vulvovaginal symptoms and the initiation date of vaginal estrogen. Medication reports were reviewed for use of concurrent therapies for vulvovaginal symptoms and/or vasomotor symptoms.

The preparation of vaginal estrogen (conjugated estrogen, estradiol cream, estradiol tablet, estradiol ring), dose and frequency were recorded, along with the date of treatment initiation and cessation. Inpatient encounters and outpatient clinic visits were reviewed for patient-reported or provider-noted improvement or worsening in symptoms. Serum estrogen levels were noted during treatment, where available. All data were stored electronically using REDCap.[20]

Categorical variables are presented as n/N (%) with 95% confidence intervals (95% CIs). Continuous variables are presented as mean ± standard deviation (SD) or median (range). The Student t-test was used for parametric continuous outcomes, the Mann-Whitney U-test for non-parametric outcomes, and the Chi square test for all categorical outcomes. Associations between outcomes were measured using Pearson correlation. All tests were considered significant at the $p<0.05$ level. JMP 13.0 was used for all statistical analyses.

RESULTS

Patient Demographics

Of the 244 women included in the final analysis, 52.0% (n=127) had a history of endometrial cancer, 25.4% (n=62) cervical cancer, 18.8% (n=46) ovarian cancer, and 3.6% had (n=9) ovarian tumors of low malignant potential. Patient demographics are displayed in Table 1. The mean age at diagnosis was 55.5±12.5 years, and was significantly higher in those with a history of endometrial cancer (60.9±9.6 ears) compared with those with cervical cancer (48.1±12.0 years), ovarian cancer (55.5±13.1 years), or low malignant potential tumors (42±13.2 years) ($p<0.001$). The mean body mass index was 29.2±8.6 mg/kg^2 for all patients. Among the entire cohort, 80.7% (n=197) had not used either local or systemic hormone therapy prior to their cancer diagnosis; only 10.2% (n=25) had a history of prior vaginal estrogen use for genitourinary syndrome of menopause.

Oncologic Variables and Cancer Treatment

Table 2 displays oncologic variables and cancer treatment details. In patients with endometrial cancer, the majority had endometrioid histology (84.3%, n=107), followed by serous carcinoma (7.1%, n=9), clear cell carcinoma (2.4%, n=3), and carcinosarcoma (3.1%, n=4). The majority of patients had grade 1 (55.1%, n=70) or 2 (18.1%, n=23) histology, stage IA (76.4%, n=97) or IB (10.2%, n=13) disease, and had surgical staging performed (99.2%, n=126). Adjuvant radiation was administered in 35.4% (n=45) of women and 25.9% (n=33) received chemotherapy.

In women with a history of ovarian cancer, high-grade serous (60.9%, n=28) and endometrioid (10.9%, n=5) histologies were the most prevalent; 3.7% (n=9) of the patients had a history of borderline or low malignant potential ovarian tumors. The majority of patients had stage I disease (30.4%, n=14). Approximately three-quarters of the cohort (73.9%, n=34) underwent chemotherapy; carboplatin and paclitaxel were administered most frequently.

In the cervical cancer cohort, 58.1% (n=36) squamous cell carcinoma and 40.3% (n=25) had adenocarcinoma. The majority of patients had stage I disease (74.2%, n=46). Hysterectomy was performed in approximately two-thirds of the patients (64.5%, n=40). The majority of patients received pelvic radiation (64.5%, n=40).

Patient Symptoms and Vaginal Estrogen Usage

Patient-reported symptoms and vaginal estrogen usage patterns are displayed in Table 3. Mean age at prescription was 59.5±13.0 years, without significant differences between cohorts (p=0.18). The median time from completion of cancer treatment to prescription was 2.4 years (range 14 days to 13.1 years). Median duration of use was 488 days or 1.3 years (IQR 194–1287 days). Gynecologic oncologists were the most frequent prescribers of vaginal estrogen (54.1%, n=132). The most common indications for treatment with vaginal estrogen were dyspareunia (41.0%, n=100), vaginal atrophy (38.5%, n=94), vaginal dryness (32.8%, n=80), and/or vaginal pain (20.9%, n=51).

Table 1 Demographic information in gynecologic cancer survivors with history of endometrial, ovarian, and cervical carcinoma

Parameter	All patients (n=244)	Endometrial cancer (n=127)	Cervical cancer (n=62)	Ovarian cancer (n=46)	Ovarian tumors of low malignant potential (n=9)	P value
Age at diagnosis (years)	55.5±12.5	60.9±9.6*	48.1±12.0	55.5±13.1	42±13.2*	<0.001*
BMI (kg/m^2)	29.2±8.6	30.7±8.3	27.6±10.1	27.2±5.9	30.7±9.1	0.06
Smoking status						
Never	193 (79.1)	105 (82.7)	45 (72.6)	35 (76.1)	8 (88.9)	0.04*
Remote history	37 (15.2)	20 (15.7)	9 (14.5)	8 (17.4)	0 (0)	
Active smoker	14 (5.7)	2 (1.6)	8 (12.9)*	3 (6.5)	1 (1.1)	
Medical co-morbidities						
HTN	82 (33.6)	53 (41.7)*	13 (21.0)	14 (30.4)	2 (2.2)*	0.03*
DM	30 (12.3)	21 (16.5)	4 (6.5)	4 (8.7)	1 (1.1)	0.2
CAD	18 (7.3)	10 (7.9)	2 (3.2)	6 (13.1)	0 (0)	0.21
PVD	1 (0.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.82
VTE	9 (3.7)	4 (3.2)	3 (6.5)	3 (5.5)	0 (0)	0.67
Renal disease	9 (3.7)	4 (3.2)	3 (4.8)	2 (4.3)	0 (0)	0.86
Pulmonary disease	14 (5.6)	7 (5.5)	5 (8.1)	1 (2.2)	1 (1.1)	0.53
Breast cancer	7 (2.9)	4 (3.2)	0 (0)	3 (6.5)	0 (0)	0.23
Hematologic malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Other solid organ malignancy	7 (2.9)	3 (2.4)	2 (3.2)	2 (4.3)	0 (0)	0.86
History of HRT						
None	197 (80.7)	92 (72.4)	59 (95.1)*	37 (80.4)	9 (100.0)*	0.001*
Vaginal E	25 (10.2)	16 (12.6)	1 (1.6)*	8 (17.4)	0 (0)*	0.02*
Systemic E+P	16 (6.6)	14 (11.0)*	2 (3.2)	0 (0)	0 (0)	0.03*
Systemic E alone	4 (1.6)	3 (2.4)	0 (0)	1 (2.1)	0 (0)	0.64
Transdermal E	1 (0.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.82
Transdermal E+P	1 (0.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.82
Duration of prior HRT (years)	0.5 (0–6)	0 (0–0.3)	0 (0–0.2)	0 (0–0.4)	N/A	0.30

Statistics presented as n (%). Age and BMI presented as mean±SD. Prior treatment presented as median+IQR.
*Significant at the p<0.05 level.
BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; E, estrogen; HRT, hormone replacement therapy; HTN, hypertension; N/A, not applicable; P, progesterone; PVD, peripheral vascular disease; VTE, venous thromboembolism.

Formulations of local vaginal estrogen prescribed included conjugated estrogen (43.4%, n=106), estradiol cream (35.7%, n=87), estradiol tablets (15.6%, n=38), and ring (7.5 µg) (1.6%, n=4). In those prescribed conjugated estrogen cream 0.625 mg, the majority were prescribed 1 g (n=66, 62.2%) or 0.5 mg (n=40, 37.8%) either two or three times a week. For those prescribed estradiol cream, the majority were prescribed 100 µg/g, 1 g (n=64, 73.5%) or 0.5 g (n=23, 26.4%) two times a week. In those prescribed estradiol tablets, most patients were prescribed 10 µg (n=35, 92.1%) two times a week; three patients (7.9%) were prescribed 25 µg prior to discontinuation. All patients who received the estradiol ring were prescribed 7.5 µg changed every 3 months. Concurrent systemic hormonal therapy (n=27) was administered in 11.1% of patients that included estradiol patch (0.025 mg/day two times a week) (n=18), oral estradiol 0.5 mg (n=2), oral conjugated equine estrogens 0.3 mg (n=4), conjugated estrogens and medroxyprogesterone acetate (n=2), and estradiol spray (1.53 mg/day) (n=1). Use of vaginal dilators was more frequent in patients with cervical cancer (22.6%, n=14) compared with other disease sites (p=0.002).

Symptomatic improvement was documented in approximately one-third of women (29.1%, n=71); however, symptom status remained unknown in 61.1% (n=149). Systemic serum estrogen levels were available for 11 patients in the cohort; in those patients the median estrogen level was 6.0 (range <5–83) pg/mL.

Recurrence and Adverse Outcomes

Table 4 displays adverse outcomes with a median follow-up of 80.5 (IQR 44.9–132.4) months. For all patients, the incidence of recurrence was 10.2% (n=25); specifically, for those with a history of endometrial cancer, ovarian cancer, and cervical cancer recurrence was 7.1% (n=9), 21.7% (n=10), and 9.7% (n=6), respectively

Table 2 Oncologic and treatment characteristics in patients with a history of endometrial, ovarian, and cervical carcinoma

Characteristic	Endometrial cancer (n=127)	n (%)	Ovarian cancer (n=46)	n (%)	Cervical cancer (n=62)	n (%)
Histology	Endometrioid	107 (84.3)	HG serous	28 (60.9)	AC	25 (40.3)
	USC	9 (7.1)	LG serous	1 (2.2)	SCC	36 (58.1)
	UCC	3 (2.4)	Mucinous	3 (6.5)	Other	1 (1.6)
		4 (3.1)	OCC	3 (5.5)		
	Mucinous	1 (0.8)	Granulosa	3 (6.5)		
	LMS	1 (0.8)	Endometrioid	5 (10.9)		
Grade	FIGO 1	70 (55.1)	FIGO 1	4 (8.7)		
	FIGO 2	23 (18.1)	FIGO 2	2 (4.3)		
	FIGO 3	14 (11.0)	FIGO 3	24 (52.2)		
Stage	IA	97 (76.4)	IA	14 (30.4)	IA1	4 (6.5)
	IB	13 (10.2)	IB	0 (0)	IA2	3 (4.8)
	II	0 (0)	IC1	4 (8.9)	IB1	29 (46.8)
	IIIA	3 (2.4)	IC2	0 (0)	IB2	10 (16.1)
	IIIB	0 (0)	IC3	3 (6.5)	IIA	3 (4.8)
	IIIC1	7 (5.5)	IIA	1 (2.2)	IIA1	1 (1.6)
	IIIC2	4 (3.1)	IIB	0 (0)	IIB	5 (8.1)
	IVA	0 (0)	IIC	3 (5.5)	IIIA	1 (1.6)
	IVB	2 (1.6)	IIIA	0 (0)	IIIB	5 (8.1)
			IIIB	3 (6.5)	IVA	0 (0)
			IIIC	15 (32.6)	IVB	0 (0)
			IVA	1 (2.2)		
			IVB	1 (2.2)		
ER status	Positive	9 (8.0)	Positive	0 (0)		
	Negative	3 (2.7)	Negative	10 (21.7)		
	Unknown	115 (90.6)	Unknown	36 (78.3)		
PR status	Positive	6 (5.4)	Positive	1 (2.2)		
	Negative	5 (4.5)	Negative	9 (19.6)		
	Unknown	116 (91.3)	Unknown	36 (78.3)		
Surgery	Age (years)	61.7±21.0	Age (years)	51.9±13.8	Age (years)	49.7±14.8
	LAP	55 (53.3)	LAP	36 (78.3)	LAP	25 (40.3)
	RL	29 (22.8)	RL	3 (6.5)	RL	11 (17.7)
	MPL	30 (23.6)	MPL	7 (15.2)	MPL	5 (8.1)
	SPL	12 (9.4)	SPL	0 (0)	SPL	3 (4.8)
	No surgery	1 (0.80)	No	0 (0)	None	18 (29.0)
Surgical procedures	Hysterectomy	126 (99.2)	Hysterectomy	38 (82.6)	Hysterectomy	40 (64.5)
	P LND	69 (54.3)	P LND	27 (58.7)	P LND	33 (53.2)
	PA LND	44 (34.6)	PA LND	25 (54.3)	PA LND	7 (11.3)
	USO	5 (3.9)	USO	3 (6.5)	USO	2 (3.2)
	BSO	118 (92.9)	BSO	43 (93.5)	BSO	22 (35.5)
RT	Any radiation	45 (35.2)	Any radiation	0 (0)	Any radiation	40 (64.5)
	VBT	41 (32.3)			VBT	34 (54.8)
	Pelvic RT	34 (26.8)			EBRT	39 (62.9)
	Other	1 (0.4)			Other	1 (1.6)

Continued

Table 2 Continued

Characteristic	Endometrial cancer (n=127)	n (%)	Ovarian cancer (n=46)	n (%)	Cervical cancer (n=62)	n (%)
CT	Any CT	54 (42.5)	Any CT	34 (73.9)	Any CT	35 (56.5)
	Carboplatin/ddTaxol	1 (0.8)	Carboplatin/ddTaxol	3 (6.5)	Cisplatin	33 (53.2)
	Carboplatin/q21 Taxol	24 (18.9)	Carboplatin/q21 Taxol	25 (54.3)	Carboplatin/q21 Taxol	2 (3.2)
	Carboplatin/Taxotere	1 (0.8)	Carboplatin/Taxol IP	1 (2.2)		
	Gemcitabine	1 (0.8)	Cisplatin/Taxol IP	3 (6.5)		
	Adriamycin	1 (0.8)	Carboplatin/Gemcitabine	1 (2.2)		
	Bevacizumab	3 (2.4)	Topotecan	1 (2.2)		
	Other	2 (1.8)	Adriamycin	2 (4.3)		
			Bevacizumab	4 (8.9)		
			Cisplatin	1 (2.2)		
			Other	2 (4.3)		

Statistics presented as n (%), except for age which is presented as mean±SD.
AC, adenocarcinoma; BSO, bilateral salpingo-oophorectomy; CS, carcinosarcoma; CT, chemotherapy; EBRT, external beam radiation therapy; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; HG, high-grade; IP, intraperitoneal; LAP, laparotomy; LG, low-grade; LMS, leiomyosarcoma; P LND, pelvic lymphadenectomy; PA LND, para-aortic lymphadenectomy; MPL, multi-port laparoscopy; OCC, ovarian clear cell carcinoma; PR, progesterone receptor; RL, robotic-assisted laparoscopy; RT, radiation therapy; SCC, squamous cell carcinoma; SPL, single-port laparoscopy; UCC, uterine clear cell carcinoma; USC, uterine serous carcinoma; USO, unilateral salpingo-oophorectomy; VBT, vaginal brachytherapy.

(p=0.03). Among women with recurrent endometrial cancer, the majority had advanced stage disease (IIIA: n=2, IIIC1: n=3, IIIC2: n=1) and high-risk histology (serous: n=2, clear cell: n=2, FIGO 3: n=2, carcinosarcoma: n=3). The incidence of recurrence was lower among patients with stage I/II disease (2.4%, n=3) versus stage III/IV (4.7%, n=6). Similarly, among women with recurrent ovarian cancer, the majority had advanced-stage disease (IIIC: n=8) and high-grade serous histology (n=8). Recurrence rates were lower in women with stage I/II (n=2/32, 4.3%) versus stage III/IV disease (17.4%, n=8).

The incidence of adverse outcomes was low: four patients (1.6%) were diagnosed with venous thromboembolism, four with deep venous thrombosis (1.6%), and two patients having simultaneous (0.8%) pulmonary emboli. The characteristics of patients who were subsequently diagnosed with deep venous thromboembolism and pulmonary embolism are displayed in online supplementary table 1. Similarly, the incidence of stroke (1.2%, n=3) and myocardial infarction were low (0.8%, n=2). The incidence of secondary diagnosis of breast cancer was 1.6% (n=4). Additionally, six patients were diagnosed with a secondary malignancy (2.5%). The characteristics of patients who developed breast cancer and secondary malignancies are displayed in Table 5.

DISCUSSION

This study sought to investigate whether vaginal estrogen use for genitourinary syndrome of menopause is associated with adverse outcomes, including cancer recurrence in women with a history of gynecologic cancer. Our cohort represents a heterogenous group of women with a low rate of adverse outcomes and recurrence. When stratified by disease site, the incidence of recurrence for endometrial cancer, ovarian cancer, and cervical cancer were low.

Genitourinary syndrome of menopause is highly prevalent in gynecologic cancer survivors and negatively impacts quality of life.[5–11] Historically, concerns have existed regarding administration of systemic or local estrogen for women with tumors that may be hormonally responsive or with an intact uterus following radiation treatment. In a recent review by del Carmen and Rice, it was concluded that women experiencing menopausal symptoms with a history of low-grade, early-stage endometrial, vaginal, vulvar, ovarian, or cervical cancer are candidates for systemic hormonal therapy.[21]

The majority of endometrial cancers are low-grade, endometrioid type and are estrogen-dependent, which has led to concerns regarding the risk of disease recurrence with exogenous estrogen therapy.[21 22] However, to date, treatment with systemic estrogen has been associated with a low risk of recurrence among women with a history of stage I/II endometrial cancer.[12 23–25] In a randomized study of patients with stage I/II endometrial cancer, recurrence was 2% in women who received systemic hormone therapy compared with 1.6% in women who did not.[12] Suriano et al demonstrated that systemic hormone therapy was associated with a significantly longer disease-free interval and lower recurrence rate compared with non-users in a cohort of women with stage I-III endometrial cancer.[25] In our study, the overall incidence of recurrence with use of vaginal estrogen for endometrial cancer was 7.1%, but the majority of patients who recurred had advanced-stage disease or high-risk histology. Recurrence was low and comparable to previous studies in patients with stage I/II endometrial cancer (2.4%). While the incidence of recurrence was higher (4.7%) in women with stage III/IV endometrial cancer following vaginal estrogen treatment, this incidence was not higher compared with historical cohorts with recurrence rates exceeding 25% among patients with advanced disease.[26 27] Our findings demonstrate that use of vaginal estrogen

Table 3 Patient symptoms and vaginal estrogen usage in patients with history of endometrial, ovarian, and cervical carcinoma

Variable	All patients (n=244)	Endometrial cancer (n=127)	Ovarian cancer (n=46)	Ovarian tumors of low malignant potential (n=9)	Cervical cancer (n=62)	P value
Age at prescription (years)	59.5±13.0	58.4±13.3	63.1±11.8	56.9±16.5	59.5±12.5	0.18
Treatment						
Conjugated estrogen cream	106 (43.4)	56 (44.1)	18 (39.1)	2 (22.2)	30 (48.4)	0.45
Estradiol cream	87 (35.7)	45 (35.4)	17 (37.0)	4 (44.4)	21 (33.9)	0.93
Estradiol tablet	38 (15.6)	18 (14.2)	11 (25.5)	3 (33.3)	6 (9.7)	0.09
Estradiol ring	4 (1.6)	3 (2.4)	1 (2.2)	0 (0)	0 (0)	0.64
Length of treatment (days)	488 (194–1287)	576 (189–1764)	513 (277–1249)	182 (164–642)	409 (204–1050)	0.33
Prescribing provider						
Gynecologic oncologist	132 (54.1)	65 (51.1)	20 (43.5)	6 (66.7)	41 (66.1)	0.09
Generalist OB/GYN	54 (22.1)	22 (17.3)	18 (39.1)	2 (22.2)	12 (19.4)	
Urogynecologist/FPMRS	36 (14.8)	24 (18.9)	5 (10.9)	1 (11.1)	6 (9.7)	
Urologist	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (1.6)	
Internal medicine	16 (6.6)	13 (10.2)	2 (4.3)	0 (0)	1 (1.6)	
Family medicine	5 (2.0)	3 (2.4)	1 (2.2)	0 (0)	1 (1.6)	
Reason for prescription						
Dyspareunia	100 (41.0)	17 (37.0)	17 (37.0)	**8 (88.9)***	29 (46.8)	**0.01***
Atrophy	94 (38.5)	16 (34.8)	16 (34.8)	2 (22.2)	27 (43.5)	0.58
Dryness	80 (32.8)	22 (47.8)	22 (47.8)	4 (44.4)	16 (25.8)	0.07
Incontinence	13 (5.3)	1 (2.2)	1 (2.2)	0 (0)	2 (3.2)	0.31
Discharge	4 (1.6)	1 (2.2)	1 (2.2)	0 (0)	2 (3.3)	0.62
Vaginal pain	51 (20.9)	8 (17.4)	8 (17.4)	2 (22.2)	12 (19.4)	0.87
Recurrent UTI	20 (8.2)	3 (6.5)	3 (6.5)	0 (0)	1 (1.6)	**0.05**
Stenosis/shortening	8 (3.3)	0 (0)	0 (0)	0 (0)	5 (8.1)	0.08
Concurrent treatments						
Systemic HRT	27 (11.1)	11 (8.7)	1 (2.2)	0 (0)	**15 (24.2)***	**0.009***
Oral contraceptives	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Progestins	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
SERMs	4 (1.6)	2 (1.6)	2 (4.3)	0 (0)	0 (0)	0.35
Effexor	7 (2.9)	4 (3.2)	1 (2.2)	1 (11.1)	1 (1.6)	0.45
Paxil	2 (0.8)	1 (0.8)	0 (0)	0 (0)	1 (1.6)	0.82
Gabapentin	1 (0.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.82

Continued

Table 3 Continued

Variable	All patients (n=244)	Endometrial cancer (n=127)	Ovarian cancer (n=46)	Ovarian tumors of low malignant potential (n=9)	Cervical cancer (n=62)	P value
Ospemifine	1 (0.4)	1 (0.8)	0 (0)	0 (0)	0 (0)	0.82
DHEA-S suppository	2 (0.8)	2 (1.6)	0 (0)	0 (0)	0 (0)	0.6
Pelvic PT	4 (1.6)	1 (0.8)	0 (0)	0 (0)	3 (4.8)	0.14
Dilators	25 (10.2)	9 (7.1)	2 (4.3)	0 (0)	**14 (22.6)***	**0.002***
Other	7 (2.9)	3 (2.4)	2 (4.3)	0 (0)	2 (3.2)	0.86
Benefit						
Unknown	149 (61.1)	83 (65.4)	25 (54.3)	3 (33.3)	38 (61.3)	0.15
Yes	71 (29.1)	30 (23.6)	16 (34.8)	6 (66.7)	19 (30.6)	
No	24 (9.8)	14 (11.0)	5 (10.9)	0 (0)	5 (8.1)	

Statistics presented as n (%). Age presented as mean±SD, Length of treatment presented as median (IQR).
*Significant at the p<0.05 level.
DHEA-S, dehydroepiandrosterone sulfate; FPMRS, female pelvic medicine and reconstructive surgery; HRT, hormone replacement therapy; OB/GYN, obstetrician gynecologist; PT, physical therapy; SERM, selective estrogen receptor modulator; UTI, urinary tract infection.

for menopausal symptoms is associated with a low incidence of recurrence in women with endometrial cancer and does not appear to increase recurrence risk beyond baseline for patients with both early and advanced disease compared with prior studies.[12 26 27]

Systemic hormone therapy in women with a history of ovarian cancer has not been associated with increased risk for recurrence, but data are limited for vaginal preparations.[28 29] Guidozzi et al randomized women with a history of ovarian cancer to systemic hormone therapy with estradiol or placebo and demonstrated no negative impact on progression-free and overall survival for all patients.[28] Additionally, on analysis by disease stage, incidence of recurrence with systemic hormone therapy was 66% and 80% for stage III and IV disease, respectively.[28] Similarly, Mascarenhas et al demonstrated that use of systemic hormone therapy following a diagnosis of ovarian cancer was associated with improved cause-specific survival compared with non-users. Comparatively, our study identified that vaginal estrogen use is associated with a low overall risk of ovarian cancer recurrence compared with previous studies for both stage I/II (4.3%) and stage III/IV disease (17.4%).[28 29] Among the patients with ovarian tumors of low malignant potential, no recurrences or adverse outcomes occurred. Women with a history of ovarian cancer with menopausal symptoms and vulvovaginal atrophy should be counseled that use of vaginal estrogen can be considered for treatment, and does not appear to increase recurrence risk compared with historical cohorts.[28 29]

Cervical cancer is more likely to be diagnosed in pre-menopausal or peri-menopausal women compared with other gynecologic malignancies.[30] To date, use of systemic hormone therapy has not been associated with increased risk of cervical cancer recurrence; however, data are limited for local vaginal estrogens. In a study by Ploch et al of 120 patients with stage I/II cervical cancer treated with systemic hormone therapy, the majority of menopausal symptoms were improved and no impact on disease outcomes was observed.[31] They noted an incidence of recurrence of 20% among women receiving systemic hormone therapy compared with 32% in controls.[31] Similarly, our study identified an overall recurrence rate of 9.7% in women with cervical cancer. Compared with historical studies that have reported recurrence rates approaching 30%, our findings demonstrate no increased risk with use of vaginal estrogen in cervical cancer survivors.[32 33] An important consideration for hormone therapy use in women with cervical cancer who are treated with definitive chemotherapy and radiation is the risk of unopposed estrogen with an intact uterus and risk of secondary uterine malignancies within the radiated field. Within our study, one patient with a history of cervical cancer treated with definitive chemoradiation developed a secondary uterine malignancy following vaginal estrogen.

Compared with previously published data for the general population, the overall incidence of adverse outcomes associated with vaginal estrogen use was low.[13 14 17 34] Prior studies have not demonstrated that local vaginal estrogen increases the incidence of embolic events.[13–19] Similarly, in this series, the incidence of deep venous thromboembolism and pulmonary embolism is low at 1.6%. Three of these events (75%) were diagnosed in women with a history of endometrial cancer. Of these patients, one embolic event was diagnosed at the time of recurrence and another was in a patient also taking systemic oral estrogen following a knee surgery. All patients were obese or had multiple medical co-morbidities

Table 4 Adverse outcomes after vaginal estrogen usage in patients with history of endometrial, ovarian, and cervical carcinoma

Variable	All patients (n=244)	Endometrial cancer (n=127)	Ovarian cancer (n=46)	Cervical cancer (n=62)	P value
Median follow-up (months)	80.5 (44.9–132.4)	88.2 (53.8–142.1)	59.8 (27.3–126.8)	79.5 (41.4–115.4)	0.26
Recurrence	25 (10.2)	9 (7.1)	10 (21.7)	6 (9.7)	**0.03***
Stage I/II		3 (2.4)	2 (4.3)	6 (9.7)	
Stage III/IV		6 (4.7)	8 (17.4)	0 (0.0)	
Complications					
Breast cancer	4 (1.6)	2 (1.6)	1 (2.2)	0 (0)	0.11
Secondary malignancy	6 (2.5)	4 (3.2)	0 (0)	1 (1.6)	0.22
Pulmonary embolism	2 (0.8)	1 (0.8)	0 (0)	1 (1.6)	0.72
Deep venous thrombosis	4 (1.6)	3 (2.4)	0 (0)	1 (1.6)	0.82
Stroke	3 (1.2)	3 (2.4)	0 (0)	0 (0)	0.43
Myocardial infarction	2 (0.8)	1 (0.8)	0 (0)	1 (1.6)	0.82

Statistics presented as n (%). Age presented as mean±SD. Length of treatment presented as median (IQR).
*Significant at the p<0.05 level.

or were active smokers. Based on these limited numbers, we are unable to draw conclusions as to whether these adverse events were related to vaginal estrogen rather than underlying medical co-morbidities and which patients appear to be at risk for adverse events. In prior studies, only trace amounts of serum estradiol were found in women undergoing treatment with vaginal estrogen using

Table 5 Characteristics of patients who developed secondary malignancies

Secondary cancer diagnosis	Medical history/genetics	Gynecologic cancer details	Vaginal estrogen treatment details	Status
Primary ER + breast cancer	History of papillary thyroid cancer, GIST, negative genetic testing	IA grade 2 mucinous OC, no adjuvant treatment	Estradiol cream 0.5 mg two times a week for 1.3 years	Alive, NED
Primary ER + breast cancer	Negative genetic testing	IA borderline tumor of the ovary, no adjuvant treatment	Estradiol tablet 10 µg two times a week for 7 years (ongoing)	Alive, NED
Primary ER + breast cancer	No genetic evaluation	IA FIGO 1 EC, no adjuvant treatment	Estradiol tablet 25 µg three times a week for 11.5 years	Alive, NED
Primary ER + breast cancer	No genetic evaluation	IA FIGO 1 EC no adjuvant treatment	Conjugated estrogen cream 0.625 mg/1 g three times a week for 9.0 years	Alive, NED
Chronic lymphocytic leukemia	No genetic evaluation	IA borderline tumor of the ovary, no adjuvant treatment	Estradiol tablet 10 µg two times a week for 9 years (ongoing)	Alive, NED
Hodgkins lymphoma	No genetic evaluation	IB FIGO 3 EC s/p VBT	Conjugated estrogen cream 0.625 mg/1 g two times a week for 1.9 years	Deceased, other causes
Colon adenocarcinoma	History of Lynch syndrome (MSH2 mutation)	IB FIGO 3 EC s/p VBT	Conjugated estrogen cream 0.625 mg/1 g two tiems a week for 14 years (ongoing)	Alive, NED
High-grade serous uterine adenocarcinoma	No genetic evaluation	IIIB SCC CC s/p cisplatin + pelvic RT + VBT	Conjugated estrogen cream 0.625 mg/1 g two times a week for 0.9 years	Alive with disease
Colon adenocarcinoma	No genetic evaluation	IB FIGO 1 EC, no adjuvant treatment	Conjugated estrogen cream 0.625 mg/1 g two times a week for 3.0 years	Deceased from colon colon adenocarcinoma
Adenocarcinoma of unknown primary	No genetic evaluation	IA FIGO 1 EC, no adjuvant treatment	Conjugated estrogen cream 0.625 mg/1 g daily for 1.5 years	Decreased from adenocarcinoma of unknown primary

CC, cervical cancer; EC, endometrial cancer; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; GIST, gastrointestinal stromal tumor; NED, no evidence of disease; OC, ovarian cancer; RT, radiotherapy; SCC, squamous cell carcinoma; s/p, status post; VBT, vaginal brachytherapy.

highly sensitive assays.[13 14 34] While limited by the small number of patients with available serum estradiol-17B levels in this retrospective study, the median level detected was low at 6.0 pg/mL, which suggests minimal absorption at the administered doses.

The retrospective design of the study precludes the authors from investigating several factors that may be important and relevant to the use of vaginal estrogen in this patient population including compliance, concurrent medication use, and serum estrogen levels. While our data demonstrate low rates of disease recurrence, given the retrospective nature of the study and lack of control cohort, we cannot rule out the possibility of selection bias in prescribing vaginal estrogen for patients with lower-risk oncologic characteristics relative to the general population included in historical cohorts. Additionally, the estrogen and progesterone receptor status was largely undetermined in the study. Although use of vaginal estrogen has been proven acceptable for use in women with estrogen receptor-positive breast cancer with low recurrence risk, this study was not powered to demonstrate similar findings in gynecologic cancers.[18 19 34] Furthermore, this retrospective study was designed to assess safety outcomes and, therefore, we are unable to draw any direct conclusions regarding clinical benefit or improvement in patient symptoms. In addition, because of the number of local estrogen preparations used, we are unable to draw conclusions for safety and adverse outcomes for any one dosage or formulation of vaginal estrogen. Despite these limitations, this study includes a large, heterogenous cohort of women with a history of gynecologic cancer and provides valuable information regarding incidence of adverse outcomes and recurrence following local vaginal estrogen use.

The results of our study demonstrate that in this heterogenous cohort of women with a history of endometrial, ovarian, or cervical cancer, vaginal estrogen is associated with a low incidence of adverse outcomes and recurrence. Our findings are generalizable given the large sample size and the broad representation of disease histologies and stages included, and therefore fills an important knowledge gap that currently exists in the literature. Further investigation is needed to prospectively evaluate efficacy of vaginal estrogen and impact on quality of life in this patient population.

Optimizing quality of life in gynecologic cancer survivors is important. In this cohort of women with a history of endometrial, ovarian, or cervical cancer, use of vaginal estrogen was associated with a low risk of adverse outcomes, including cancer recurrence, secondary malignancies, and embolic events. Based on these data, local vaginal estrogen may be considered for use in women with a history of endometrial, ovarian, or cervical cancer with no evidence of disease who are experiencing genitourinary symptoms of menopause that are impacting their quality of life. Given the frequency of genitourinary syndrome of menopause and the associated burden on quality of life in women with a history of endometrial, ovarian, or cervical cancer, additional prospective studies are needed to further delineate the role of vaginal estrogen in women with urogenital symptoms and its impact on quality of life in these patients.

Twitter Laura M Chambers @laurajmoulton

Contributors All the authors contributed to this work. LMC: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval. AH: collection and assembly of data, data analysis and interpretation, manuscript writing, final approval. CF: data analysis and interpretation, manuscript writing, final approval. CM: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval. SR: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval.

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Supplementary Table 1: Characteristics of Patients Who Developed Venous Thromboembolic Events

Patient Age, Diagnosis and Comorbidities	VTE Diagnosis	Gynecologic Cancer Details	Vaginal Estrogen Treatment Details	Status
84 year old female with history of coronary artery disease, hypertension and stroke, BMI 35, non-smoker	Unilateral DVT diagnosed when 9 years NED	Stage IA FIGO1 endometrioid adenocarcinoma, no adjuvant treatment	Conjugated estrogen cream 0.625mg/g, 0.5mg daily	Alive, NED
79 year old female with history of hypertension, BMI 45, non-smoker	DVT developed at the time of cancer recurrence	Stage IIIA clear cell carcinoma of the uterus, treated with Carboplatin/Paclitaxel for 6 cycles and pelvic RT with disease recurrence 40 months from diagnosis.	Conjugated estrogen cream 0.625mg/g, 0.5mg daily	Dead of disease
58 year old female, BMI 38, non-smoker	DVT and PE diagnosed following knee surgery when 4 years NED	Stage IA FIGO1 endometrioid adenocarcinoma, no adjuvant treatment	Estradiol ring 2mg with additional systemic estrogen	Alive, NED
64 year old female with history of hypertension, chronic kidney disease, coronary artery disease, BMI 24, active smoker	DVT and PE diagnosed at 24 months after completion of treatment	Stage IIIB SCC of the cervix s/p chemo/RT	Estradiol cream 0.1mg/gram, 1g twice weekly	Alive, NED

BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolus; NED, no evidence of disease