Breast Cancer, Aromatase Inhibitor Therapy, and Sexual Functioning: A Pilot Study of the Effects of Vaginal Testosterone Therapy

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Conflict of Interest

Melissa Dahir is a speaker for Warner Chilcott.

Key Words

Breast neoplasms, Aromatase inhibitors, Testosterone, Sexual dysfunction, Quality of life

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Abstract

Introduction. Women with breast cancer have better cancer-related outcomes with the use of aromatase inhibitors (AIs), but the physiological suppression of estradiol can negatively affect sexual functioning due to unpleasant urogenital and vaginal symptoms. Local health care practitioners have observed that the benefits of vaginal testosterone in allaying these unpleasant symptoms in women with breast cancer are similar to the benefits of vaginal estrogen in women without breast cancer.

Aim. To evaluate the effects of using a daily vaginal testosterone cream on the reported sexual health quality of life in women with breast cancer taking AI therapy.

Methods. Thirteen postmenopausal women with breast cancer on AI therapy and experiencing symptoms of sexual dysfunction were recruited from an oncology practice. The women were prescribed a 300 microgram (μg) testosterone vaginal cream daily for 4 weeks. During the first study visit, a vaginal swab was obtained to rule out the presence of *Candida* species or *Gardnerella vaginalis* in participants. Women with positive vaginal swabs were treated prior to starting the vaginal testosterone therapy.

Main outcome measure. The Female Sexual Function Index (FSFI) survey, measuring female sexual health quality of life, was administered during the first study visit and at the final study visit, after completing testosterone therapy.

Results. Twelve patients completed four weeks of daily vaginal testosterone therapy. When compared to baseline FSFI scores, there was a statistically significant improvement for individual domain scores of desire (P=0.000), arousal (P=0.002), lubrication (P=0.018), orgasm (P=.005), satisfaction (P=0.001), and pain (P=0.000).

Total domain scores reflecting sexual health quality of life also improved when compared to baseline (P=0.000).

Conclusions. The use of a compounded testosterone vaginal cream applied daily for four weeks improves reported sexual health quality of life in women with breast cancer taking AIs.

Introduction

Breast cancer is the most common type of malignancy among women in the United States [1]. The advanced technology of mammography screening offers early detection and diagnosis of breast cancer. In the United States, about 75% of breast cancers are diagnosed in postmenopausal women and 80% of them are estrogen receptor-positive [2]. The recommended treatment for postmenopausal women with hormone-receptor positive cancers is estrogen deprivation through the use of adjuvant endocrine therapy, such as an aromatase inhibitor (AI). AIs inhibit the synthesis of estrogen by preventing the aromatase enzyme from converting androgens to estrogens [3]. Third-generation AIs suppress up to 98% of circulating hormones and are considered to be first-line treatment [4].

Women with breast cancer have better cancer-related outcomes with the use of AIs, but side effects from the medication can negatively affect sexual functioning due to the physiologic suppression of estradiol [4-6]. As a result, women taking AIs are more likely to experience a decreased sexual quality of life due to unpleasant urogenital and vaginal symptoms [7-9]. In 2008, Antoine et al. surveyed women with breast cancer for reported quality of life concerns during AI treatment. When compared to non-AI users, women taking AIs had significantly higher rates of: vaginal dryness (P=0.01); decreased sexual desire (P<0.02); dissatisfaction with their sexual life (P<0.01); and sexual dysfunction (P<0.001) [7].

Baumgart et al. (2011) reported in a population-based study that nearly 600,000 women in the United States currently take AIs, and that these women are two times more likely than non-treated women to report symptoms of vulvovaginal atrophy and painful

intercourse. Baumgart and colleagues evaluated subjective symptoms related to endocrine changes, such as estrogen deficiency, using the Endocrine Subscale of the Functional Assessment of Cancer Therapy-Breast (FACT-B) tool. Fifty-eight percent of participants reported moderate to severe symptoms of vaginal atrophy, 42% reported vaginal dryness, and 62% reported pain or discomfort during intercourse [8].

Testosterone. Testosterone therapy has been prescribed off-label for women since the early 1900s. At the turn of the last century, little safety data existed on the use of testosterone in women, and health care providers prescribed testosterone based on professional observations in the clinical setting [10]. Testosterone is a U.S. Food and Drug Administration (FDA) approved drug, but currently, the FDA has not approved a vaginal testosterone medication for the treatment of vulvovaginal symptoms and negative sexual side effects related to AI use [11]. The lack of treatment options is concerning because the number of women diagnosed with breast cancer continues to increase; their longevity, also, continues to increase with the use of newer adjuvant chemotherapies [4, 12]. Testosterone is available off-label, by prescription, to women through compounding pharmacies that are licensed and regulated at the state level [13]. Pharmaceutical compounding requires sterile technique and a detailed process to ensure the right drug, weight, and dose; even distribution of the chemical throughout the base; and proper distribution of the compounded medication through the base, such as a cream.

There is limited research regarding the safety and efficacy of using local vaginal hormones to alleviate symptoms associated with AI treatment. The concurrent use of AIs with vaginal estrogen is generally not recommended because local estrogen may interfere with the drug's ability to suppress endogenous estrogen production. Available evidence

suggests that the use of topical vaginal testosterone may be an appropriate alternative to vaginal estrogen treatment in women with breast cancer who take AIs [14, 15]. At the American Society of Clinical Oncology Breast Cancer Symposium, Glaser (2010) reported findings from a proof-of-concept study using testosterone/anastrozole subcutaneous implants in women with breast cancer. The study included 43 women with breast cancer, 40 of whom had estrogen-receptor positive cancers. Serum estradiol and testosterone levels were drawn two weeks after each insertion and about 93% of serum estradiol levels were less than or equal to 30 picograms per milliliter (pg/mL) (the normal range of serum estradiol levels is less than 41 pg/mL in postmenopausal women) [16]. All women reported relief of vulvovaginal symptoms related to hormone deficiency, there was no recurrence or progression of breast cancer over three years, and no associated adverse events were reported. The researcher concluded that subcutaneous implants of anastrozole/testosterone provide therapeutic levels of testosterone and do not cause elevated estradiol levels [14].

Witherby et al. (2011) also recognized the need for an alternative to vaginal estrogen to treat vaginal atrophy in women with breast cancer who take AIs. Uncertainty about whether the use of vaginal estrogen with AIs decreases the efficacy of breast cancer treatment led to this phase I/II pilot study. Two groups of patients (N=20) received different daily dosages of testosterone in a compounded vaginal cream. Ten study participants received a daily 300μg dose of testosterone and 10 participants used a 150μg dose of testosterone daily. The researchers concluded, per participant report, that a 4-week course of vaginal testosterone improved symptoms of vaginal atrophy without increasing estradiol or testosterone levels [15].

Aim

Testosterone is an important hormone for female sexual functioning because it facilitates sexual response through increased blood flow, vaginal and clitoral engorgement, sensation, and lubrication [17, 18]. Local health care practitioners have observed that the benefits of vaginal testosterone for sexual health in women with breast cancer are similar to the benefits of vaginal estrogen in women without breast cancer. The aim of the present pilot study was to evaluate the effects of using a daily vaginal testosterone cream on the reported sexual health quality of life in women with breast cancer who take AI therapy.

Methods

The pilot study was approved by the Creighton University Institutional Review Board and registered with Clinicaltrials.gov. Participants were prospectively recruited from Nebraska Cancer Specialists in Omaha, NE, between January 11, 2013, and April 23, 2013. The target population was women with breast cancer who take AI therapy such as anastrozole, letrozole, or exemestane. Eligible participants included women who: (a) were diagnosed with breast cancer and currently on AI therapy; (b) had reported urogenital/vulvovaginal symptoms, such as vaginal dryness and pain with intercourse; (c) had reported changes in sexual health quality of life/sexual functioning since starting AI therapy; (d) were older than age 50 years; and (e) were postmenopausal (two years since last menstrual cycle). The exclusion criteria included: (a) the use of other treatments for breast cancer, such as chemotherapy or radiation, within the past 12 months, (b) a known sensitivity to medications containing testosterone, and (c) the use of exogenous hormone

replacement therapy (HRT) in the past three months, including systemic and local estrogen or testosterone therapy.

Study setting and procedures. Midwest Cancer Center Legacy in Omaha, NE, was the setting for conduct of the study, meetings with participants, and data collection. The principal investigator (PI) procured initial and ongoing study consent and served as the sole educator throughout the study. Participants gave written informed consent prior to enrolling in the study.

During the first study visit, the PI conducted interviews and performed a physical examination. The PI procured a vaginal swab (Affirm, Becton Dickinson, Franklin Lakes, NJ) prior to prescribing testosterone therapy because women with suppressed estrogen levels have an increased risk of infection. A decrease in vaginal secretions reduces lactic acid production by lactobacilli, increases the vaginal pH, and predisposes the vulvovaginal area to infection [19-21]. In the clinical setting, the PI has observed that women who develop a yeast (*Candida* species) or bacterial (*Gardnerella vaginalis*) infection while using vaginal testosterone frequently report symptoms of vaginal itching, burning, or irritation.

Participants with a negative vaginal swab were prescribed a vaginal testosterone cream, and those with positive results were treated prior to starting the intervention. Participants who were treated for a vaginal infection did not have a repeat vaginal swab because a test of cure is not standard of care when the symptoms have resolved [22, 23]. The vaginal testosterone cream was prepared by Precision, a licensed compounding pharmacy in Omaha, NE, and given to the participants at no cost. The study drug was supplied in prefilled syringes and each 0.5 milliliter (mL) dose delivered 300μg of

testosterone daily. The PI demonstrated proper application of the vaginal testosterone cream and participants were instructed to apply 0.5 mL to the vaginal opening and clitoris once daily for four weeks (28 days). A treatment application protocol was followed to ensure consistency among participants in the application of the vaginal testosterone cream. A mirror was used to demonstrate application of the topical testosterone vaginal cream. After the physical examination, the patient was reinstructed on how to apply the vaginal testosterone cream using a diagram of the vulva.

Main Outcome Measure

The primary end point of the study was to evaluate the impact of using vaginal testosterone cream on sexual health quality of life. Participants completed the Female Sexual Function Index (FSFI) questionnaire prior to starting testosterone therapy (pretest) and repeated the questionnaire after using the testosterone cream for four weeks (posttest). The FSFI is a 19-item multidimensional self-administered questionnaire and takes about 15 minutes to complete. The questionnaire assesses six dimensions of sexual functioning over the previous four weeks. The dimensions are related to desire, arousal, lubrication, orgasm, and satisfaction; a total FSFI score less than 26.5 is suggestive of female sexual dysfunction.

The FSFI questionnaire was constructed by a group of experts in female sexual functioning to ensure face validity and that the questions were not biased, and to determine the ease of administration and scoring [24]. The questionnaire was revised, administered to a larger sample, and re-administered after two to four weeks to establish test-retest reliability. Reliability has been supported in numerous studies [25-27]. The original researchers granted permission to use the FSFI questionnaire free of charge, and

requested that publications using the FSFI questionnaire be emailed to the original researchers.

Statistics

The quasi-experimental pilot study involved a one-group pre-posttest design using the FSFI questionnaire and participants serving as their own controls. The data were collected, recorded, and analyzed using SPSS 21.0 for Macintosh (SPSS, Inc, Chicago IL, USA). The demographics and characteristics of participants were analyzed by descriptive statistics. The FSFI scores were analyzed by paired *t*-test and presented as mean, standard deviation, *t*-score, and probability (*P*) value. The *P* value was considered statistically significant if $P<0.05$.

Results

There were no participant reports of serious adverse events to vaginal testosterone therapy. Of the 13 women enrolled in the study, one withdrew due to recurrent *Gardnerella vaginalis*. Per study protocol, her bacterial vaginal infection was treated prior to starting testosterone therapy, and the participant used the study drug for two weeks. After two weeks, the participant reported symptoms of a recurrent vaginal infection and burning discomfort with application of the testosterone cream.

Table 1 shows the participant demographics. The participants were between the ages of 50 and 69. The mean age of participants was 59.67 years of age. All of the participants were married and most of them (91.7%) had been married for more than 20 years. Forty-one percent were married 21 to 25 years, 16.7% were married 31 to 35 years, and 16.7% were married 36 to 40 years. Most of the participants were overweight

(41.7%) or obese (41.7%) by BMI (body mass index) criteria. All participants were high school graduates and most of them (33.3%) completed a bachelor's degree. Two of the participants shared their thoughts about participating in the study. One participant stated, "I did not tell my husband about the study because I did not want to get his hopes up. He has been patient and I feel bad for him. I hope you can help me." Another participant stated, "My husband doesn't know I am here today. I want to surprise him on Valentine's Day."

Table 2 shows additional characteristics of the participants. One-third of the participants were surgically postmenopausal (surgical removal of ovaries). Anastrozole was the most commonly prescribed AI therapy (91.7%), 8.3% were taking letrozole, and none of the participants were taking exemestane. Twenty-five percent of the participants were positive for *Gardnerella vaginalis* at the initial screening, treated successfully prior to study intervention, and none of them were positive for *Candida* species. Upon completion of the study, 91.7% of the participants decided to continue use of vaginal testosterone therapy and several participants offered qualitative feedback (See Table 3).

All FSFI domain scores increased after using the testosterone vaginal cream and the findings were statistically significant. The individual mean pre-treatment to post-treatment domain scores were as follows: desire: 1.35 to 2.65, P=0.000; arousal: 1.2 to 2.83, P=0.002; lubrication: 1.18 to 2.68, P=0.018; P=0.005 for orgasm; P=0.001 for satisfaction; and P=0.000 for pain (See Table 3).

The total FSFI posttest scores improved for all participants when compared to baseline FSFI scores. Two of the participants had a total posttest score greater than 26.5

(a total FSFI score less than 26.5 is suggestive of sexual dysfunction) (See Figure 1). The total mean FSFI scores improved from pre-treatment to post-treatment (8.69 to 18.78, *P*=0.000). Although this finding was statistically significant, the mean post-treatment score was less than 26.5 and suggests continued female sexual dysfunction (See Table 4).

Discussion and Implications

Health care providers, regardless of their specialty, should proactively assess sexual health in women with breast cancer who are taking AIs because they may experience a decrease in quality of life and sexual functioning due to side effects from adjuvant endocrine therapy, typically AIs [7-9]. However, AIs are currently the first-line treatment for hormone receptor-positive tumors in postmenopausal women due to better cancer-related outcomes [4, 28]. Although research regarding the use of testosterone replacement in women with breast cancer who take AIs is limited, the findings from this pilot study suggest the use of daily testosterone 300 μg vaginal cream for four weeks reduces unpleasant urogenital and vaginal symptoms and improves related sexual health quality of life in women with breast cancer on AI therapy. Next, the pilot study revealed an unexpected secondary outcome regarding the discovery of *Gardnerella vaginalis* in several participants during the baseline assessment. The clinical assessment findings align with prior research suggesting that women with compromised ovarian functioning have an increased risk for developing a vaginal infection; as such, the presence of any vaginal infection must be ruled out prior to starting testosterone therapy [19-21]. Finally, vaginal testosterone may be a safe and efficacious alternative to estrogen in women suffering from the negative sexual side effects related to the use of AIs [14, 15].

Limitations of this pilot study included the narrow time frame for enrollment, the exclusion of surgically menopausal women under the age of 50, and the presence of recurrent *Gardnerella vaginalis*. The small sample size was another limitation; however, the purpose of conducting a pilot study is to critique the study procedure, identify problems with data collection, and improve the design for an expanded study [29]. Some patients declined participation in the study due to the traveling distance for study visits. Other patients declined participation because they identified situational factors that would likely inhibit sexual activity during the four-week study. The situational factors included caring for a daughter with poor health, no sexual activity due to a long-distance relationship, and a second surgery for breast reconstruction had been scheduled during the enrollment time frame. The following potential threats to validity were identified: participants may not represent women with breast cancer who take AIs in the general population; sexual functioning may have been affected by history or events such as relationship conflict, stress, or vacation; and non-adherence with using the vaginal testosterone cream as demonstrated and prescribed.

Conclusions

Sexual health is a state of physical, emotional, mental, and social well-being [30]. The domains of sexual functioning (desire, arousal, lubrication, orgasm, satisfaction, and pain) often do not occur as a single diagnosis [24]. Rather, each domain seems to have a "domino effect" in which multiple problems with sexual functioning can coexist [31]. It is not professional, compassionate, or ethical for health care providers to ignore or dismiss sexual functioning, and doing so omits total disease management [31, 32]. Failure to assess sexual functioning in women with breast cancer who take AI therapy

could result in the patient feeling anxious or self-doubting; relationship conflict; decreased quality of life; and worsening of physical and mental health [33-35].

The assessment of sexual health requires a positive and respectful approach from all members of the health care team [30]. A gynecologic examination is a common intervention and a good opportunity to start a dialogue with the patient regarding sexual health and sexual dysfunction [31]. The open dialogue will allow the patient to ask questions and let her know that she can discuss concerns about sexual functioning in the future [36].

In closing, women with breast cancer who experience symptoms of sexual dysfunction due to AI therapy need to know about the possible risks and benefits to evidence-based treatment options. Results from the current pilot study suggest that daily topical testosterone treatment may be an effective therapy to support sexual health quality of life for women with breast cancer who are on AI therapy. Future prospective studies with larger sample sizes and more age-inclusive criteria are needed to establish the safety and efficacy of testosterone use in women with breast cancer who take AIs and how it relates to sexual dysfunction.

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Table 1

Demographics of Project Participants

	N=12	Percentage (%)	Mean
Age (years)			59.67
Body mass index			
18.5-24.9 (normal)	2	16.7	
25-29.9 (overweight)	5	41.7	
30.0 and above (obese)	5	41.7	
Marital status			
Married	12	100	
Not married	0	0	
Length of marriage			
0-5 years	1	8.3	
6-10 years	0	0	
11-15 years	0	0	
16-20 years	0	0	
21-25 years	5	41.7	
26-30 years	1	8.3	
31-35 years	2	16.7	
36-40 years	2	16.7	
41-50 years	0	0	
51-55 years	1	8.3	
Education			
High school degree	3	25	
Associate's degree	3	25	
Bachelor's degree	4	33.3	
Master's degree	2	16.7	

Table 2

Participant Characteristics

	N=12	Percentage (%)
Oophorectomy		
Yes	4	33.3
No	8	66.7
Aromatase Inhibitor		
Anastrozole (Arimidex)	11	91.7
Letrozole (Femara)	1	8.3
Exemestane (Aromasin)	0	0
Vaginal swab test		
No vaginal infection	9	75
Gardnerella vaginalis	3	25
Candidiasis species	0	0
Continued vaginal testosterone upon completion of study		
Yes	11	91.7
No	1	8.3

Table 3

Qualitative Feedback from Participants

- I never knew I had options. I hope you can help more women like me.
- After using the cream I was almost pain free – thank you for that.
- I no longer use Vagisil and I feel like my vaginal tissues have healed.
- I have noticed an increase in desire, but I still have pain.
- I feel like things opened up after using the testosterone cream.
- The testosterone cream caused moisture in my vagina within 24 hours of use. Prior to using the cream, there was no moisture.
- I thought there was no hope for me. Now I have moisture in my vagina and hardly any pain.
- I was really happy I did this. I always enjoyed cuddling with my husband, but I feel like I am more alert and aware about sexual thoughts. I have noticed increased clitoral sensitivity. I still have tenderness around my vaginal opening, but I am hoping it will get better.

Table 4

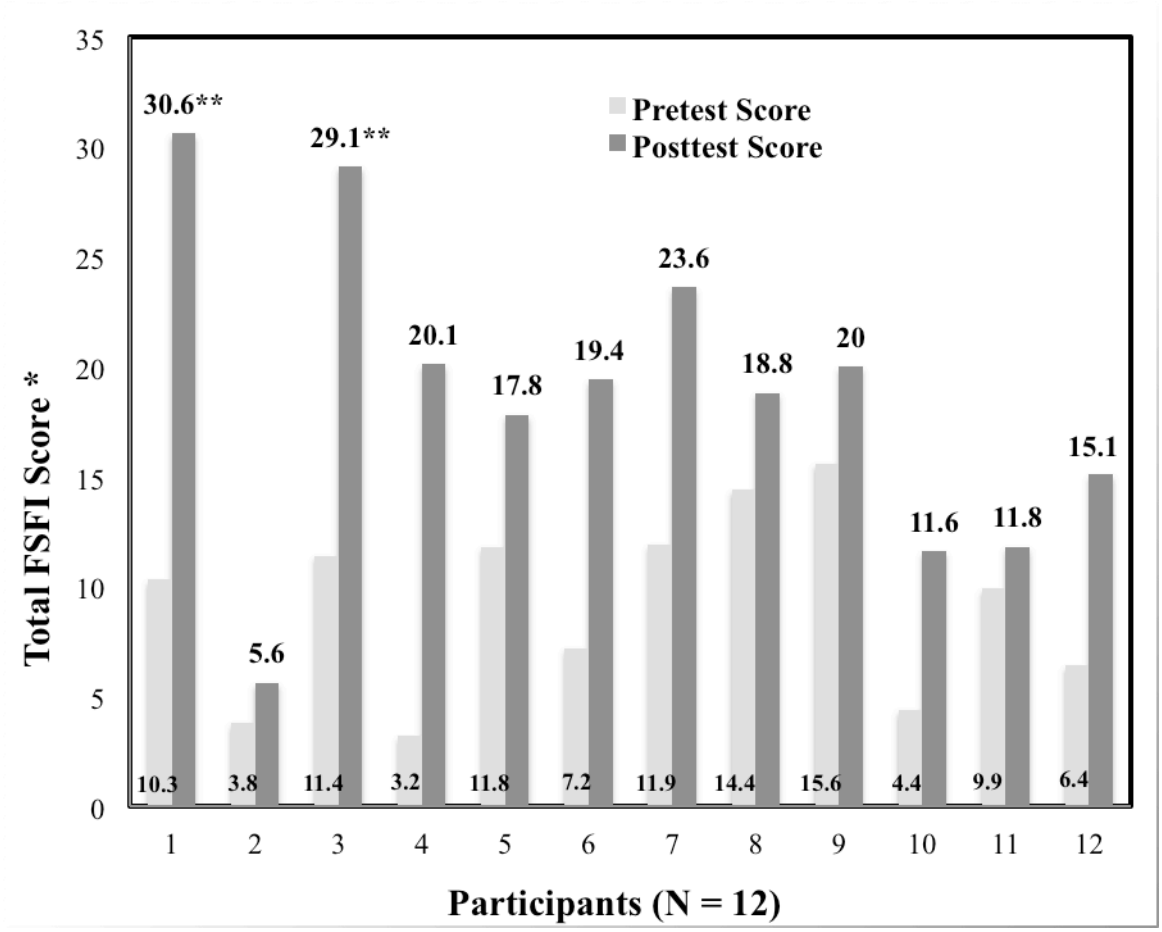
Female Sexual Function Index (FSFI) Questionnaire Results

	Mean score pre-treatment (SD)	Mean score post-treatment (SD)	*t* Score	*P* Value*
	N=12	N=12		
FSFI Domains				
Sexual desire (Score range 1.2 - 6)	1.35 (.37)	2.65 (.87)	-5.117	.000
Arousal (Score range 0 - 6)	1.2 (.68)	2.83 (1.26)	-4.113	.002
Lubrication (Score range 0 - 6)	1.18 (.62)	2.68 (1.93)	-2.770	.018
Orgasm (Score range 0 - 6)	1.73 (1.77)	2.93 (2.05)	-3.518	.005
Satisfaction (Score range 0.8 - 6)	2.3 (1.31)	4.2 (1.29)	-4.857	.001
Pain (Score range 0 - 6)	.93 (.88)	3.5 (2.28)	-4.960	.000
Total FSFI Score† (Score range 2 - 36)	8.69 (3.80)	18.78 (7.05)	-5.790	.000

*Derived from paired *t*-test
†A total FSFI score less than 26.5 suggests female sexual dysfunction

Figure 1

Total FSFI Scores for Individual Participants



*A total FSFI score less than 26.5 suggests female sexual dysfunction
**Participants with a total FSFI score greater than 26.5