

Journal Pre-proof



Management of Genitourinary Syndrome of Menopause in Female Cancer Patients: A Focus on Vaginal Hormonal Therapy

Katie K. Crean-Tate, MD, Stephanie S. Faubion, MD, Holly J. Pederson, MD, Jennifer A. Vencill, PhD, LP, Pelin Batur, MD, NCMP, CCD

PII: S0002-9378(19)31057-9

DOI: <https://doi.org/10.1016/j.ajog.2019.08.043>

Reference: YMOB 12865

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 24 May 2019

Revised Date: 4 August 2019

Accepted Date: 24 August 2019

Please cite this article as: Crean-Tate KK, Faubion SS, Pederson HJ, Vencill JA, Batur P, Management of Genitourinary Syndrome of Menopause in Female Cancer Patients: A Focus on Vaginal Hormonal Therapy, *American Journal of Obstetrics and Gynecology* (2019), doi: <https://doi.org/10.1016/j.ajog.2019.08.043>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc.

1 Management of Genitourinary Syndrome of Menopause in Female Cancer Patients: A Focus on
2 Vaginal Hormonal Therapy

3
4 Katie K CREAN-TATE, MD
5 Gynecologic Oncology, Women's Health Institute
6 Cleveland Clinic
7 Cleveland, OH

8
9 Stephanie S FAUBION, MD
10 Center for Women's Health and Division of General Internal Medicine
11 Mayo Clinic
12 Rochester, MN

13
14 Holly J PEDERSON, MD
15 Medical Breast Services
16 Cleveland Clinic
17 Cleveland, OH

18
19 Jennifer A VENCILL, PhD, LP
20 Department of Psychiatry and Psychology and Division of General Internal Medicine
21 Mayo Clinic
22 Rochester, MN

23
24 Pelin BATUR, MD, NCMP, CCD
25 Ob/Gyn & Women's Health Institute
26 Cleveland Clinic
27 Cleveland, OH

28
29 Disclosure Statement:
30 KKCT has no disclosures
31 SSF consults for Mithra Pharmaceuticals, AMAG, and Procter & Gamble
32 HJP consults for Myriad Genetics
33 JAV has no disclosures
34 PB has no disclosures

35
36 Financial Support:
37 There was no financial support for this article.

38
39 Corresponding Author:
40 Katie Crean-Tate, MD
41 9500 Euclid Avenue, Desk A81
42 Cleveland, OH 44195
43 Work Phone: 216-973-2692, Mobile Phone: 916-856-7626
44 Fax Number: 216-636-1296
45 Email Address: creantk@ccf.org

46

47 Word Count: 4,552

48 Condensation: Discussion of national guideline-based management options for female cancer
49 patients with genitourinary syndrome of menopause, with emphasis on safety and efficacy of
50 vaginal hormonal therapy.

51
52 Short Title: GSM in Female Cancer Patients: Focus on Vaginal Hormonal Therapy

53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92

Journal Pre-proof

93 Abstract:

94
95 Genitourinary syndrome of menopause is a condition describing the hypoestrogenic effects
96 on the female genitals and lower urinary tract leading to symptoms such as vaginal dryness,
97 vulvar and vaginal burning, dyspareunia and dysuria. Genitourinary syndrome of menopause
98 is experienced by over half of postmenopausal women, and is even more pervasive in women
99 with cancer. Due to treatments such as surgery, chemotherapy, radiation, and hormonal
100 therapy, women may experience early menopause resulting in earlier and more severe
101 symptoms. Understanding the scope of this issue in female breast and gynecologic cancer
102 survivors and identifying treatment options for this complex patient population are
103 paramount. Tailored patient treatments include nonhormonal therapies (vaginal moisturizers,
104 lubricants, pelvic floor physical therapy, dilator therapy, counseling), systemic and local
105 hormonal therapies. Consensus recommendations by medical societies and associated
106 evidence are reviewed, with emphasis on safety and efficacy of local vaginal hormonal
107 therapies, and management variations noted depending on cancer type and characteristics.
108 With knowledge and understanding of the unmet need associated with under-recognition and
109 under-treatment of genitourinary syndrome of menopause, providers caring for women with
110 cancer are in a position to improve the quality of life of their patients by providing safe and
111 effective treatments.

112
113 Key Words: atrophic vaginitis, breast cancer, cancer survivorship, dehydroepiandrosterone,
114 dyspareunia, endometrial cancer, estrogen-progestin therapy, genitourinary syndrome of
115 menopause, gynecologic cancer, nonhormonal vaginal therapy, quality of life, sexual health,
116 sexual dysfunction, vaginal hormonal therapy.

117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138

139 **Introduction**

140

141 With over 1 million U.S. women living with gynecologic cancer and over 3 million living with
142 breast cancer, quality of life in female cancer survivors is an essential aspect of patient care.
143 Among the multiple quality of life issues experienced after cancer, nearly 90% of survivors note
144 sexual health as a major concern.¹ This is seen in gynecologic and breast cancer survivors, as
145 well as other types of cancer (e.g., those involving the pelvis or lower abdomen, including anal
146 or colorectal malignancies). Many of the treatments provided for female cancers affect the
147 hormonal milieu, sometimes leading to early menopause. Hormonal therapy to treat breast cancer
148 also affects sexuality.¹⁻⁴ Challenges with sexual health are multifactorial in cancer survivors.

149

150 Genitourinary syndrome of menopause (GSM) is a condition resulting from menopause-related
151 hypoestrogenic effects on the female genitals and lower urinary tract, including the labia minora,
152 clitoris, vestibule/introitus, vagina, urethra, and bladder. Symptoms can include vaginal dryness,
153 vulvar and vaginal burning and irritation, lack of lubrication, dyspareunia, urinary urgency,
154 frequency, and dysuria, and recurrent urinary tract infections. In 2014, the International Society
155 for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society
156 (NAMS) adopted the term GSM to better encompass the array of genitourinary symptoms
157 attributed to the loss of estrogen associated with menopause.⁵

158

159 GSM affects over 50% of postmenopausal women, and is even more pervasive in the female
160 cancer population.^{2,6,7} As breast cancer is often diagnosed after menopause, women with breast
161 cancer may experience GSM prior to diagnosis, and breast cancer treatments may intensify
162 symptoms. Broeckel et al⁸ compared women with breast cancer treated with chemotherapy to
163 age-matched controls without cancer and found that breast cancer patients experienced worse
164 sexual function, with vaginal dryness as one of the most significant predictors of poorer sexual
165 function. Similarly, endocrine therapies such as tamoxifen and aromatase inhibitors (AI) may
166 worsen symptoms of GSM; AIs in particular are associated with difficulty with lubrication,
167 dyspareunia, and global dissatisfaction with one's sex life.⁹ Surgical treatment of breast or
168 gynecologic cancers that involve oophorectomy in premenopausal women leads to early
169 menopause which is associated with sexual dysfunction and GSM.^{10,11} Chemotherapy and
170 radiation therapy can result in ovarian insufficiency, similarly leading to GSM symptoms in
171 premenopausal patients or intensified symptoms in postmenopausal patients.¹²

172

173 Cancer survivors endure a multitude of insults on their reproductive system throughout their
174 course of disease, and sexual health generally and GSM specifically are often overlooked. We
175 will discuss management options for GSM in women with cancer, focusing here on women with
176 breast and gynecologic cancer, including nonhormonal and hormonal options (systemic and local
177 vaginal). We will also review clinical guidelines on this topic and discuss other considerations
178 for sexual health in female cancer survivors.

179

180 **Nonhormonal treatments for GSM**

181

182 Nonhormonal regimens are an important first line therapy for symptoms of vulvar and vaginal
183 dryness and related dyspareunia in all women, and particularly in those with hormone-dependent
184 cancers. These include vaginal moisturizers and lubricants, topical anesthetics, pelvic floor

185 physical therapy, and counseling. A study of 175 women with gynecologic cancers who received
186 focused education on vaginal moisturizers, lubricants, pelvic floor exercises, vaginal dilator
187 therapy, and psychosexual education after cancer care demonstrated significant improvements in
188 sexual function, sexual activity, vaginal and vulvar assessment scores and vaginal pH compared
189 to baseline.²

190
191 Lubricants work to relieve discomfort and pain by reducing friction against thinned, atrophic
192 genital tissue. These are available as water-, silicone-, mineral oil- or plant oil-based products.
193 The World Health Organization recommends lubricant use with condoms for postmenopausal
194 women.¹³ In contrast, vaginal moisturizers are applied regularly, providing pain relief from
195 vaginal penetration as well as general atrophy. Moisturizers work by hydrating the vaginal
196 mucosa and lowering the vaginal pH,¹⁴ and are available as plant-based or synthetic polymers.
197 Two studies found that Replens, an FDA approved vaginal moisturizer, caused equivalent
198 subjective improvement of vaginal dryness when compared with vaginal estrogen therapy.^{15,16}

199
200 Another nonhormonal treatment option for GSM is topical lidocaine. In a randomized study of
201 survivors of breast cancer with severe GSM and dyspareunia, 4% aqueous lidocaine applied
202 three minutes prior to penetration was associated with an 88% reduction in dyspareunia versus
203 33% with placebo.¹⁷

204
205 Micro-ablative fractional CO2 laser and non-ablative vaginal Erbium YAG laser have been
206 explored in women with and without a cancer history who have GSM. The mechanism of action
207 of laser therapy is thought to be through the remodeling and synthesis of collagen.¹⁸ In an
208 observational study of women with GSM who underwent fractional CO2 laser treatment,
209 significant symptomatic improvements in pain, dryness, dyspareunia, and sexual function were
210 found at 3 months and 1 year.¹⁸ Limited data also suggest that laser treatments are effective in
211 breast cancer survivors.¹⁹⁻²¹ Case reports of pain, scarring, and sexual dysfunction after laser
212 treatment have been reported.²² Further studies are needed to assess the long term risk versus
213 benefits of vaginal laser and thermal treatments.

214
215 Treatment of GSM in cancer survivors is often complex, and a multidisciplinary approach is
216 often needed.²³ Pelvic floor physical therapy and counseling address other associated sexual
217 health issues such as pelvic floor myalgia and underlying mood disorders or relationship issues.
218 Please see “Special Considerations” below for further discussion of these topics.

219 220 **Vaginal hormonal therapies**

221
222 Although systemic hormone therapy (HT) is typically avoided in women with estrogen sensitive
223 cancers (i.e., breast, endometrial), discussion regarding safety and efficacy of vaginal hormonal
224 therapy is important when nonhormonal treatments fail to provide sufficient relief. Systemic HT
225 may not adequately control GSM symptoms in up to 45% of patients, whereas low dose vaginal
226 hormonal therapy is highly effective in providing symptomatic relief of sexual dysfunction,
227 lower urinary tract infections, and other genitourinary symptoms and is associated with minimal
228 systemic absorption. Several factors may play a role in the decision to use vaginal hormone
229 therapy after breast cancer (Table 1).²⁴ These factors are used to assess overall lower vs higher
230 risk of recurrence, with a focus on factors such as hormone receptor status, anti-estrogen therapy

231 use, and severity of symptoms. These factors should be considered together, as, for example, a
232 patient with advanced or metastatic cancer with extended life expectancy but with severe
233 symptoms and negative hormone status should be considered for hormone therapy given the
234 impact on quality of life and less likely recurrence due to hormone activity.

235
236 *Vaginal estrogens*

237
238 Vaginal estrogen therapy is administered locally to the vulvar and vaginal tissues via cream, ring,
239 insert or tablet. Most preparations are delivered locally in a low dose, with minimal systemic
240 absorption.²⁵ FDA-approved dosing regimens are often higher and/or more frequent than those
241 used in clinical practice. Examples of different vaginal estrogen therapies and their variable rates
242 of systemic absorption are summarized in Table 2.

243
244 Many studies have shown the overall safety and efficacy of vaginal estrogen in treating GSM. In
245 a Cochrane review including 30 randomized control trials and over 6000 patients, different
246 vaginal estrogen preparations were compared to each other and to placebo and were found to be
247 similarly efficacious in GSM treatment with no differences in adverse events. Older studies using
248 the 25 mcg vaginal estrogen tablet (no longer available) reported a slight increase in serum
249 estradiol levels, although data are difficult to interpret as several studies utilized older assays that
250 may have shown falsely elevated levels.^{26,27} The 10 mcg estradiol tablet is associated with serum
251 estradiol concentrations that remain within the postmenopausal range when measured by gas
252 chromatography and mass spectrometry, and has good evidence for clinical benefit.²⁸ Santen et
253 al assessed symptomatic improvement in genitourinary symptoms with a questionnaire as well as
254 vaginal cytology, pH, endometrial biopsy and serum LH, FSH, estradiol and estrone levels
255 throughout treatment with different doses of vaginal estrogen; they found that 10 mcg provided
256 improvement in both symptoms and objective endpoints, while maintaining an atrophic
257 endometrium and estrogen levels within the postmenopausal range (3-10 pg/mL).²⁹ An analysis
258 assessing endometrial biopsies in women after 52 weeks of treatment with 10 mcg vaginal
259 estradiol tablets showed an atrophic endometrium in 86% of women with less than 1%
260 demonstrating endometrial hyperplasia or carcinoma, similar to the background incidence of
261 endometrial hyperplasia and carcinoma in postmenopausal women.³⁰ While most regimens of
262 vaginal estrogen result in estradiol levels within the normal postmenopausal range (<20pg/ml),³¹
263 the exact safety threshold of serum estradiol in those with a history of breast cancer is unknown.
264 Vaginal estrogen products associated with lower serum estradiol levels may be preferable for
265 hormone receptor-positive breast cancer survivors, including the 4 mcg vaginal inserts, 10 mcg
266 inserts and tablets, and the vaginal ring providing 7.5 mcg estradiol daily.

267
268 Vaginal estrogen therapy has not been found to increase primary breast cancer risk or breast
269 cancer recurrence in survivors. In a review of over 18,000 women from a Finnish registry,
270 vaginal estrogen was not associated with an increased risk of breast cancer.³² This finding was
271 supported by both the Women's Health Initiative Observational Study and the Nurse's Health
272 Study where vaginal estrogen use was not associated with increased breast cancer risk.^{33,34} In
273 breast cancer survivors, vaginal estrogen therapy has not been associated with an increased risk
274 in breast cancer recurrence or mortality.^{35,36} In a nested case-control study of women with breast
275 cancer receiving tamoxifen or AI treatment, no increased recurrence risk was found in vaginal
276 estrogen users versus non-users.³⁷

277
278 Data regarding vaginal estrogen therapy and risk of recurrence of endometrial and ovarian
279 cancers is limited. Extrapolating from studies on systemic HT in these populations, most
280 endometrial and ovarian cancer survivors would benefit from vaginal hormonal therapy if
281 indicated (see Table 3). Vaginal estrogen therapy in the setting of cervical, vaginal, and vulvar
282 cancers is considered safe as these gynecologic cancers are not considered hormonally-
283 sensitive.^{41,42}

284 285 *Vaginal DHEA*

286
287 Dehydroepiandrosterone (DHEA) is an inactive precursor from the adrenal gland that is
288 transformed to active androgen in the peripheral tissues, exerting action locally in the same cells
289 where synthesis takes place. Androgens are then aromatized to form estrogens. This mechanism,
290 known as intracrinology, leads to local cellular effects with subsequent intracellular inactivation
291 of the hormones, leading to minimal active hormone release into the systemic circulation.

292
293 Treatment with vaginal DHEA (prasterone) has shown improvement in vaginal health and sexual
294 function. In vivo studies of vaginal effects after oophorectomy found that DHEA increased
295 mucification of epithelium, muscularis thickness, and collagen fiber compactness in the lamina
296 propria, thus affecting three layers of the vaginal wall for a robust, physiologic local response.⁴³
297 In a prospective, double-blind randomized control trial, daily vaginal DHEA 0.5% 6.5 mg was
298 administered for 12 weeks and compared with placebo. DHEA was associated with significant
299 improvement in vaginal secretions, epithelial thickness, color, vaginal pH, and vaginal cytology
300 with increased vaginal parabasal and superficial cells.⁴⁴ In another open label study, 52 weeks of
301 daily vaginal DHEA use revealed significant improvements in all domains of sexual function
302 studied, including desire, arousal, lubrication, orgasm, pain and satisfaction.⁴⁵

303
304 Head to head studies of the safety and efficacy of vaginal estrogens versus DHEA are not
305 available. Studies assessing the safety of FDA-approved DHEA in cancer survivors are limited.
306 In one randomized, controlled trial, 464 breast and gynecologic cancer survivors who
307 experienced GSM were given either compounded vaginal DHEA 3.25 mg, 6.5mg DHEA, or
308 plain moisturizer over 12 weeks. While all three arms showed improvement in vaginal symptoms
309 at 12 weeks, women who used 6.5mg DHEA reported significantly improved sexual health.
310 There was no increase in provider-graded toxicity or self-reported side effects, and similar results
311 were appreciated if the patient was on concurrent AI therapy.⁴⁶ The authors reported that serum
312 DHEA-S and testosterone levels were significantly increased in women on 6.5 mg DHEA
313 compared to those using plain moisturizers. Estradiol levels significantly increased in those on
314 6.5 mg/day DHEA, though levels remained in the lower half of the postmenopausal range. No
315 elevations in serum estradiol levels were seen in women on AIs.⁴⁷

316
317 In contrast, other studies (not done in cancer survivors) indicate there is no significant change in
318 serum steroid levels, including estradiol, estrone, DHEA, and testosterone.⁴⁸ DHEA 6.5 mg
319 (0.5%) use for up to 52 weeks in 422 women was associated with endometrial atrophy or
320 inactive endometrium on endometrial biopsies.⁴⁹

321

322 Taken together, the studies to date on vaginal DHEA indicate significant improvements in
323 objective determinants of vaginal health as well as subjective symptomatic improvement in
324 GSM, with minimal change in serum estrogen or androgen levels. Additional studies of DHEA
325 use in cancer survivors are needed, as well as studies directly comparing vaginal DHEA and
326 estrogen.

327 328 *Vaginal testosterone*

329
330 Vaginal testosterone is an off-label therapy sometimes used for GSM given that female
331 genitourinary tissues are known to be rich in testosterone receptors.⁵⁰ Clinical data on local
332 testosterone use is limited. Given the aromatization of testosterone to estradiol, there is concern
333 about safety when used after a diagnosis of hormone dependent cancer. In a randomized trial of
334 80 postmenopausal women who received 12 weeks of compounded vaginal testosterone versus
335 placebo lubricant, those receiving compounded testosterone had improved vaginal assessment
336 scores, improved vaginal pH and vaginal flora.⁵¹ A few studies assessed local testosterone use in
337 breast cancer patients with vaginal atrophy on AIs and indicated improved symptoms including
338 dyspareunia, dryness, vaginal pH, and sexual function scores.⁵²⁻⁵⁴ However, these studies either
339 failed to fully describe the serum testosterone levels or found levels to be elevated well above
340 physiologic range, with one study indicating 12% of patients also had persistently elevated
341 estradiol levels after testosterone therapy.⁵⁴ Given these findings, the administration of vaginal
342 testosterone is not routinely recommended after breast cancer.

343 344 **Systemic hormone therapy**

345
346 Systemic hormone therapy (HT) is often considered for women with menopausal symptoms or
347 for women experiencing early (< age 45 years) or premature (< age 40) menopause to protect
348 against the potential adverse health consequences of early estrogen deprivation.⁵⁵ Although
349 vaginal hormonal therapies are more effective at treating GSM, systemic HT is available when
350 patients have vasomotor symptoms impacting quality of life, or in women with early or
351 premature menopause.⁵⁶ Many guidelines recommend avoiding systemic HT in women with
352 hormone responsive cancers.^{24,57-59} The evidence for these recommendations is conflicting, and
353 depends on cancer type.

354
355 The safety of systemic HT in breast cancer survivors is still debated, and use is generally
356 discouraged in these women. The primary subtypes of breast cancer include luminal (luminal A
357 and luminal B), human epidermal growth factor 2 (HER2) over-expressing, and triple negative
358 (ER, progesterone receptor (PR), and HER2 negative). These subtypes are clinically important in
359 determining management at diagnosis, with targeted treatment such as endocrine therapy for
360 luminal subtypes as these make up the majority of estrogen receptor (ER) positive tumors.
361 Subtypes with hormone receptor activity, which make up about 80% of breast cancers, should
362 avoid systemic hormone therapy. On the other hand, hormone therapy is not theoretically linked
363 with a higher risk of recurrence in women with hormone receptor negative tumors, though data
364 supporting this are scant.⁶⁰ Three large studies are typically referenced relating risk of hormone
365 therapy in breast cancer. The first, the Women's Health Initiative (WHI) study, showed that
366 combined estrogen and progestin HT increased the risk for primary invasive cancer by 8 per
367 10,000 person-years in healthy postmenopausal women after 5.2 years. Long term follow up has

368 revealed a *lower* risk of breast cancer in women taking estrogen alone for 7.1 years, with a
369 hazard ratio 0.79 in estrogen users compared to placebo (95% CI 0.65–0.97).⁶¹ The second two
370 studies are two randomized trials looking specifically at breast cancer survivors, which
371 demonstrated conflicting results. In the Hormonal Replacement Therapy After Breast Cancer—Is
372 It Safe? (HABITS) trial, breast cancer survivors with menopausal symptoms were randomized to
373 HT or placebo. The relative hazard for breast cancer recurrence was 3.3 (95% CI 1.5–7.4) at
374 median follow up of 2.1 years, with 26 women in the HT group and 7 in the non-HT group
375 diagnosed with a new breast cancer during the trial. The trial was stopped during accrual due to
376 unacceptable risk.⁶² The Stockholm trial, which also randomized breast cancer survivors to
377 hormone therapy versus placebo, showed no difference in breast cancer recurrence risk at a
378 median of 4.1 years, or after 10.8 years in a follow-up study.^{63,64} Given both HABITS and the
379 Stockholm trial were prematurely closed due to the preliminary findings from the HABITS trial,
380 the ultimate determination of risk in this population remains unclear. However given the concern
381 for increased risk in the breast cancer survivor population, systemic hormone therapy is not
382 recommended.

383
384 Endometrial cancer is estrogen sensitive in 90% of cases, thus concern regarding risk of
385 recurrence with HT is understandable; however, studies do not support this claim. Barakat et al.
386 initiated a randomized trial of estrogen versus placebo after surgery in early stage endometrial
387 cancer, however the study did not reach accrual due to the concomitant publication of WHI trial
388 results. Recurrence rates were not significantly different, with 2.3% in the HT group (with 1.3%
389 developing a new malignancy), compared to 1.9% recurrence in the placebo group (1.6%
390 developed new malignancy). Due to early closure, no conclusions could be made, though the low
391 rate of recurrence and diagnosis of new malignancy was highlighted.⁶⁵ A meta-analysis that
392 included nearly 900 endometrial cancer survivors receiving HT compared to over 1000 nonusers
393 found no increased risk of recurrence in the HT versus control group.³⁸ There is a paucity of data
394 regarding HT use in less common uterine cancers such as endometrial stromal sarcoma and
395 uterine leiomyosarcoma. Studies indicate prolonged survival with hormone suppression in
396 hormone responsive endometrial stromal sarcoma, and one case series found that patients
397 withdrawn from HT responded with disease stabilization and experienced a partial response
398 when aromatase inhibitors were provided. Thus systemic HT is avoided in these cancer types.^{66–}
399 ⁶⁹ Uterine leiomyosarcomas often overexpress estrogen and progesterone receptors, however
400 studies have found oophorectomy at the time of hysterectomy did not improve 5 year overall
401 survival and, in a Surveillance, Epidemiology, and End Results review, was associated with
402 significantly lower survival rates.^{70,71} However, given the lack of definite data in this aggressive
403 subtype, many recommend caution in providing systemic hormone therapy to this group.⁷²

404
405 When considering ovarian cancer, the predominant histological subtype is serous which has been
406 found to have no correlation with worse survival outcomes in patients taking systemic HT.
407 Randomized studies in ovarian cancer survivors found equivalent disease free intervals and
408 overall survival, with one multi-center randomized study of pre- and postmenopausal patients
409 finding an improvement in overall survival in the HT arm at median follow-up of 19.1 years
410 (HR: 0.63, 95% CI 0.44–0.90, p=0.011) as well as relapse free survival (HR: 0.67, 95% CI 0.47–
411 0.97, p=0.032).^{39,40} As such, systemic hormonal therapy for symptomatic ovarian cancer
412 survivors is not only safe but is associated with a survival benefit, and should be recommended
413 to premenopausal, and certainly at least offered to symptomatic postmenopausal patients.
414 Ovarian germ cell and sex-cord stromal tumors are rare and thus data is further limited. However

415 HT for germ cell tumors is generally considered safe.^{42,73} However, ovarian granulosa cell
416 tumors are hormonally active; patients with a history of this ovarian cancer subtype are typically
417 advised to avoid systemic HT.⁷⁴
418

419 Most cervical, vulvar and vaginal cancers, are not considered hormonally sensitive. In a study
420 using systemic HT in cervical cancer patients, no significant increased risk of recurrence or
421 decreased 5 year survival were seen, with significant improvement in post-radiation rectal,
422 bladder and vaginal effects (17% vs 45% in control arm), indicating the benefits of HT use.⁷⁵ HT
423 use is acceptable in these patients if no other contraindications to use exist. Vaginal and cervical
424 clear cell adenocarcinoma is exceedingly rare, however there is a near 40-fold increased risk of
425 development of this type of cancer in woman who were exposed to diethylstilbestrol (DES), a
426 synthetic estrogen used during pregnancy fifty years ago.⁷⁶ Given the rarity of this cancer, no
427 conclusions can be drawn regarding effects of HT, thus recommendations for use of systemic HT
428 in cervical and vulvovaginal adenocarcinoma are limited.
429

430 **Selective estrogen receptor modulators**

431
432 Ospemifene is a selective estrogen receptor modulator (SERM) that is approved for the treatment
433 of GSM. Similar to other SERMs, it has shown antiestrogenic effects on the breast in preclinical
434 studies, though it appears to be less potent than tamoxifen or raloxifene.⁷⁷ It has favorable effects
435 on bone turnover and breast density, without any data on fracture risk.²⁴ Studies suggest
436 endometrial safety, but only have one year of follow up.⁷⁸ It is not FDA-approved for use in
437 women with or at high risk for breast cancer (though is not contraindicated in Europe for women
438 who have completed their breast cancer treatment). Similar to other SERMs, it may increase hot
439 flashes and risk of thrombosis.
440

441 **Clinical guidelines**

442
443 Five major consensus recommendations help guide the treatment of GSM in cancer
444 survivors.^{24,57-59,79} There is agreement that nonhormonal treatments should be offered first,
445 including counseling, pelvic floor relaxation techniques and vaginal dilator use.⁵⁹ When
446 nonhormonal measures fail to adequately relieve symptoms, local vaginal hormones may be
447 considered after shared decision making with the patient and her oncologist. All
448 recommendations suggest caution regarding the use of vaginal estrogen in women with breast
449 cancer on AI therapy given that the goal of treatment is to maximally suppress estradiol levels.
450 Because tamoxifen exerts its effects by competitively binding to the estrogen receptor, an
451 increase in serum estradiol is less likely to affect patient treatment response.⁵⁸
452

453 Some of these medical society expert recommendations make specific points that may be helpful
454 in guiding clinical practice. The American College of Obstetrics and Gynecology and the
455 NAMS/ISSWSH guidelines note that women on AIs with severe GSM symptoms may consider
456 discussing a trial of tamoxifen with their oncologist (with or without vaginal hormone
457 treatment).^{24,58} The International Menopause Society endorses the importance of starting therapy
458 early prior to development of irreversible genitourinary changes.⁵⁷ The National Comprehensive
459 Cancer Network released survivorship guide updates in 2019 stating that if local estrogen-based
460 treatment is necessary, rings and suppositories are preferred over creams. Local vaginal DHEA

461 preparations can also be used with caution in survivors with a history of estrogen-dependent
462 cancers, with limited safety data.⁷⁹ There are insufficient data to recommend vaginal estrogen
463 versus DHEA. Checking estradiol levels in those on vaginal hormone treatments is
464 discouraged.²⁴

465

466 **Special considerations: Contributors to sexual dysfunction**

467

468 While GSM can have a significant impact on the sexual health after cancer, other factors are
469 important to consider. In women undergoing gynecologic surgeries requiring resection of a
470 portion of the vulva or vagina, scarring and shortening of the vagina can occur. Radiation
471 therapy may result in vaginal fibrosis, stenosis, and vulvar or clitoral pain sensitivity.¹² Women
472 with cervical cancer may develop dyspareunia after radiotherapy, as well as difficulty with
473 sexual desire and arousal;⁸⁰ limited data suggest that orgasm using a clitoral suction device may
474 help symptoms.⁸¹ Other comorbid conditions include endocrine disorders (diabetes, metabolic
475 syndrome, hypo- and hyperthyroidism) and medication effects, which include antihypertensives,
476 narcotics and SSRIs (effects on sexual desire and orgasm).⁶ Addressing each of these potential
477 contributors to sexual dysfunction is important to fully address a woman's sexual health
478 concerns.

479

480 The diagnosis and treatment of cancer is a stressful life event which can lead to challenges with
481 mood, intimacy and decreased sexual desire and arousal. Chemotherapy can result in loss of hair,
482 weight changes, and associated issues with body image. Body image issues may also arise when
483 patients require surgery, including removal of breasts, ovaries, genitalia, and placement of
484 ostomies with radical surgery. Additionally, breast sensitivity is lost with mastectomy resulting
485 in a lost erogenous zone for many women. Given the complex and multifactorial nature of sexual
486 health concerns, support for a multidisciplinary treatment approach, including medical providers,
487 sex therapists, and pelvic floor physical therapists, continues to grow.⁸²⁻⁸⁴ Women are often
488 hesitant to report sexual health concerns and specifically GSM to their healthcare providers due
489 to embarrassment, shame, and/or a mistaken belief that treatment options do not exist.⁸⁵ Many
490 suffer for years with sexual pain and resulting avoidance of intimacy and relational distress.^{86,87}
491 Even when medical treatment has been established, shame-based emotions can negatively impact
492 treatment adherence (e.g., women who report embarrassment or even outright disgust about their
493 vulva may struggle to apply local hormonal treatments to the genitals).

494

495 Sex therapy is a specialized form of psychotherapy designed to help patients with a wide variety
496 of sexual and relationship concerns.⁸⁶ Using cognitive behavioral theories, sex therapists work
497 with patients to address the avoidant cycle of sexual interaction within which many find
498 themselves trapped (especially in the presence of dyspareunia). Sex therapy often involves
499 psychoeducation and skills-building related to sexual communication, identifying one's own
500 sexual likes, dislikes, and fears, as well as helping patients to identify and alter links between
501 problematic thoughts, emotions, behaviors, and their sexual symptoms. Building skills for
502 relaxation and mindfulness can further improve symptoms of avoidance and anxiety that many
503 patients may have developed around sexual situations. Certified sex therapists can be found on
504 the website of the American Association of Sexuality Educators, Counselors, and Therapists
505 (AASECT.org).

506

507 Pelvic floor physical therapy applies the knowledge and skill of specialized physical therapists to
508 evaluate and treat patients with pelvic floor dysfunction. With individually focused assessments,
509 therapists can provide education, exercises in both strengthening and relaxation, manual
510 therapies (such as massage), and pelvic floor biofeedback.⁸⁸ Manual physical therapy techniques
511 can markedly or completely relieve up to 80% of patients' musculoskeletal pelvic pain.⁸⁹ Pelvic
512 floor rehabilitation improves sexual pain disorders in up to 77% of women, and increases sexual
513 desire and orgasm.^{90,91} A careful exam to diagnose concomitant pelvic floor dysfunction is
514 recommended to identify individuals who would benefit from referral to a pelvic floor physical
515 therapist.²⁴ Specialized therapists can be found at the American Physical Therapy Association
516 website (www.womenshealthapta.org).⁹²

517

518 **Conclusion**

519

520 Women with a history of breast and gynecologic cancers often suffer from symptoms of GSM.
521 Guidelines agree that nonhormonal therapies are first-line treatment, though in many women
522 these options will not adequately control symptoms. Hormonal therapies must be used with
523 caution in women with estrogen-dependent cancers. For many cancer survivors, local vaginal
524 estrogen or DHEA therapy can be considered with informed shared decision making. Clinicians
525 should consult the woman's oncologist when considering these therapies. These discussions and
526 management decisions can be complex, but are of paramount importance to the quality of life of
527 cancer survivors with GSM.

528

529

530

531

532

533

534

535

536

537

538

539

540

541

542

543

544

545

546

547

548

549

550

551

552

553 References

- 554
- 555 1. Stabile C, Goldfarb S, Baser RE, et al. Sexual health needs and educational intervention
556 preferences for women with cancer. *Breast Cancer Res Treat.* 2017;165(1):77–84.
- 557 2. Carter J, Stabile C, Seidel B, Baser RE, Goldfarb S, Goldfrank DJ. Vaginal and sexual health
558 treatment strategies within a female sexual medicine program for cancer patients and
559 survivors. *J Cancer Surviv.* 2017;11(2):274–283.
- 560 3. Raggio GA, Butryn ML, Arigo D, Mikorski R, Palmer SC. Prevalence and correlates of
561 sexual morbidity in long-term breast cancer survivors. *Psychol Health.* 2014;29(6):632-650.
562 doi:10.1080/08870446.2013.879136
- 563 4. Oberguggenberger A, Martini C, Huber N, et al. Self-reported sexual health: Breast cancer
564 survivors compared to women from the general population – an observational study. *BMC*
565 *Cancer.* 2017;17(1). doi:10.1186/s12885-017-3580-2
- 566 5. Portman DJ, Gass ML, Panel VATCC. Genitourinary syndrome of menopause: new
567 terminology for vulvovaginal atrophy from the International Society for the Study of
568 Women’s Sexual Health and the North American Menopause Society. *Climacteric.*
569 2014;17(5):557–563.
- 570 6. DeSimone M, Spriggs E, Gass JS, Carson SA, Krychman ML, Dizon DS. Sexual dysfunction
571 in female cancer survivors. *Am J Clin Oncol.* 2014;37(1):101–106.
- 572 7. Cook ED, Iglehart EI, Baum G, Schover LL, Newman LL. Missing documentation in breast
573 cancer survivors: genitourinary syndrome of menopause. *Menopause N Y N.*
574 2017;24(12):1360-1364. doi:10.1097/GME.0000000000000926
- 575 8. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term
576 breast cancer survivors treated with adjuvant chemotherapy. *Breast Cancer Res Treat.*
577 2002;75(3):241-248.
- 578 9. Baumgart J, Nilsson K, Evers AS, Kallak TK, Poromaa IS. Sexual dysfunction in women on
579 adjuvant endocrine therapy after breast cancer. *Menopause.* 2013;20(2):162–168.
- 580 10. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of
581 premature or early menopause and considerations for management. *Climacteric.*
582 2015;18(4):483–491.
- 583 11. Graziottin A. Menopause and sexuality: key issues in premature menopause and beyond. *Ann*
584 *N Y Acad Sci.* 2010;1205(1):254–261.
- 585 12. Falk SJ, Dizon DS. Sexual dysfunction in women with cancer. *Fertil Steril.*
586 2013;100(4):916-921. doi:10.1016/j.fertnstert.2013.08.018

- 587 13. Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause:
588 how important is vaginal lubricant and moisturizer composition? *Climacteric J Int*
589 *Menopause Soc.* 2016;19(2):151-161. doi:10.3109/13697137.2015.1124259
- 590 14. Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment.
591 *Pharmacotherapy.* 2001;21(4):464-480.
- 592 15. Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of
593 vaginal atrophy in postmenopausal women. *Maturitas.* 1996;23(3):259-263.
- 594 16. Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women.
595 *Fertil Steril.* 1994;61(1):178-180.
- 596 17. Goetsch MF, Lim JY, Caughey AB. A Practical Solution for Dyspareunia in Breast Cancer
597 Survivors: A Randomized Controlled Trial. *J Clin Oncol Off J Am Soc Clin Oncol.*
598 2015;33(30):3394-3400. doi:10.1200/JCO.2014.60.7366
- 599 18. Sokol ER, Karram MM. Use of a novel fractional CO2 laser for the treatment of
600 genitourinary syndrome of menopause: 1-year outcomes. *Menopause N Y N.* 2017;24(7):810-
601 814. doi:10.1097/GME.0000000000000839
- 602 19. Pagano T, De Rosa P, Vallone R, et al. Fractional microablative CO2 laser for vulvovaginal
603 atrophy in women treated with chemotherapy and/or hormonal therapy for breast cancer: a
604 retrospective study. *Menopause.* 2016;23(10):1108–1113.
- 605 20. Pagano T, De Rosa P, Vallone R, et al. Fractional microablative CO2 laser in breast cancer
606 survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local
607 treatments: a retrospective study. *Menopause.* 2018;25(6):657–662.
- 608 21. Pieralli A, Fallani MG, Becorpi A, et al. Fractional CO 2 laser for vulvovaginal atrophy
609 (VVA) dyspareunia relief in breast cancer survivors. *Arch Gynecol Obstet.* 2016;294(4):841–
610 846.
- 611 22. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: a case series of patient
612 complications following vaginal laser treatment for atrophy. *Menopause N Y N.*
613 2019;26(4):423-427. doi:10.1097/GME.0000000000001293
- 614 23. Bober SL, Kingsberg SA, Faubion SS. Sexual function after cancer: paying the price of
615 survivorship. *Climacteric J Int Menopause Soc.* May 2019:1-7.
616 doi:10.1080/13697137.2019.1606796
- 617 24. Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of
618 menopause in women with or at high risk for breast cancer: consensus recommendations
619 from The North American Menopause Society and The International Society for the Study of
620 Women's Sexual Health. *Menopause.* 2018;25(6):596-608.
621 doi:10.1097/GME.0000000000001121

- 622 25. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal
623 women. *Cochrane Database Syst Rev*. 2016;(8):CD001500.
624 doi:10.1002/14651858.CD001500.pub3
- 625 26. Wills S, Ravipati A, Venuturumilli P, et al. Effects of vaginal estrogens on serum estradiol
626 levels in postmenopausal breast cancer survivors and women at risk of breast cancer taking
627 an aromatase inhibitor or a selective estrogen receptor modulator. *J Oncol Pract*.
628 2012;8(3):144-148. doi:10.1200/JOP.2011.000352
- 629 27. Kendall A, Dowsett M, Folkerd E, Smith I. Caution: Vaginal estradiol appears to be
630 contraindicated in postmenopausal women on adjuvant aromatase inhibitors. *Ann Oncol Off*
631 *J Eur Soc Med Oncol*. 2006;17(4):584-587. doi:10.1093/annonc/mdj127
- 632 28. Eugster-Hausmann M, Waitzinger J, Lehnick D. Minimized estradiol absorption with ultra-
633 low-dose 10 microg 17beta-estradiol vaginal tablets. *Climacteric J Int Menopause Soc*.
634 2010;13(3):219-227. doi:10.3109/13697137.2010.483297
- 635 29. Santen RJ, Pinkerton JV, Conaway M, et al. Treatment of urogenital atrophy with low-dose
636 estradiol: preliminary results. *Menopause N Y N*. 2002;9(3):179-187.
- 637 30. Simon J, Nachtigall L, Ulrich LG, Eugster-Hausmann M, Gut R. Endometrial safety of ultra-
638 low-dose estradiol vaginal tablets. *Obstet Gynecol*. 2010;116(4):876-883.
639 doi:10.1097/AOG.0b013e3181f386bb
- 640 31. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on
641 plasma estradiol levels. *Climacteric*. 2015;18(2):121-134.
642 doi:10.3109/13697137.2014.947254
- 643 32. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using
644 estrogen-only therapy. *Obstet Gynecol*. 2006;108(6):1354-1360.
645 doi:10.1097/01.AOG.0000241091.86268.6e
- 646 33. Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and
647 cardiovascular events in participants who used vaginal estrogen in the Women's Health
648 Initiative Observational Study. *Menopause N Y N*. 2018;25(1):11-20.
649 doi:10.1097/GME.0000000000000956
- 650 34. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease
651 risk in the Nurses' Health Study. *Menopause N Y N*. December 2018.
652 doi:10.1097/GME.0000000000001284
- 653 35. Ponzzone R, Biglia N, Jacomuzzi ME, Maggiorotto F, Mariani L, Sismondi P. Vaginal
654 oestrogen therapy after breast cancer: is it safe? *Eur J Cancer Oxf Engl 1990*.
655 2005;41(17):2673-2681. doi:10.1016/j.ejca.2005.07.015
- 656 36. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone
657 replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality.
658 *J Natl Cancer Inst*. 2001;93(10):754-762.

- 659 37. Le Ray I, Dell'Aniello S, Bonnetain F, Azoulay L, Suissa S. Local estrogen therapy and risk
660 of breast cancer recurrence among hormone-treated patients: a nested case-control study.
661 *Breast Cancer Res Treat.* 2012;135(2):603-609.
- 662 38. Shim S-H, Lee SJ, Kim S-N. Effects of hormone replacement therapy on the rate of
663 recurrence in endometrial cancer survivors: a meta-analysis. *Eur J Cancer Oxf Engl 1990.*
664 2014;50(9):1628-1637. doi:10.1016/j.ejca.2014.03.006
- 665 39. Guidozi F, Daponte A. Estrogen replacement therapy for ovarian carcinoma survivors: A
666 randomized controlled trial. *Cancer.* 1999;86(6):1013-1018.
- 667 40. Eeles RA, Morden JP, Gore M, et al. Adjuvant Hormone Therapy May Improve Survival in
668 Epithelial Ovarian Cancer: Results of the AHT Randomized Trial. *J Clin Oncol Off J Am Soc*
669 *Clin Oncol.* 2015;33(35):4138-4144. doi:10.1200/JCO.2015.60.9719
- 670 41. Guidozi F. Estrogen therapy in gynecological cancer survivors. *Climacteric J Int*
671 *Menopause Soc.* 2013;16(6):611-617. doi:10.3109/13697137.2013.806471
- 672 42. Kuhle CL, Kapoor E, Sood R, Thielen JM, Jatoi A, Faubion SS. Menopausal hormone
673 therapy in cancer survivors: A narrative review of the literature. *Maturitas.* 2016;92:86-96.
674 doi:10.1016/j.maturitas.2016.07.018
- 675 43. Berger L, El-Alfy M, Martel C, Labrie F. Effects of dehydroepiandrosterone, Premarin and
676 Acolbifene on histomorphology and sex steroid receptors in the rat vagina. *J Steroid*
677 *Biochem Mol Biol.* 2005;96(2):201-215. doi:10.1016/j.jsbmb.2005.02.018
- 678 44. Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone
679 (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal
680 atrophy, and of the genitourinary syndrome of menopause. *Menopause N Y N.*
681 2018;25(11):1339-1353. doi:10.1097/GME.0000000000001238
- 682 45. Bouchard C, Labrie F, Derogatis L, et al. Effect of intravaginal dehydroepiandrosterone
683 (DHEA) on the female sexual function in postmenopausal women: ERC-230 open-label
684 study. *Horm Mol Biol Clin Investig.* 2016;25(3):181-190. doi:10.1515/hmbci-2015-0044
- 685 46. Barton DL, Sloan JA, Shuster LT, et al. Evaluating the efficacy of vaginal
686 dehydroepiandrosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG
687 N10C1 (Alliance). *Support Care Cancer Off J Multinatl Assoc Support Care Cancer.*
688 2018;26(2):643-650. doi:10.1007/s00520-017-3878-2
- 689 47. Barton DL, Shuster LT, Dockter T, et al. Systemic and local effects of vaginal
690 dehydroepiandrosterone (DHEA): NCCTG N10C1 (Alliance). *Support Care Cancer Off J*
691 *Multinatl Assoc Support Care Cancer.* 2018;26(4):1335-1343. doi:10.1007/s00520-017-
692 3960-9
- 693 48. Labrie F, Martel C, Bérubé R, et al. Intravaginal prasterone (DHEA) provides local action
694 without clinically significant changes in serum concentrations of estrogens or androgens. *J*
695 *Steroid Biochem Mol Biol.* 2013;138:359-367.

- 696 49. Portman DJ, Labrie F, Archer DF, et al. Lack of effect of intravaginal
697 dehydroepiandrosterone (DHEA, prasterone) on the endometrium in postmenopausal
698 women. *Menopause N Y N*. 2015;22(12):1289-1295. doi:10.1097/GME.0000000000000470
- 699 50. Hodgins MB, Spike RC, Mackie RM, MacLean AB. An immunohistochemical study of
700 androgen, oestrogen and progesterone receptors in the vulva and vagina. *BJOG Int J Obstet*
701 *Gynaecol*. 1998;105(2):216–222.
- 702 51. Fernandes T, Costa-Paiva LH, Pinto-Neto AM. Efficacy of vaginally applied estrogen,
703 testosterone, or polyacrylic acid on sexual function in postmenopausal women: a randomized
704 controlled trial. *J Sex Med*. 2014;11(5):1262–1270.
- 705 52. Witherby S, Johnson J, Demers L, et al. Topical testosterone for breast cancer patients with
706 vaginal atrophy related to aromatase inhibitors: a phase I/II study. *The oncologist*.
707 2011;16(4):424–431.
- 708 53. Dahir M, Travers-Gustafson D. Breast cancer, aromatase inhibitor therapy, and sexual
709 functioning: a pilot study of the effects of vaginal testosterone therapy. *Sex Med*.
710 2014;2(1):8–15.
- 711 54. Melisko ME, Goldman ME, Hwang J, et al. Vaginal testosterone cream vs estradiol vaginal
712 ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for
713 early-stage breast cancer: a randomized clinical trial. *JAMA Oncol*. 2017;3(3):313–319.
- 714 55. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of
715 premature or early menopause and considerations for management. *Climacteric J Int*
716 *Menopause Soc*. 2015;18(4):483-491. doi:10.3109/13697137.2015.1020484
- 717 56. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone
718 therapy position statement of The North American Menopause Society. *Menopause N Y N*.
719 2017;24(7):728-753. doi:10.1097/GME.0000000000000921
- 720 57. Sturdee DW, Panay N, International Menopause Society Writing Group. Recommendations
721 for the management of postmenopausal vaginal atrophy. *Climacteric J Int Menopause Soc*.
722 2010;13(6):509-522. doi:10.3109/13697137.2010.522875
- 723 58. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice,
724 Farrell R. ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women
725 With a History of Estrogen-Dependent Breast Cancer. *Obstet Gynecol*. 2016;127(3):e93-96.
726 doi:10.1097/AOG.0000000000001351
- 727 59. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of
728 Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol Off J Am Soc*
729 *Clin Oncol*. 2016;34(6):611-635. doi:10.1200/JCO.2015.64.3809
- 730 60. Kwan K, Ward C, Marsden J. Is there a role for hormone replacement therapy after breast
731 cancer? *J Br Menopause Soc*. 2005;11(4):140-144.

- 732 61. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health
733 outcomes during the intervention and extended poststopping phases of the Women's Health
734 Initiative randomized trials. *Jama*. 2013;310(13):1353–1368.
- 735 62. Liotta M, Escobar PF. Hormone replacement after breast cancer: is it safe? *Clin Obstet*
736 *Gynecol*. 2011;54(1):173-179. doi:10.1097/GRF.0b013e3182083cbb
- 737 63. von Schoultz E, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal hormone
738 therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst*.
739 2005;97(7):533-535. doi:10.1093/jnci/dji071
- 740 64. Fahlén M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast
741 cancer: 10 year follow up of the Stockholm randomised trial. *Eur J Cancer*. 2013;49(1):52-
742 59. doi:10.1016/j.ejca.2012.07.003
- 743 65. Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS, Gynecologic Oncology Group
744 Study. Randomized double-blind trial of estrogen replacement therapy versus placebo in
745 stage I or II endometrial cancer: a Gynecologic Oncology Group Study. *J Clin Oncol Off J*
746 *Am Soc Clin Oncol*. 2006;24(4):587-592. doi:10.1200/JCO.2005.02.8464
- 747 66. Stewart LE, Beck TL, Giannakopoulos NV, Rendi MH, Isacson C, Goff BA. Impact of
748 oophorectomy and hormone suppression in low grade endometrial stromal sarcoma: A
749 multicenter review. *Gynecol Oncol*. 2018;149(2):297-300. doi:10.1016/j.ygyno.2018.03.008
- 750 67. van Meurs HS, van der Velden J, Buist MR, van Driel WJ, Kenter GG, van Lonkhuijzen
751 LRCW. Evaluation of response to hormone therapy in patients with measurable adult
752 granulosa cell tumors of the ovary. *Acta Obstet Gynecol Scand*. 2015;94(11):1269-1275.
753 doi:10.1111/aogs.12720
- 754 68. van Meurs HS, van Lonkhuijzen LRCW, Limpens J, van der Velden J, Buist MR. Hormone
755 therapy in ovarian granulosa cell tumors: a systematic review. *Gynecol Oncol*.
756 2014;134(1):196-205. doi:10.1016/j.ygyno.2014.03.573
- 757 69. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic
758 low-grade endometrial stromal sarcoma: single center experience with 10 cases and review
759 of the literature. *Gynecol Oncol*. 2006;101(3):464-469. doi:10.1016/j.ygyno.2005.11.010
- 760 70. Kapp DS, Shin JY, Chan JK. Prognostic factors and survival in 1396 patients with uterine
761 leiomyosarcomas: emphasis on impact of lymphadenectomy and oophorectomy. *Cancer*.
762 2008;112(4):820-830. doi:10.1002/cncr.23245
- 763 71. Garg G, Shah JP, Liu JR, et al. Validation of tumor size as staging variable in the revised
764 International Federation of Gynecology and Obstetrics stage I leiomyosarcoma: a
765 population-based study. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc*.
766 2010;20(7):1201-1206. doi:10.1111/IGC.0b013e3181e9d0ba

- 767 72. Del Carmen MG, Rice LW. Management of menopausal symptoms in women with
768 gynecologic cancers. *Gynecol Oncol.* 2017;146(2):427-435.
769 doi:10.1016/j.ygyno.2017.06.013
- 770 73. Non-Epithelial Ovarian Cancer | ESMO Clinical Practice Guidelines | ESMO.
771 <https://www.esmo.org/Guidelines/Gynaecological-Cancers/Non-Epithelial-Ovarian-Cancer>.
772 Accessed July 28, 2019.
- 773 74. Deli T, Orosz M, Jakab A. Hormone Replacement Therapy in Cancer Survivors - Review of
774 the Literature. *Pathol Oncol Res POR.* January 2019. doi:10.1007/s12253-018-00569-x
- 775 75. Ploch E. Hormonal replacement therapy in patients after cervical cancer treatment. *Gynecol*
776 *Oncol.* 1987;26(2):169-177.
- 777 76. Diethylstilbestrol (DES) and Cancer. National Cancer Institute.
778 <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet>.
779 Published October 5, 2011. Accessed July 28, 2019.
- 780 77. Eigeliene N, Kangas L, Hellmer C, Kauko T, Erkkola R, Härkönen P. Effects of ospemifene,
781 a novel selective estrogen-receptor modulator, on human breast tissue ex vivo. *Menopause.*
782 2016;23(7):719–730.
- 783 78. Simon JA, Lin VH, Radovich C, Bachmann GA, Group OS. One-year long-term safety
784 extension study of ospemifene for the treatment of vulvar and vaginal atrophy in
785 postmenopausal women with a uterus. *Menopause.* 2013;20(4):418–427.
- 786 79. Melisko ME, Narus JB. Sexual Function in Cancer Survivors: Updates to the NCCN
787 Guidelines for Survivorship. *J Natl Compr Cancer Netw JNCCN.* 2016;14(5 Suppl):685-689.
- 788 80. Schover LR, Fife M, Gershenson DM. Sexual dysfunction and treatment for early stage
789 cervical cancer. *Cancer.* 1989;63(1):204-212. doi:10.1002/1097-
790 0142(19890101)63:1<204::AID-CNCR2820630133>3.0.CO;2-U
- 791 81. Schroder M, Mell LK, Hurteau JA, et al. Clitoral therapy device for treatment of sexual
792 dysfunction in irradiated cervical cancer patients. *Int J Radiat Oncol Biol Phys.*
793 2005;61(4):1078–1086.
- 794 82. Brotto LA, Yong P, Smith KB, Sadownik LA. Impact of a multidisciplinary vulvodynia
795 program on sexual functioning and dyspareunia. *J Sex Med.* 2015;12(1):238-247.
796 doi:10.1111/jsm.12718
- 797 83. Goldstein I, Dicks B, Kim NN, Hartzell R. Multidisciplinary overview of vaginal atrophy
798 and associated genitourinary symptoms in postmenopausal women. *Sex Med.* 2013;1(2):44-
799 53. doi:10.1002/sm2.17
- 800 84. Rullo J, Faubion SS, Hartzell R, et al. Biopsychosocial Management of Female Sexual
801 Dysfunction: A Pilot Study of Patient Perceptions From 2 Multi-Disciplinary Clinics. *Sex*
802 *Med.* 2018;6(3):217-223. doi:10.1016/j.esxm.2018.04.003

- 803 85. Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of
804 clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet*
805 *Gynecol.* 2016;215(6):704-711. doi:10.1016/j.ajog.2016.07.045
- 806 86. Althof SE. Sex therapy and combined (sex and medical) therapy. *J Sex Med.*
807 2011;8(6):1827-1828. doi:10.1111/j.1743-6109.2011.02306.x
- 808 87. van Lankveld JJDM, Granot M, Weijmar Schultz WCM, et al. Women's sexual pain
809 disorders. *J Sex Med.* 2010;7(1 Pt 2):615-631. doi:10.1111/j.1743-6109.2009.01631.x
- 810 88. Faubion SS, Shuster LT, Bharucha AE. Recognition and Management of Nonrelaxing Pelvic
811 Floor Dysfunction. *Mayo Clin Proc.* 2012;87(2):187-193. doi:10.1016/j.mayocp.2011.09.004
- 812 89. Tu FF, As-Sanie S, Steege JF. Musculoskeletal causes of chronic pelvic pain: a systematic
813 review of existing therapies: part II. *Obstet Gynecol Surv.* 2005;60(7):474-483.
- 814 90. Beji NK, Yalcin O, Erkan HA. The effect of pelvic floor training on sexual function of
815 treated patients. *Int Urogynecol J Pelvic Floor Dysfunct.* 2003;14(4):234-238; discussion
816 238. doi:10.1007/s00192-003-1071-2
- 817 91. Rosenbaum TY. REVIEWS: Pelvic Floor Involvement in Male and Female Sexual
818 Dysfunction and the Role of Pelvic Floor Rehabilitation in Treatment: A Literature Review.
819 *J Sex Med.* 2007;4(1):4-13. doi:10.1111/j.1743-6109.2006.00393.x
- 820 92. - Section on Women's Health. <https://www.womenshealthapta.org/>. Accessed May 8, 2019.
- 821 93. Faubion SS, Sood R, Kapoor E. Genitourinary Syndrome of Menopause: Management
822 Strategies for the Clinician. *Mayo Clin Proc.* 2017;92(12):1842-1849.
823 doi:10.1016/j.mayocp.2017.08.019
- 824
- 825
- 826
- 827
- 828
- 829
- 830
- 831
- 832
- 833
- 834
- 835
- 836
- 837
- 838
- 839
- 840

841 **Table 1**
 842 **Factors to consider prior to prescribing vaginal hormones in breast cancer patients**

	More desirable candidates	Less desirable candidates
Stage of disease	Stage 0-2, or metastatic with limited life expectancy	Stage 3, or metastatic with extended life expectancy
Grade of disease	Low-intermediate grade	High grade
Lymph node involvement	No	Yes
Hormone receptor status	Negative	Positive
Endocrine therapy	Tamoxifen	Aromatase inhibitors
Risk of recurrence	Low	High
Time since diagnosis	Remote	Recent
Symptom severity	Severe	Mild
Nonhormone therapies	Failed	Effective
Effect on quality of life	Severe	Mild

843 Adapted from NAMS/ISSWSH Consensus Recommendations²⁴

844
 845
 846
 847
 848
 849
 850
 851
 852
 853
 854
 855
 856
 857
 858
 859
 860
 861
 862
 863
 864
 865
 866
 867
 868
 869
 870
 871
 872
 873
 874

875 **Table 2**
876 **Characteristics of the local vaginal hormonal treatments**

Formulation	Brand name	Generic Available	Usual Clinical Dosing	Comments
<i>Low-Dose Vaginal Estrogen</i> (serum estradiol <20pg/ml)				
4 mcg estradiol insert	Imvexxy	No	1 insert daily for 2 weeks, then 1 insert twice weekly	Formulated as a medium-chain triglyceride
7.5 mcg estradiol ring	Estring	No	1 ring per vagina every 90 days	Should not be confused with Femring, which is a systemic vaginal estrogen ring
10 mcg insert and tablet	Imvexxy and Vagifem	Yuvafem	1 insert daily for 2 weeks, then 1 insert twice weekly	
<i>Moderate-Dose Vaginal Estrogen</i> (serum estradiol >20pg/ml, intermittently)				
0.5g (0.3mg) CEE cream	Premarin vaginal cream (0.625 mg/g)	No	0.5-1g 1-3 times per week	FDA approved frequency includes daily for 21 days then off 7 days, but may lead to higher systemic absorption
<i>Higher-Dose Vaginal Estrogen</i> (serum estradiol can intermittently reach premenopausal levels)				
≥ 1 gm (0.625mg) CEE cream	Premarin vaginal cream (0.625 mg/g)	No	0.5-1g 1-3 times per week	FDA approved dose is up to 2g which may lead to higher systemic absorption
≥ 0.5 gm (50 mcg) estradiol cream	Estrace cream (100mcg/gm)	Estradiol	0.5-1g daily for 2 weeks, then twice per week	FDA approved dose: 2-4g daily, then 1g 1-3 times per week
<i>Vaginal DHEA</i>				
6.5mg (0.5%) DHEA insert	Intrarosa, Prasterone	No	1 insert daily	

877 Adapted from ACOG Committee Opinion #659⁴⁵, Santen et al³¹, Faubion et al⁹³

878 CEE = conjugated equine estrogen

879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923

924 **Table 3**
 925 **Recommendations for local hormone therapy based on female cancer type and**
 926 **characteristics**

Recommendations for local hormonal therapy (HT) based on female cancer type and characteristics		
Patient Population	Recommendation	Note
<i>General Guidelines</i>	Individualize therapy (see Table 1)	
	Use nonhormonal therapy first-line	
	Involve treating oncologist in decisions regarding HT use	
	Avoid off-label medications (vaginal testosterone, estriol)	
	Consider laser therapy, with appropriate counseling regarding limited data on use	
Further recommendations after above general guidelines have been considered and nonhormonal therapies have failed:		
Breast Cancer		
<i>ER+ breast cancer, on tamoxifen</i>	If favorable factors (see Table 1), local HT* is an option	Tamoxifen is an ER antagonist in breast tissue, any absorbed estrogen may be blocked
<i>ER+ breast cancer, on aromatase inhibitor (AI)</i>	Caution in considering local HT; review with oncologist, consider switching to tamoxifen	AIs block conversion of androgen to estrogen, goal is very low serum estradiol levels; GSM symptoms often severe
<i>Triple-neg breast cancer</i>	Local HT is an option, counsel on limited data	No known negative effects, data limited
Uterine Cancer		
<i>Type I (estrogen-dependent) endometrial cancer</i>	Local HT is an option, counsel on limited data	Prematurely closed randomized trial with HT vs placebo showed no increased recurrence risk, small sample size ⁶⁴
<i>Type II (estrogen-independent) endometrial cancer</i>		
<i>Uterine carcinosarcoma</i>		No known negative effects, data limited
<i>Endometrial stromal sarcoma</i>	Caution in considering local HT, counsel on limited data	Hormonally active tumor, data limited
<i>Uterine leiomyosarcoma</i>	Caution in considering local HT, counsel on limited data	Tumor is often ER/PR+, data limited
Ovarian Cancer		
<i>High Grade Serous</i>	Local HT is an option. Consider systemic HT if premenopausal or postmenopausal with symptoms.	Survival benefit and improved relapse-free survival seen in symptomatic pre- and postmenopausal patients on systemic HT after surgery ⁴⁰
<i>Endometrioid</i>	Caution in considering local HT,	Hormonally active tumor,

<i>Sex cord stromal (eg granulosa cell)</i>	counsel on limited data	data limited
<i>Germ cell</i>	Local HT is an option	No known risks, data limited
Cervical Cancer		
<i>Squamous cell</i>	Local HT is an option	Systemic HT has equivalent recurrence risk and survival compared to control ⁷⁴ No known risks given not hormonally active, no contraindication to HT
<i>Adenocarcinoma</i>		
Vulvar/Vaginal Cancer		
<i>Squamous cell</i>	Local HT is an option	No known risks, data limited
<i>Adenocarcinoma</i>		
Special Populations		
<i>Clear cell adenocarcinoma (cervical, vulvar or vaginal)</i>	Caution in considering local HT, counsel on limited data	Possibly hormonally responsive, data limited
<i>DES exposure</i>		

927 Adapted from NAMS/ISSWSH Consensus Recommendations²⁴, ACS/ASCO Breast Cancer
 928 Survivorship Guidelines⁵⁹, Deli et al⁷³
 929 HT, hormone therapy; ER, estrogen receptor; AI, aromatase inhibitor; GSM, genitourinary
 930 syndrome of menopause; PR, progesterone receptor; DES, diethylstilbestrol.
 931 *Local hormone therapies are vaginal estrogen and intravaginal DHEA (prasterone).