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Journal
Lasers in Surgery and Medicine, 51(2)

ISSN
0196-8092

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Publication Date
2019-02-01

DOI
10.1002/lsm.23003

Peer reviewed

HHS Public Access

Author manuscript

Lasers Surg Med. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Lasers Surg Med. 2019 February ; 51(2): 120–126. doi:10.1002/lsm.23003.

1.7 Micron Optical Coherence Tomography for Vaginal Tissue Characterization *in Vivo*

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Abstract

Objectives: Optical coherence tomography (OCT) can noninvasively visualize *in vivo* tissue microstructure with high spatial resolution that approaches the histologic level. Currently, OCT studies in gynecology are few and limited to a conventional 1.3 μm center wavelength swept light source which provides high spatial resolution but limited penetration depth. Here, we present a novel endoscopic OCT system to provide improved penetration depth with high resolution.

Methods: A novel IVOCT system was developed based on a 1.7 μm swept source laser, which is capable of deeper tissue penetration due to its longer wavelength. To evaluate the performance of this novel OCT system, we imaged human vaginas *in vivo* with both conventional 1.3 μm and 1.7 μm endoscopic OCT systems.

Results: With the 1.7 μm endoscopic OCT system, imaging depth was improved by more than 25%, allowing better visualization of the lamina propria and clear contrast of the epithelium layer from the surrounding tissues.

Conclusion: The significantly improved performance of the novel 1.7 um OCT imaging system demonstrates its potential use as a minimally-invasive monitor of vaginal health in gynecologic practice.

Keywords

Gynecology; optical coherence tomography; vagina; epithelium; 1.7 micron swept-source laser; penetration depth

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Conflict of Interest: Dr. Chen has a financial interest in OCT Medical Imaging, Inc., which, however, did not support this work.

Introduction:

The vagina is a dynamic, tubular structure made up of an epithelium, lamina propria, muscularis and adventitia layer [1]. The vaginal epithelium is non-keratinized, stratified squamous epithelium and contains three layers: an active basal layer, superbasal layer, and superficial layer [2]. These layers are estrogen receptor sensitive such that post-menopausal epithelium demonstrates a decreased proportion of superficial epithelial cells on histologic evaluation [3]. The lamina propria is composed of fibroblasts, which produce collagen and elastin, and houses small vessels and nerves. Despite knowledge that collagen contributes to epithelial tensile strength and elastin provides elasticity, pathologic changes associated with conditions like Genitourinary Syndrome of Menopause (GSM) are not well understood [4]. While studies looking at collagen and elastin density before and after menopause have varying results, the leading hypothesis is that diminishing estrogen levels affect normal degradation and regeneration of the extracellular matrix [5]. Estrogen deficiency promotes structural and functional changes in the urogenital tissue which relates to reduced vascularization, decreased elasticity and thinning of vaginal epithelium [6]. A substantial decline in glycogen production promotes changes in vaginal pH, decreased lactobacilli and increased susceptibility to inflammation. Subsequent symptoms of GSM include: dryness, dyspareunia, itching, and lower urinary track symptoms.

To date, studies to evaluate the epithelium mainly rely on invasive biopsies for histologic evaluation. Therefore, there is a need for non-invasive techniques capable of evaluating the vaginal wall clinically. In recent years, more and more noninvasive imaging technologies, such as fluorescence, OCT, Doppler OCT, ultrasound, and photoacoustic imaging, have been developed to provide morphology and molecular contrast of biological tissue [7–11]. Among them, OCT has the advantage over histologic tissue analysis (obtained by biopsy) in acquiring high resolution, microscopic images with a non-invasive approach [12]. This technique has already demonstrated success in dermatology, ophthalmology, breast surgery and cardiology but limited use in gynecology. For example, Vincent et al. validated epithelial thickness measurement with OCT using a sheep model and subsequently demonstrated consistent visualization of the epithelial-lamina propria interface and changes in epithelial thickness after treatment with nonoxynol-9 [13, 14]. Despite these novel findings, OCT imaging of the human vagina *in vivo* has not been reported. Recently, Li et al. published results of a novel OCT system with a 1.7 μm center wavelength swept light source by imaging coronary arteries *ex vivo* [8], which penetrates deeper into tissue based on the utilization of a longer wavelength. Thus, more structural information can be obtained. When extrapolating this technology to gynecology, we hypothesized that 1.7 μm endoscopic OCT system can better characterize the vaginal wall for evaluating laser treatment compared with current methods [15–17]. Therefore, we developed a 1.7 μm endoscopic OCT technology to visualize the morphology of the vaginal wall *in vivo* to demonstrate capability for disease diagnosis and treatment evaluation. In addition, *in vivo* imaging of human vagina from a 1.7 μm endoscopic OCT system is compared with a 1.3 μm endoscopic OCT system to demonstrate the advantages of the 1.7 μm endoscopic OCT system.

Materials and Methods:

System setup and imaging probe

The novel OCT system consists of a fiber optic-based Mach-Zehnder interferometer (MZI) with a 1.7 μm center wavelength swept light source (Santec, Inc. HSL-40–90-B, 90 kHz, 120 nm bandwidth) as shown in Figure 1(a). The output energy is split by a 90:10 coupler. The reference arm (low energy), which consists of a collimator, lens and mirror, has a fixed delay. The sample arm (high energy) includes a fiber optics rotary joint and imaging probe for transmitting the light to the tissue. Two circulators with a center wavelength of 1650 nm are used to separate the illumination light and back scattered/back reflection light. The collected light from the sample arm and reference arm generates interference in a 50/50 coupler with a center wavelength of 1650 nm. The interference signal is detected by a balanced photodetector which is able to remove the noise by subtracting the two optical input signals from each other. In order to better evaluate the performance of this novel endoscopic OCT system, another MZI-based OCT system with a 1.3 μm center wavelength vertical-cavity surface-emitting laser (VCSEL) swept source (Thorlabs Inc., 100 kHz, 100 nm bandwidth) was built to perform the same experiments. A 12 bit data acquisition board is used to detect and record the interference signal. The software is written entirely in C++ for data acquisition, image processing, and display in real-time using a graphics processing unit. A logarithmic transform is applied to the OCT signal in all of the figures to make low-reflective layers visible.

A 1.2-mm-diameter proximal scanning flexible endoscopic OCT imaging probe was developed. Figure 1(b) shows the schematic of the imaging probe. The OCT laser beam propagates through the single mode fiber, is focused by a gradient index (GRIN) lens, and then reflected towards the tissue surface by a mirror. All of the elements are housed in a metal cap and fixed by epoxy. The cap is connected to a double-wrapped torque coil to transmit the torque from the rotary motor to drive the imaging probe for performing cross-sectional imaging. The 3D scanner consists of a fiber optics rotary joint (Princetel Inc., MJXA-FAPB-131-DC-FA), rotary motor (MicroMo Electronics, Inc.), and translation stage (Zaber Technologies Inc.).

In vivo human experiment

This was a prospective pilot study to evaluate the vagina using OCT on healthy women. Women were recruited from the Division of Female Pelvic Medicine and Reconstructive Surgery at UC Irvine and participated voluntarily. A brief history was obtained to confirm pre-menopausal status. Before performing OCT, a vaginal lavage with 60ml of sterile water was performed to minimize the presence of transudate. Participants were placed in the dorsal lithotomy position while obtaining OCT images. The imaging probe within a sterile sheath was placed in the vagina to the level of the uterine cervix and withdrawn at a standard speed of 1mm/s. A single operator performed all procedures. Imaging was done using the 1.7 μm and 1.3 μm endoscopic OCT systems.

All methods were carried out in accordance with the University of California, Irvine (UCI) Institutional Review Board (IRB) under protocol HS# 2017–3686.

Results

Two pre-menopausal female subjects were enrolled in the study. Figure 2 shows the cross-sectional OCT images and penetration depth from two endoscopic OCT systems. Figures 2 (a)-2(c) show the OCT vagina cross-sectional images and quantitative analysis of penetration depth from subject 1. In Figures 2 (a) and 2 (b), the epithelium and lamina propria are clearly identified; however, less of the lamina propria is obtained by the 1.3 μm endoscopic OCT system. Figure 2 (c) is a quantitative analysis that shows the penetration depth of both OCT systems from the areas indicated by the red dashed lines demonstrating a deeper penetration depth obtained by the 1.7 μm endoscopic OCT system. Figures 2 (d)-2 (f) represent the OCT vagina cross-sectional images and quantitative analysis from subject 2. Again, the vaginal epithelium and lamina propria are clearly identified and the deeper penetration depth for the 1.7 μm endoscopic OCT system is demonstrated.

In order to better evaluate the performance of the 1.7 μm endoscopic OCT system, a quantitative analysis of penetration depth was performed. The penetration depth is determined by calculating the imaging depth in which the signal to noise ratio of the OCT signal is above −25 dB (noise level of OCT images). The corresponding results are shown in Figure 3. Around 1000 cross-sectional images from each subject were collected, and 50 equally spaced cross-sectional images were used to calculate the averaged penetration depth of each cross-sectional image which was obtained by averaging the penetration depth of all of the A-line signals of each cross-sectional image. Figure 3 shows the averaged penetration depth from two subjects with the two endoscopic OCT systems. From the figure, it can be found that the averaged penetration depth is 1.65 mm with the 1.7 μm endoscopic OCT system and 1.3 mm with the 1.3 μm endoscopic OCT system. A more than 25% improvement in the penetration depth is demonstrated, allowing better visualization of the lamina propria and clear contrast of the epithelium layer from the surrounding tissues.

Figures 4 shows representative OCT images obtained by both endoscopic OCT systems from two subjects. Comparing the OCT images from the two endoscopic OCT systems, much more information can be obtained along the axial direction with the 1.7 μm endoscopic OCT system. Video is available online that shows real time cross-sectional OCT images (Video 1).

Figure 5 shows 3D OCT images of the human vagina. Figures 5 (a), 5 (b), 5 (d) and 5 (d) are 3D OCT images with different views. Figures 5 (e) and (f) are cross-sectional OCT images of a longitudinal view (indicated by the blue and green dashed squares, respectively) obtained by the 1.7 μm endoscopic OCT system in which typical layers can be identified. For some areas, the vaginal epithelium and lamina propria cannot be clearly separated. There are two possible reasons. First, due to vaginal folding, the OCT beam hits the tissue surface at a slightly different imaging distance from the OCT probe. When the tissue is not at the focal plane, SNR of the vaginal image may decrease which can cause an unclear boundary between the epithelium and lamina propria. In addition, transudate in the vagina scatters and absorbs OCT light which also explains the reason of decreased SNR at some locations. In the future, we will apply an axicon lens to generate an extended focal plane.

To obtain the microstructure of the vagina at different depths, an *en face* OCT image was rendered and is depicted in Figures 6 (d)-(g). Sheath distortion is due to pressure from the vaginal wall. An algorithm was performed to find the edge of the sheath and flatten the edge, as shown in Figures 6 (a) and (b). In Figure 6 (d), the unfolded 3D image depicts the different layers of the vagina. Figures 6 (e), (f) and (g) show 2D longitudinal cross-sectional images from varying depths, indicated by green arrows in Figure 6 (d). Video is provided online to show OCT longitudinal cross-sectional images through the whole imaging depth (Video 2).

Discussion

To our knowledge, this pilot study represents the first demonstration of endoscopic OCT imaging and the first attempt to evaluate the 1.3 μm and 1.7 μm endoscopic OCT systems for *in vivo* imaging of human vagina. In comparing our OCT images to vaginal histology available in the literature, both endoscopic OCT systems demonstrate the vaginal epithelium and lamina propria [18, 19]. This is inferred from the density and depth of the visualized layers. The 1.7 μm endoscopic OCT system penetrates deeper than the 1.3 μm OCT system and may provide more information within the layers of the vagina.

There are many potential clinical uses for 1.7 μm endoscopic OCT imaging on vaginal tissue. Currently, pathologic changes in the vagina are determined by gross physical examination and histologic evaluation. While areas that are suspicious for malignancy warrant biopsy and histologic evaluation, other conditions, such as GSM, pelvic organ prolapse or stress urinary incontinence (SUI), do not. It is hypothesized that abnormal, progressive remodeling of collagen, elastin and vascularity within the extracellular matrix lead to altered architecture and decreased support [20]. Hypoestrogenic states, such as a GSM, exacerbate this abnormal remodeling. Jackson et al. hypothesized that estrogen should increase the quantity of collagen; however, their results showed decreased concentrations of collagen [5]. This highlights the remaining uncertainty about what happens at the microscopic level to cause these medical conditions.

Non-invasive techniques like ultrasound and OCT are promising tools to further delineate the pathophysiology of abnormal tissue remodeling at the microscopic level. Ultrasound represents an imaging system that is commonly used in gynecology. Panayi et al. attempted and validated the use of ultrasound to evaluate the vagina; however, this technique provides little information beyond vaginal wall thickness due to poor axial resolution [21]. OCT can also be used as a point of care test: its spatial resolution and ability to detect images on a micrometer scale are far superior to ultrasound. Our study was able to demonstrate high resolution images of the vagina, *in vivo*, and show deeper penetration depth with the 1.7 μm versus 1.3 μm endoscopic OCT systems. These findings highlight the potential for 1.7 μm imaging to evaluate changes in the vaginal extracellular matrix of human subjects over time. In addition, 1.7 μm OCT may be able to visualize more blood vessels at the deeper region of laminar propria. Since the blood vessel plays an important role in maintaining tissue function, the 1.7 um OCT system may provide more accurate evaluation of treatment effects by visualizing more vasculatures. However, there are a number of challenges we need to overcome before translating the 1.7 um OCT system into gynecology clinics, including

further improvement of penetration depth and spatial resolution for visualizing more morphological features of the vaginal wall, implementation of a swept light source with sufficient phase stability and an advanced image processing algorithm for imaging microvasculature, and automation of image analysis for accurate and rapid diagnosis. Future studies will focus on system improvement and quantification of microvasculature. We will also validate our findings with hematoxylin and eosin histology. Quantitative changes in collagen, elastin, glycogen enriched epithelial cells, and vascular density within the lamina propria may provide answers to how the vagina changes with various medical conditions and their subsequent treatments.

Conclusion

We have developed a 1.7 μm endoscopic OCT system and demonstrated the first *in vivo* imaging of human vagina. The significantly improved performance of the novel 1.7 um OCT imaging system demonstrates its potential use as a minimally-invasive monitoring of vaginal health in gynecologic practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

The authors thank the individuals enrolled in the gynecology study for the advancement of education and research.

Funding: National Institutes of Health (R01HL-125084, R01HL-127271, R01EY-026091, R01EY-021529, R01EY028662, P41EB-015890); Air Force Office of Scientific Research (FA9550–17-1–0193), Alma Lasers, Buffalo Grove, IL.

References

[1]. De Landsheere L, Munaut C, Nusgens B, Maillard C, Rubod C, Nisolle M, et al. Histology of the vaginal wall in women with pelvic organ prolapse: a literature review. International urogynecology journal. 2013;24:2011–20. [PubMed: 23649687]

[2]. Anderson DJ, Marathe J, Pudney J. The Structure of the Human Vaginal Stratum Corneum and its Role in Immune Defense. Am J Reprod Immunol 2014;71:618–23. [PubMed: 24661416]

[3]. Weber MA, Limpens J, Roovers JPWR. Assessment of vaginal atrophy: a review. International urogynecology journal. 2015;26:15–28. [PubMed: 25047897]

[4]. Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference P. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause 2014;21:1063–8. [PubMed: 25160739]

[5]. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. Bjog-Int J Obstet Gy 2002;109:339–44.

[6]. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clinic proceedings 2010;85:87–94. [PubMed: 20042564]

[7]. Li Y, Gong XJ, Liu CB, Lin RQ, Hau W, Bai XS, et al. High-speed intravascular spectroscopic photoacoustic imaging at 1000 A-lines per second with a 0.9-mm diameter catheter. J Biomed Opt 2015;20.

[8]. Li Y, Jing J, Heidari E, Zhu J, Qu YQ, Chen ZP. Intravascular Optical Coherence Tomography for Characterization of Atherosclerosis with a 1.7 Micron Swept-Source Laser. Sci Rep-Uk 2017;7.

[9]. Li Y, Jing J, Qu YQ, Miao YS, Zhang BY, Ma T, et al. Fully integrated optical coherence tomography, ultrasound, and indocyanine green-based fluorescence tri-modality system for intravascular imaging. Biomed Opt Express 2017;8:1036–44. [PubMed: 28271001]

[10]. Chen ZP, Milner TE, Srinivas S, Wang XJ, Malekafzali A, vanGemert MJC, et al. Noninvasive imaging of in vivo blood flow velocity using optical Doppler tomography. Opt Lett 1997;22:1119–21. [PubMed: 18185770]

[11]. Li Y, Jing J, Yu JX, Zhang BY, Huo TC, Yang Q, et al. Multimodality endoscopic optical coherence tomography and fluorescence imaging technology for visualization of layered architecture and subsurface microvasculature. Optics letter 2018;43:2074–7.

[12]. Kirillin M, Motovilova T, Shakhova N. Optical coherence tomography in gynecology: a narrative review. J Biomed Opt 2017;22.

[13]. Vincent KL, Vargas G, Wei JN, Bourne N, Motamedi M. Monitoring vaginal epithelial thickness changes noninvasively in sheep using optical coherence tomography. Am J Obstet Gynecol 2013;208.

[14]. Vincent KL, Stanberry LR, Moench TR, Breitkopf CR, Loza ML, Wei JN, et al. Optical Coherence Tomography Compared With Colposcopy for Assessment of Vaginal Epithelial Damage A Randomized Controlled Trial. Obstet Gynecol 2011;118:1354–61. [PubMed: 22105265]

[15]. Hardy LA, Chang CH, Myers EM, Kennelly MJ, Fried NM. Computer simulations of thermal tissue remodeling during transvaginal and transurethral laser treatment of female stress urinary incontinence. Lasers Surg Med 2017;49:198–205. [PubMed: 26900038]

[16]. Gaspar A, Brandi H, Gomez V, Luque D. Efficacy of Erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. Lasers Surg Med 2017;49:160–8. [PubMed: 27546524]

[17]. Lang P, Dell JR, Rosen L, Weiss P, Karram M. Fractional CO2 laser of the vagina for genitourinary syndrome of menopause: Is the out-of-pocket cost worth the outcome of treatment? Lasers Surg Med 2017;49:882–5. [PubMed: 28881431]

[18]. Patton DL, Thwin SS, Meier A, Hooton TM, Stapleton AE, Eschenbach DA. Epithelial cell layer thickness and immune cell populations in the normal human vagina at different stages of the menstrual cycle. Am J Obstet Gynecol 2000;183:967–73. [PubMed: 11035348]

[19]. Tadir Y, Gaspar A, Lev-Sagie A, Alexiades M, Alinsod R, Bader A, et al. Light and Energy Based Therapeutics for Genitourinary Syndrome of Menopause: Consensus and Controversies. Laser Surg Med 2017;49:137–59.

[20]. Chen B, Yeh J. Alterations in Connective Tissue Metabolism in Stress Incontinence and Prolapse. J Urology 2011;186:1768–72.

[21]. Panayi DC, Digesu GA, Tekkis P, Fernando R, Khullar V. Ultrasound measurement of vaginal wall thickness: a novel and reliable technique. International urogynecology journal. 2010;21:1265–70. [PubMed: 20502876]

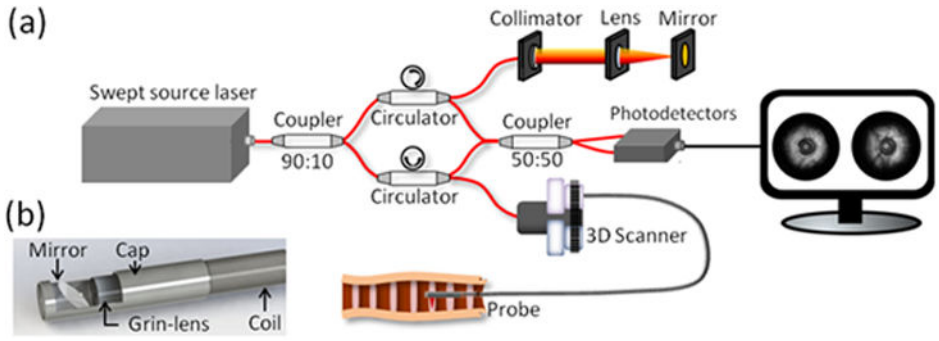

Figure 1: Schematic of the 1.7 μm OCT system.

(a) System and (b) the imaging probe. 3D scanner consists of a fiber optics rotary joint, rotary motor, and translation stage.

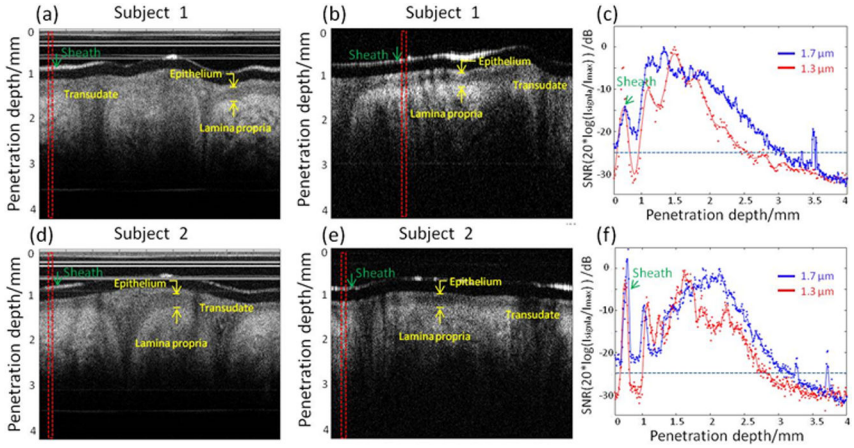

Figure 2: OCT images of human vagina and quantitative analysis of penetration depth.

(a) and (d) OCT images with the 1.7 μm endoscopic OCT system. (b) and (e) OCT images with the 1.3 μm endoscopic OCT system. (c) and (f) Quantitative analysis of penetration depth for the two endoscopic OCT systems.

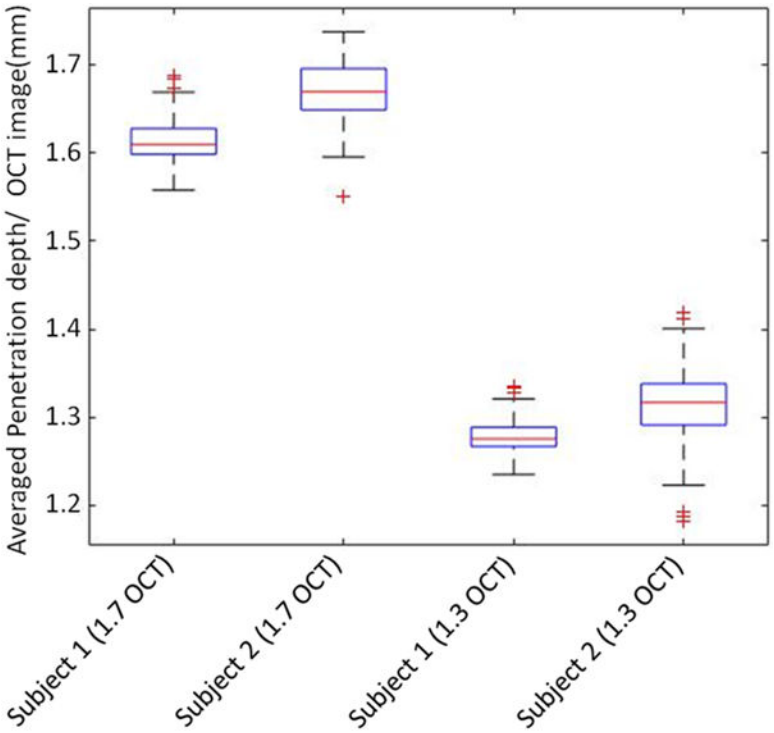

Figure 3:
Quantitative analysis of penetration depth with the 1.7 μm endoscopic OCT system and the 1.3 μm endoscopic OCT system.

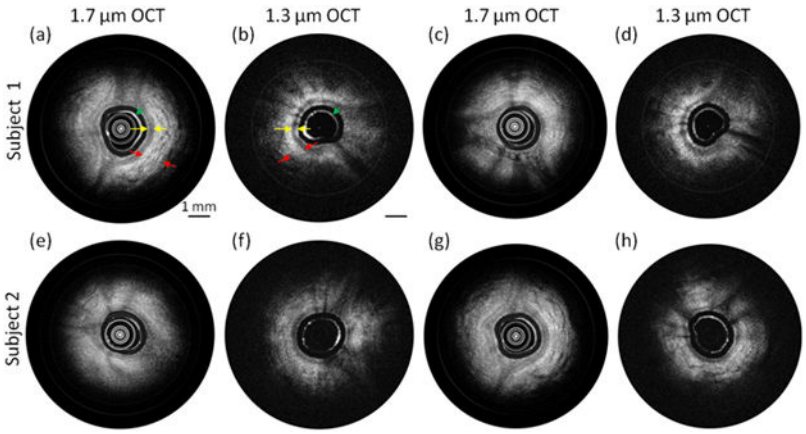

Figure 4: OCT images of human vagina with two OCT systems.

(a) and (c) OCT images obtained from subject 1 with the 1.7 μm OCT system. (b) and (d) OCT images obtained from subject 1 with the 1.3 μm OCT system. (e) and (g) OCT images obtained from subject 2 with the 1.7 μm OCT system. (f) and (h) OCT images obtained from subject 2 with the 1.3 μm OCT system. Green arrow: sheath. Yellow arrow: epithelium. Red arrow: lamina propria.

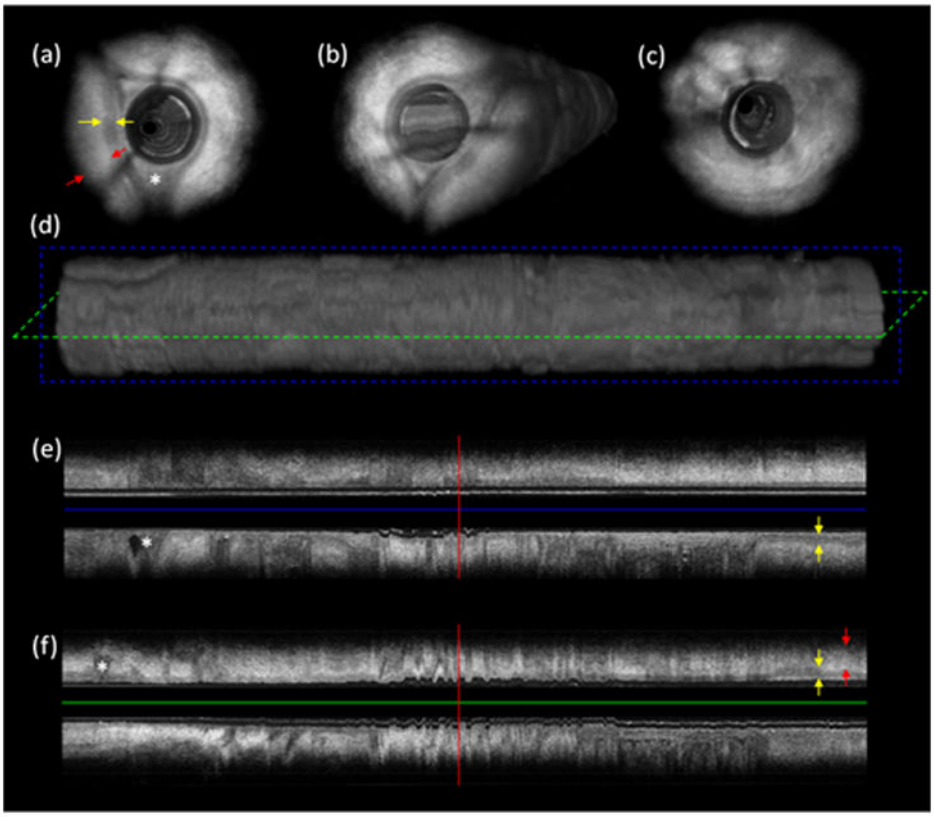

Figure 5: 3D OCT images.

(a), (b), (c) and (d) show 3D OCT images with different views from the 1.7 μm endoscopic OCT system. (e) And (f) Corresponding longitudinal OCT images (*: transudate).

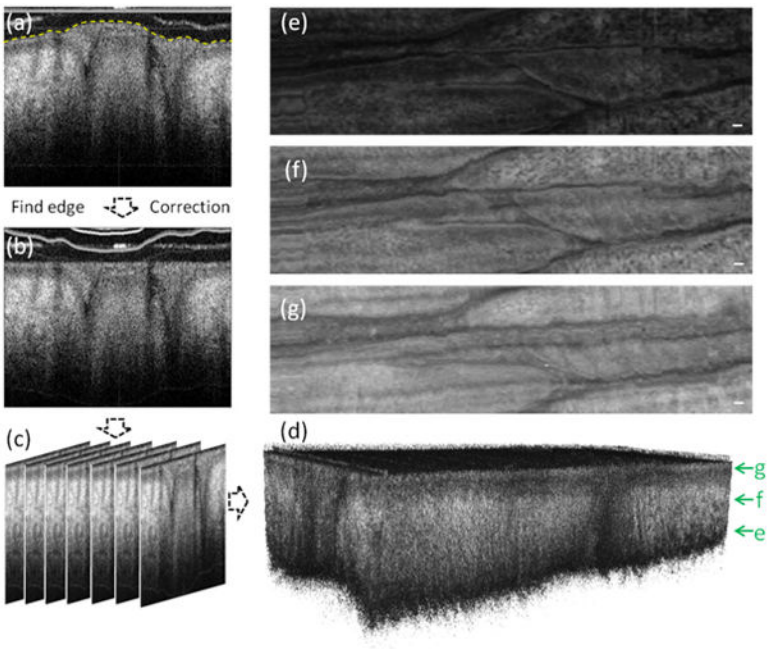

Figure 6: *En face* 3D OCT image of human vagina.

(a) Original cross-sectional OCT images. (b) Calibrated cross-sectional OCT image. (c) OCT images. (d) *En face* 3D OCT image. (e), (f) and (g) Cross-sectional OCT images at different depths, indicated by green arrows in (d). Scale bar: 1mm.