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Optical Vaginal Biopsy Using Optical Coherence Tomography

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Abstract

Objective—Optical coherence tomography is a noninvasive technology that visualizes tissue microstructure with high spatial resolution. We designed a novel vaginal system that demonstrates a clear distinction between vaginal tissues planes. In this study, we sought to compare vaginal tomographic images of premenopausal, perimenopausal, and postmenopausal women, demonstrate feasibility of tracking vaginal tissue changes after treatment with fractional-pixel CO_2 laser therapy, and obtain a histologic correlation of these findings.

Methods—Enrolled subjects underwent imaging and were divided into 3 groups based on menopausal status. Women with genitourinary syndrome of menopause who received fractional-pixel CO_2 laser therapy were assessed before and after treatment. A cadaveric vagina was used to obtain tomographic and histologic images to assess for accuracy. Our primary outcome was mean vaginal epithelial thickness. Statistical analysis was performed using analysis of variance and t tests, respectively.

Results—Among 6 women, the mean vaginal epithelial thickness decreased with menopause ($P < 0.01$). Although change in epithelial thickness after fractional-pixel CO_2 laser treatment varied between the 2 subjects evaluated, it increased significantly for the subject who reported improvement of vaginal symptoms ($P < 0.01$). Using a cadaveric specimen, optical biopsy was correlated to an hematoxylin and eosin–stained biopsy of the same vaginal site.

Conclusions—This study establishes feasibility of optical coherence tomography in providing an optical biopsy of the vaginal epithelium and lamina propria. In addition, it demonstrates vaginal changes as women enter menopause. This report is the initial phase of a longitudinal cohort study to evaluate changes in vaginal microstructure after energy-based treatment.

Genitourinary syndrome of menopause (GSM) is a broad term that describes symptoms that arise from a physiologic decline in estrogen levels.[1] Estrogen deficiency leads to reduced

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vascularization, lubrication, tissue elasticity, and thinning of the vulva, vagina, and urethra. Although GSM is not a life-threatening condition, it has a negative impact on a woman's quality of life with regard to general health and sexual function.[2] Low-dose vaginal estrogen is the mainstay of treatment to restore a local hormonal effect.[3] However, some patients are unable to use estrogen or do not obtain adequate relief of symptoms. For these patients, there are few satisfactory alternatives. Recently, fractional lasers and other energy-based treatments of the vulva and vagina are being offered, off-label, as a minimally invasive treatment for GSM and related conditions.[4,5] Although fractional laser therapy has demonstrated clear benefit in areas of medicine, such as dermatology, it remains controversial in female pelvic medicine. Specifically, a large number of energy-based devices of various laser wavelengths (CO_2, Er:YAG, Hybrid), different technologies (scanning, pixel print), and radiofrequencies (monopolar, bipolar, matrix radiofrequency) are available with limited quality evidence to support their widespread use.[6] Without a clear indication to routinely perform multiple invasive biopsies for benign genitourinary changes, the pathophysiology of disease severity, response to treatment, and factors leading to refractory symptoms remain poorly understood. Thus, this is an area of research that would greatly benefit from noninvasive imaging technology.

Optical coherence tomography (OCT) system provides a real-time, optical biopsy of tissue microstructures, with high spatial resolution within a large scanning area.[7,8] By providing detailed cross-sectional images up to 2 mm in depth, OCT accurately measures epithelial thickness. In addition, OCT angiography can directly visualize microvasculature and quantify blood flow.[9,10]

Optical coherence tomography technology is Food and Drug Administration approved for use in other fields of medicine, such as dermatology and ophthalmology; however, its use in gynecology is very limited and off-label. Vincent et al[11,12] validated the use of OCT to evaluate sheep vaginal epithelial thickness (VET) and subsequent epithelial changes after treatment with nonoxynol-9. These studies were limited to 2-dimensional cross-sectional OCT images of animal tissue or ex vivo human tissue. More recently, OCT was used to correlate suspicious bladder lesions with histologic specimens.[13] Sensitivity of malignancy and invasion beyond the lamina propria was 100%, whereas specificity was 65%. This study highlights the ability of OCT to obtain histopathologic information without an actual biopsy and its potential diagnostic power in benign conditions such as GSM. Thus, OCT can be an important tool to (*a*) monitor the progression of disease, (*b*) evaluate treatment effect, and (*c*) individualize treatment strategies.

We previously published the design and results of our novel endoscopic OCT system, capable of imaging the human vagina, in vivo.[14] In this study, we sought to determine the feasibility of assessing menopausal changes in vaginal tissue as well as the effect of fractional-pixel CO_2 laser therapy. Secondarily, we tested the histologic accuracy of OCT imaging.

METHODS AND MATERIALS

This was an institutional review board-approved, prospective pilot study using OCT to assess the vaginal epithelium in adult women. Subjects were recruited from the Department of Gynecology at the University of California, Irvine, between October 2017 and 2018. The study aims were to use OCT to (*a*) compare VET among premenopausal, perimenopausal, and postmenopausal women, (*b*) assess for change in VET in postmenopausal women with GSM and undergoing fractional-pixel CO_2 laser treatment (FemiLift; Alma Lasers), and (*c)* correlate OCT imaging histologically, using a cadaveric specimen. Menopausal status was based on Stages of Reproductive Aging Workshop guideline.[15] Women were classified as premenopausal if they had a menstrual period in the past 12 months and reported no menstrual cycle variability. Menstruating women who reported menstrual cycle length variability were considered perimenopausal, and women without a menstrual cycle in the past 12 months were considered postmenopausal. Women were excluded for the following reasons: history of pelvic irradiation, pregnant, breastfeeding, and on hormone replacement therapy (systemic or local) within the last 3 months.

After informed consent was obtained and menopausal status was confirmed, subjects were asked to perform a vaginal douche using 60 mL of sterile water. During the initial prototype testing of the novel OCT system, significant artifact was encountered from physiologic vaginal discharge. It was found that vaginal douching consistently resolved this issue; thus, it was standardized into the imaging protocol. The subjects were then positioned in dorsal lithotomy for the OCT imaging procedure.

A schematic of the OCT system and vaginal probe are shown in Figure 1. The OCT system has been previously described and delivers light to the custom-built vaginal probe.[14] The handheld vaginal probe consists of a clear protective tube (12.5 X 150 mm), an optical core, and single-mode fiber that connects to the OCT system. The optical core of the endoscope is rotated using an external optical rotary joint system. The optical core contains rotational bearing to minimize motion artifact and is manually withdrawn at a speed of approximately 2 mm/s. The result is a 360-degree tomographic image of the entire vaginal length, to a depth of 2 mm, obtained in less than 60 seconds. For each subject, a disposable OCT vaginal probe was coated with a small amount of surgical lubricant and placed in the vagina to the level of the cervix. This procedure was performed twice to ensure that satisfactory images were captured. All clinical procedures were performed by the same physician and OCT technician to minimize variability.

Premenopausal and perimenopausal women presented for a single research visit during which OCT imaging was performed. Postmenopausal women undergoing fractional-pixel CO_2 laser treatment for GSM received a baseline OCT scan in addition to a repeat scan 4 to 6 weeks after laser treatment. The CO_2 laser treatment involved a single pulse and had the following settings: first pass 80mJ/pixel of energy and second-pass 100mJ/pixel of energy. Four to 6 weeks after treatment, women who received CO_2 laser were asked to complete an adapted Patient Global Impression of Improvement (PGI-I), regarding their symptoms of GSM. The PGI-I is a single question survey to determine treatment response from very much better (1) to very much worse (7).[16] Although it is not validated for GSM, it is widely used and validated in women with stress urinary incontinence and prolapse.[17]

The primary outcome was mean VET. The mean VET was calculated from the 30 randomly selected, cross-sectional OCT images along the vaginal wall using MATLAB software. These locations were standardized across all subjects. The software reported VET as a mean and standard deviation (SD) and assumed a normal distribution. For aim 1, meant VET was compared among the following 3 groups of women: premenopause, perimenopause, and menopause using analysis of variance ($P < 0.05$). For aim 2, the change in mean VET after treatment with fractional-pixel CO_2 laser for GSM was assessed with paired t tests ($P < 0.05$). A 95-year-old fresh-frozen cadaver was used in aim 3 to correlate OCT and histologic images. First, a scanning OCT image of a 2 X 2-cm area of the midvagina was obtained. The same area was then excised and stained with hematoxylin and eosin. The OCT and hematoxylin and eosin images were qualitative compared, and the mean VET was assessed with Students t test ($P < 0.05$).

RESULTS

Six subjects were recruited to assess mean VET across premenopausal, perimenopausal, and postmenopausal women (Table 1)

There were 3 premenopausal women in their early 30s (A1–A3), 2 perimenopausal women in their late 40s (B1–B2), and 1 menopausal 70-year-old woman (C). The mean (SD) VET for subjects A1 to A3 was 316 (82) μm, 174 (44) μm for subjects B1 to B2, and 106 (32) μm for subject C. The difference in meant VET between, premenopausal, and perimenopausal, as well as perimenopausal and postmenopausal, groups were statistically significant ($P < 0.01$) (Fig. 2). No adverse events including pain, infection, or bleeding were reported.

Two menopausal subjects with GSM and undergoing fractional pixel CO_2 laser treatment were recruited for OCT imaging before and after treatment (Fig. 3). The first patient was a 70-year-old woman who had undergone physiologic menopause in her 50s. She demonstrated a significant increase in her mean VET of 72.7 μm ($P < 0.01$) after a single treatment with CO_2 laser therapy. In addition, she reported that her symptoms were “much better” on PGI-I. The second patient was a 45-year-old woman who had undergone surgical menopause 5 years prior. Her baseline VET (287 [65] μm) was similar to the premenopausal group ($P = 0.30$). After treatment with fractional-pixel CO_2 laser therapy, her VET marginally decreased by 8.5 μm ($P = 0.241$). She reported “no change” in her GSM symptoms on PGI-I. Of note, patient 2 had been using a vaginal estrogen ring, which was removed approximately 6 weeks before her baseline OCT scan. This information was not disclosed to the investigators until after study completion.

Using the cadaveric vaginal specimen, the qualitative appearance of the vaginal epithelium and underlying microstructures appeared similar between OCT and histologic images (Fig. 4). Consistent with the histologic view, OCT images showed a clear distinction between vaginal epithelium and lamina propria. Quantitatively, the mean (SD) VET of 55.6 (18.9) μm on OCT correlated with the histologic mean VET of 61.3 (14.7) μm ($P = 0.41$).

DISCUSSION

This study confirms the feasibility of using OCT to image vaginal tissue microstructures and its correlation with histology. In addition, OCT can quantify changes in VET that may occur after CO_2 laser therapy for GSM.

Our findings demonstrate that VET significantly decreases with progression to menopause. This, likely, correlates with declining levels of systemic estrogen. Among the 2 women with GSM, patient 1's thin VET on OCT represents an expected finding of a postmenopausal woman with GSM. Conversely, patient 2 is atypical: she underwent surgical menopause for cancer risk reduction 5 years prior and was found to have a premenopausal VET despite reporting severe symptoms of GSM. Technically, patient 2 met exclusion criteria because she had been using vaginal estrogen; however, this was not disclosed to the study investigators until completion of the study procedures; thus, decision was made to include her in the pilot group. Including her results provides valuable preliminary information about vaginal OCT imaging, represents a real-world example of the heterogeneous population experiencing GSM, and highlights the conundrum of refractory symptoms in some women, despite the use of vaginal estrogen.

The application of vaginal estrogen is known to restore the vaginal structure, mechanical properties, and lactobacilli-dominated microbiome.[18] We can surmise that the use of vaginal estrogen may have restored patient 2's VET to premenopausal state; however, why she remained symptomatic is an important point of interest. It further corroborates the notion that GSM is a complex condition, impacted by a combination of various tissue components beyond vaginal epithelial thinning, including the following: tissue integrity, hemodynamics, and the vaginal microbiome.[19,20] In addition, it is interesting that her VET by OCT imaging did not increase with CO_2 laser therapy nor did her GSM symptoms improve. Unlike some forms of nonablative energy-based treatments, depth of microablation with fractional CO_2 laser can be controlled by increasing the energy per pixel. Vaginal epithelial thickness changes, and/or clinical improvement may also occur after additional treatment sessions. The proof of concept described so far suggest that real-time OCT imaging may guide the treatment protocol to optimize the outcome.

In most energy-based protocols, multiple treatment sessions, at varying time intervals, are recommended. However, these protocols have not been objectively validated. After a single-treatment session, the change in VET shown on OCT may represent a new generation of "real-time" noninvasive monitoring to test the validity of treatment recommendations.

The primary weakness of this study is the small sample size, essentially representing a sample of convenience. Although it is not possible to draw clear conclusions about the pathophysiology of GSM or confirm accuracy of OCT as an optical biopsy, the results clearly demonstrate that OCT can provide real-time, noninvasive, optical images of vaginal tissue microstructures.

This pilot study is the initial phase of a longitudinal cohort study using OCT to investigate vaginal microstructure changes that occur after CO_2 laser treatment for GSM. In addition to measuring VET, we will assess vaginal vasculature and biomechanics of elastic fibers using

OCT angiography and OCT elastography and perform microbiome analysis to provide comprehensive information about GSM pathophysiology. Based on our preliminary results, we hypothesis that individual patient response to laser treatment depends on their baseline tissue conditions.

Our novel OCT system is capable of noninvasively extracting valuable information about vaginal tissue microstructure before and during various treatment. This type of technology is lacking in the field of pelvic medicine and has great potential. As we work toward confirming the accuracy of this technology, we believe that it will become a valuable tool to monitor treatment response and contribute to individualized treatment plans.

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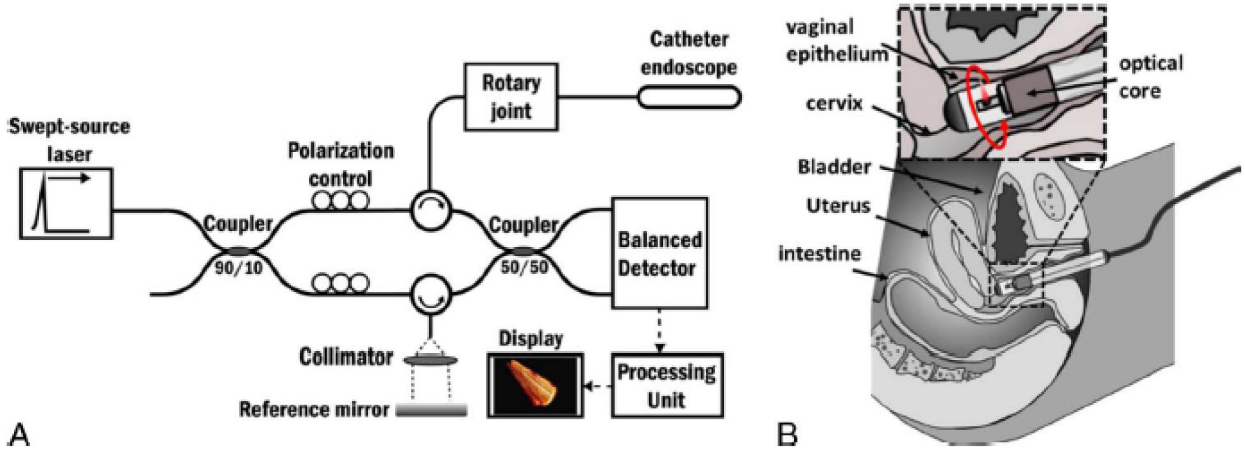


FIGURE 1.

Novel optical coherence tomography system (A) and vaginal probe (B).

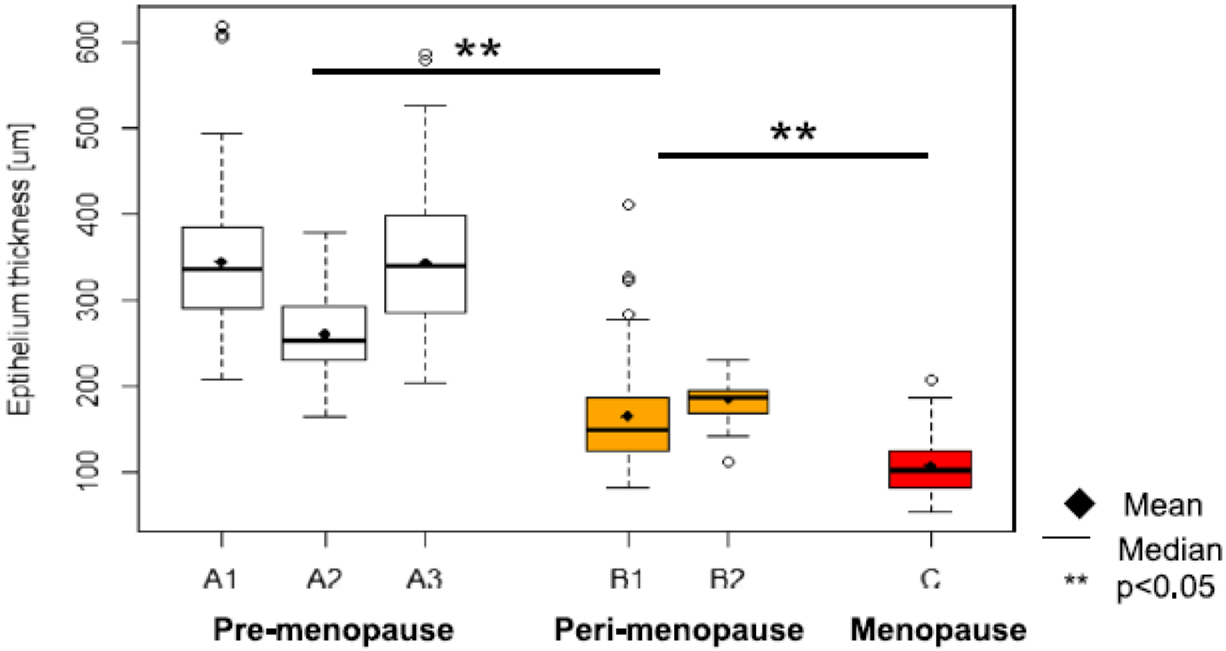


FIGURE 2.

Vaginal epithelial thickness based on menopausal status.

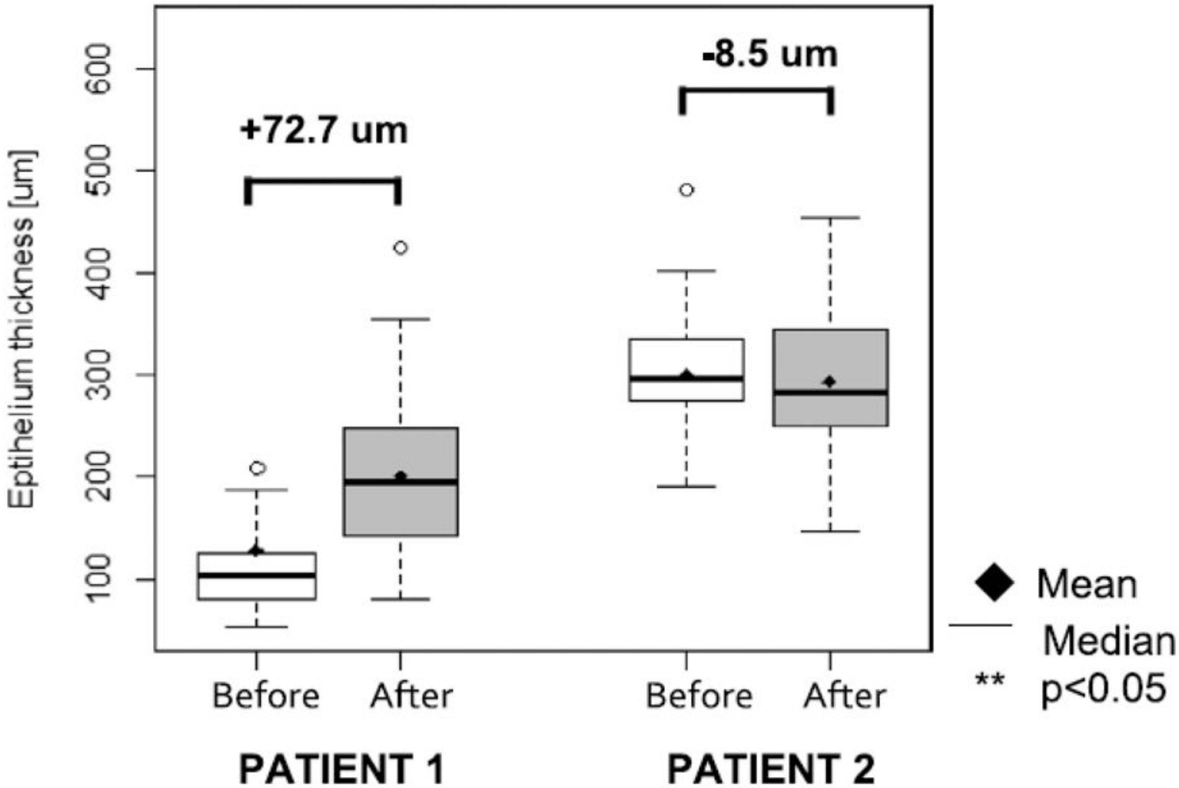
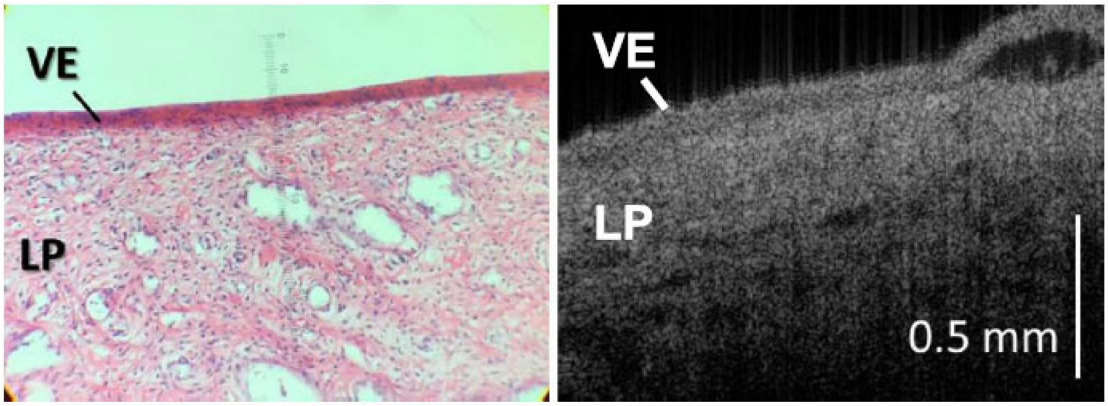


FIGURE 3.

Vaginal epithelial thickness before and after CO_2 laser treatment for GSM.



VE: vaginal epithelium LP: Lamina propria

FIGURE 4.

Correlation between histologic and OCT images using a cadaveric vagina. LP, lamina propria; VE, vaginal epithelium.

TABLE 1.

Descriptive Data of Aim 1 Cohort

Menopausal Status	Age, y	Mean VET, μm
Premenopausal	33.3	316.9
A1	34	348
A2	35	260.1
A3	31	342.6
Perimenopausal	48.5	174.2
B1	49	164.1
B2	48	184.4
Postmenopausal	70	106.8
C		