Locating Pain in Breast Cancer Survivors Experiencing Dyspareunia
A Randomized Controlled Trial

Martha F. Goetsch, MD, MPH, Jeong Y. Lim, PhD, and Aaron B. Caughey, MD, PhD

OBJECTIVE: To locate sites of genital tenderness in breast cancer survivors not using estrogen who experience dyspareunia and to test the hypothesis that tenderness is limited to the vulvar vestibule rather than the vagina and is reversed by topical anesthetic.

METHODS: Postmenopausal survivors of breast cancer with moderate and severe dyspareunia were recruited for an examination including randomization to a double-blind intervention using topical aqueous 4% lidocaine or normal saline for 3 minutes to the areas found to be tender. Comparisons of changes in patients’ reported numerical rating scale values were made with the Wilcoxon rank-sum test with significance set at $P<.05$.

RESULTS: Forty-nine patients aged 37–69 years (mean 55.6±8.6 years) had a median coital pain score of 8 (interquartile range 7–9, scale 0–10). On examination, all women had tenderness in the vulvar vestibule (worst site 4 o’clock median 6, 4–7). In addition, one had significant vaginal mucosal tenderness and two had pelvic floor myalgia. All had vulvovaginal atrophy with 86% having no intravaginal discharge. Aqueous lidocaine 4% reduced the vestibular tenderness of all painful sites. For example, pain at the worst site changed from a median of 5 (4–7) to 0 (0–1) as compared with saline placebo, which changed the worst site score from 6 (4–7) to 4 (3–6) ($P<.001$). After lidocaine application, speculum placement was nontender in the 47 without either myalgia or vaginal mucosal tenderness.

CONCLUSION: In breast cancer survivors with dyspareunia, exquisite sensitivity was vestibular and reversible with aqueous lidocaine. Vaginal tenderness was rare despite severe atrophy.

(Obstet Gynecol 2014;123:1231–6)
DOI: 10.1097/AOG.0000000000000283

LEVEL OF EVIDENCE: I

A well-known symptom of low estrogen in postmenopause is dyspareunia. The therapy that has proven itself to be most effective is estrogen, but women with a history of breast cancer are warned not to use estrogen products. Genital complaints are frequent in breast cancer survivors, and there is an unmet need to address this problem.1

Studies of entry dyspareunia as a pain phenomenon have led to a focus on the vulvar vestibule both in premenopausal and postmenopausal women.2–4 Our group has published histopathologic findings that indicate that postmenopausal dyspareunia can be localized provoked vulvodynia.5

To reconsider concepts of genital atrophy and dryness as explanations for postmenopausal dyspareunia, our first research goal was to clarify the specific locations of tenderness in postmenopausal survivors of breast cancer who have consistent distressing dyspareunia. We performed focused examinations of the vulva, vagina, and pelvic floor using a study drug intervention. Our hypotheses are that mucosal tenderness is limited to the vulvar vestibule rather than the vagina and that it reverses temporarily with application of topical anesthetic, signifying a local pain condition rather than a condition of dryness.
MATERIALS AND METHODS

A randomized, double-blind, controlled study was conducted at the Women’s Health Research Unit of the Department of Obstetrics and Gynecology in Portland, Oregon, from January 2012 to June 2013. The institutional review boards of the Knight Cancer Institute and Oregon Health & Science University approved the study protocol.

This report describes the initial screening examination and focused use of topical lidocaine to be followed by randomized home intervention phases of the study. Postmenopausal patients experiencing dyspareunia were recruited by flyers in independent and hospital-affiliated oncology offices of three large health systems in Portland and in cancer support groups, both independent and hospital-affiliated. Inclusion criteria included a more than 1-year history of invasive breast cancer, use of no estrogen products for a minimum of 4 months, consistent pain with intercourse for at least 6 months severe enough to result in reduced penetrative intimacy (moderate dyspareunia) or abstinence (severe dyspareunia), 6,7 English-speaking, and age 18–70 years. Postmenopausal status was defined as more than 1 year without menses with accompanying climacteric symptoms, prior bilateral oophorectomy, or, in patients younger than age 55 years with ovaries but a prior hysterectomy, use of a luteinizing hormone agonist to suppress ovaries to allow antiestrogen medications. Participants were excluded if they had pelvic pain and deep dyspareunia, a diagnosis of pelvic floor myalgia, or vulvar dermatoses that could cause pain with intercourse.

Potential patients were administered an entry questionnaire with questions regarding demographics, gynecologic and menopause history, cancer history, dyspareunia, and medications. They underwent a screening examination as follows: a visual examination of the external genitalia evaluated atrophy relative to thinning, shrinkage of contours, and coloration (pallor, reddened, or focally reddened). Evidence of vulvar scarring was felt to indicate an inflammatory dermatosis and was cause for exclusion. The vulvar vestibule was examined by means of the cotton swab touch test at eight designated sites. A moist, small cotton-tipped applicator was lightly rolled over the following surfaces of the vestibule in consistent order: the anterior vestibule between the urethra and clitoris at 1:00, 11:00, and 12:00 and the paraphymen vestibule at 3:00, 4:00, 8:00, 9:00, and 6:00, referencing a clock face (Fig. 1). This order was so that the zones likely to be least tender were touched before the zones expected to be most tender so as not to immediately elevate the patient’s anticipation of pain. Participants were asked to respond using the Numerical Rating Scale with anchors of 0 (no pain) and 10 (the worst pain you have experienced).

After the initial touch test, the patients were randomized without restriction to have one of two study liquids applied to the vestibule mucosa for 3 minutes using three saturated large cotton swabs held in place by the examiner. The clear odorless liquids were labeled liquid A and liquid B. All participants (patient, examiner, and registered nurse assistant/scribe) were blinded to the examination liquids. Randomization was computer-generated by the research pharmacy using www.randomization.com. Allocation was concealed using sequentially numbered, sealed, opaque envelopes, opened only after the initial swab touch test was positive for tenderness. After the first liquid was applied for 3 minutes and a touch test repeated and scored, the other blinded liquid was applied and a touch test repeated and scored. Each patient received both study liquids without a washout period, and touch tests were performed and scored a total of three times. The primary outcome was the proportional change in tenderness at each vestibule site after the initial study liquid was applied. So as to allow pain-free insertion to assess upper genital structures, any spots of remaining tenderness were treated with topical lidocaine 4% until there was no annoying sensation to swab touch. Failure of topical lidocaine to correct allodynia indicated a diagnosis of generalized vulvodynia and was an exclusion item.

Fig. 1. The eight touch test sites in the vulvar vestibule are numbered in red, corresponding to the sequential order of touch. At each site in black is the median touch score (interquartile range) at baseline for the cohort. Artist: Robin M. Jensen. © 2014 Robin M. Jensen. Used with permission. Goetsch. Pain Site in Menopausal Dyspareunia. Obstet Gynecol 2014.
An internal examination was then performed in a serial manner; first, a digital examination of the perineal and lower paravaginal muscles, right and left, was performed, asking the patients to identify whether they felt pressure or tenderness or pain. Then a Pederson speculum modestly lubricated with water-based office lubricant was introduced for a visual examination of the vaginal mucosa, evaluating loss of vaginal rugae, color, and presence of any pooled or adherent discharge. Sensitivity of the vaginal mucosa was evaluated by asking the patient to rate the sensation (0–10) when two small cotton-tipped applicators were drawn lightly along the right and then the left vaginal wall from the upper vagina to the lower vagina. With these swabs, vaginal moisture was collected for microscopic and pH assessment. The microscopic examination evaluated a saline preparation, a potassium hydroxide preparation, and a Rakoff stain preparation for maturation of epithelial cells. The vaginal moisture sample from one swab was dabbed into a saline drop on each of three slides; to one was added potassium and to another was added Rakoff stain, a triphenylmethane dye. The second swab was rolled on pH paper that had color demarcations indicating pH 3–6.

The speculum was removed, and a digital examination assessed the upper paravaginal muscles for tenderness, checked for bladder tenderness, and for tenderness on bimanual examination. A secondary outcome was the location of additional sites of tenderness once the vestibule was nontender. Serum was drawn for follicle-stimulating hormone and estradiol testing.

Demographic characteristics were examined between randomized groups using Student’s t test or Wilcoxon rank-sum test depending on the normality of distribution for continuous variables and χ² or Fisher’s exact test for categorical variables. Comparisons of changes in patients’ reported numerical rating scale values used the two-tailed Wilcoxon rank-sum test with significance set at P < .05, because the distributions of changes in patients’ numerical rating scale were far from normal. Study data were collected and managed using REDCap electronic data capture tools hosted at Oregon Health & Science University. All statistical analyses were performed using SAS 9.3.

Sample size was calculated to achieve more than 90% power with a significance level of .05 using a two-tailed, two-sample t test. A total sample size of 44 was estimated to achieve 94% power to detect at least 1.5-points mean difference between treatment and placebo with consideration of a 10% placebo effect from a previously reported mean ± standard deviation of 8.0 ± 1.4 for untreated patients. This given sample size also achieved more than 90% power with non-parametric tests. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials suggests that reductions in pain intensity of at least 15–20%, or 1–2 points in the 0–10 scale, reflect clinically important changes. To compensate for possible withdrawal of 10% of patients in the at-home portion of the dyspareunia study, 50 participants were needed.

RESULTS

Fifty-one women were recruited for the screening examination. One was excluded as a result of undiagnosed lichen sclerosus, an exclusion criterion. One was excluded as a screen failure because she had mild dyspareunia. Forty-nine were examined fully and Table 1 details their demographic data. Ages ranged from 37 to 69 years (mean 55.6 ± 8.6 years). All were significantly hypoestrogenic as shown by low estradiol levels, median 5 (interquartile range 5–9.6; n = 46). For 46% who had ovarian function at diagnosis of breast cancer, therapy for their cancer induced ovarian failure. Before their cancer diagnosis, some patients had used supplemental estrogen after natural or surgical menopause, and the table notes the duration of time off estrogen before entering the study, which for some was shorter than the duration of ovarian absence or failure. One patient discontinued use of local estrogen and had a washout period of 4 months to qualify to enter the study. Types of prior breast carcinoma were ductal (80%) or lobular (18%) with one patient having both and two not being sure what their pathology was.

All patients had moderate or severe dyspareunia. The median coital pain score was 8 (interquartile range 7–9; scale 0–10). Details of the dyspareunia history are presented in Table 1. Six reported having had dyspareunia before their cancer diagnosis and for each, it was with surgical or natural menopause and was either mild or well treated with estrogen supplements until the cancer diagnosis, at which time antiestrogen therapy or reverting to natural menopause status worsened the dyspareunia significantly. Patients were compared with respect to presence or absence of ovaries and there was not a difference in scores for pain (0–10) with intercourse (P = .397) or baseline touch testing (P = .735). Patients presently using an aromatase inhibitor were compared with patients on no current hormone-manipulating therapy, and intercourse pain was not different (P = .134) nor was touch test pain (P = .327). Present use of a selective estrogen receptor modulator, namely tamoxifen in six and toremifene in one, was associated with less pain with intercourse, 6 (4–8) compared with 8 (7–10; P = .023), but no difference in touch test pain (P = .538) compared with no
current hormone-manipulating therapy. By recollection, 63% of patients said dyspareunia developed gradually but related the timeframe as months, not years, and 22% recalled having dyspareunia on resuming intercourse after chemotherapy or oophorectomy. Fifty percent stated that they had discontinued intercourse because of pain.

All patients had pallor, thinning, and shrinkage of the introital tissues indicating atrophy. Localized redness was visible next to the hymen remnants in 72%. No patients had a visible vaginal discharge at the introitus. Figure 1 shows the anatomic locations, order, and results of touch testing. Table 2 shows the median results both before and after initial application of a randomized liquid, saline, or 4% aqueous lidocaine. Base-line scores were not statistically different between groups. We considered saline to be a placebo. All sites could be made pain-free using 4% aqueous lidocaine before the internal examination was initiated.

The digital examination of perineal muscles was painful in one patient (2%), and levators (puborectalis) were painful in 12 (24%). Insertion of the speculum was pain-free in all patients except two with muscle tenderness and one described subsequently with mucosal tenderness. By visual inspection all patients had vaginal atrophy as judged by lack of rugae and pale or erythematous mucosa. Intravaginal discharge was absent in 42 (86%). Visible discharge was present in seven (14%) with appearance ranging from white and creamy (three) to gray (one) or watery (one) and serosanguineous (one). Those with the gray and watery discharges were on a selective estrogen receptor modulator. No examples of desquamative inflammatory vaginitis, candidal infection, or bacterial vaginosis were found.

The majority of patients (67%) rated light touch of the vaginal mucosa as minimally tender with a median numerical score of 1. The others said they could scarcely feel the swab strokes. One patient was distinctly more uncomfortable, rating touch at 5 and 8 and describing all insertional maneuvers such as prior intercourse and gynecologic examinations as very painful. To assess her pain more specifically, two large 4% lidocaine-saturated swabs were inserted into the vagina, one up to the cuff and the second to midvagina. They were left for 3 minutes, and after they were removed, the speculum and digital examinations in this patient were nontender.

From the moisture gathered along the vaginal sidewalls, pH values were checked using litmus paper.

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Saline (n=25)</th>
<th>4% Lidocaine (n=24)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.7±8.9</td>
<td>56.5±8.5</td>
<td>.467</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>22 (88)</td>
<td>21 (87.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>0</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>More than 1 race</td>
<td>2 (8)</td>
<td>1 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than 12th grade</td>
<td>23 (92)</td>
<td>20 (83.3)</td>
<td>.417</td>
</tr>
<tr>
<td>9–12th grade</td>
<td>2 (8)</td>
<td>4 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Years with present partner</td>
<td>25.2±11.7</td>
<td>26.1±12.9</td>
<td>.799</td>
</tr>
<tr>
<td>Years since diagnosis of breast cancer</td>
<td>6 (4–14)</td>
<td>2 (2–6.5)</td>
<td>.013</td>
</tr>
<tr>
<td>Specifics of postmenopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer before menopause</td>
<td>16 (64)</td>
<td>9 (37.5)</td>
<td>.064</td>
</tr>
<tr>
<td>Prior oophorectomy</td>
<td>10 (40)</td>
<td>7 (29.2)</td>
<td>.483</td>
</tr>
<tr>
<td>Presently on a selective estrogen receptor modulator</td>
<td>3 (12)</td>
<td>4 (16.7)</td>
<td>.702</td>
</tr>
<tr>
<td>Presently on an aromatase inhibitor</td>
<td>8 (32)</td>
<td>10 (41.7)</td>
<td>.483</td>
</tr>
<tr>
<td>Duration of postmenopause (y)</td>
<td>11 (5–16)</td>
<td>8 (1.5–16.5)</td>
<td>.428</td>
</tr>
<tr>
<td>Pain with sex at baseline‡</td>
<td>7 (7–9)</td>
<td>8 (7–9.5)</td>
<td>.359</td>
</tr>
<tr>
<td>Duration of dyspareunia (y)</td>
<td>4 (2–10)</td>
<td>2 (1–4)</td>
<td>.013</td>
</tr>
<tr>
<td>Stopped having penetrative intimacy (yes)</td>
<td>12 (48)</td>
<td>13 (54.2)</td>
<td>.666</td>
</tr>
<tr>
<td>Months since last coitus attempted</td>
<td>1 (0.5–4)</td>
<td>2 (1–6.5)</td>
<td>.264</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>62.4±32.2</td>
<td>60.6±22.3</td>
<td>.831</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation, n (%), or median (interquartile range) unless otherwise specified.

* P values were derived using Student’s t test or Wilcoxon rank-sum test for continuous variables and χ² or Fisher’s exact test for categorical variables.

† Menopause is defined as ovarian failure, either natural or induced from chemotherapy, or caused by oophorectomy.

‡ Numerical Rating Scale 0–10.
Values ranged from 4 to 6 with 84% having a pH of 5 or greater, consistent with low estrogen. Maturation indices showed 63% of patients to have 75% or more parabasal cells; 24% had a majority of intermediate cells. Rare mature epithelial cells were noted in 16% of patients’ smears and 84% had no superficial epithelial cells in any fields. Representative photomicrographs are shown in Figure 2.

Upper pelvic floor muscles (pubococcygeus, ileococcygeus) were tender or painful for 12 (24%), but they did not always share lower levator tenderness. Two patients were deemed to have severe myalgia because of pain and muscle tightness, presenting difficulty accommodating a two-finger examination and having pain with downward pressure of the speculum. Some bladder discomfort or mild pain was noted in three patients (6%). One patient had a tender uterus (2%) and no patients had adnexal tenderness.

DISCUSSION

Finding that the vulvar vestibule, not the vagina, is the location of exquisite genital tenderness in this cohort of breast cancer survivors challenges assumptions that vaginal dryness and vaginal atrophy cause tenderness. The term “dryness” is justified by the scant cellularity and lack of visible vaginal discharge in most of these patients. Similarly, the cohort uniformly demonstrated both vulvar and vaginal atrophy by criteria described by the North American Menopause Society. Despite the severity of hypoestrogenism, only one participant had exquisite mucosal pain in the vagina.

Pain researchers have raised questions about atrophy and location. Kao et al concluded after a review of the literature that atrophy is not a satisfactory construct to explain pain. Embryologic origin may help explain differences in sensitivity, because the vagina derives from mesoderm and vestibule from endoderm. Kao’s clinical study found that 98% of menopausal patients with dyspareunia had similar numerical scores for vestibular pain as did patients in this study.

Tenderness localized to the vestibule and associated with dyspareunia fulfills Friedrich’s criteria for...
vulvodynia. The International Society for the Study of Vulvovaginal Disease requires absence of gross anatomic findings to diagnose localized provoked vestibulodynia, and atrophy has been considered such a finding. Expanding the rubric of vulvodynia to include postmenopausal women will require further research, including histologic data and studies showing that interventions to the vestibule alay dyspareunia. This study is an initial step in mapping the locations and degrees of vestibular allodynia in breast cancer survivors using a validated testing technique and a pain scale recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

Use of topical lidocaine was important in distinguishing potential zones of pain. It prevented what may be a common confusion of confounding locations of tenderness by examining an internal genital structure while causing entryway pain with the instrument or fingers needed to examine that internal structure. In our clinical experience, localized use of aqueous 4% lidocaine has been very helpful in office evaluations of reports of genital dryness or pain.

Survivors of breast cancer who have dyspareunia constitute a particular population. After cancer is diagnosed, an aim of therapy is to shift patients rapidly into a hypoestrogenic state. The finding of a lack of association between examination touch scores and particular strategies to achieve profound hypoestrogenism may imply that the specific anticancer therapies are not as important as the resultant low estrogen state when considering dyspareunia.

This study was not without limitations. It was small, focusing on breast cancer survivors, so its generalizability to all postmenopausal women is limited. The consistent designation of study liquids as A and B could have weakened the degree of blinding of the examiner. The assessment of vaginal tenderness could have been strengthened by addition of descriptors of sensation. Perhaps because the study was small, the randomized groups were not equivalent in all demographics. More women in the saline-first group had a premenopausal diagnosis of breast cancer, and this affected the amount of time since diagnosis and the duration of dyspareunia. Despite this, the groups were equivalent regarding the degree of dyspareunia and the numbers abstaining from intercourse because of pain, which are factors more indicative of equivalent status at the time of study examinations. A larger study should correct this discrepancy and could also clarify the prevalence of pan-vaginal mucosal tenderness that was found in one patient.

Finding that the vestibule is the primary location of genital tenderness in hypoestrogenic breast cancer survivors with postmenopausal dyspareunia adds more justification to the need to understand this small anatomic zone. The demonstration that topical lidocaine alleviates the provoked pain during examinations is promising and deserves further study to validate these findings and develop recommendations for clinical use. Old concepts attributing pain to vaginal dryness and atrophic vaginitis deserve reconsideration.

REFERENCES