

**OB/GYN & WOMEN'S HEALTH INSTITUTE
CLEVELAND CLINIC**

**A Randomized Clinical Trial Comparing
Vaginal Laser Therapy to Vaginal Estrogen Therapy (VeLVET)
in Women with Genitourinary Syndrome of Menopause (GSM)**

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INVESTIGATOR'S SIGNATURE PAGE

Protocol Number or Version: _____

Protocol Date: _____

**A Randomized Clinical Trial Comparing
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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Investigator: _____ Date: _____

Printed Name and Title

Signed: _____ Date: _____
Name and Title

[PAGE TO BE PRINTED AND SIGNED WITH EACH FINAL PROTOCOL VERSION]

Name and Address of Institution: _____

Background and Significance

Vulvovaginal atrophy, referred to more recently as genitourinary syndrome of menopause (GSM), results from the involution of the vaginal epithelium and tissues of the vulva and vagina due to declining levels of systemic estrogen during menopause [1]. The vagina may decrease in caliber, and the vaginal opening may become more narrow and constricted. These changes in the vulvovaginal environment can have a significant negative impact on a woman's sexual health and quality of life. [9-13]. Other common changes include: progressive loss of elasticity and rugae, decreased glandular secretions leading to decreased lubrication, vaginal dryness and dyspareunia, as well as vaginal burning, discharge, itching, irritation, and dysuria [2-5]. Moreover, the weakened tissues are prone to developing traumatic tears, bleeding, petechiae, infection, and pain [2]. The prevalence of vulvovaginal symptoms has been consistently reported in approximately 50% of menopausal women. [3, 6-10].

Choice of therapy for GSM depends on symptom severity and treatment efficacy and safety. First-line treatment for symptomatic women with GSM, recommended by the North American Menopause Society, includes vaginal moisturizers, vaginal lubricants, and continued sexual activity. If these therapies fail, estrogen treatment should be considered in patients without contraindications. Topical estrogen therapy is designed to temporarily alleviate symptoms and reverse atrophic anatomical changes [14]. Despite proven effectiveness with symptom relief [14, 15], compliance rates for estrogen are variable, ranging between 52-74% [16]. Furthermore, long-term data (> 1 year) of these topical estrogen therapies are lacking. [15]. Additionally, no information is available in high-risk patients [14], e.g. those with known breast or uterine cancer in whom estrogen therapy is relatively contraindicated and where the management depends on a woman's preference, potential benefits, understanding of potential risks, and recommendations from oncology specialists [14].

Fractional CO₂ lasers have demonstrated safety and remodeling tissue properties in many body regions, such as the skin of the face, neck and chest, with the effect of producing new collagen and elastic fibers [17-20]. Moreover reports on the use of Er:YAG laser, similar to a CO₂ laser for its superficial effect, showed improvement in two aspects of pelvic floor dysfunction (urinary incontinence and vaginal laxity) [21,22]. Recently, the regenerative effects of intravaginal fractional CO₂ laser on the vaginal epithelium and lamina propria in postmenopausal women with GSM has been reported by Salvatore *et al* [23]. The same investigators found that microablative fractional CO₂ laser was feasible, efficacious, and safe in improving GSM symptoms in postmenopausal women at 12-week follow-up [24]. Additionally, intravaginal fractional CO₂ laser therapy caused a significant decrease in the severity of dyspareunia related to vaginal dryness in these patients, and was subsequently associated with a consistent improvement in sexual function and sexual satisfaction of menopausal women with GSM [25, 26].

Hypothesis: The CO₂ fractional vaginal laser therapy is non-inferior to vaginal estrogen therapy in the treatment of GSM.

Study Design and Aim:

This is a multi-centered, randomized prospective single blinded clinical trial comparing CO2 fractionated vaginal laser therapy and vaginal estrogen therapy in the treatment of vulvovaginal atrophy/GSM

Study Outcomes:

The primary outcome is subjective improvement of vaginal dryness using a 10 cm Visual analog scale.

The secondary outcomes that will be assessed include

1. An objective evaluation of vaginal atrophy/estrogenization measured by the globally validated “Vaginal Health Index” (VHI) score [reference Bachmann Maturitas 1995 attached]
2. The effect of GSM symptoms on QoL using the DIVA questionnaire [28]
3. The effect of treatment on the vaginal maturation index, at baseline and 6 month follow up
4. The effect of treatment on vaginal wall elasticity, using standard vaginal dilators to determine vaginal caliber
5. The effect of treatment on the female sexual function, by means of the Female Sexual Function Index (FSFI)[29]
6. Calculation of the percentage of patients who are sexually active or resume intercourse after therapy. A sexual function question not included in FSFI has been added to evaluate this.
7. The effect of the treatment on urinary symptoms by means of the Urogenital Distress Inventory (UDI-6) [30]
8. The degree of difficulty encountered by the physician in performing the MonaLisa laser treatment assessed via a 5-point Likert scale,
9. The rate of satisfaction of patients with treatment assessed by the Patient Global Impression of Improvement (PGI), using a 5-point Likert scale.

Subject SelectionInclusion Criteria

- Menopausal with absence of menstruation for at least 12 months
- Presence of vaginal atrophy symptoms [subjective assessment of vaginal dryness ≥ 7 cm on VAS)
- Prolapse stage \leq II, according to the pelvic organ prolapse quantification (POP-Q) system[31]
- No pelvic surgery within 6 months prior to treatment (vulva biopsy may be included after 2 weeks)
- Understanding and acceptance of the obligation to return for all scheduled follow-up visits

- English speaking and able to give informed consent

Exclusion Criteria

- Personal history of vulvovaginal condyloma, vaginal intraepithelial neoplasia (VAIN), vaginal carcinoma, lichen sclerosis, lichen planus, history of vaginal radiation, history of cervical cancer, other gynecologic cancer, or pelvic radiation
- Acute or recurrent urinary tract infection (UTI), or genital infection (e.g. bacterial; vaginosis, herpes genitalis, candida).
- Personal history of Scleroderma
- Any serious disease, or chronic condition, that could interfere with the study compliance
- Previously undergone reconstructive pelvic surgery within the past 6 months
- Previously undergone reconstructive pelvic surgery with transvaginal mesh kits and sacrocolpopexy with synthetic mesh for prolapse, excluding synthetic slings (unless current untreated exposure or extrusion)
- Have used vaginal estrogen cream, ring or tablet within 1 month prior to entering the study
- Vaginal moisturizers, lubricants or homeopathic preparations within 2 weeks of therapy
- Personal history of thrombophlebitis
- Personal history of heart failure or myocardial infarction within 12 months of procedure
- Use or anticipated use of antiplatelet therapy, anticoagulants, thrombolytics, vitamin E or nonsteroidal anti-inflammatory drugs within 2 weeks pre-treatment
- Contraindication to vaginal estrogen therapy
- Unwilling to Take vaginal estrogen therapy
- Inability to give informed consent

Subject Recruitment and Screening

Study subjects will be recruited from patients who present to the clinical sites at the Women's Health Institute at the Cleveland Clinic, Christ Hospital, Stanford University Hospital, MedStar Washington Hospital Center, Women's and Infants' Hospital of Rhode Island and Wake Forest School of Medicine for treatment of GSM. Cleveland Clinic will serve as the central Data Coordinating Center

Study Identification and Recruitment

Potential subjects will be identified by members of the sections of Urogynecology and Reconstructive Pelvic Surgery and Benign Gynecology at the respective institutions. Eligible patients who agree to participate will be provided written informed consent administered by the collaborators listed on this IRB.

Randomization

The participants will then be randomized to either fractional CO2 vaginal laser therapy or vaginal estrogen therapy according to a computer-generated randomization schedule with random block sizes with the use of the SAS statistical software package (SAS Institute, Cary, NC). All patients will be unblinded to their assignment.

Diagnostic and Therapeutic Interventions

In addition to a standardized evaluation including the history and physical examination, patients will be asked to complete the Female Sexual Function Inventory (FSFI) questionnaire, the Day-to-day Impact of Vaginal Aging (DIVA) questionnaire, and the Urogenital Distress Inventory (UDI-6), at baseline, 3 months, and 6 months after baseline and visual analog scales (VAS) for GSM symptoms. The Patient Global Index (PGI) will also be administered at 6 months. Completion of these questionnaires should take no more than 15-20 minutes. A vaginal maturation index will be obtained at the baseline visit on a regular Pap Smear slide and fixed with cytofixative and air dried. This will be repeated during the last follow up visit at 6 months.

Vaginal Laser Protocol

Postmenopausal women will undergo treatment intravaginally with the fractional microablative CO₂ laser system (SmartXide 2 V 2 LR, MonaLisa Touch, DEKA, Florence, Italy), using the following setting: dot power 30 watt, dwell time 1000 μ s, dot spacing 1000 μ m and the smart stack parameter from 1 to 3. Stack 1 is used at baseline and stack 3 at 6 weeks and 3 months. The laser beam will be applied using a 90° vaginal probe gently inserted up to the top of the vaginal canal and subsequently withdrawn at centimeter intervals and rotated to 6 positions in an alternating clockwise and counterclockwise pattern in order to provide a complete treatment of the vaginal wall. At the investigators discretion a flat probe (vulvar probe) may be utilized to more efficiently treat the introital area and vestibule. At the level of the vaginal introitus, the dot power will be decreased to 26 watts. A treatment cycle includes three laser applications (every 40-50 days, approximately 6 weeks). The procedure will be performed in the outpatient clinic and does not require any specific preparation (e.g. analgesia/anesthesia). At the clinician's discretion, EMLA cream may be applied to introitus for thirty minutes and wiped clean and dried prior to vulvar laser therapy. Patients will be recommended to avoid coital sexual activity for at least 3 days after each laser application because a mild inflammatory reaction may last up to 48 hours after laser therapy. Topical lidocaine 5% ointment may be used for any vulvar pain post-procedure.

Post Treatment Instructions

- Each subject shall be evaluated immediately post-treatment for complications and side effects, excessive bleeding, symptomatic vaginal discharge, pain, etc.
- Each study subject will be asked to assess discomfort of treatment using a 5-point Likert scale.
- The patient will be instructed on the specific activity limitations following the procedure, sedentary activities are recommended for a least a few days.
- The subject will not engage in vigorous exercise or contact sports for at least 72 hours, or until approved by the physician.
- The subject will refrain from douching for at least 72 hours after the procedures.
- Subjects will not engage in intercourse for at least 72 hours post procedure.
- The subject may shower but may not bathe the day following the procedure. They will use regular shower gel or soap.

Vaginal Estrogen Protocol

The women in the vaginal estrogen group will be prescribed and asked to administer one of three common choices of vaginal estrogen therapy based on patient's formulary and preference of cream or tablet form:

- 1) Conjugated estrogen cream (Premarin[®]): 0.5 g of cream intravaginally daily (using applicator or fingertip) for two weeks (fourteen days) then 0.5 g twice weekly for 24 ± 2 additional weeks, **or**
- 2) Estradiol cream (ESTRACE[®]): 1.0 g of cream intravaginally daily (using applicator or fingertip) for two weeks (fourteen days) then 1.0 g twice weekly for 24 + 2 additional weeks, **or**
- 3) Estradiol vaginal tablet (Vagifem[®]): one tablet (10 microgram) inserted daily into the vagina for two weeks (fourteen days) then 1 tablet inserted intravaginally twice weekly for 24 + 2 additional weeks.

Vaginal examinations

Vaginal Health Index (VHI) score including vaginal pH will be obtained using litmus paper during baseline and each follow-up examination and recorded. This will be obtained during baseline, 6 week, 3 month, and 6 month follow-up by a **blinded examiner** prior to assessment of vaginal wall elasticity with silastic dilators. A limited vaginal exam will be performed to assess the condition of the vaginal area. This exam will include a vaginal calibration, performed with a standard vaginal dilator (Syracuse Medical). The investigator will determine the largest dilator of the five sizes available (XS, S, M, L, XL), that the subject can comfortably have placed in her vagina. The subject then assesses how much pain she is experiencing when the dilator is placed in her vagina, using a 5-point Likert scale.

- GSM symptom (vaginal dryness, vaginal burning, vaginal itching, dysuria) will be assessed using the VAS.
- Patient evaluation of the overall treatment (PGI) using a 5-point Likert scale will be conducted at 6 week, 3 month and 6 month follow-up visits.
- After each treatment, the PI or co-investigator will be asked to evaluate the ease of treatment using a 5-point Likert scale.
- After each treatment, the subject will be asked the degree of discomfort experienced as a result of treatment using a 5-point Likert scale.
- Events will be evaluated and recorded.

Questionnaires and evaluations

Questionnaires will be administered by a **research nurse coordinator who is blinded to the patient's therapy**. Sexual function, GSM, and urinary function will be evaluated with the 10-cm VAS, Female Sexual Function Index (FSFI), Day-to-day Impact of Vaginal Aging (DIVA), and Urogenital Distress Inventory (UDI-6), both at baseline prior to 1st laser treatment or commencing with vaginal estrogen (depending on treatment group), and at 12 weeks from

baseline (+/- 1 week) but prior to 3rd laser treatment (if applicable), and at 3 months follow-up after 3rd laser treatment (if applicable). Note that all patients will follow up 6 months from baseline visit for final assessment

The DIVA questionnaire will be administered at baseline, 3 month, and 6 month follow-up visit period, in addition to the FSFI, UDI-6, VHI, and PGI during final assessment. All questionnaires are supplied in the appendix.

Calendar of Study Procedures

	Baseline	6 weeks	3 months	6 months
Informed Consent	X			
H & P	X			
MonaLisa Touch vaginal laser ¹	X	X	X	
Vaginal estrogen therapy ^{2, 3, 4}	X	X	X	
Vaginal symptom VAS	X	X	X	X
Vaginal health index VHI	X	X	X	X
Vaginal maturation index	X			X
DIVA questionnaire	X		X	X
Vagina dilator calibration	X	X	X	X
FSFI	X		X	X
UDI-6	X		X	X
Likert scale (laser patient)	X	X	X	
PGI		X	X	X
Likert scale (laser provider ease)	X	X	X	
Adverse events	X	X	X	X
Sexual activity	X	X	X	X

¹A treatment cycle includes three laser applications (every 5-7 weeks).

²Conjugated estrogen cream (Premarin[®]): 0.5g of cream intravaginally daily (using applicator or fingertip) for two weeks (fourteen days) then 0.5 g twice weekly for 24 ± 2 additional weeks, **or**

³Estradiol cream (ESTRACE[®]): 1.0 g of cream intravaginally daily (using applicator or fingertip) for two weeks (fourteen days) then 1.0 g twice weekly for 24 + 2 additional weeks, **or**

⁴Estradiol vaginal tablet (Vagifem[®]): one tablet (10 microgram) inserted daily into the vagina for two weeks (fourteen days) then 1 tablet inserted intravaginally twice weekly for 24 + 2 additional weeks.

Data Collection & Management:

Baseline data will include the following:

- Patient age, race, vaginal parity, menopausal state, BMI, history of previous use of vaginal estrogen
- FSFI, DIVA, and UDI-6 questionnaires
- VAS for GSM symptoms and VHI for objective GSM findings

Data points recorded during the procedure will include:

- Likert Scales for physician assessment of patient comfort during the procedure.
- Adverse events including inability to complete the procedure due to discomfort or constricted vagina

Post-procedure data will include the following:

- The rate of satisfaction of patients with treatment by mean of the Patient Global Impression of Improvement (PGI), using a 5-point Likert scale.
- The degree of difficulty encountered by the physician in performing the treatment, by mean of a 5-point Likert scale.
- Additionally, untoward side effects of treatment such as new bothersome vaginal irritation and significant vaginal bleeding will be recorded.

Protection of each subject's personal health information will be a priority in this study. One master Excel file containing subject personal information including name and medical record number will be kept in a password-protected file, on a designated protected research drive on a password-protected computer in a locked office at each respective institution. In that file, each subject will be assigned a subject identification number that will be used for the purposes of data collection in order to de-identify subjects.

All paper forms used for data collection will be kept in a research cabinet dedicated to this project, which will be locked at all times, in a locked office at the Cleveland Clinic (or other institution). All forms will contain de-identified information. Identification numbers will correspond to the subjects listed in the master excel file.

All study data will be transferred and managed electronically using REDCap (Research Electronic Data Capture). Each subject will be entered into REDCap using the assigned identification number from the master excel file. REDCap is a secure, web-based application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation, audit trails, and a de-identified data export mechanism to common statistical packages. The system was developed by a multi-institutional consortium which was initiated at Vanderbilt University and includes the Cleveland Clinic. The

database is hosted at the Cleveland Clinic Research Datacenter in the JJN basement and is managed by the Quantitative Health Sciences Department. The system is protected by a login and Secure Sockets Layers (SSL) encryption. Data collection is customized for each study as based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at the Cleveland Clinic.

Statistical Analysis Plan

Sample Size Rationale

We plan to enroll and randomize 196 patients in this non-inferiority trial comparing vaginal estrogen therapy to laser treatment of vaginal atrophy. The primary outcome will be subjective assessment of vaginal dryness as assessed by 10 cm visual analog scale at 6 months after initiating treatment. Assuming an alpha of 0.025 and a standard deviation of 2.0 [24], 85 subjects in each group will provide a 90% power to reject the null hypothesis (H0) that the true difference in vaginal dryness VAS score (Vaginal Estrogen – Vaginal Laser) is less than or equal to 1.0 cm on the VAS (effect size 0.5) in favor of the alternative hypothesis (H1): the true difference is greater than 1.0 cm using a one sided two sample t-test. Anticipating a 15% loss to follow-up and/or drop-rate over the period of the study, the total enrollment goal is 196 participants.

Analysis Plan

This study is a non-inferiority study design. The predefined non-inferiority margin is a difference of 1.0cm on a 10cm VAS. To minimize bias towards a finding of non-inferiority, data from women who were eligible and received the assigned treatment (per protocol) will be used for the analysis of the primary outcome. The primary outcome will be presented as the difference in VAS scores between treatments (Vaginal Estrogen – Vaginal Laser). The hypothesis of non-inferiority of the two treatment groups will be tested by comparing the lower limit of the two-sided 95% confidence interval (equivalent of a one-sided significance level of 0.025%) of the absolute difference with the margin set at -1.0cm. A secondary analysis of the primary outcome according to original treatment assignment (intent to treat) will also be performed as well as standard superiority testing using Student's t-test. If differences in baseline patient characteristics are noted, linear regression analysis adjusting for these differences will also be performed. Secondary outcomes will be analyzed using the intent to treat population using Pearson's Chi-square test for categorical data, Student's t-test for parametric continuous data, or Wilcoxon rank sum test for ordinal or nonparametric continuous data. Changes in patient reported outcome questionnaires (FSFI, DIVA, UDI-6, etc.) will be compared between treatments using repeated measures ANCOVA.

SAFETY AND ADVERSE EVENTS

Definitions

Adverse events include prolonged vaginal bleeding beyond 48 hours, heavy vaginal bleeding, bothersome vaginal irritation, bacterial vaginosis, vaginal yeast infection, post-procedural fever, and skin burn.

Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will also be recorded in the source document.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs up to 30 days after the subjects final study visit, and is considered to be related to or possibly related to the study treatment or study participation, will be recorded and reported immediately.

Reporting of Serious Adverse Events

Notification to Data Coordinating Center

A Serious Adverse Event (SAE) form must be completed by the investigator and emailed to the DCC within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by email to:

Dr. Paraiso – paraism@ccf.org

Lynn Borzi – borzil@ccf.org

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the DCC.

DATA SAFETY MONITORING

The Data Safety Monitoring Board (DSMB) is the primary data and safety advisory group for the **Female Foundation for Health Awareness (FFHA)** trial entitled "**A Randomized Clinical Trial Comparing Vaginal Laser Therapy to Vaginal Estrogen Therapy (VeLVET) in Women with Genitourinary Syndrome of Menopause (GSM)**". The DSMB reviews study data, evaluates the treatments for excess adverse experiences according to treatment group, judges whether the overall integrity and conduct of the study remain acceptable and makes recommendations to the FFHA and the Cleveland Clinic Data Coordinating Center.

- The DSMB will consist of 3 members that are not participating in this trial. All members have experience and expertise in their field of practice and in the conduct of clinical trials. Members were selected by the Cleveland Clinic Data Coordinating Center in conjunction with Marie Fidela Paraiso, M.D., Principal Investigator, Co-Investigators of the study and the FFHA.
- The DSMB will meet via teleconferences after 5 subjects from each site is enrolled, or sooner if warranted.
- During the initial portion of the conference call, members of the operational team will give an overview of the status of the trial and be available to answer questions from DSMB members. The Cleveland Clinic DCC will provide a general study status update and enrollment update at the beginning of the call. On conference calls, the Cleveland Clinic DCC will describe the reports to members. The Cleveland Clinic DCC will be present for the presentation of results and entire discussion portion of all calls to answer questions. He/she will not be present for the DSMB discussion and vote. Only voting members of the DSMB and the Cleveland Clinic DCC recorder may be present during the presentation of results and actual vote.
- After each conference call, the Cleveland Clinic DCC recorder, Lynn Borzi, reviewed by Dr. Paraiso, and distributed to the DSMB, will prepare minutes. The Chairperson will send a letter to the Cleveland Clinic DCC recommending changes and continuation/discontinuation of the trial. At the end of the study, a copy of the minutes will be forwarded to the Cleveland Clinic DCC for archive.

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Appendix

Baseline Examination Data

Pt. ID # _____

Treatment Group

Vaginal Laser Vaginal Estrogen

Age _____ BMI _____

Race

Caucasian African-American Hispanic Asian

Other, specify _____

Marital status

Single Married Divorced Widowed

Menopausal Status

Premenopausal Perimenopausal Postmenopausal (no menses for 6 months)

Current use of oral or transdermal hormonal therapy

Yes No

History of vaginal estrogen use

Yes No

Sexually active

Yes No

Exam:

Vaginal pH _____

Vaginal caliber XS S M L XL

Maturation Index Results:

_____ Data prior to and after Vaginal Laser or Vaginal Estrogen therapy (6 wk, 3 mos, 6 mos):

Exam

Vaginal pH _____

Vaginal caliber XS S M L XL

Local anesthetic used? Yes No N/A (Estrogen arm)

Vulvovestibular laser therapy? Yes No N/A (Estrogen arm)

Adverse event laser arm:

Inability to complete the procedure due to discomfort or constricted vagina

Yes No

Other: Specify _____

PATIENT ID: _____

PATIENT GLOBAL IMPRESSION OF IMPROVEMENT

Patient Global Impression of Improvement

Circle how you feel your symptoms are after treatment:

Much Worse	Worse	Same	Better	Much Better
1	2	3	4	5

Level of satisfaction after treatment

How would you define the level of satisfaction with the treatment?

Very Dissatisfied	Dissatisfied	Same	Satisfied	Very Satisfied
1	2	3	4	5

10 cm VISUAL ANALOG SCALE (VAS)

0 indicating absent symptoms (no bother) and 10 indicating the worst the symptoms could be (bothers as much as you can imagine). Please indicate your degree of bother with an X marked on the 10 cm line below next to each symptom.

	No Bother	Mild Bother	Moderate Bother	Most Bother
Vaginal dryness	0			10
Vaginal itching	0			10
Vaginal irritation	0			10
Painful urination	0			10

Additional question regarding sexual function not included in the FSFI.
This question will be asked at baseline, 6 weeks, 3 months, and 6 months.

Over the past 4 weeks have you been sexually active? (yes/no)

The reason if your answer no

- no partner
- no interest
- due to pain
- due to other reason, please specify_____

VAGINAL HEALTH INDEX SCALE

	Overall elasticity*	Fluid secretion type & consistency	pH	Epithelial mucosa	Moisture
1	None	None	6.1	Petechiae noted before contact	None, mucosa inflamed
2	Poor	Scant, thin yellow	5.6 – 6.0	Bleeds with light contact	None, mucosa not inflamed
3	Fair	Superficial, thin white	5.1 – 5.5	Bleeds with scraping	Minimal
4	Good	Moderate, thin white	4.7 – 5.0	Not friable, thin mucosa	Moderate
5	Excellent	Normal (white flocculent)	≤ 4.6	Not friable, normal mucosa	Normal

*Lower score corresponds to greater urogenital atrophy
Bachmann G. Maturitas 1995; 22:Suppl S1-5.

Female Sexual Function Index (FSFI) ©

Subject Identifier _____

Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

- Very high
- High
- Moderate
- Low
- Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

- No sexual activity
- Very high
- High
- Moderate
- Low
- Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- Did not attempt intercourse
- Very high
- High
- Moderate
- Low
- Very low or none at all

Thank you for completing this questionnaire

Medicine Compliance Log:

Weeks 1 and 2, please place an X in the box for each day you inserted vaginal cream or tablet

Weeks 3-6

Weeks 7-12

Weeks 13-18

Weeks 19-24

Urogenital Distress Inventory (UDI-6 Short Form): UDI-6

- 1) Do you usually experience frequent urination? Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
- 2) Do you usually experience urine leakage associated with a feeling of urgency; that is, a strong sensation of needing to go to the bathroom? Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
- 3) Do you usually experience urine leakage related to coughing, sneezing, or laughing?
Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
- 4) Do you experience small amounts of urine leakage (that is, drops)? Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
- 5) Do you experience difficulty emptying your bladder? Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
- 6) Do you usually experience pain or discomfort in the lower abdomen or genital region?
Yes No
If yes, how much does this bother you? Not at all Somewhat
Moderately Quite a bit
If yes, then is your pain relieved after emptying your bladder? Yes No

No= 0, Not at all= 1, Somewhat= 2, Moderately= 3, Quite a bit= 4

Add all scores and multiply by 6 then multiply by 25 for the scale score

Missing items are dealt with by using the mean from the answered items only

Higher score = higher disability

Also see scoring of PFDI-20.

Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl AJ. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. *Neurourol and Urodynam* 1995;14:131-139.

Grade A rating for symptoms of UI for women

Donavan J, et al Symptom and quality of life assessment. In *Incontinence vol 1 Basics and Evaluation* eds Abrams P, Cardozo L, Khoury S, Wein A. Health Publications Ltd Paris France 2005.

APPENDIX A

The Day-to-Day Impact of Vaginal Aging questionnaire

We are interested in understanding the impact of vaginal symptoms such as vaginal dryness, soreness, irritation, and itching on your day-to-day life. For each question below, please check the answer that best describes how your activities, relationships, and feelings have been affected by any of these symptoms during the past 4 weeks.

Part A. During the past 4 weeks, how much have vaginal symptoms such as dryness, soreness, irritation, or itching made it uncomfortable for you to or interfered with your ability to

1. Walk at your usual speed?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
2. Wear the clothing or underwear you want?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
3. Use the toilet or wipe yourself after using the toilet?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
4. Sit for more than an hour?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
5. Get a good night's sleep?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely

Part B. During the past 4 weeks, how often have vaginal symptoms such as dryness, soreness, irritation, or itching caused you to feel

6. Depressed or down?	<input type="checkbox"/> ₀ Never	<input type="checkbox"/> ₁ Rarely	<input type="checkbox"/> ₂ Sometimes	<input type="checkbox"/> ₃ Fairly often	<input type="checkbox"/> ₄ Very often
7. Embarrassed?	<input type="checkbox"/> ₀ Never	<input type="checkbox"/> ₁ Rarely	<input type="checkbox"/> ₂ Sometimes	<input type="checkbox"/> ₃ Fairly often	<input type="checkbox"/> ₄ Very often
8. Frustrated or resentful?	<input type="checkbox"/> ₀ Never	<input type="checkbox"/> ₁ Rarely	<input type="checkbox"/> ₂ Sometimes	<input type="checkbox"/> ₃ Fairly often	<input type="checkbox"/> ₄ Very often
9. Bad about yourself?	<input type="checkbox"/> ₀ Never	<input type="checkbox"/> ₁ Rarely	<input type="checkbox"/> ₂ Sometimes	<input type="checkbox"/> ₃ Fairly often	<input type="checkbox"/> ₄ Very often

Part C. The following questions ask about the impact of your symptoms on vaginal sexual intercourse and other types of sexual activity such as self-stimulation or masturbation. During the past 4 weeks, have vaginal symptoms such as dryness, soreness, irritation, or itching affected

10. Your desire or interest in having sexual intercourse or other types of sexual activity (including self-stimulation or masturbation)?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
11. How frequently you had sexual intercourse or other types of sexual activity (including self-stimulation or masturbation)?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
12. Your ability to become aroused during sexual activity (including self-stimulation or masturbation)?	<input type="checkbox"/> ₀ Not at all <input type="checkbox"/> Not applicable. I have not had sexual activity of any kind recently.	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
13. Your ability to be spontaneous about sexual activity (including self-stimulation and masturbation)?	<input type="checkbox"/> ₀ Not at all <input type="checkbox"/> Not applicable. I have not had sexual activity of any kind recently.	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
14. Your ability to relax and enjoy sexual activity (including self-stimulation or masturbation)?	<input type="checkbox"/> ₀ Not at all <input type="checkbox"/> Not applicable. I have not had sexual activity of any kind recently.	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₂ Quite a bit	<input type="checkbox"/> ₄ Extremely
15. The amount of pleasure you experienced during sexual activity (including self-stimulation or masturbation)?	<input type="checkbox"/> ₀ Not at all <input type="checkbox"/> Not applicable. I have not had sexual activity of any kind recently.	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
16. Your desire or interest in being in a sexual relationship?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
17. Your confidence that you could sexually satisfy a partner?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely
18. Your overall satisfaction with your sex life?	<input type="checkbox"/> ₀ Not at all	<input type="checkbox"/> ₁ A little bit	<input type="checkbox"/> ₂ Moderately	<input type="checkbox"/> ₃ Quite a bit	<input type="checkbox"/> ₄ Extremely

Part D. The following statements describe ways in which your vaginal symptoms may have affected your feelings about yourself and your body. Please indicate how true each of the following statements has been for you during the past 4 weeks.

19. My vaginal symptoms make me feel like I'm getting old.	<input type="checkbox"/> ₀ Not at all true	<input type="checkbox"/> ₁ A little true	<input type="checkbox"/> ₂ Somewhat true	<input type="checkbox"/> ₃ Mostly true	<input type="checkbox"/> ₄ Definitely true
20. I feel undesirable because of my vaginal symptoms.	<input type="checkbox"/> ₀ Not at all true	<input type="checkbox"/> ₁ A little true	<input type="checkbox"/> ₂ Somewhat true	<input type="checkbox"/> ₃ Mostly true	<input type="checkbox"/> ₄ Definitely true
21. When I think about my vaginal symptoms, I feel like I have lost something.	<input type="checkbox"/> ₀ Not at all true	<input type="checkbox"/> ₁ A little true	<input type="checkbox"/> ₂ Somewhat true	<input type="checkbox"/> ₃ Mostly true	<input type="checkbox"/> ₄ Definitely true

22. My vaginal symptoms make me feel like my body is deteriorating.	<input type="checkbox"/> ₀ Not at all true	<input type="checkbox"/> ₁ A little true	<input type="checkbox"/> ₂ Somewhat true	<input type="checkbox"/> ₃ Mostly true	<input type="checkbox"/> ₄ Definitely true
23. I feel less sexy because of my vaginal symptoms.	<input type="checkbox"/> ₀ Not at all true	<input type="checkbox"/> ₁ A little true	<input type="checkbox"/> ₂ Somewhat true	<input type="checkbox"/> ₃ Mostly true	<input type="checkbox"/> ₄ Definitely true

Recommended scoring:

Total scores for each domain scale are computed by calculating the average of scores for the corresponding individual items. The possible range for all domain scales is 0 to 4, with higher scores denoting greater impact of vaginal symptoms.

Two versions of the sexual functioning scale are available: (1) a short five-item version that can be administered to all postmenopausal women regardless of sexual activity status and (2) a longer nine-item version that includes four additional items (12, 13, 14, and 15) that are only appropriate for women with a history of recent sexual activity.

Activities of daily living domain: items 1, 2, 3, 4, 5

Emotional well-being domain: items 6, 7, 8, 9

Sexual functioning domain (short version): items 10, 11, 12, 16, 17, 18

Sexual functioning domain (longer version): items 10, 11, 12, 13, 14, 15, 16, 17, 18

Self-concept and body image domain: items 19, 20, 21, 22, 23

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- If other investigators are interested in obtaining the survey, please refer them to the source document to ensure that they obtain the most recent version and scoring instructions.

APPENDIX B

Hypothesized correlations between Day-to-Day Impact of Vaginal Aging domain scales and other measures of convergent-divergent constructs

Additional measures	Day-to-Day Impact of Vaginal Aging domain scales			
	Activities of daily living	Emotional well-being	Sexual functioning	Self-concept and body image
Vaginal Symptom Bothersomeness Scale ^a	++	++	++	++
Female Sexual Problems Measure ^b	•	•	++	+
Hospital Anxiety and Depression Scale depression subscale ^c	•	++	•	+
Hospital Anxiety and Depression Scale anxiety subscale ^c	•	++	•	+

(++) Moderate to strong correlation; (+) weak correlation; (•) no specific hypothesis.

^aThis five-item measure assesses the presence and bothersomeness of vaginal dryness, itching, irritation, soreness, and pain during sexual intercourse in the past month. Higher scores indicate greater overall bother associated with symptoms.

^bThis four-item measure assesses difficulty with sexual arousal, lubrication, orgasm, and pain with sexual activity in the past 3 months. Higher scores indicate more severe sexual activity-specific problems.

^cThis measure consists of a seven-item subscale assessing depression and a seven-item subscale assessing cognitive anxiety in the past 4 weeks. Higher scores indicate greater depression or anxiety.