Official title: A Randomized Placebo-Controlled Trial Evaluating Radiofrequency and Hybrid Fractional Laser for Vaginal Rejuvenation

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The University of Texas Southwestern Medical Center at Dallas

Institutional Review Board

Principal Investigator:

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[redacted]

1. Introduction and Purpose:

Recently there has been an explosion of new minimally invasive technologies for the management of postmenopausal vulvovaginal symptoms, vaginal wall laxity, sexual dysfunction, and even mild to moderate urinary incontinence with very limited scientific studies to back the merits of these technologies and their claims.

Goals:

1. To evaluate the efficacy of radiofrequency (RF) and hybrid fractional laser (HFL) treatment for vaginal rejuvenation [redacted]
2. To establish objective methods to monitor vaginal rejuvenation following treatments by optimizing biopsy sample size and histological/gene expression methods.

Hypothesis:

We hypothesize that it is possible that vaginal rejuvenation via RF or HFL treatment could be a placebo effect. There are claims of improvement in urinary incontinence, appearance, and an array of vulvovaginal symptoms. To date, there is a paucity of objective data to support these

claims. We are unaware of any long-term studies following the outcomes after treatment.

Scientific gap:

[redacted]

The purpose of our pilot study is to use subjective and objective tests to address some of these unanswered questions. [redacted]

By collecting data at these short-term and long-term time points we will fill an important scientific gap regarding whether these treatments have an actual effect or not.

[redacted]

2. Background:

Vaginal rejuvenation is a catch-all term of trendy procedures which claim to provide relief of many issues affecting women's health, ranging from postmenopausal vulvovaginal symptoms (i.e. dryness, burning, itching), stress urinary incontinence, sexual dysfunction or discomfort, vaginal laxity, and labial appearance, amongst others.[3,4] [redacted]

[redacted]

References

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Dysfunction. *Lasers Surg Med*. 2016. Epub.

2. Krychman M, Rowan CG, Allan BB, DeRogatis L, Durbin S, Yacoubian A, Wilkerson D. Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controoled Trial. *J Sex Med.* 2017 Feb;13(2):215-225. doi: 10.1016/j.jsxm.2016.11.322.

3. Millheiser LS, Pauls RN, Herbst SJ, Chen BH. Radiofrequency treatment of vaginal laxity after vaginal delivery: Nonsurgical vaginal tightening. *J Sex Med* 2010;7(9): 3088–3095.

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5. N. Zerbinati, M. Serati, M. Origoni, M. Candiani, T. Iannitti, S. Salvatore, F. Marotta, A. Calligaro. Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. *Lasers Med. Sci*. 2015; 30:429–436

6. Paul M, Blugerman G, Kreindel M, Mulholland RS. Three-dimensional radiofrequency tissue tightening: a proposed mechanism and applications for body contouring. *Aesthetic Plastic Surg.* 2011;35(1):87-95

7. Peet J. Evaluation of the Safety and Efficacy of Hybrid Fractional 2940 nm and 1470 nm Lasers for Treatment of Vaginal Tissue: Pilot Study. [White paper].

3. Concise Summary of Project:

This is a single-center, randomized, prospective study designed to evaluate the efficacy of radiofrequency and hybrid fractional laser for vaginal rejuvenation. [redacted]

[redacted]

4. Study Procedures:

[redacted]

The purpose of the study and specific inclusion and exclusion criteria and potential risks/benefits will be discussed with the potential study subject. All interested subjects will be given the Consent Form with adequate time for review. The Investigator and/or his designee will address questions and concerns raised by the subject. Those subjects who elect to participate will sign the Consent Forms prior to any study procedures.

Treatment Groups

IntraGen: [redacted] patients will each undergo a three-part treatment of the vulvovaginal area. [redacted]

IntraGen Placebo: [redacted] patients will undergo a three-part placebo treatment, space 1 month apart (+/- 10 days) of the vulvovaginal area. [redacted]

[redacted]

DiVa: [redacted] patients will undergo a three-part treatment, spaced 1 month apart (+/- 10 days) of the vulvovaginal area. [redacted]

DiVa Placebo: [redacted] patients will undergo a three-part placebo treatment, spaced 1 month apart (+/- 10 days) of the vulvovaginal area. [redacted]

All

Each patient will undergo testing at baseline and will be followed conservatively with no further therapy until they reach 6 months (+/- 10 days) [redacted] Those in the treatment group will be followed to 9 months (+/- 10 days) after the initiation of treatment with appropriate analysis. Those in the placebo group will be provided 3 monthly treatments with both [redacted] RF and [redacted] HFL .These post placebo dual therapy patients will be conservatively followed with no further treatment until they reach 6 months (+/- 10 days) after the initiation of the dual [redacted] RF and [redacted] HFL treatments. 6 months (+/- 10 days) post dual therapy they will return for subjective and objective testing. These patients will return for 9 month visit (+/- 10 days) after the initiation of dual therapy. P[redacted]

[redacted]

[redacted]

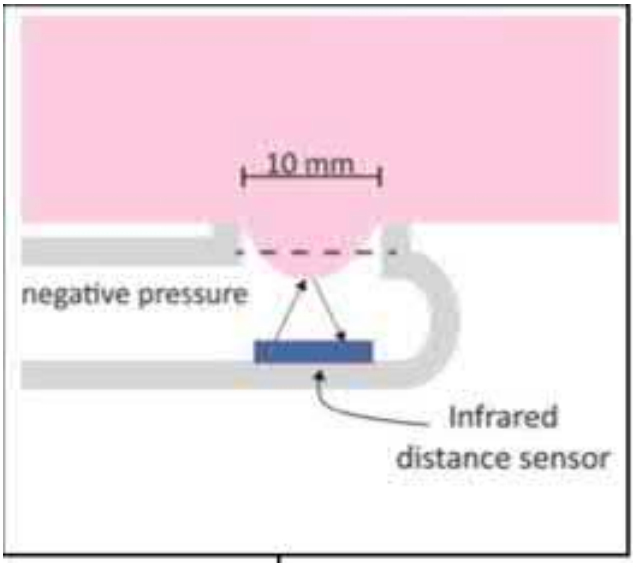
Visit Timelines

[redacted]

[redacted]

[redacted]

[redacted]



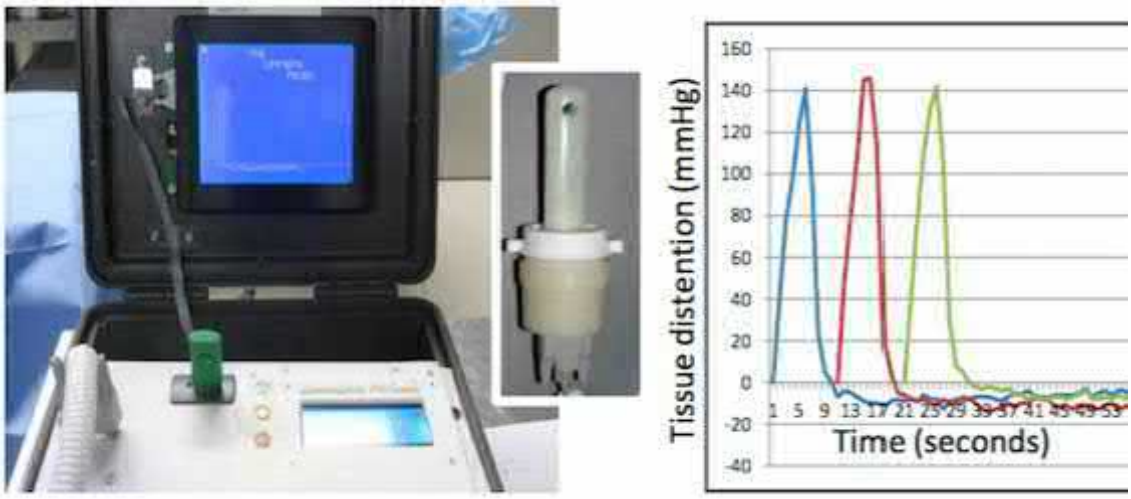
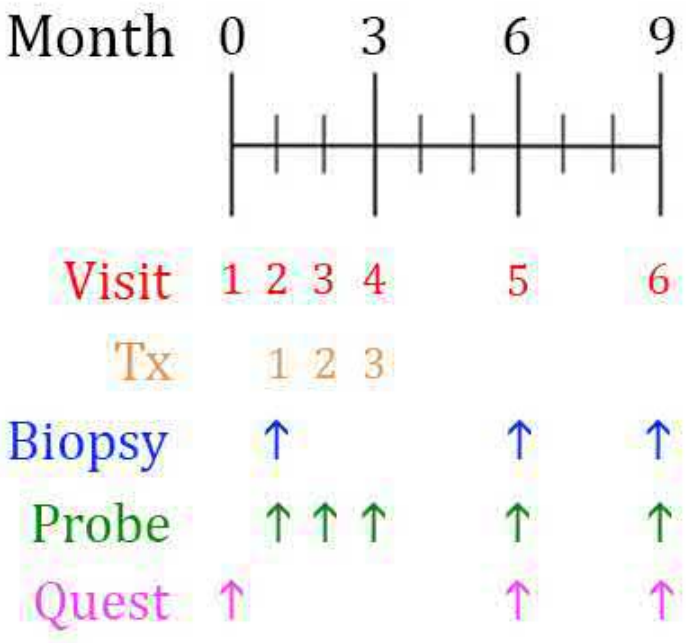
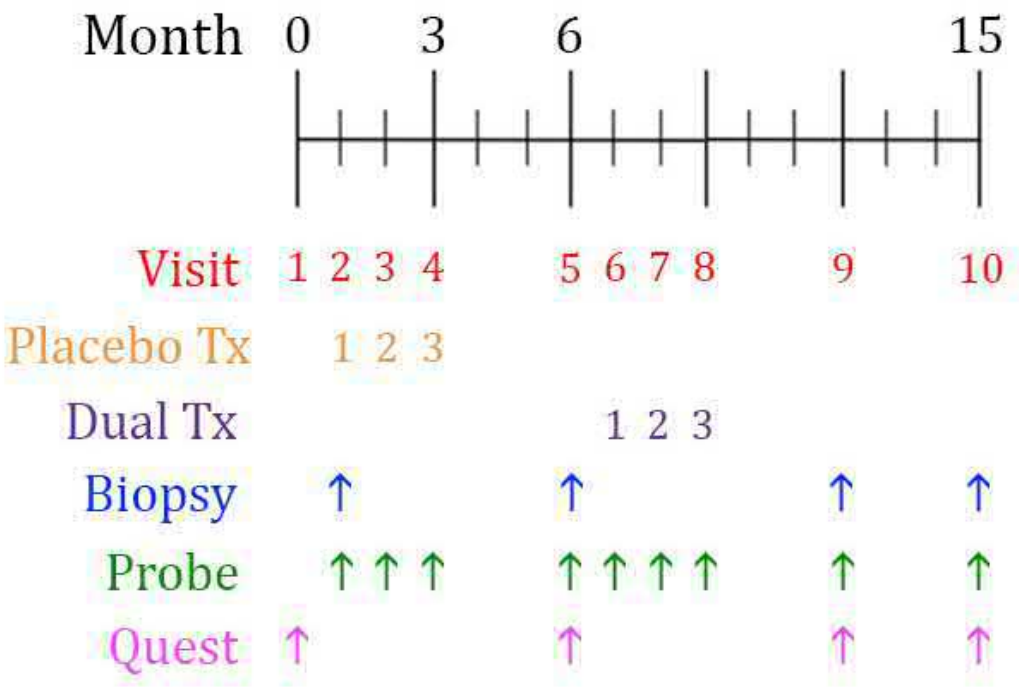


Figure 1: Zimmern Probe



Timeline Protocol 1 – Treatment Arm



Timeline Protocol 2 – Placebo Arm

Primary outcome measure:

1) Improvement in Vulvovaginal Symptoms

• The Vulvovaginal Symptoms Questionnaire is a validated questionnaire which was created to study vulvovaginal symptoms in postmenopausal women including their discomfort, emotions, life-impact and sexual-impact. [redacted]

Erekson EA, Yip SO, Wedderburn TS, et al. The Vulvovaginal Symptoms Questionnaire: a questionnaire for measuring vulvovaginal symptoms in postmenopausal women. Menopause 2013;20:973-979.

Erekson EA, Li FY, Martin DK, Fried TR. Vulvovaginal symptoms prevalence in postmenopausal women and relationship to other menopausal symptoms and pelvic floor disorders. Menopause 2015; 23:368-375.

2) Perceived changes in vaginal laxity

• This will be measured by both biometric probe analysis for elasticity and subjective questionnaire: the Vaginal Laxity Questionnaire (VLQ)

Millheiser LS, Pauls RN, Herbst SJ, Chen BH. Radiofrequency treatment of vaginal laxity after vaginal delivery: nonsurgical vaginal tightening. J Sex Med 2010 Sep;7(9):3088-95

Secondary outcome measures

Perceived changes in urinary incontinence

• This will be measured by subjective questionnaire: Urogenital Distress Short Form (UDI-6) and Incontinence Impact Questionnaire Short Form (IIQ-7)

Perceived improvement in sexual dysfunction

• This will be measured by subjective questionnaire: Female Sexual Function Index (FSFI)

[redacted]

5. <u>Sub-Study Procedures:</u> None

6. <u>Criteria for Inclusion of Subjects:</u>

Women should be between 40 and 65 years of age

Women should be post-menopausal

Women should be amenorrheic for at least 12 months

Postmenopausal women presenting with one or more of the following:

- Vulvar itching
- Vulvar burning or stinging
- Vulvar Pain
- Vulvar irritation
- Vulvar dryness
- Discharge from subject's vulva or vagina
- Odor from subject's vulva or vagina

7. Criteria for Exclusion of Subjects:

- Unable to commit to future appointments within one year
- Planning on moving away from Dallas within one year
- History of other energy-based vaginal therapy within one year
- Vaginal hormone replacement therapy must have a one month washout period prior to treatment and discontinued use for duration of study, systemic replacement is not excluded
- Prior labiaplasty, or vaginal injections of fat or fillers within 6 months
- Prior anti-incontinence surgery in the last 12 months
- Urinary incontinence requiring more than 2 pads/day
- Clinically significant pelvic organ prolapse (POP)
- Urinary tract infection in the past 3 months
- Unstable diabetes
- Ongoing chemotherapy
- Immunodeficiency status (steroid intake, ongoing chemotherapy)
- Diffuse pain syndrome or chronic pain requiring daily narcotics
- Chronic vaginitis including bacterial vaginosis, HPV, herpes, or other active STI
- Recent abnormal Papanicolaou test result
- Recent abnormal pelvic exam (i.e. concerning lesions)
- Vulvar dermatologic pathology requiring local steroid use
- Undiagnosed abnormal genital bleeding
- If less than two years postmenopausal, not using a medically approved method of contraception (i.e. oral, transdermal, implanted contraceptives, intrauterine device, diaphragm, condom, etc.)
- Pregnancy
- History of genital fistula or a thin rectovaginal septum
- Uncontrolled psychiatric conditions (well-controlled depression/anxiety is not excluded)

- Body Mass Index > 35
- Actively participating in or planning on participating in pelvic floor muscle strengthening exercise
- Presence of pacemaker, AICD, or other electrical health maintenance device

8. Sources of Research Material:

Medical history and demographic data (age, ethnicity, BMI, gravidity parity (both current and past), menopausal status, hysterectomy/ovarian status, allergies, current medications, major illnesses/hospitalizations, previous surgeries, smoking status, systemic hormone replacement therapy (HRT), current sexual activity, and medical co-morbidities). Subjective assessments including Vulvovaginal Symptom Questionnaire, Female Sexual Function Index, Vaginal Laxity Questionnaire, Urogenital Distress Inventory Short Form, and Incontinence Impact Questionnaire Short Form. Objective assessments including Zimmern Probe measurement and vulvovaginal biopsy studies for histology and gene expression studies.

9. Recruitment Methods and Consenting Process:

[redacted]

At the time of their recruitment, subjects will be notified of the risks and benefits of the study and will be provided with the consent form for their consideration. Informed consent and HIPAA Authorization will be done in the presence of the principal investigator, co-investigators or designated clinical trial coordinator under the University of Texas Southwestern Medical Center at Dallas guidelines. A copy of the signed consent and HIPAA Authorization will be given to the subject, and the original will be kept in the source documents. All subjects will be

repeatedly asked if they have any questions regarding the study procedures.

10. <u>Potential Risks:</u>

The risks of radiofrequency, high frequency laser treatment, and dual therapy administering both radiofrequency and a high frequency laser of the vulvovaginal region include discomfort, mild edema, temporary erythema, spot bleeding, potential for transient over-active bladder, injury to bowel and bladder, and painful intercourse due to over-treatment. Less commonly, scarring, burns, and infection could occur. Should infection occur, treatment with antibiotics and even surgical intervention (i.e. I&D) may be required.

The risks of vaginal wall punch biopsy include pain, bleeding, bruising, infection, and possible scarring.

The RF or HFL treatment procedure will be performed by a medical provider who has been trained by [redacted] in the application of the device. The punch biopsy and probe application will be performed by this same doctor. There is no known risks associated with the suction probe to measure the anterior biomechanical vaginal wall tissue properties in situ.

There is also a potential risk of Loss of Confidentially during data collection. However, this risk can be minimized by de-identification of the patient data, and access limited to members of the research team.

11. <u>Subject Safety and Data Monitoring</u>

All study records will be identified by a study identification number. [redacted]

[redacted]

12. <u>Procedures to Maintain Confidentiality:</u>

All study records and information will be identified by the subject number. All subject identifiers will be removed from all documents. The link between subject name and study ID number will be kept in separate password-protected files. [redacted] All electronic study data will be password protected with access limited to members of the research team. Electronic data will be password protected.

[redacted]

14. <u>Biostatistics:</u>

The primary outcome of this study is the VSQ. We have estimated the standard deviation to be 2.5 based on prediction of pre-treatment scores ranging from 4 to 14. To detect a difference of 3 points on this measure with 80% power, 20 subjects per group will be required.

One way analysis of variance will be used for comparison of groups both for the VSQ and the Q-PCR data. Questionnaire results will be compared by comparing the results at each time point compared to pretreatment assessment.

UT Southwestern affiliated clinical statisticians have been and will continue to be consulted throughout the statistical analysis process.