

MINERVA GINECOLOGICA

VOL. 68 · 2016

**TECHNOLOGICAL EVOLUTION IN THE
RADIOFREQUENCY TREATMENT OF
VAGINAL LAXITY AND MENOPAUSAL
VULVO-VAGINAL ATROPHY AND OTHER
GENITOURINARY SYMPTOMS:
FIRST EXPERIENCES WITH A NOVEL DYNAMIC
QUADRIPOLE DEVICE**

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EDIZIONI · MINERVA · MEDICA

ORIGINAL ARTICLE

Technological evolution in the radiofrequency treatment of vaginal laxity and menopausal vulvo-vaginal atrophy and other genitourinary symptoms: first experiences with a novel dynamic quadripolar device

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ABSTRACT

BACKGROUND: This paper was a spontaneous, non-sponsored exploratory study to investigate the safety and efficacy of two schedules of thermal treatment with a new low-energy dynamic quadripolar radiofrequency (DQRF) device in: A) premenopausal women referring perception of vaginal introital laxity and related symptoms, with special reference to dysuria and urinary incontinence and unsatisfactory sexual activity (vaginal laxity arm of the study); B) postmenopausal women with vaginal atrophy and dryness and other vulvo-vaginal atrophy and *genitourinary syndrome of menopause* (VVA/GSM) related symptoms (VVA/GSM arm of the study).

METHODS: As for the vaginal laxity arm of the study, 12 women with perception of very to slightly loose vaginal introital laxity underwent five 20-min DQRF thermal treatment sessions every 14±1 days. A Vaginal Laxity Questionnaire (VLQ, certified Italian translation) and short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) were used to assess urinary incontinence, sexual gratification and the contribution of any concomitant pelvic organ prolapse. As for the VVA/GSM arm of the study, 13 women with objective evidence of VVA and vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms underwent four 10-min DQRF sessions every 10±1 days. Specifically designed visual analogue scales (VAS) for VVA/GSM symptoms and overall satisfaction with sexual life were used.

RESULTS: No adverse effects, including thermal burns or injuries, were reported during or after treatments in either arm of the study. Eleven of the enrolled women completed the five planned DQRF treatment sessions in the vaginal laxity arm of the study; 12 women completed the four DQRF sessions planned in the VVA/GSM arm of the study. Clinically and statistically significant improvements in self-perceived sensation of looseness and symptoms like dysuria/urinary incontinence and sexual function in the vaginal laxity arm of the study as well as VVA/GSM symptoms and overall satisfaction with sexual life in the VVA/GSM arm of the study. Improvements were already reported at the first assessment visit before the end of the planned DQRF sessions of each arm of the study, after, respectively, 56±4 and 30±3 days.

CONCLUSIONS: The DQRF treatment was well tolerated, with no pain during the procedure and no untoward effect reported over the 2-month follow-up periods in both the vaginal laxity and VVA/GSM arms of the study. Improvements in self-reported VLQ and PISQ-12 scores (vaginal laxity arm) and VAS self-evaluation of VVA/GSM symptoms and overall satisfaction with sexual life (VVA/GSM arm of the study) were rapid and persistent. This suggests rapid and persistent vaginal rejuvenation as the basis of subjective improvement in symptoms and decreased sexual distress in both indications, including dysuria and urinary incontinence in menopausal women. Such promising exploratory findings deserve confirmation in larger studies.

(Cite this article as: Vicariotto F, Raichi M. Technological evolution in the radiofrequency treatment of vaginal laxity and menopausal vulvo-vaginal atrophy and other genitourinary symptoms: first experiences with a novel dynamic quadripolar device. Minerva Ginecol 2016;68:225-36)

Key words: Pulsed radiofrequency treatment - Urinary incontinence - Menopause.

Well-defined clusters of events occur in all women in the weeks after vaginal childbirth and the months and years after menopause. The almost inevitable stretching during delivery of the dense connective tissue of the vaginal wall, introitus and labia majora, that then heals in varying degrees of laxity and worsen with each successive birth, may be considered physiological or quasi-physiological. Though distinct from vaginal and other genito-pelvic structures bulging into the vaginal canal and introitus more properly defined as prolapse, vulvovaginal laxity may seriously affect the woman's self-image, self-esteem and overall quality of life. This is due to compromised genital aesthetics and discomfort and irritation in everyday life, as well as to the negative impact on the woman's sexual experience and couple relationship. Much the same can be said of the menopausal estrogen drop associated with vulvar and vaginal involution and decreased circulatory engorgement, lubrication and elasticity, frequently leading to vulvo-vaginal atrophy (VVA) and related symptoms (dryness, irritation, itching, burning, discharge, dysuria).

Decreased genito-pelvic sensation during sexual activity is common in women with vaginal laxity. In a multinational survey of members of the International Urogynecological Association (IUGA), more than four out of five interviewed practitioners described vaginal laxity — mainly a delivery-related problem, though compounded by natural aging — as an under-reported and troubling condition that impacts the couple relationship. The interviewed IUGA members also described vaginal laxity as the most important change of body integrity experienced by women after vaginal delivery.¹

As regards VVA and genitourinary syndrome of menopause (GSM), symptoms may trouble up to 50% of postmenopausal women.^{2, 3} A 2015 survey in women with VVA symptoms found EQ-5D (EuroQol-5D) scores to be linearly related to symptom severity assessed with the Menopause Rating Scale. The decrements in EQ-5D scores associated with moderate to severe VVA symptoms were comparable to those observed in other serious

conditions such as arthritis, chronic obstructive pulmonary disease, asthma, and irritable bowel syndrome.⁴ The surveyed prevalence of VVA/GSM symptoms in the general menopausal population ranged between 40% (Germany) and 54.4% (Spain), with half of women reporting their symptoms as either moderate or severe.⁴ Vaginal dryness is the most commonly reported VVA symptom in Europe (70%), with 32% of women in Italy, Germany, Spain and the UK naïve to any kind of treatment.^{3, 5}

Besides impacting on the woman's quality of life and psychological wellbeing, introital and vaginal laxity after delivery and menopausal VVA/GSM frequently expose to unwelcome consequences in terms of long-term morbidity. Vaginal laxity is often detected in conjunction with atrophic vaginitis, stress incontinence and/or inappropriate micturition reflex with bladder instability. A lax vagina may in fact be the main determinant of both stress and urge female urinary incontinence.⁶ As regards VVA and GSM, recent vaginal infections were much more likely in a survey of a selected population of 722 women diagnosed with GSM out of 913 looking for routine gynecological examinations in Italian menopause health centers (OR 2.48, 50% CI: 1.33-4.62, vs. non-GSM controls). Itching and dysuria as risk factors for further morbidity were also highly prevalent (56.6% and 36.1%, respectively).⁷

The paper illustrates the outcomes, with special reference to safety, of the first study with the last technological evolution of non-ablative radiofrequency treatment in women with either vaginal laxity or VVA/GSM (see Appendix). The study, designed as a spontaneous, non-sponsored, short-term exploratory investigation, was carried out in a private outpatient setting and targeted to women experiencing quite severe quality of life disruption because of significant GSM- and vaginal laxity-related symptoms. Emphasis was on safety and the medical value of the new technology as elective procedure when either condition is a serious problem for the woman's wellbeing and quality of life.

The paper also discusses how the efficacy and safety outcomes of the study relate to the

biophysics of dynamic quadripolar application of highly targeted heat-generating radiofrequency fields to vulvar and vaginal subepithelial tissue layers.

Materials and methods

Study goal and design and study population

A spontaneous, exploratory, open-label investigation was prospectively conducted in outpatient office-based subjects at the investigator's private practice to probe the safety and efficacy of a newly developed dynamic quadripolar device as non-surgical, non-laser radiofrequency treatment in: A) women with subjective perception of laxity of vaginal introitus and other laxity-associated symptoms with special reference to urinary incontinence; B) postmenopausal women with subjective perception of vaginal dryness and other VVA/GSM-related symptoms. All study materials were appropriately peer reviewed for ethical problems. All candidate women gave full informed consent.

Candidate women with vaginal laxity were screened from early January to mid-May 2015; candidate women with VVA/GSM for enrolment from late mid-February to late May 2015. A total of 12 women with vaginal laxity and 13 with VVA/GSM were enrolled; follow-up of the last subjects ended in July 2015. The dimensions of the two samples were defined without any clear-cut indications from either published papers or systematic clinical experience about the value and role of the new radiofrequency technology in the two indications. The two schedules of thermal dynamic quadripolar radiofrequency (DQRF) treatment were designed based on the evidences of pre-clinical experiences in animal vaginal models.

Activities specific to the vaginal laxity arm of the study

SCREENING AND ENROLMENT PROCEDURES

Candidate women were to be less than 54 years old and premenopausal. They were to

have had at least one full-term vaginal delivery (more than 36 weeks gestation) completed at least one year before study enrolment and to currently have negative pregnancy tests and a normal Papanicolaou Smear Cytology Test (obtained no more than two months before enrolment). Candidate women were to be in a stable monogamous heterosexual relationship, to have reasonable sexual activity (at least two vaginal intercourses per month using an acceptable method of birth control), and to have no evidence of significant pelvic organ prolapse (*i.e.*, beyond the hymenal ring). Dosage of any medication, such as antihypertensives and psychotropics, known to affect sexuality should have been stable for at least 1 month prior to treatment with no dosage change likely or planned in the forthcoming weeks. Candidates should not have been taking medications known to affect collagen metabolism and healing such as non-steroidal anti-inflammatory drugs and steroids for at least one month. The vaginal canal, introitus and vestibule were to be free of injuries and bleeding. Previous pelvic surgery within four years also prevented enrolment.

Candidates were fit for enrolment if they reported a perception of vaginal introital laxity that they defined as "very loose", "moderately loose", or "slightly loose" on a certified Italian translation of the Vaginal Laxity Questionnaire (VLQ), a Likert-type Scale with seven levels of response ("Very loose", "Moderately loose", "Slightly loose", "Neither loose nor tight", "Slightly tight", "Moderately tight", "Very tight").⁸ Subjects with severe urinary incontinence with suspected intrinsic sphincteric deficiency (ISD) and positive empty bladder stress tests were excluded.

OUTCOME ASSESSMENT

VLQ was the main outcome measure instrument; the short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) was also used as a validated standard assessment instrument for symptoms like dysuria/urinary incontinence and for gratifi-

cation with sexual life as well as to discriminate the contribution of any concomitant pelvic organ prolapse.⁹ Categorical levels of response were translated into ordinal scores for statistical analysis (for the VLQ scale, for instance, “Very loose”=1, “Moderately loose”=2, “Slightly loose”=3, “Neither loose nor tight”=4, “Slightly tight”=5, “Moderately tight”=6, “Very tight”=7). After the first one, the 20-min DQRF sessions were repeated every 14±1 days for a total of 5 sessions.

Activities specific to the VVA/GSM arm of the study

SCREENING AND ENROLMENT PROCEDURES

Candidate women were to be more than 50 years old and to have experienced no menstruation for at least 12 months. A wish to maintain an active sexual life should have been coexisting with vaginal dryness and/or dyspareunia rated as moderate/severe most bothersome symptoms¹⁰ and objective evidence of VVA (thinning/loss of vaginal rugae, mucosal pallor, friability and/or petechiae, low vaginal pH, low vaginal maturation index). Any systemic or local hormonal replacement therapy should have been stopped for at least six months and no vaginal moisturiser, lubricant or any other local preparations should have been used in the previous month. Prolapse staged ≥II according to the pelvic organ prolapse quantification system¹¹ also prevented enrolment.

OUTCOME ASSESSMENT AND TIMING OF DQRF SESSIONS

Clinical severity of VVA/GSM symptoms (vaginal dryness, burning and itching, dyspareunia, dysuria) was self-assessed by the enrolled subjects using 10-cm visual analogue scales (VAS) with “No symptom” at the left extreme of the scale and “Symptom as severe as it could be” at the right extreme as previously reported in several VVA studies including breast cancer survivors.¹² The overall satisfaction with sexual life was similarly assessed by enrolled women using a 10-cm VAS with

“Worst level of satisfaction” at the left extreme of the scale and “Best level of satisfaction” at the right extreme. After the first one, the 10-min DQRF sessions were repeated every 10±1 days for a total of 4 sessions.

Screening and outcome assessment activities common to both arms of the study

Screening assessment included a physical and pelvic examination, demographics, and medical and obstetric/gynecological history. Exclusion criteria included pelvic surgery within four years of the study, acute or recurrent urinary tract infections, active genital infections, chronic vulvar pain or vulvar lesions or disease (dermatitis, human papillomavirus, herpes simplex, vulvar dystrophy), inadequate thickness of the recto-vaginal septum as assessed by pelvic examination. Any systemic condition or mood/psychiatric disorder interfering with informed consent and study compliance also prevented enrolment in either arm of the pilot study.

Basal assessment was performed immediately before the first DQRF procedure in both arms of the study immediately before the first DQRF session. Three office follow-up visits were planned: immediately before the last procedure (*i.e.*, after 56±4 days in women with vaginal laxity and after 30±3 in women with VVA/GSM) and after 30±1 and 60±1 days following this first follow-up assessment (Figure 1).

In-office safety assessment included recording of vital signs and adverse events with special reference to any experience of pain or discomfort during and after the procedure. Post-treatment safety assessments were carried out the next day by telephone calls and by questioning for any need of analgesics, anti-inflammatory drugs or other medications at the following DQRF session.

Statistical analysis

Descriptive statistics (means and standard deviations for continuous variables, frequency distributions and percentages for categorical

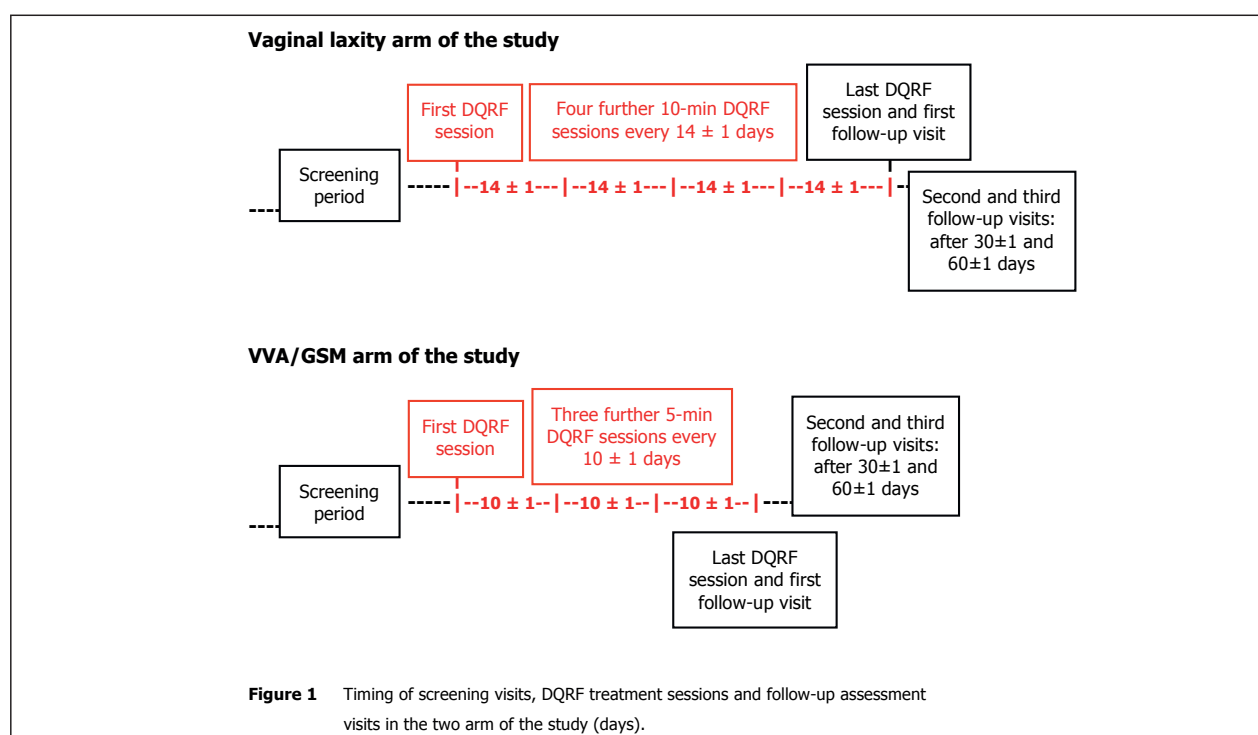


Figure 1.—Timing of screening visits, DQRF treatment sessions and follow-up assessment visits in the two arm of the study (days).

variables) were generated for demographics, medical history, and physical examination findings. The nonparametric Wilcoxon Signed Rank Test for repeated measurements on a single population was applied to both repeated measures of ordinal data (VLQ, PISQ-12 and SF-12 mean scores) and continuous variables (VAS mean scores); the McNemar Test was used to test for differences in ordinal mean scores. Two-sided 95% confidence levels were used with $p < 0.05$ as cut-off for statistical significance.

Results

Eleven women completed the 5 planned sessions of DQRF treatment in the vaginal laxity arm of the study; 12 women completed the 4 planned sessions in the VVA/GSM arm of the study. One woman was lost to follow-up in each arm of the study without any further information. Table I illustrates the demographics and other characteristics relevant to the investigations of the two study populations at the screening visits immediately before the first treatment session.

TABLE 1.—Main characteristics of the two populations in the two arms of the study. SD, standard deviation; HRT, hormone replacement therapy.

Vaginal laxity arm, study population	
Women completing the five planned DQRF sessions	11
Age (years, mean \pm SD)	41.7 ± 5.5
Body Mass Index (kg/m^2 , mean \pm SD)	24.1 ± 2.0
Parity (n, %)	
0	1 (9%)
1	3 (27%)
2	4 (36%)
3	3 (27%)
Current sexual activity (n, %)	11 (100%)
Frequency of sexual activity per week	1-4
VVA/GSM arm, study population	
Women completing the four planned DQRF sessions	12
Age (years, mean \pm SD)	60.4 ± 6.5
Body Mass Index (kg/m^2 , mean \pm SD)	23.0 ± 1.8
Previous live births (n, %)	9 (75%)
Parity	1.7 (1-3)
Current sexual activity (n, %)	7 (58%)
Previous systemic HRT (n, %)	3 (25%)
Months of systemic HRT (months, range)	31 (3-54)

As regards evaluation of safety as the main goal of this explorative study, no burns, blisters or other complication were reported during or after treatments in both arms of the

study. All DQRF sessions were described as relaxing and comfortable in both arms of their study. All women were able to resume all everyday activities, including sexual life, immediately after each DQRF treatment session.

Vaginal laxity arm of the study

Secondary vaginal laxity-related conditions (orgasmic dysfunction, stress incontinence, atrophic vaginitis) were reported at the screening visit by 10 out of the 12 enrolled women with self-reported perception of vaginal laxity (9 out of the 11 subjects who actually completed the study).

Compared to basal assessment, VLQ mean scores as index of subjective perception of vaginal tightness significantly improved by at least one level in all women, as observed already at the first follow-up visit before the

end of the five DQRF sessions. Six out of the 11 women who completed the five planned DQRF sessions reported VLQ scores that were 2-4 levels higher than before treatment at the first assessment visit. A marginally non-significant trend to further improvement was apparent during the 2-month post-treatment follow-up, with 9 women reporting VLQ scores that were 2-4 levels higher than basal assessment after 60 ± 1 days (Figure 2A).

A statistically significant improvement in overall sexual function (mean Total PISQ-12 Score) could be demonstrated at the first evaluation visit, immediately before the last DQRF procedure, compared with basal assessment (34.5 ± 6.8 vs. 38.5 ± 6.1 , $P < 0.05$). Nine out of the 11 women who completed the five planned sessions showed an improvement of 2 to 4 points (Figure 2B).

Four individual PISQ-12 scores showed statistically significant improvements at the first assessment visit (Q2 or frequency of climax, Q6 or urinary incontinence related to sexual activity, Q7 or fear of urinary and stool incontinence, Q9 or emotional reactions during sex); four individual scores showed a tendency to improve (Q1 or sexual desire, Q3 or sexual excitation, Q4 or variety of sexual activities, Q8 or sense of vaginal bulging preventing sex); for three PISQ-12 categories there was no change (Q5 or pain during intercourse, Q10 or partner's erection problems, Q11 or partner's premature ejaculation).

Similar mean total PISQ-12 scores were reported at the second and third assessment visit after 1 and 2 months of follow-up (40 ± 5.5 and 40.5 ± 5.6 , not significant compared to the first assessment visit, $P < 0.05$ compared with basal assessment).

Pain with intercourse subscores, already very low at screening, did not change over the follow-up period, meaning lack of even a very low-level of chronic inflammation induced, or anyway associated with the DQRF procedure. At the second visit, one woman missed more than two answers and was excluded from PISQ-12 assessment in accordance with PISQ-12 scoring instructions.⁹

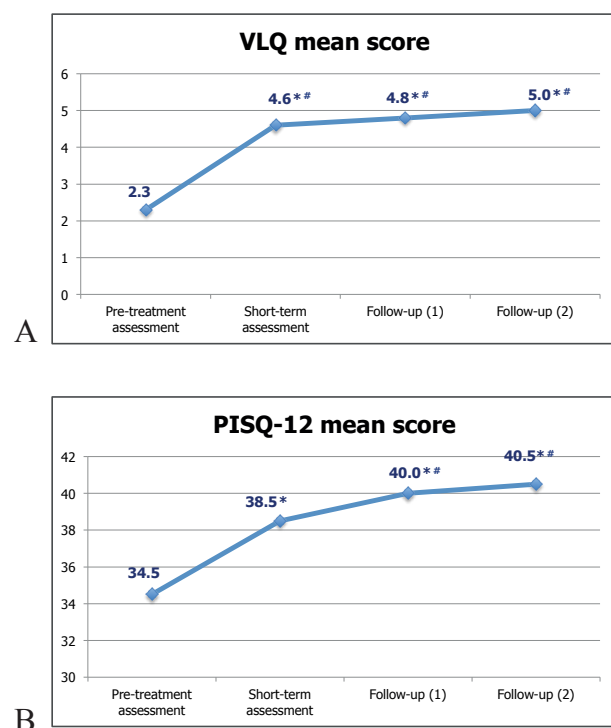


Figure 2.—Mean Vaginal Laxity Questionnaire (VLQ) scores (A), and mean Total Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) scores (B) immediately before the first DQRF procedure (Pretreatment assessment), immediately before the last planned DQRF procedure (Short-term assessment) and after 30 ± 1 and 60 ± 1 days of post-treatment follow-up (Follow-up (1) and Follow-up (2)). * $P < 0.05$ vs. basal assessment; #non-significant vs. first assessment visit.

VVA/GSM arm of the study

Before treatment, 8 out of the 13 screened and enrolled women (61.5%) and 7 out of the 12 women who completed the four planned sessions (58.3%) were sexually active; 5 of the screened women reported to have had no sexual intercourse for at least three months due to severe VVA/GSM symptoms. As regards VVA/GSM symptoms, vaginal dryness was reported by all 13 enrolled women before treatment, vaginal itching and vaginal burning by 10, dyspareunia by 11, and dysuria/incontinence by 8.

At the first assessment visit before the first DQRF session, 10 of the enrolled women reported to have resumed coital sexual activity (83.3%). At the last follow-up visit 11 women reported to be variably but anyway sexually active; only one woman reported physical and emotional discomfort during a few attempts at having intercourse and would not consider herself sexually active.

Compared to basal assessment, clinically and statistically significant improvements were observed for mean VAS scores of most VVA/GSM symptoms and for the overall satisfaction with sexual life at the first evaluation visit before the last DQRF session. Further improvements for all scored items, or at least a tendency to further improvement, could be appreciated at the two post-treatment visits during the follow-up period (Table II).

The mean VAS score for overall satisfaction with sexual life improved from 4.3 ± 1.4 at baseline up to 7.0 ± 2.0 after 30 ± 3 days ("First assessment visit") and 7.7 ± 2.4 at the last fol-

low-up visit, 90 ± 4 days after the first DQRF session (Figure 3).

Discussion

The radiofrequency technology for non-surgical thermal treatment and vaginal rejuvenation in women with either vaginal laxity or VVA/GSM is well established and widely considered safe and effective.^{8, 13}

In spite of the relative paucity of enrolled women with vaginal laxity and VVA/GSM, this exploratory study suggests that the novel dynamic quadripolar evolution of radiofrequency treatment is safe and well tolerated in both indications of vaginal rejuvenation with an excellent 2-month follow-up safety profile.

Even minimally invasive technologies may expose to bleeding, pain and burning.¹⁴ By minimizing the risk of thermal injuries, the new DQRF technology may offer further safety benefits over the current unipolar radiofrequency and laser technologies for non-surgical thermal treatment of introital and vaginal laxity and VVA/GSM.

Preclinical evidences provide convincing evidences of the biophysics of the DQRF concept. In infrared thermophotographs, the thermal effect in the treated genital areas appears to be highly localized onto the target mucosal surfaces and to rapidly dissipate after the end of the procedure without residual irritation or more severe injuries (Figure 4). The whole procedure has been usually reported by all women enrolled in the two arms of the study as painless and often devoid of any thermal sensation.

TABLE II.—*Detection and clinical severity of VVA/GSM symptoms in the study population of the VVA/GSM arm of the investigation. Mean scores (\pm standard deviation); data in cm assessed on 10-cm specifically designed visual analogue scales.*

	N.	Pre-treatment assessment	Short-term assessment	Follow-up (1)	Follow-up (2)
Vaginal dryness	12	8.8 ± 2.4	4.3 ± 1.8 **	3.4 ± 1.7 ** °	3.2 ± 1.9 ** °
Vaginal itching	10	7.5 ± 2.7	3.7 ± 1.9 **	3.0 ± 1.6 ** °	2.6 ± 1.3 ** °°
Vaginal burning	10	7.2 ± 2.5	3.4 ± 1.8 **	3.0 ± 1.7 ** #	2.8 ± 1.4 ** °
Dyspareunia	11	8.7 ± 2.2	4.5 ± 1.9 **	3.0 ± 1.8 ** #	3.1 ± 1.9 ** °
Dysuria/incontinence	8	5.5 ± 2.6	3.0 ± 1.9 *	2.9 ± 1.6 * #	2.6 ± 1.5 ** °

N.: women reporting symptom; * $P < 0.05$ vs. basal assessment; ** $P < 0.01$ vs. basal assessment; ° $P < 0.05$ vs. first assessment visit; °° $P < 0.01$ vs. first assessment visit; # non-significant vs. first assessment visit.

Preclinical investigations relating to the time course and spatial distribution of the thermal effect in the subepithelial layers also suggested the tentative treatment schedules ad-

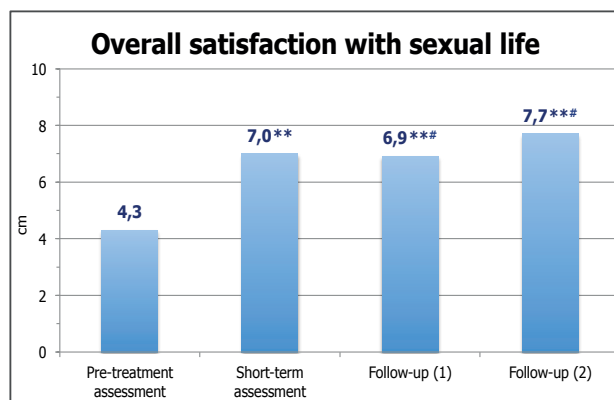


Figure 3.—Mean scores for overall satisfaction with sexual life (expressed as cm on a 10-cm visual analogue scale) before the first DQRF procedure (Pretreatment assessment) and at the first and second follow-up visit after 30±1 and 60±1 days of follow-up (Follow-up 1 and Follow-up 2). *P<0.05 vs. basal assessment; #non-significant vs. first assessment visit.

opted in this exploratory study. More formal dose-finding studies are warranted to fine-tune radiofrequency wavelengths and times of applications to maximize efficacy in both menopausal vaginal atrophy and laxity of the vaginal introitus and wall.

Somewhat different sets of biological effects should be pursued in the two conditions. As also suggested for other thermal therapy technologies, vaginal rejuvenation in introital and vaginal laxity implies re-activation of fibroblast and connective tissue function and development of new networks of collagen and elastin fibres in the subepithelial layers of introitus and vagina.^{13, 15}

Collagen re-activation is also the goal in vaginal rejuvenation in VVA/GSM, but possibly an even more important goal is vasodilatation. Increases of local blood flow facilitate the diffusion of the inactive sex steroid precursor dehydroepiandrosterone (DHEA) to vulvo-vaginal cells for local intracrine estrogen

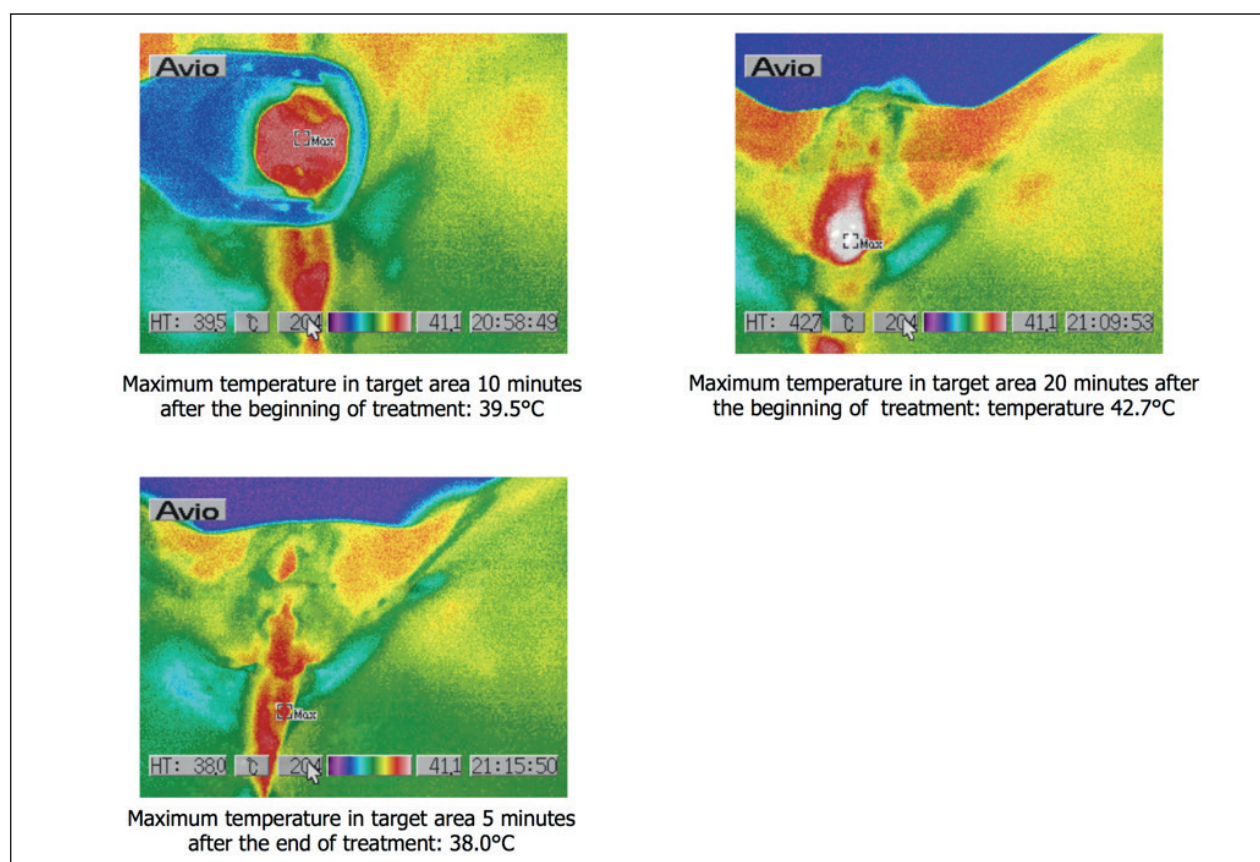


Figure 4.—Infrared temporised thermophotographs of the perineal, vulvar and vaginal areas of a woman enrolled in the vulvo-vaginal laxity arm of the study during her first 20-min DQRF session. Operational position: dorsal lithotomy position.

production. Thermally induced vasodilatation also facilitates the diffusion of DHEA-derived estrogens produced in local adipose tissue to the atrophic vaginal mucosa. From the time of menopause, DHEA from the adrenal glands becomes the only significant source of sex steroids for all hormone-dependent female tissues except the uterus. Ease of diffusion of DHEA and DHEA-derived sex steroids to vulvo-vaginal target cells may be crucial to counteract menopausal symptoms such as osteoporosis, muscle loss, vaginal atrophy, fat accumulation and hot flashes.^{16, 17}

The women with introital and vaginal laxity enrolled in the study defined their perception as “very loose”, “moderately loose”, or “slightly loose” on an internationally recognized self-assessment instrument as the VLQ. However few, as it is usually the case in exploratory studies, these women were a faithful sample of the universe of women with subjective perception of vaginal laxity in the gynecologist’s everyday clinical practice.

Improvements were rapid for both mean VLQ scores as index of vaginal laxity and PISQ-12 scores as index of overall sexual function and ancillary VVA-related disturbances like sex-related urinary and stool incontinence. Statistical and clinical VLQ and PISQ-12 improvements could be already shown at the first assessment visit immediately before the last DQRF procedure, only about 40 days after the first one, suggesting rapid onset of clinical benefits.

Improvements in VLQ and PISQ-12 scores vs. pre-DQRF basal assessment were similar at the first, the second and the third follow-up visits, suggesting persistence of clinical benefits with a base in anatomical re-modelling. Individual scores for intensity of orgasms and emotional experience during intercourse improved similarly to scores for dysuria and incontinence, confirming that anatomical re-modelling may be behind such ample benefits. Rapid and persistent improvement of vaginal laxity perception and laxity-related symptoms with DQRF treatment is in line with previous clinical evidences with highly effective unipolar radiofrequency and laser treatments.^{8, 13, 14}

When informally questioned during follow-up visits, women with pre-treatment introital vaginal laxity were usually happy to confirm gratifying, even unexpected, improvements in self-perceived sense of looseness, reduction of orgasmic dysfunction, better overall sexual satisfaction with a more relaxed couple relationship, as well as more pleasing genital aesthetics and improvement or disappearance of sex-associated stool and urinary incontinence. The operator also commonly referred visual improvements in looseness of labia majora, introitus and vagina: even at the first visit before the last planned DQRF treatment session.

As regards the VVA/GSM arm of the study, consistent improvements of all symptoms, as well as of sexual gratification, were reported by almost the whole VVA/GSM sample. Once again, the improvement of symptoms and the benefits for the sexual life were rapid — already after about a month and even before the end of the planned DQRF program — and persisted over the 2-month follow-up period.

The persistency of benefits once again suggests anatomical re-modelling and real correction of atrophy. Although no evaluation of thinning/loss of vaginal rugae, mucosal pallor and friability, low vaginal maturation index and other VVA-related symptoms was formally planned, anecdotic observations by investigators confirm anatomical rejuvenation. The menopausal fall of sex hormones, especially estrogens, impacts on mucosal elasticity by fusion, hyalinization and fragmentation of collagen and elastin fibers, and loss of highly hydrated matrix glycosaminoglycans.^{18, 19} As a consequence, urogenital atrophy-related symptoms develop in 40-57% of post-menopausal women and even in 15% of pre-menopausal ones.¹⁸

The benefits for vaginal health in menopausal women suggested by this exploratory study could even be indirectly self-sustaining over the long time. By letting the woman resume and maintain an active sexual life, DQRF vaginal rejuvenation may activate a series of physiological protective mechanisms that help to counteract the loss of mucosal elasticity and hydration associated with sex hormone depri-

vation.²⁰

However promising the results of this exploratory study with the new technologically advanced radiofrequency device in women with either vulvo-vaginal laxity or VVA/GSM, whether the benefits for wellbeing, self-esteem, sexual health and couple relationship are long-lasting remains an open question. Only further studies with a longer follow-up, hopefully in comparison with other effective non-surgical treatments, will be able to answer the question. Decreased sexual functioning in young breast cancer survivors as well as in pre-menopausal women with chemotherapy-related or surgical amenorrhea is another issue that this new technology could possibly contribute to relieve.²¹

Another field of application of non-surgical technologies for vaginal rejuvenation relates to the wish by many women, who have no real genitalia disorders, to obtain a more subjectively pleasing aesthetic appearance. This may indeed be the foremost field of application of non-surgical procedures for vaginal rejuvenation, and even for elective surgery.

Recent studies have shown that aesthetic reasons were behind the decision by 90% of patients to undergo elective surgery for vaginal tightening and perineal support.²² Labial reduction surgical procedures performed in the UK have doubled in the current decade,²³ whilst vaginal rejuvenation procedures increased by almost 30% in just one year in the USA in the last decade, from 793 in 2005 up to 1030 in 2006, according to the American Society of Plastic Surgeons.²⁴ The dynamic quadripolar evolution of the established radiofrequency technology is likely to have brilliant future also in aesthetic medicine, if the dynamic quadripolar concept — “persistent rejuvenation whilst minimising the risk of thermal injuries” — will survive the test of time. Well-designed dose-finding studies are a must also for any development in aesthetic medicine.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: March 11, 2016. - Manuscript received: March 7, 2016.

Appendix.—DQRF device and procedure

The radiofrequency generator is driven by a patented dynamic quadripolar technology emitting radiofrequency DQRF with frequencies that vary between 1MHz and 1.3MHz and a maximum emitting power of 55W. The device is equipped with both a movement and a temperature detector sensor for high safety. Specifically designed treatment tips equipped with medically certified AISI Type 316 stainless steel dynamic quadripolar electrodes are mounted on anatomical probes used for intravaginal, introital and vulvar applications.

Procedures were office-performed with no need for previous preparations like analgesia or local anesthesia; subjects were placed on the examining table in dorsal lithotomy position. Vagina, perineum, and perianal area were cleansed using an alcohol-free cleanse. The treatment area, defined by a vaginal circumference at the hymenal ring of about 12 cm, was about 20 cm². The probe tipped by the dynamic quadripolar electrode system is applied onto the mucosa of the vaginal introitus starting behind the hymenal ring using a coupling gel to ensure the RF delivery. Radiofrequency energy is applied over the treatment area with circular and back-and-forth continuous movements, keeping the probe in contact

with the vaginal mucosal walls. The target temperature is reached setting the power from 15% to 18% according to the patient's sensitivity. The target range in VVA/GSM subjects is lower (40° C to 42° C) and is reached by setting a power between 12-15% according to the patient's sensitivity.

The new DQRF technology does not need a grounding pad attached on the subject's upper thigh, thereby leading to current flows through the thigh tissues and delivery of heavy energy loads because of Ohm's resistances in tissues. Electric fields generate only within the electrodes area. The configuration of the four electrodes is continuously and electronically controlled between alternating receiver and transmitter states. This allows repelling electric fields to form that, once in the ideal combination, direct energy deep in the subepithelial layers of the introitus, vagina and vulva. The operator can fine-tune the low-energy thermal effect generated by the localized electric fields both volumetrically and in terms of depth. Such fine-tuning is facilitated by a complete set of anatomically designed probes and tips equipped with the dynamic quadripolar electrode system.

MINERVA

GINECOLOGICA

VOLUME 69 · No.4 · PAGES 342-349 · AUGUST 2017

DYNAMIC QUADRIPOLEAR RADIOFREQUENCY TREATMENT OF VAGINAL LAXITY/MENOPAUSAL VULVO-VAGINAL ATROPHY: 12-MONTH EFFICACY AND SAFETY

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E D I Z I O N I · M I N E R V A · M E D I C A

ORIGINAL ARTICLE

Dynamic quadripolar radiofrequency treatment of vaginal laxity/menopausal vulvo-vaginal atrophy: 12-month efficacy and safety

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ABSTRACT

BACKGROUND: Twelve-month extension of a previous spontaneous exploratory study investigating safety and efficacy of a new low-energy dynamic quadripolar radiofrequency (DQRF) device in: A) premenopausal women with symptoms of vaginal laxity, with special reference to dysuria, urinary incontinence and unsatisfactory sexual life (vaginal laxity arm of the study); B) postmenopausal women with vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) and VVA/GSM-related symptoms (VVA/GSM arm of the study). DQRF treatment schedule in both study arms: 4 to 6 procedures of 15 to 20 min every 14 days (vaginal laxity, range 12-17 days; VVA/GSM, range 13-16). Operative temperatures in vaginal target tissues during procedure: vaginal laxity, 42 °C (range 40-43 °C); VVA/GSM, 40 °C (range 40-42 °C).

METHODS: In the vaginal laxity arm of the study, 25 women with subjective sensation of vaginal introital laxity (very to slightly loose). Assessment of urinary incontinence, satisfaction with sexual relationship and contribution of pelvic organ prolapse: Vaginal Laxity Questionnaire (VLQ, Italian certified translation) and short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation). Further evaluation of sexual gratification: Sexual Satisfaction Questionnaire (SSQ). In the VVA/GSM arm of the study, 32 women with objective evidence of VVA and vaginal dryness and/or dyspareunia as most bothersome symptoms. Assessment of VVA/GSM symptoms and overall satisfaction with sexual life: specifically designed 10-cm visual analogue scales.

RESULTS: All 4 to 6 planned DQRF sessions were well tolerated in both the vaginal laxity and VVA/GSM arms of the study, with no troubling pain, thermal injury or other immediate adverse effects during all the procedures. All screened women completed the planned DQRF treatment sessions in both arms of the extension study. There was no participant attrition with only a few occasionally missing visits over the 12-month follow-up period. Improvements were rapid in self-perception of introital looseness and related symptoms like dysuria/urinary incontinence and unrewarding sexual relationship (vaginal laxity patients) and atrophy-related symptoms including painful and unsatisfactory sexual activity (VVA/GSM patients). Participating women consistently reported wide-spectrum strong clinical improvements by the end of the planned DQRF sessions. Clinical improvements remained steady for the whole follow-up period in postmenopausal women; a statistically non-significant tendency to slight deterioration in VLQ, PISQ-12 and SSQ mean scores was detected after 6 to 9 months of follow-up in the vaginal laxity arm of the study.

CONCLUSIONS: Safety was excellent during all DQRF procedures and over the 12 months following the end of the treatment sessions. VLQ, PISQ-12 and SSQ scores (women with vaginal laxity), VAS self-evaluation of VVA/GSM symptoms and overall satisfaction with sexual life (women with VVA/GSM symptoms) improved rapidly, reaching almost normal levels by the last DQRF session and suggesting rapid, but also persistent, vaginal rejuvenation in both indications. A late tendency to some slight deterioration in women treated for vaginal laxity suggests such women might benefit from new DQRF treatments 6 to 9 months after the previous cycle.

(Cite this article as: Vicariotto F, De Seta F, Faoro V, Raichi M. Dynamic quadripolar radiofrequency treatment of vaginal laxity/menopausal vulvo-vaginal atrophy: 12-month efficacy and safety. Minerva Ginecol 2017;69:342-9. DOI: 10.23736/S0026-4784.17.04072-2)

Key words: Vulva - Vagina - Atrophy - Urinary incontinence - Rejuvenation.

The radiofrequency technology for non-surgical thermal treatment and vaginal rejuvenation in women with either vaginal laxity or VVA/GSM is well established and widely considered safe and effective.^{1, 2} Increased awareness of these undertreated conditions and technological advances stimulate a steady flow of new surveys and high-level studies.³⁻⁵ A previous paper in 2016 in this journal described for the first time the efficacy and safety of a new technologically advanced low-energy radiofrequency device (EVA™, technology patented by Novavision Group S.p.A., Misinto, Monza-Brianza, Italy) in women experiencing severe quality of life disruption because of either postpartum vaginal laxity or vulvo-vaginal atrophy/genitourinary syndrome of menopause (VVA/GSM). This pioneer short-term investigation was carried out in a private outpatient setting as a spontaneous non-sponsored study.⁶

The 2016 paper also discussed the biophysics leveraged by the patented VDR™ (Vaginal Dynamic Radiofrequency) quadripolar 1.0-1.3 MHz radiofrequency technology of the new device (maximum emitting power, 55 W) to generate radiofrequency fields with high spatial precision in vulvar and vaginal sub-epithelial layers. Movement and temperature detector sensors specifically designed for high safety (RSS™, Radiofrequency Safety System technology) eliminate any need for systemic analgesia or local anesthesia in the target area — usually a circle of some 12 cm around the hymenal ring.⁶

The herein described two-arm study is the 12-month open-label extension of the previous one with a substantial increase of evaluated women in both indications. In the pioneering office-based pilot study that led to the current extension, 11 women with vaginal laxity and 12 women with VVA/GSM completed a total of, respectively, 5 treatment sessions and 4 sessions every 14±1 and 10±1 days. In this long-term extension, new enrolments have complemented the few participants of the exploratory study up to more than double women with vaginal laxity and almost three times more in the VVA/GSM arm of the study. As the previ-

ous investigation, this 12-month extension was also conducted in a private outpatient setting.

Materials and methods

Candidate women with vaginal laxity were screened and treated since early January 2015 and the follow-up was over by mid-January 2017; the total period for candidate women with VVA/GSM was since mid-February 2015 to early February 2017, for both indications within the pool of outpatients regularly attending the investigator's private practice. All candidate women referred either subjective perception of laxity of vaginal introitus and other laxity-associated symptoms or postmenopausal vaginal dryness and other VVA/GSM-related symptoms. All pelvic organ prolapses beyond the hymenal ring, chronic vulvar pain, vulvar lesions (dermatitis, human papillomavirus, herpes simplex, vulvar dystrophy) and poor thickness of the recto-vaginal septum at pelvic examination led to exclusion of candidates. Any active genital or urinary tract infection required treatment before enrolment. All study materials were peer-reviewed for ethical problems and all candidates gave informed consent.

Vaginal laxity arm of the study

SCREENING CRITERIA

As in the previous short-term exploratory study, the last full-term vaginal delivery (more than 36 weeks gestation) of all premenopausal candidates should have occurred at least one year before study enrollment with currently negative pregnancy tests; candidates should also be reporting a sensation of introital laxity defined as “very loose”, “moderately loose”, or “slightly loose” — first three categorical levels of response out of the seven of the Likert-type Scale Vaginal Laxity Questionnaire or VLQ in a certified Italian translation.⁷ Ancillary screening criteria included age less than 54 years, a normal Papanicolaou smear cytology assay obtained no more than 2 months before enrolment, a stable monogamous heterosexual

relationship with at least two vaginal intercourse per month using an acceptable birth control method, and stable doses of any medication known to affect sexuality such as antihypertensives and psychotropics for at least one month. Treatment with medications known to affect collagen metabolism and healing such as non-steroidal anti-inflammatory drugs and steroids, as well as injuries and bleeding of vaginal canal, introitus and vestibule, pelvic surgery in the last 4 years, and severe urinary incontinence with suspected intrinsic sphincteric deficiency and positive empty bladder stress tests also prevented enrollment.

OUTCOME EVALUATION

The Italian certified translation of VLQ was the main evaluation instrument; the 12-question short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12, Italian certified translation) was also useful to discriminate the contribution of any concomitant pelvic organ prolapse to vaginal laxity symptoms like dysuria, urinary incontinence and poor sexual satisfaction with couple relationship.⁸ An Italian translation of the Sexual Satisfaction Questionnaire (SSQ, 6-level ordered responses: none, poor, fair, good, very good, excellent) was also used to evaluate sexual satisfaction from vaginal intercourse. Categorical responses were translated into ordinal scores for statistical analysis (for instance for the VLQ Scale, very loose=1, moderately loose=2, slightly loose=3, ..., moderately tight=6, very tight=7).

VVA/GSM arm of the study

SCREENING CRITERIA

As in the previous short-term exploratory study, in all postmenopausal candidates (no menstruation for at least 12 months and currently no hormonal replacement therapy) a desire for a still active sexual life should have been coexisting with vaginal dryness, dyspareunia and other VVA/GSM symptoms and/or objective evidence of mucosal atro-

phy (thinning or loss of vaginal rugae, mucosal pallor, etc.).

OUTCOME EVALUATION

Clinical severity of VVA/GSM symptoms (vaginal dryness, burning and itching, dyspareunia, dysuria) was self-assessed by participants at each visit using 10-cm visual analogue scales (VAS) with "no symptom" at the left extreme of the scale and "symptom as severe as it could be" at the right extreme, as in several previous VVA studies including in breast cancer survivors.⁹ The overall satisfaction with sexual life was also evaluated by VAS ("worst level of satisfaction" at the left extreme of the 10-cm scale and "best level of satisfaction" at the right extreme).

An overall basal evaluation was performed immediately before the first DQRF procedure in all enrolled women participating in either arm of the study. On the same occasion, all women were asked for a judgement about how they remembered to have felt, compared with their current situation, before either delivery and development of vaginal laxity or development of VVA/GSM.

DQRF operative procedure

Four to six treatment sessions were planned every 14 ± 2 days for both indications. Power was applied, using a coupling gel, for 15 to 20 minutes starting behind the hymenal ring, with circular back-and-forth continuous movements and keeping the tip probe in contact with the vaginal mucosa. Power settings were 14% to 20% of the device maximum power (55 W) to treat vaginal laxity and 12% to 18% to treat VVA/GSM. Follow-up appointments were planned after 1, 2, 6, 9 and 12 months. Safety, with special attention to pain and discomfort, was assessed in all women at each study visit and by telephone calls over the following days.

Statistical analysis

Descriptive statistics (means and standard errors of the mean for continuous variables,

frequency distributions and percentages for categorical variables) were generated for demographics, medical history, and physical examination findings. The nonparametric Wilcoxon Signed Rank Test for repeated measurements on single populations was applied to both repeated measures of ordinal data (VLQ, PISQ-12 and SSQ mean scores) and continuous variables (VAS mean scores); the McNemar test was used to test for differences in ordinal scores. Two-sided 95% confidence levels were used with $P<0.05$ as cut-off for statistical significance.

Results

All women in both arms of the study completed their planned DQRF treatment sessions with only some occasional missing visits. Table I illustrates the demographics of the two study populations as recorded before the first DQRF session. All DQRF sessions were described as comfortable and no burns or other complications were reported. All women resumed their everyday activities, including sexual couple relationship, immediately after all DQRF treatment sessions.

TABLE I.—*Demographics and characteristics of study participants.*

Vaginal laxity arm, demographics	
Women completing the planned DQRF sessions	25
Age (years, mean \pm SD)	41.4 \pm 5.8
BMI (kg/m ² , mean \pm SD)	24.5 \pm 5.0
Parity (N., %)	
0	1 (4%)
1	5 (20%)
2	10 (40%)
3	6 (24%)
≥ 4	3 (12%)
Current sexual activity (N., %)	24 (96%)
Frequency of sexual activity per week	1-4
VVA/GSM arm, demographics	
Women completing the planned DQRF sessions	32
Age (years, mean \pm SD)	61.1 \pm 6.9
BMI (kg/m ² , mean \pm SD)	23.9 \pm 4.6
Previous live births (N., %)	23 (72%)
Mean parity (range)	1.7 (1-4)
Current sexual activity (N., %)	18 (56%)
Previous HRT (N., %)	9 (28%)

SD: standard deviation; HRT: hormone replacement therapy.

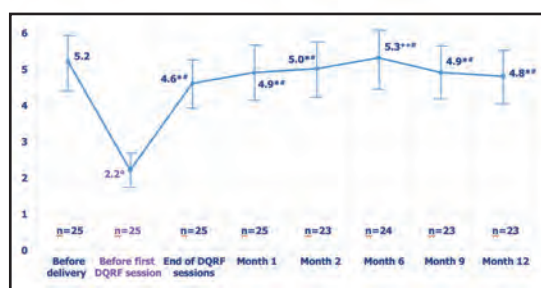


Figure 1.—Vaginal Laxity Questionnaire (VLQ) 7-level rating scale (very loose=1 to very tight=7), mean scores \pm SEM. Women's estimate before developing vaginal laxity ("before delivery") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions"), and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session. * $P<0.01$ vs. "before delivery". * $P<0.05$ vs. "before first DQRF session"; #non-significant vs. "before delivery"; ++ $P<0.01$ vs. "before first DQRF session" and $P<0.05$ vs. "end of DQRF sessions".

Vaginal laxity arm of the study

One or more disorders associated with vaginal laxity such as orgasmic dysfunction and stress incontinence were reported before starting the DQRF treatment sessions by 21 out of the 25 women (84%) participating to the study. Before the last DQRF session 17 women (68%) already reported VLQ scores as index of subjective perception of vaginal tightness that were at least 3 levels higher than before the first DQRF session (4.6 ± 1.8 vs. 2.2 ± 0.9 ; $P<0.05$). VLQ scores slowly yet steadily improved over the 6 months after the last DQRF treatment session, with 21 women (84%) reporting VLQ scores at "month 6" visit that were at least 3 levels higher than before the first DQRF session (VLQ mean score, 5.3 ± 2.0 ; $P<0.01$ vs. basal assessment, $P<0.05$ vs. last DQRF session). Subjective perception of tightness showed a slow trend towards some deterioration at "month 9" and "month 12" visits with 19 women (76%) reporting VLQ scores at the "month 12" visit at least 3 levels higher than before the first DQRF session (VLQ mean Score, 4.8 ± 1.9 ; non-significant vs. last DQRF treatment session) (Figure 1).

The overall sexual function and sexual satisfaction from vaginal intercourse also showed marked improvements at the first evaluation

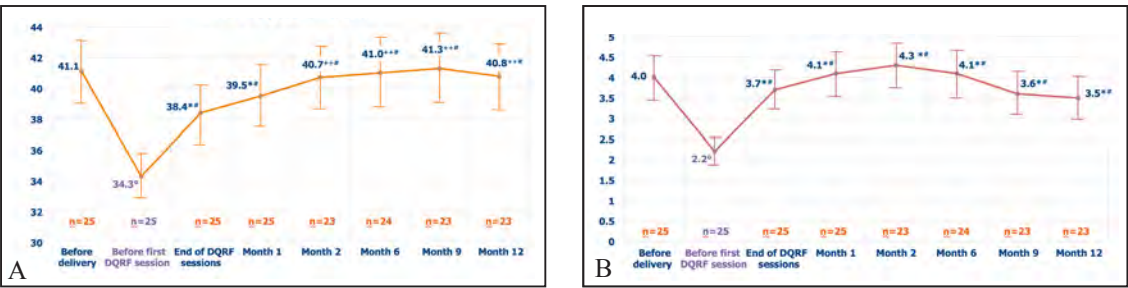


Figure 2.—A) Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, short form (PISQ-12) and (B) Sexual Satisfaction Questionnaire (SSQ) 6-point rating scale (none=1 to excellent=6), mean scores±SEM. Women’s estimate before developing vaginal laxity (“before delivery”) and evaluations immediately before the first and the last DQRF treatments (“before first DQRF session”, “end of DQRF sessions”), and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session. °P<0.01 vs. “before delivery”. *P<0.05 vs. “before first DQRF session”; #non-significant vs. “before delivery”; **P<0.01 vs. “before first DQRF session” and P<0.05 vs. “end of DQRF sessions”.

visit with, respectively, mean total PISQ-12 and SSQ scores (“end of DQRF sessions” vs. “before first DQRF session”) of 38.4±6.5 vs. 34.3±5.8 and 3.7±1.6 vs. 2.2±0.9, P<0.05 (Figures 2A, 2B). Twenty and 19 women out of 25 showed a short-term improvement (before the last DQRF session) of at least 3 points in, respectively, PISQ-12 and SSQ scores.

VVA/GSM arm of the study

Clinically significant improvements were observed for all VVA/GSM symptoms at the first evaluation visit (“end of DQRF sessions”) compared with the overall clinical picture at basal assessment (“before first DQRF session”). A steady progress of all scored symptoms towards the premenopausal situation, estimated by the “before VVA/GSM” VAS

scores, was apparent over the whole follow-up period (Table II).

Ten of the 32 screened women (31.2%) reported being forced to renounce any attempt at sexual intercourse during the three months before the first DQRF treatment visit because of severe VVA/GSM symptoms. Only 25 women reported at least some sexual activity, often unwillingly. All women reported vaginal dryness before treatment while 27 reported vaginal itching and burning, 29 dyspareunia, and 17 dysuria/incontinence.

At the first short-term assessment before the first DQRF session, 27 women out of 32 reported to have resumed having intercourse (84.4%); all women but four had resumed coital activity by the “month 2” visit (87.5%). Only two women reported strong physical and emotional discomfort during attempts at intercourse at

TABLE II.—Clinical severity of VVA/GSM symptoms, self-assessed mean scores±SEM (10-cm visual analogue scales). Women’s estimate before developing VVA/GSM (“before VVA/GSM”) and evaluations immediately before the first and the last DQRF treatments (“before first DQRF session”, “end of DQRF sessions”) and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.

	Vaginal dryness	Vaginal itching	Vaginal burning	Dyspareunia	Dysuria/incontinence
Before VVA/GSM (N.=25)	2.9±1.4	2.1±0.9	2.5±1.1	2.1±0.9	2.4±1.0
Before first DQRF session	8.9±2.4 °	7.6±2.8 °	7.2±2.5 °	8.8±2.2 °	5.9±2.5 °
End of DQRF sessions	4.3±1.9 *#	3.8±1.8 *	3.5±1.8 *#	4.4±1.7 *	2.9±1.9 *#
Month 1 (N.=25)	3.4±1.7 *#	3.0±1.7 *#	3.0±1.8 *#	2.9±1.8 *#	2.8±1.5 *#
Month 2 (N.=23)	3.2±1.6 *#	2.6±1.8 *#	2.9±1.6 *#	2.8±1.8 *#	2.7±1.6 *#
Month 6 (N.=24)	3.0±1.5 *#	2.4±1.6 *#	2.6±1.7 *#	2.4±1.5 *#	2.5±1.8 *#
Month 9 (N.=23)	3.1±1.1 *#	2.3±1.3 *#	2.5±1.2 *#	2.4±1.3 *#	2.4±1.4 *#
Month 12 (N.=23)	3.1±1.3 *#	2.3±1.2 *#	2.6±1.1 *#	2.3±1.2 *#	2.5±1.3 *#

°P<0.01 vs. “before VVA/GSM”; *P<0.05 vs. “before first DQRF session”; #non-significant vs. “before VVA/GSM”.

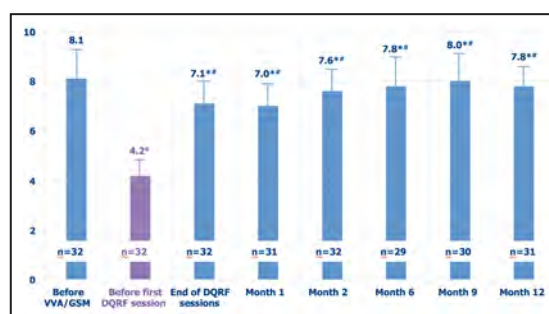


Figure 3.—Overall satisfaction with sexual life, self-assessed mean scores \pm SEM (10-cm VAS). Women's estimate before developing VVA/GSM ("before VVA/GSM") and evaluations immediately before the first and the last DQRF treatments ("before first DQRF session", "end of DQRF sessions") and at follow-up visits 1, 2, 6, 9 and 12 months after the last DQRF session.

*P<0.01 vs. "before VVA/GSM"; *P<0.05 vs. "before first DQRF session"; #non-significant vs. "before VVA/GSM".

the "month 6" through "month 12" follow-up visits. Mean VAS scores for overall satisfaction with sexual life improved from 4.2 ± 1.2 at baseline ("before first DQRF session") to 7.0 ± 2.1 before the end of the DQRF program ("end of DQRF sessions") and up to 7.6-8.0 after the sixth month of follow-up (Figure 3).

Discussion

The 12-month extension of the previous exploratory investigation of the new dynamic quadripolar evolution of radiofrequency treatment for vaginal rejuvenation confirms the new DQRF technology as most effective in both investigated indications postdelivery: vaginal laxity and postmenopausal atrophy of female genital tissues with associated genitourinary symptoms. The 12-month safety follow-up was also excellent. The long-term clinical benefits of the new technology are in line with the previous evidences with highly effective unipolar radiofrequency and laser devices.^{1, 10, 11}

No disturbing thermal injury or pain occurred during all the many performed procedures and, according to treated women, the procedure was painless and often free of any thermal sensation. The new DQRF technology might well be a safety advance over laser technologies that, even if minimally invasive, may

cause bleeding, pain and burning.¹⁰ It might also be an advance over available unipolar radiofrequency system because the new DQRF device does not need a grounding pad on the subject's upper thigh, thus avoiding all risk of current flows triggering Ohm's resistances in crossed tissues.

The technological trick is generating electric fields only within the medically certified stainless steel dynamic quadripolar electrodes tipping the anatomically designed probes. After the probes are applied to the vaginal, introital and vulvar mucosa, the configuration of the four electrodes is continuously and electronically controlled between alternating receiver and transmitter states. This allows repelling electric fields to be generated that concentrate energy in topographically localized electric fields in the subepithelial layers of the introitus, vagina and vulva. The operator can thus fine-tune the thermal effect associated with these low-energy electric fields in terms of both tissue volume and mucosal depth. Clinical pharmacology investigations with infrared thermophotographs of treated genital areas confirmed the thermal effect to be highly localized at the desired mucosal depth, and to dissipate rapidly without residual irritation.⁶

VLQ scores as main index of vaginal laxity, and PISQ-12 and SSQ scores as index of overall sexual function and ancillary VVA-related disturbances like sex-related urinary and stool incontinence, rapidly improved in participant women with introital and vaginal laxity even before the end of the planned DQRF sessions. Rapidly improved genital aesthetics and control of sex-associated stool and urinary incontinence were both reported as most gratifying by many women independently of the more relaxed couple relationship. Aside from any real medical consideration and remembering that aesthetic reasons were behind the decision by 90% of patients to undergo elective surgery for vaginal tightening and perineal support,¹² obtaining a more subjectively pleasing aesthetic appearance thanks to non-surgical techniques of cosmetic genitoplasty may even become the foremost field of application of vaginal rejuvenation.

Anatomical re-modeling defines vaginal rejuvenation. Anatomical re-modeling is most likely associated with thermal re-activation of fibroblasts and development of new networks of collagen and elastin fibers in the subepithelial layers of introitus and vagina.^{11, 13} The program of 4 to 6 DQRF sessions was over in less than two months, yet the vaginal rejuvenation effect persisted for a whole year after the last treatment. A few participant women reported some slight deterioration in perceived vaginal laxity and sexual satisfaction from vaginal intercourse (VLQ and SSQ mean scores), though there was no deterioration of improved ancillary symptoms like dysuria and urinary incontinence (PISQ-12 mean scores). This suggests consolidating the re-modelling and symptomatic benefits of the previous DQRF vaginal rejuvenation program with some further sessions after 6 to 9-12 months.

The Women's EMPOWER Survey most recently showed that women's awareness and understanding of VVA/GSM is still poor in spite of quite a lot of VVA surveys and wide media coverage of the problem over recent years.¹⁴⁻¹⁶

Vaginal rejuvenation as an option in VVA/GSM also benefits from direct thermal re-activation of fibroblasts and collagen, elastin, and matrix neosynthesis, but thermal vasodilatation is also a goal. The peri- and postmenopausal fall of estrogens impacts on mucosal elasticity by matrix glycosaminoglycans depletion and by hyalinization, fragmentation and fusion of collagen and elastin fibres.^{17,18} These events are associated with urogenital atrophic symptoms even in 15% of premenopausal women.¹⁷ Facilitating diffusion to the atrophic vaginal mucosa of adrenal dehydroepiandrosterone (DHEA) and DHEA-derived estrogens produced in local adipose tissue is likely to counteract vaginal atrophy, and possibly even postmenopausal osteoporosis, muscle loss, fat accumulation and hot flashes.^{19, 20} All women but two in the VVA/GSM arm of the study reported control of dyspareunia and resumption of coital activity and gratifying couple relationship at the end of the 12-month follow-up period, but benefits were already impressive

before the last treatment session, no later than one month and a half or two months after beginning the DQRF program.

Conclusions

The study data suggest there is no tendency to clinical deterioration even after one year since the last DQRF treatment session. This observation suggests persistent anatomical remodeling and real counteracting of atrophy. As in the pioneer exploratory study, no formal evaluations of thinning/loss of vaginal rugae, mucosal pallor and friability and low vaginal maturation index were formally planned, yet anecdotal observations by the investigator confirmed anatomical rejuvenation.

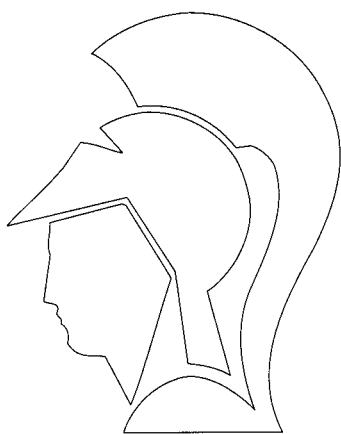
The follow-up of this office-based investigation is still going on with the goal of further defining the clinical and safety profile of the new DQRF device in both indications with the forthcoming evidences after 18 and 24 months.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.



Evolutions in diagnosis and treatment of vaginal laxity

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Received: ; Published:

Abstract

Introduction:

The use of Dynamic Quadripolar Radiofrequency (DQRF) is a new therapy for the treatment of vulvovaginal conditions such as laxity and sexual dysfunctions, while Vaginal tactile imaging allows biomechanical assessment of vaginal tissues and pelvic floor muscles.

The purpose of this study is to explore changes in vaginal tissue elasticity, pelvic floor support and muscle strength after applied vaginal radiofrequency treatments.

Case Report: In January 2017, a 42-year-old Caucasian Patient was treated for vaginal laxity. She had given birth to three children, the most recent being six years before vaginal rejuvenation was performed. She had experienced no previous non-surgical vaginal rejuvenation treatments and no past medical history that would be significant to this procedure such as recent surgical labiaplasty, etc., no known drug allergies, no sexual health history until the procedure, and cervical smears has never shown any abnormalities. DQRF procedures were performed at 2 week intervals for 4 consecutive treatments. The Vaginal Tactile Imager (VTI) was used to assess the vaginal walls, pelvic floor support structures and pelvic floor muscle (PFM) contractions before and two weeks after the final DQRF treatment. The VTI probe allows for an estimation of: a) vaginal tissue elasticity as a pressure gradient under vaginal wall deformation, b) pelvic floor support conditions as a pressure gradient under deformation of the posterior compartment, and c) PFM strength as a pressure feedback under voluntary and involuntary (cough) contractions.

Conclusion: Dynamic Quadripolar Radiofrequency treatment is a promising novel technology with clinical results improving tissue elasticity, pelvic floor support and PFM strength upon assessment with tactile imaging. VTI allows monitoring of biomechanical transformation of tissues before and after the radiofrequency treatment and may predict the effectiveness of therapy for individual patients.

Keywords: Vaginal Tactile Imaging, Radiofrequency, Vaginal Laxity, Vaginal Rejuvenation

Introduction

The use of Dynamic Quadripolar Radiofrequency (DQRF) is a new therapy for the treatment of vulvovaginal conditions, while Vaginal tactile imaging (VTI) allows biomechanical assessment of vaginal tissues and pelvic floor muscles.

The purpose of this study is to explore changes in vaginal tissue elasticity, pelvic floor support and muscle strength after vaginal DQRF treatments upon assessment with tactile imaging.

Standardized instruments for assessing biomechanical conditions of the pelvic floor and all urogynecologic aspects of female sexual dysfunction are lacking. In the last decade, a new modality for tissue characterization termed Elasticity Imaging (EI) or Elastography has emerged. EI allows visualization and assessment of mechanical properties of soft tissue. Mechanical properties of tissues (elastic modulus, viscosity), are highly sensitive to tissue structural changes in several physiological and pathological processes. Evaluating the biomechanical properties of the vaginal wall and its immediate surrounding connective tissue has been particularly difficult. The specific goal of VTI is to provide a reproducible and quantifiable means to visualize and measure vaginal tissue elasticity. VTI most closely mimics manual palpation because the TI probe, with a pressure sensor array, acts like human fingers during a clinical examination. The probe slightly compresses soft tissue and detects changes in the pressure pattern ("stress imaging," "computerized palpation," or "mechanical imaging").

Case Report

Methods

In January 2017, a 42-year-old Caucasian Patient was treated for vaginal laxity. She had given birth to three children, the most recent being six years before vaginal rejuvenation was performed. She had no previous non-surgical vaginal rejuvenation treatments and no past medical history that would be significant to this procedure such as recent surgical labiaplasty, etc., no known drug allergies, no sexual health history, until the procedure, and cervical smears has never shown any abnormalities. DQRF procedures were performed at 2 week intervals for 4 consecutive treatments.

The Vaginal Tactile Imager (VTI) developed by Egorov et al. was used to assess the vaginal walls, pelvic floor support structures and pelvic floor muscle (PFM) contractions before and two weeks after the final DQRF treatment.

VTI is performed on a patient the dorsal lithotomy position with empty bladder and rectum. The full VTI examination takes 2 to 3 minutes to complete. The VTI probe is calibrated before every clinical application. The VTI procedure consists of 3 independent parts (i) probe insertion, (ii) probe rotation, and (iii) muscle contractions, with 8 different tests listed below.

VTI allows the acquisition of pressures applied to the vaginal walls and the acquisition of probe location to visualize vaginal and pelvic floor support structures and to record pelvic floor muscle contractions. The VTI software provides visualization, analysis, information, and reporting tools. The acquired data and analysis information can be used for quantitative assessment of the vaginal and pelvic floor conditions. The VTI device is associated with a movable computer display cart. The VTI probe is equipped with 96 pressure sensors along both sides of the probe, an orientation sensor, and temperature sensors with micro-heaters. During the patient examination procedure, data are sampled from the probe sensors and displayed on the VTI computer display in real time. The probe surfaces that contact the vaginal walls are preheated to human body temperature. A lubricating jelly is used for patient comfort and to provide reproducible boundary-contact conditions with deformed vaginal tissue.

The VTI probe allows for an estimation of: a) vaginal tissue elasticity as a pressure gradient under vaginal wall deformation, (test 1 and 2), b) pelvic floor support conditions as pressure gradient under a deformation of the posterior compartment (test 3), and c) PFM strength as a pressure feedback under voluntary and involuntary (cough) contractions (tests 4 to 8). Orthogonal cross-sections of the 3-D tactile image allow visualization of anatomy and elasticity distributions. Tactile imaging reveals not only the elasticity conditions of vaginal wall itself, but the elasticity distribution of underlying tissue structures. These images may be considered as documentation of the current elasticity state of the vaginal walls and surrounding

support tissues. 8 VTI parameters were proposed to characterize vaginal conditions:

Test 1 allows the calculation of: 1. Maximum resistance force to insertion ($F_{l_{max}}$ in newtons, N); 2. Insertion work (Wl in millijoules, mJ); 3. Maximum stress-to-strain ratio, ie gradient, elasticity ($G_{l_{max}}$ kilopascals per millimeter, kPa/mm). Test 2 allows the calculation of: 1. Maximum intravaginal pressure at rest (kilopascals, kPa); 2. Anterior vs posterior force at rest (newtons, N); 3. Left vs right force at rest (newtons, N)

Test 3 allows the calculation of: 1. Maximum intravaginal pressure at pelvic muscle contraction (kilopascals, kPa); 2. Muscle contraction force (newtons, N).

A Standard Vaginal Laxity Questionnaire (VLQ) translated in French was also used. It obtains perceptions on level of vaginal laxity/ tightness assessed with 7-level ordered responses (very loose, moderately loose, slightly loose, neither loose nor tight, slightly tight, moderately tight, or very tight).

The patient was successfully treated with 4 consecutive DQRF treatments with 15 days interval.

The non parametric Wilcoxon Signed Rank Test for repeated measurements on single populations was applied to both repeated measures in Improvement in Elasticity and Pelvic Floor Muscles Strength after treatment, and average calculation of vaginal elasticity. Two-sided levels were used for all statistical tests with $p < 0.01$ as cut-off for significance.

Results

The vaginal tissues elasticity improved from a VLQ score of 1 (very loose) to 6 (moderately tight), and improved in pressure and calculated pressure gradients with color map going wider in yellow and red colours for pressure in test 1 (figure 1), gradient and pressure in test 2 (Figure 2) and pressure in test 3 (Figure 3). There are statistically significant improvements in pressure at test 1 by 100%, from 20% to 500% in gradient in test 2, and 60% in test 3 (Table 1). The PFM strength for voluntary muscle contractions (figure 4) and PFM strength for involuntary contractions (contraction with a cough, figure 5) showed higher peak pressures after treatment. PFM increased respectively by 242% and 172% (table 1).

The measurement of elasticity (Gradient in kPa/mm in test 1) of the underlying tissues surrounding the vagina, significantly improved by 88%. Maximum intravaginal pressure at pelvic muscle contraction (kPa) increased by 10.5% and muscle contraction force (N) increased by 8.3%. (Table 2)

Comfort level of the VTI examination procedure was classified as more comfortable as manual palpation; No report for the VTI exam as painful.

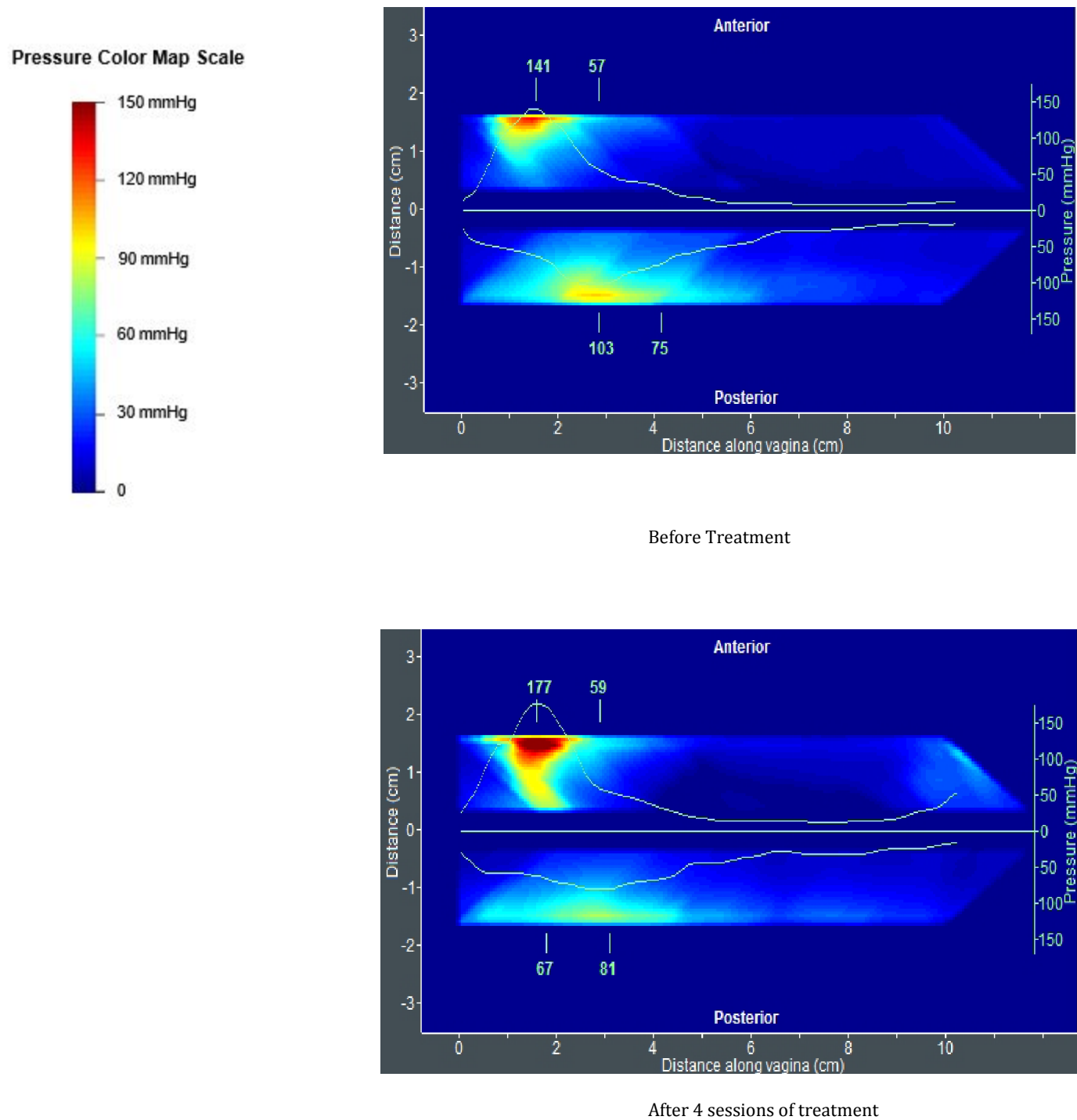


Figure 1: Pressure patterns for vaginal tactile imaging probe elevation (test 1) and calculated pressure along the anterior and posterior compartments before and after radiofrequency treatment

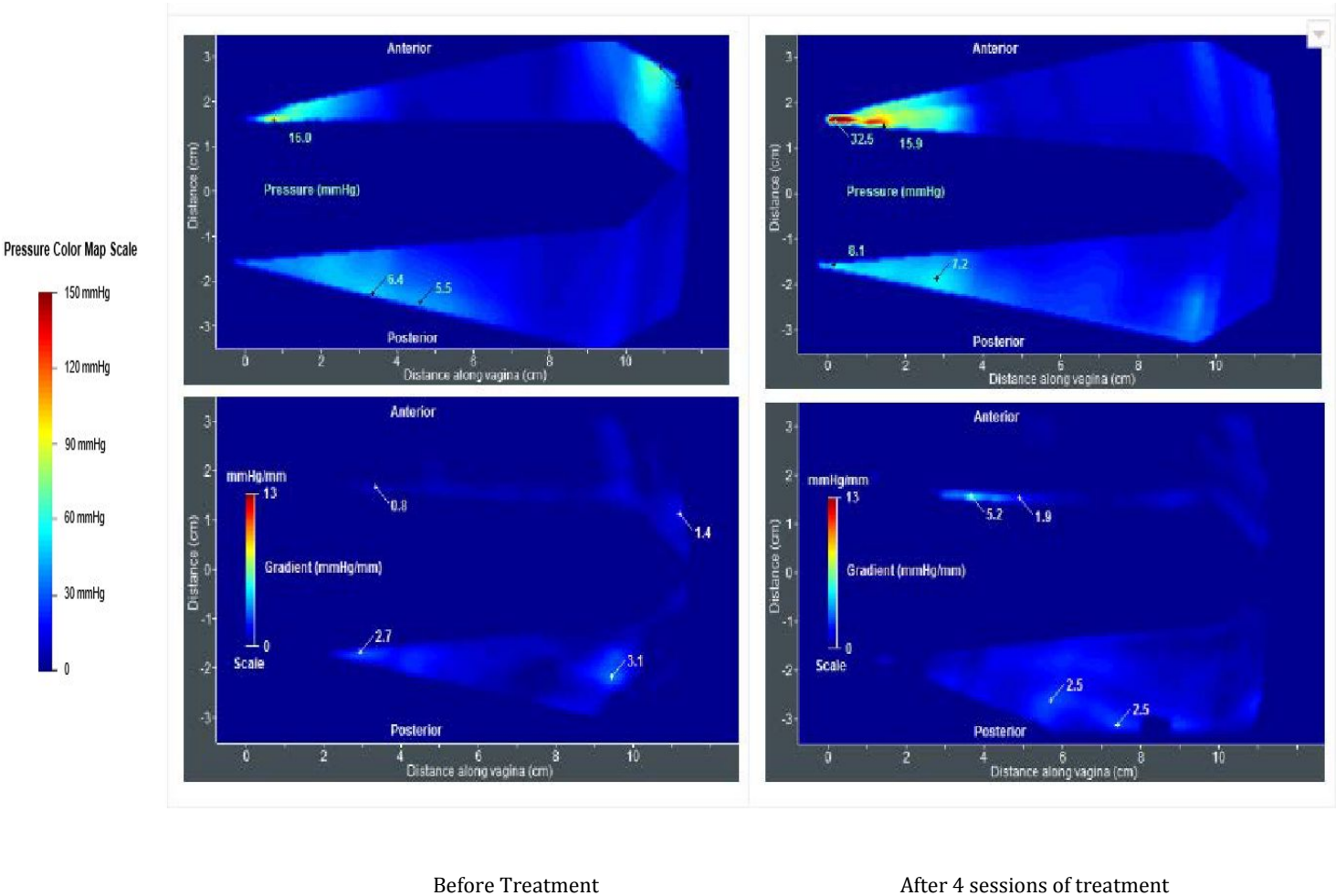
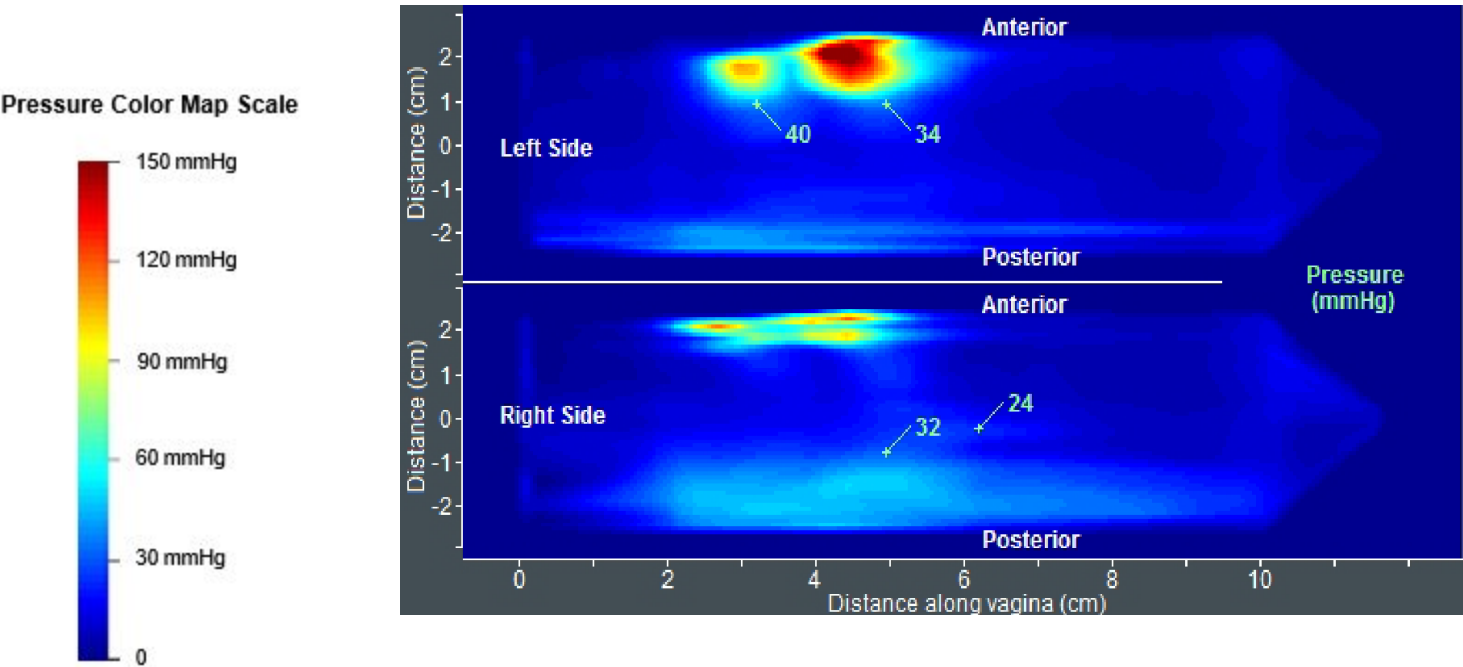
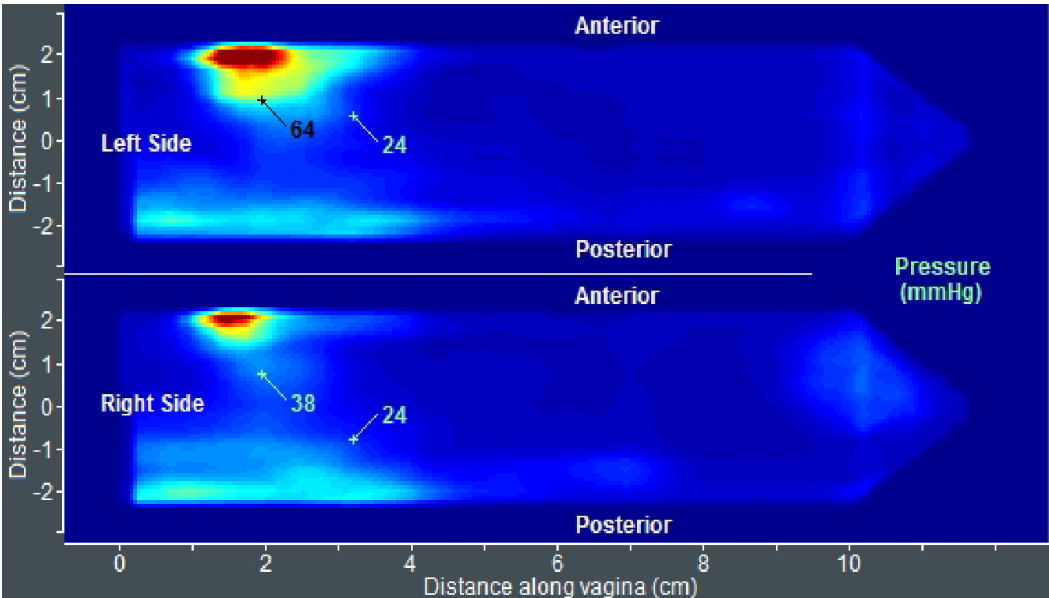


Figure 2: Pressure patterns for vaginal tactile imaging probe elevation (test 2) and calculated pressure and pressure gradients along the anterior and posterior compartments before and after radiofrequency treatment



Before Treatment



After 4 sessions of treatment

Figure 3: Pressure patterns for vaginal tactile imaging probe rotation (test 3) and calculated pressure along the vaginal walls before and after radiofrequency treatment

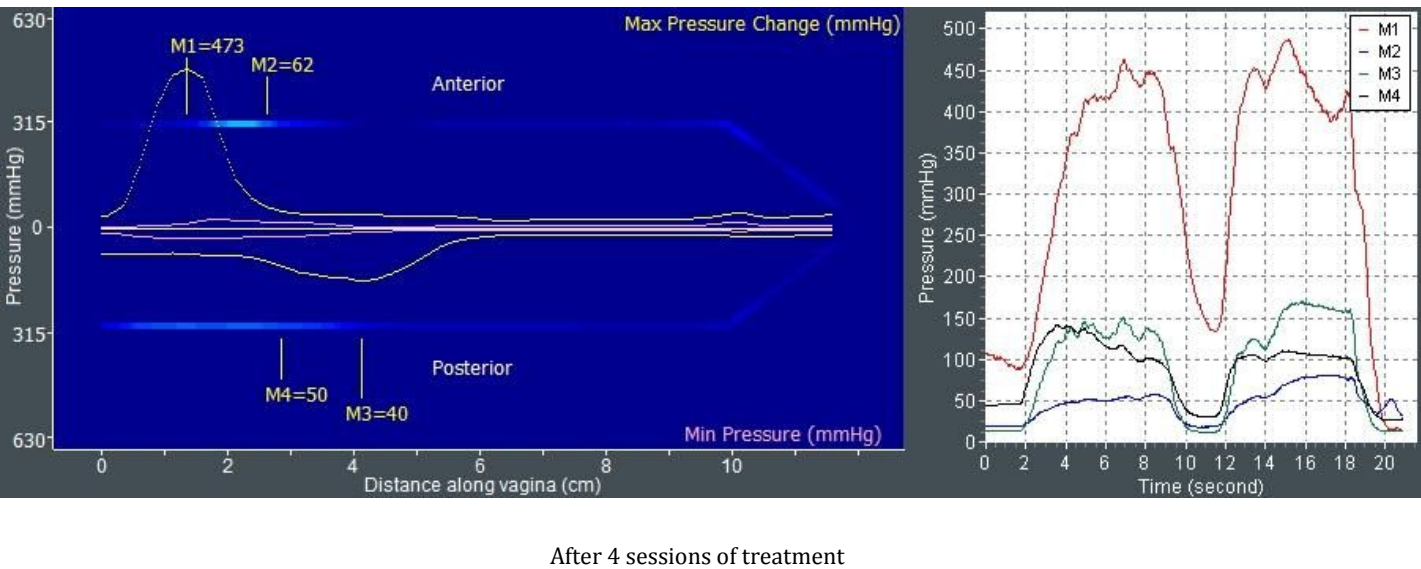
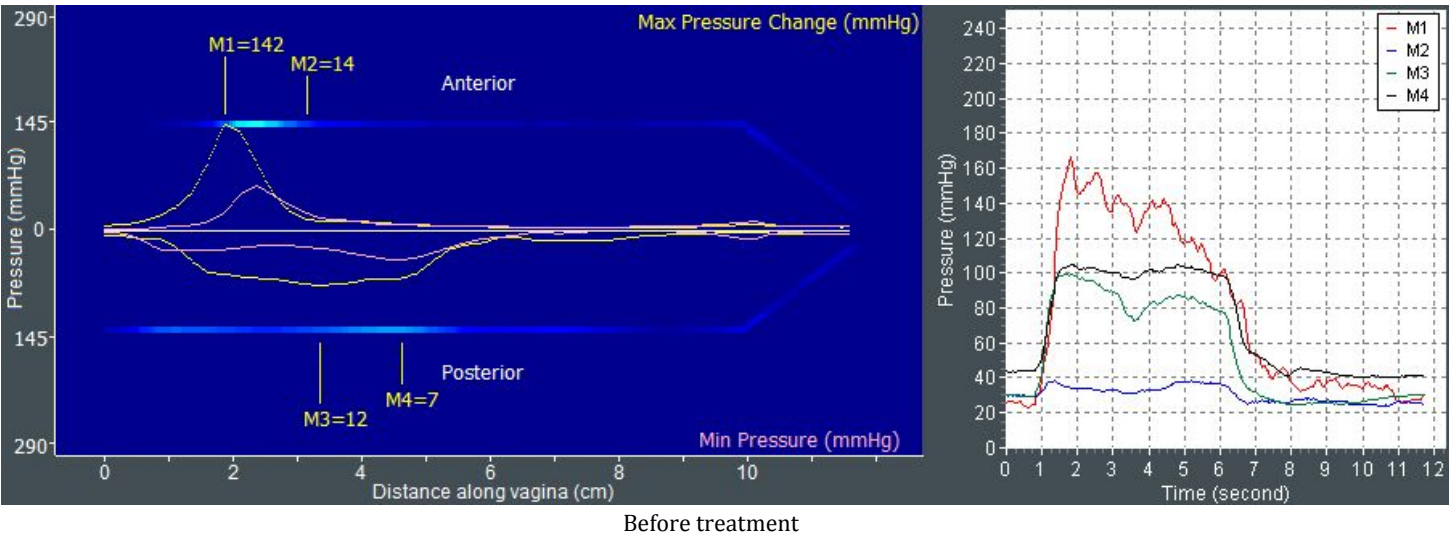
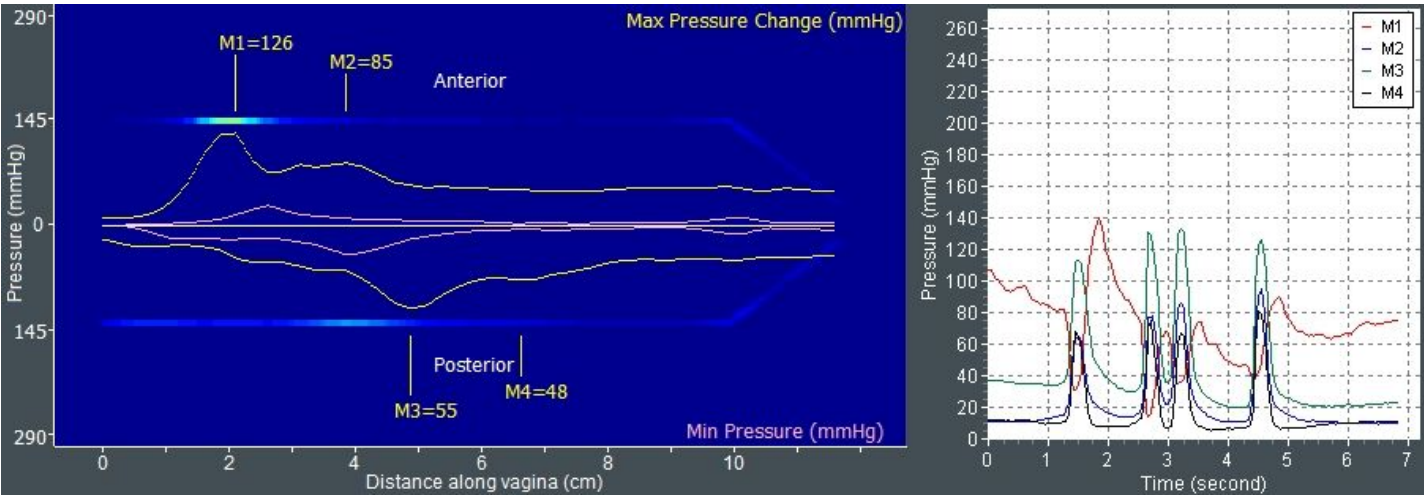
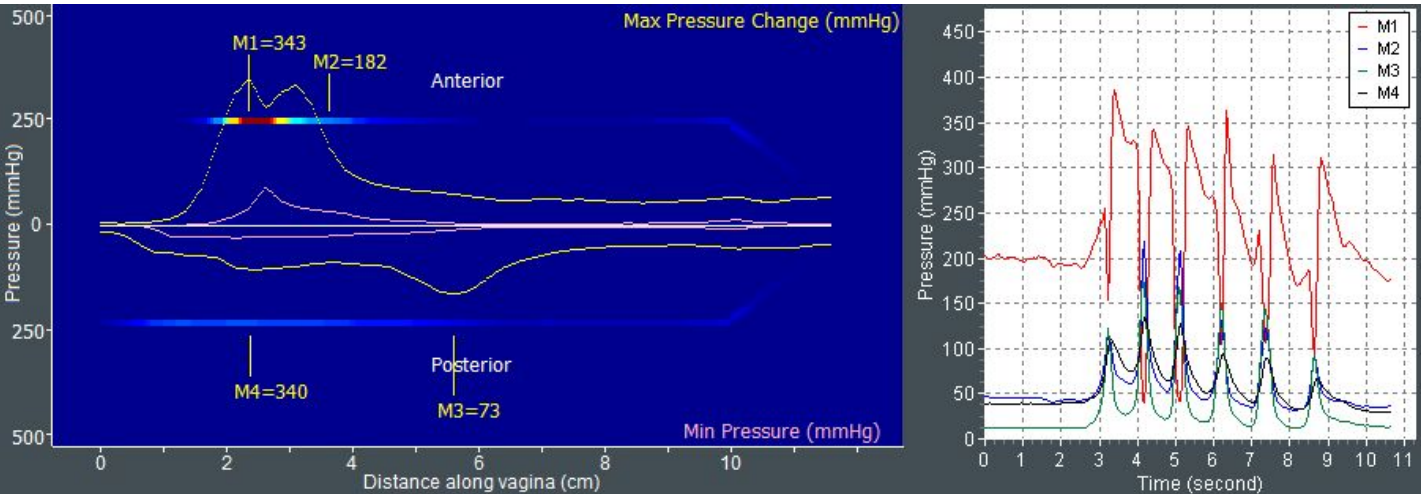


Figure 4: Pelvic Floor muscles strength for voluntary contraction (test 5)



Before treatment



After 4 sessions of treatment

Figure 5: Pelvic Floor muscles strength for involuntary contraction (test 5)

	Before treatment	After 4 sessions of treatment
Pressure at VTI Test 1	141	177
Pressure at VTI Test 2	16	32.5
Gradient at VTI Test 2	0.8	5.2
Pressure at VTI Test 3	40	64
PFM strength voluntary contraction	142	473
PFM strength involuntary contraction	126	343

Table 1: Improvement in Elasticity and Pelvic Floor Muscles Strength after treatment
Numbers in red shows statistical significance (p<0.01)

	F _{max} (N)		W (mj)		Gradient (kPa/mm)	
	Before	After	Before	After	Before	After
Test 1	0.665	0.928	32.9	39.9	0.98	1.84

	P _{max} at rest (N)		F (N) at rest vert		F (N) at rest horiz	
	Before	After	Before	After	Before	After
Test 3	23.76	26.24	1.56	1.69	0.69	0.68

Table 2: Average calculation of Vaginal Tissue Elasticity
Numbers in red show statistical significance (p<0.01)

Discussion

Increasingly, thermal non invasive treatments are used for vaginal modification. However, objective assessment of vaginal conditions before and after the applied treatment does not exist yet. Objective anatomic measures, biomechanical, and functional characterization are essential to understand the difference between normal and abnormal conditions. The VTI approach resembles soft tissue palpation, which has been the most prevalent medical diagnostic technique for accessible human organs and the musculoskeletal system. but clinical examination cannot be translated into objective and comprehensive information for a medical report for other clinicians. And that's where tactile imaging acquisition with stored data has a great interest in translating the sense of touch into a digital image.

Tactile imaging displays tissue anatomy and elasticity distribution by keeping the stress-strain relation for deformed tissue. The 3-dimensional tactile image can be transformed into an elasticity image with the use of a linear transformation for a region of interest. Functional tactile imaging is a translation of muscle activity into a dynamic pressure pattern. VTI allowed in our report better comprehension of vaginal walls and pelvic floor muscle changes, when Vagina Laxity Questionnaire (or other questionnaires) is not enough accurate for detailed analysis. It is always useful to have reproducible, stored DATA for comparison and further studies.

Vaginal laxity is common symptom in urogynecology everyday practice. It is often associated with younger age, vaginal parity, symptoms of prolapse. Vaginal laxity occurs in all women in the weeks after vaginal childbirth and after menopause. The stretching of the dense connective tissue of the vaginal walls and introitus during delivery varies in degrees of laxity and can worsen with successive deliveries. Although it may be considered physiological vulvovaginal laxity may deeply affect self-esteem and quality of life, due to discomfort in everyday life, and to negative impact on sexual relationships. Then, loss of sensation is common in women with vaginal laxity. and vaginal laxity is described by practitioners as the most important change of body integrity experienced by women after vaginal childbirth.

Radiofrequency (RF) used for medical treatments is an advanced technology based on converting the energy of an electromagnetic wave into heat: radiofrequency waves interact with the tissues, generating controlled thermal change. Unlike lasers, which produce heat by selectively targeting a specific chromophore, non ablative radiofrequency generates heat as a result of the tissue's resistance to movement of the electrons subject to the RF field.

As also suggested for other thermal therapy technologies, DQRF vaginal rejuvenation in introital and vaginal laxity implies re-activation of fibroblast and connective tissue function and development of new networks of collagen and elastin fibers in the subepithelial layers of introitus and vagina.

One of the current gold standard treatments for after childbirth abnormal conditions are daily sessions of pelvic floor training (PFT). Significant improvement are mostly usually noticed after 2 months. Targeting continent antenatal women early in pregnancy and offering a structured PFT programme may prevent the onset of urinary incontinence in postpartum. However, the cost-effectiveness of this is unknown. Population approaches (recruiting antenatal women regardless of continence status) may have a smaller effect on urinary incontinence, although the reasons for this are unclear. It is uncertain whether a population-based approach for delivering postnatal PFT is effective in reducing urinary incontinence. The new DQRF technique can bring valuable clinical outcomes for patients because of less discomfort for women and less disruption of their daily life and routine. This may require further investigations to compare both methods.

DQRF seems to hold advantage regarding its non ablative characteristics compared to CO2 lasers, and deeper effects in the dermis compared to Erbium Lasers. Comparative studies could be interesting to conduct to assess these differences.

Conclusion

Dynamic Quadripolar Radiofrequency treatment seems promising to improve tissue elasticity, pelvic floor support and PFM strength upon assessment with tactile imaging. VTI allows monitoring of biomechanical transformation of tissues before and after the radiofrequency treatment and may predict the effectiveness the therapy for individual patients.

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