

# Management of Vaginal Atrophy, Vaginal Hyperlaxity and Stress Urinary Incontinence with Intravaginal High-Intensity Focused Ultrasound (HIFU)

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## Abstract

*We have studied High-Intensity Focused Ultrasound (HIFU) technology for the treatment of urogenital atrophy (GSM), stress urinary incontinence (SUI) and vaginal hyperlaxity (VH). This is a novel gynecological application that produces a regenerative thermal effect on superficial vaginal tissues, and also on deeper layers that cannot be reached with laser and RF equipment due to their physical nature. The results of this prospective pilot study, involving a cohort of 30 patients that were clinically analyzed, answered validated questionnaires and underwent pre- and post-treatment biopsies, confirm the assumptions about its potential therapeutic effect and offer positive and valid conclusions to consider its use necessary as the preferred therapy or complementary to laser and other therapies with published evidence. With 80-90% of individuals presenting an adequate therapeutic response after only two outpatient sessions of painless intravaginal treatment and follow-up controls confirming the persistence of the benefits achieved within a year after the procedure, we feel encouraged to keep monitoring the cohort and design new perspective, randomized and comparative protocols evaluating HIFU against other thermal solutions and using the current gold standard in urogenital atrophy: estriol. Results are promising and motivate further research*

## Keywords

*High-Intensity Focused Ultrasound; Genitourinary syndrome of menopause; Vaginal atrophy; Stress urinary incontinence; Vaginal hyperlaxity; Vaginal regeneration; Quality life.*

## I. Introduction

The regeneration of genital tissue using energy-based devices (EBD) is revolutionary in gynecological treatments applied to a genitourinary syndrome of menopause (GSM), including mild to moderate stress urinary incontinence (SUI). GSM is a condition with very high prevalence (75%) on which the main international gynecologic associations are working [1] and which has been recently redefined and renamed as such [2] (previously called urogenital atrophy). From the first bold but innovative publications about the use of lasers in vaginal regeneration, such as Gaspar Adrian et al. [3], to the ones that started a real paradigm shift in 2014, including those by Stefano Salvatore, Nicola Zerbinati, Gambacciani, Palacios and others [4-9], who presented histologic and clinical evidence, the value of the so-called thermal effect on genital tissue rejuvenation and functional restoration is indisputable. Prestigious gynecological associations such as NAMS (North American Menopause Society), with their Practice Pearl report “Vulvar and vaginal fractional CO<sub>2</sub> laser treatments for GSM” [10], and even international associations such as IUGA (International Urogynecology Association)

and FIGO (International Federation of Gynecology and Obstetrics), make room for these issues in their conferences. In July 2018, the FDA showed their critical position [11] requesting more studies to prove their effectiveness and safety, which is the journey all of us pioneers and researchers have embarked upon. The discussion about which light and energy devices are adequate and/or better for these achievements has also been carried out, agreed upon and published by Yona Tadir et al. in a multicentric study [12] we were part of that work. However, further studies are still needed for these procedures to be considered Evidence-Based Medicine (EBM) because their probability is “low” or “very low” from a statistical point of view [13].

Until now, almost everything that has been published is based on the regeneration and functional recovery of the vaginal mucosa and little is said about the possibilities of seeking these effects in deep tissues beyond the mucosa, where most of the real non-GSM problems, such as stress urinary incontinence (SUI) and prolapses (POP), are rooted and where the restoration of vaginal mucosa is not

enough to give long-term solutions. This is the approach we followed to study other technologies with therapeutic possibilities in deeper tissues, seeking to strengthen the pelvic floor support structures described by John DeLancey and following the modern theory of urinary continence of Petros and Ulmsten [14-18]. Given their wavelength, CO<sub>2</sub> and Erbium lasers (with many indexed scientific publications) concentrate all the energy on the mucosa and have no action on areas beyond it. The physical nature of radiofrequency (RF) allows a deeper action than that of 10600 nm and 2940 nm lasers but, although studies have already been published in important journals [19-22], the theoretically adequate in-depth thermal effect is still under discussion.

For this reason, we decided to study High-Intensity Focused Ultrasound (HIFU) technology as energy equipment (in this case, thermal energy generated by ultrasound waves) in order to provide an adequate, controlled and regulated thermal action at a known depth in areas where lasers cannot reach and where non-invasive RF is still being studied and analyzed [23]. With such purpose, and based on our knowledge derived from HIFU in facial aesthetics, supported by many publications in over six years [24-26], we took this device to the area of intra-vaginal regeneration treatment to assess its effect on GSM and the instability of the pelvic floor, including its consequences in SUI.

## II. Material and Methods

A prospective pilot study of GSM and SUI treatment in postmenopausal patients using vaginal HIFU. Performed at **Dr. Alberto Eurnekian Hospital, Gynecology Service, in Ezeiza, Province of Buenos Aires, and the Gynesthetic Center for Gynecological Regenerative Studies and Treatments** between November 10, 2017, and December 30, 2018. The design of the study and treatment protocol was presented and approved by the Dr. Eurnekian Hospital Ethics Committee based on all international standards for research studies. All patients signed Informed Consent forms, and the treatment was free of charge.

### Sample and Inclusion Criteria:

- Thirty patients with GSM visiting the facilities for consultation were randomly enrolled in this study, provided they fulfilled the strict inclusion criteria selected for its execution.

- Out of the total of 30 patients studied and treated, 17 (56.66%) had been clinically diagnosed with SUI.

Age: range 50-67 (mean: 59)

Weight: range 58-87 (mean: 70) BMI: range 23-29 (mean: 26.3)

- **Clinical diagnosis of GSM** according to the description of signs and symptoms accepted by the IMS in 2015 (2).

- **SUI diagnosis** was clinical (not urodynamic), comprising a verbal and physical examination to assess anterior vaginal wall damage and urethral hypermobility. This was measured using the **Q-Tip test** (swab angle greater than 30 degrees with Valsalva) and a **1-hour PAD**

**test**, with “mild,” “moderate” or “severe” diagnoses according to O'Sullivan's criteria [27] based on pad weight gain. **Only patients with mild and moderate incontinence were admitted.**

-Patients with **Prolapses (POP)** were assessed according to Blaivas classification [28,29] to determine the degree of dystopia and its relationship with SUI. **Limit set at Blaivas II.**

-For **Vaginal Laxity** assessment, we followed the definitions of Dr. Santiago Palacios [30]

Postmenopausal patients with a minimum of three years since last menstruation and at least two of GSM symptoms: vaginal dryness; vaginal burning or irritation; recurrent vaginal or urinary tract infections; vaginal discharge; dyspareunia; high urinary frequency; urgency; urge incontinence and more than two episodes of nocturnal urination.

**Weight and fat mass** of the patients were analyzed using body mass index (BMI), with 18.5-29 as BMI margins, i.e., normal weight and overweight patients (not obese).

- **Vaginal pH** was measured using an electronic tester with a 0.01 pH resolution.

**Analysis of signs and symptoms as per validated questionnaires:**

**a.-ICIQ-SF: International Consultation on Incontinence Questionnaire - Short Form** [31]

**b.-PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire** [32]

**c.-FSFI: Female Sexual Function Index** [33]

-Clinical assessment of vaginal mucosa based on **VHI: Vaginal health index** [34]

-A **biopsy** of the right lateral vaginal wall was performed at 3 cm from the introitus with a 3 mm disposable punch under lidocaine anesthesia. Histological studies performed were **Hematoxylin and Eosin (H&E) Staining; Masson's Trichrome Staining and Immunohistochemistry with Novocastra Technique for Estrogen Hormone Receptors.** The same cytopathologist performed all the histological studies.

All the evaluations were performed before the first therapy and 45 days after the second one to carry out the comparative studies and assess the results of the study.

- Therapy pain tolerance was assessed using a visual analogue pain scale.

#### **Treatment Protocol:**

Two therapy sessions separated by 30-45 days were conducted following the same protocol.

The equipment used was **SVELTIA Feminine HIFU (Figure 1a)**. Manufactured in the City of Cordoba, Province of Cordoba, Argentina. HIFU equipment with the vaginal device, including 4 MHz 3.0 and 4.5 mm-depth vaginal transducers (**Figure 1b**). Validated and authorized by the Ministry of Health, Secretariat for Health Regulation and Management. ANMAT. The Argentine Republic. MP# 2089-15. Modification. File no.: 1-0047-3110-000145-18-8 - Date: 7-24-2018

The equipment allows all parameters for intravaginal use to be selected by software (**Figure 1c**). Intravaginal rotation: 0-360°;

Angle: 3-20°; Focal treatment line length: 5-25 mm; Pitch: 1-5 mm; Output power: 0.20-2.0 J. Two 340° treatment rounds were performed, one 7.5 cm deep into the vagina, according to the insertion mark on the application device (**Figure 1d**), and a second one following the same protocol 5 cm deep in the outer part of the vagina, according to the vaginal device marking. The rounds started at the 11 o'clock position and finished at the 1 o'clock position, never firing at the sub-urethral area (12 o'clock) for biosafety reasons. The treatment lines were 25 mm long, each one with a density of one focal point per millimeter (Pitch 1). The intravaginal rotation angle of the device between shots was 6° (Angle 6), which produced a total of 56 lines shot after a complete rotation in the vagina (340° Round). The protocol used 1.5 Joules in each shot during the first session and up to 2 Joules during the second treatment session depending on pain tolerance.

**1.- All patients received a complete Vaginal Treatment using a transducer with a focal depth of 3 mm. The protocol followed as described above.**

**2.- Patients with SUI received additional treatment with a 4.5 mm-depth transducer. Bilateral paraurethral with a rotation of 40° degrees (Round) every 3° (Angle) avoiding the sub-urethral area and completing, on each side, 13 treatment lines with a Length of 20 mm, a Pitch of 1 mm and a total Energy output of 2 J at each focal point.**

**3.- Patients with Vaginal Hyperlaxity received treatment with the 4.5 mm-depth**

**transducer in the entire vagina using the following parameters: Round 340, Angle 6, Length 25 mm, Pitch 1, and Energy 2 J.**

**Evolutionary control of the therapy:**

Six months after completing the treatment and taking the post-treatment biopsy, the follow-up and evolutionary control of the results were carried out with clinical control. The control included a verbal and physical examination.

**Statistical analysis:**

Performed using a Wilcoxon signed-rank test for paired samples and a t-student test.



### III. Results

#### Patients with GSM: n= 30

##### Therapy results as per questionnaires:

##### - ISIQ-SF questionnaire. Global analysis by score

Pre-treatment median 5.50. Post-treatment median 1.0. Pre-treatment mean 7.70 +/-6.62 and post-treatment mean 2.57 +/-2.45. **Paired Wilcoxon test. P <0.001. STATISTICALLY SIGNIFICANT (Figure 2)**

##### - PISQ-12 questionnaire. Global analysis by score

Pre-treatment median 39.5. Post-treatment median 46. Pre-treatment mean 37.80 +/-5.25 and post-treatment mean 44.87 +/-4.42. Favorable score variations in 90% of the patients (27/30). **Paired Wilcoxon test. P <0.001. STATISTICALLY SIGNIFICANT (Figure 3)**

##### - FSFI questionnaire. Global analysis and by domain

**Global analysis:** Pre-treatment median 23. Post-treatment median 58. Pre-treatment mean 23.47 +/-17.88 and post-treatment mean 58.53 +/-15.31. **Paired Wilcoxon test. P <0.001. STATISTICALLY SIGNIFICANT (Figure 4)**

All FSFI Domains (**lubrication, dyspareunia, orgasm, desire, arousal, satisfaction**), when analyzed separately, showed positive changes in the mean and median values of the analysis for 100% of the questionnaires completed, the Wilcoxon test results being P <0.001 STATISTICALLY SIGNIFICANT in each group. The **Lubrication** and **Pain** domains showed higher median and mean values than

those of the **Desire, Arousal, and Satisfaction** domains (**Figure 5**).

##### - Vaginal Health Index (VHI): Global score assessment:

Pre-treatment mean 12.07 +/-2.64 and post-treatment mean 18.6 +/-1.98. All patients showed an improvement in all 5 points of analysis. **Paired Wilcoxon test. P <0.001. STATISTICALLY SIGNIFICANT (Figure 6)**

##### -Vaginal pH measurement:

Pre-treatment median 5.6 +/-0.44. Post-treatment median 5.24 +/-0.33. Trophic changes identified in 24/30 (80%). P <0.001 **Paired T-Student Test. STATISTICALLY SIGNIFICANT (Figure 7)**

#### Patients with SUI= 17 (56.66%)

##### **Pre-treatment POP:**

1/17 (6%) Blaivas 0.  
8/17 (47%) Blaivas I.  
8/17 (47%) Blaivas II.

##### **Post-treatment POP:**

1/17 (6%) Blaivas 0.  
12/17 (70.6%) Blaivas I.  
4/17 (23.5%) Blaivas II (4/8 [50%] passed to Blaivas I).

##### **Q-Tip test:**

**Pre-HIFU** 16/17 (94%) with Q-Tip >30  
**Post-HIFU** 10/17 (58.8%) with Q-Tip >30

##### **Analysis of incontinence symptom results:**

**-ICIQ-SF:** Statistically significant global variations in questionnaire result.

Pre-treatment median 13. Post-treatment median 4. Pre-treatment mean 12.18 +/-4.76 and post-treatment mean 3.71 +/-2.76. Paired Wilcoxon test. P <0.001. **STATISTICALLY SIGNIFICANT (Figure 8)**

**-Clinical analysis** (verbal and physical examination)  
8/17 (47.0%) no longer presented SUI.  
6/17 (35.2%) presented SUI improvement.  
3/17 (17.6%) presented no clinical improvement.

**-Analysis of 1-hour PAD test (Figure 9)**

**1-hour PAD test**

**Pre-treatment, Positive in 70.6%: 12/17**

6/17 Mild (2-10 grams)

6/17 Moderate (11-50 grams)

**Post-treatment, Positive in 35%: 6/17**

2/17 Mild

4/17 Moderate

**Patients with Vaginal Hyperlaxity (n= 6 patients)**

20% (6/30 patients) met diagnostic criteria for this syndrome, which has been recently described by Santiago Palacios. No measurement of vaginal pressure was made, and the patients were only diagnosed based on verbal examination. Five out of these six patients (83%) presented no further symptoms after HIFU therapies. Control after six months, 5/5 (100%) asymptomatic

**Pain during treatment (global sample n=30):**

The Visual Analogue Scale (VAS) was used, with the following results

Range 1-4

Mean: 2.5

Median: 2

The patients with the highest VAS result belonged to the SUI and Vaginal Hypermobility group when using the 4.5 mm-depth transducer. The most referred pain was to the anal region when emitting energy on the posterior wall and the outermost round of the vagina.

**Pathologic anatomy**

**Hematoxylin-Eosine (H-E) Technique:** 27 (90%) out of the 30 patients in the study showed histologic hypotrophy in the biopsy. Only 2 (6.66%) presented histologic atrophy. One patient (3.33%) was reported as an insufficient sample. Post-treatment biopsies showed trophic changes in 27 patients (90%).

**Figure 10-11** belong to the same patient (Before and After). In **Figure 10 (Before)**, the arrows show the low stratification of the epidermis and, in the lamina propria, the image density typical of Type I collagen, and minimal vascularization. In **Figure 11 (After)**, the arrow marks show an increase in the stratification of the epidermis with a large amount of intracellular glycogen, and some vacuolar areas in the deepest part of the epidermis (near the lamina propria), which can be appreciated in the images of the cavitation points produced by the HIFU thermal effect. The arrow in the lamina propria indicates the increased vascularization that was one of the most visible histological images in all samples. **Figure 12 (After)** evidences the trophic changes more clearly: stratification and glycogen in epidermal cells, vacuolization in the area before the papillary dermis, and a

lamina propria presenting high vascularization as well as vacuolization in certain areas. With the Mason technique (**Figure 13-14**), all samples show the response to the treatment in the epidermis, the papillary dermis and the lamina propria, which is typical of the trophism recovery after using HIFU (stratification, glycogen, thicker papillary dermis, vacuolization and lamina propria with high vascularization and elastic collagen image). **Figure 15-16** shows the effects of the treatment on the same patient with Masson's Trichrome. The arrows pointing at the lamina propria (**Figure 16**) mark the characteristic aspect of elastic collagen fibers (collagen III) which, besides their light blue shade, have a cottony or wound/unwound thread pattern, a multi-stratified epidermis and a thicker papillary dermis. **Figure 15** shows the bright blue staining and thick, linear bars that are typical of fibrous collagen (collagen I).

The immunohistochemistry study (Novacastra Technique) showed positive estrogen receptors (ER) in 20% (6 patients) of hypotrophic patients before treatment, as seen in **Figure 17**. After therapy, ER expression using this technique increased to 63% (19 patients), and profound regenerative histological changes were made, as evidenced in **Figure 18**.

#### **Follow-up - Clinical status six months after the therapy:**

Patients were called in for a verbal and physical examination six months after taking the second biopsy. Twenty-seven patients came to the follow-up control visit. All the benefits obtained at the end of the treatment persisted in 100% of the analyzed cases.



#### IV. Discussion

HIFU bases its action on a focused thermal effect at a certain depth producing cavitation and apoptosis, and thermal coagulative microdamage caused by a 60-70 °C temperature, a technique originally used in oncology for tumor removal [35,36]. This action, now taken to the aesthetic and regenerative arena, is determined by the concentration of energy emitted by a round and concave ultrasound transducer of 20 mm in diameter that directs convergent ultrasonic waves to a specific focal depth according to the position of the transducer crystal, i.e. closer or further away from the emission plate that comes into contact with the vaginal mucosa, since the range of the energy cone produced by the crystal is always the same (**Figure 19**).

These convergent mechanical waves produce the molecular vibration of the water, which raises the temperature of the tissue and produces its physical modifications.

The equipment generates these cone-shaped ultrasonic waves in a pulsed way, and the operator moves the transducer crystal along a longitudinal axis (**Figure 20**) to displace the convergence point (the focal point) and ultimately produce regeneration lines based on ablative thermal energy points. Each shot taken with the equipment is a longer or shorter line of points (Length) that are more or less separated from each other (Pitch), according to a series of parameters entered in a software. Other setpoints include the proximity and the

number of lines shot to the tissue with the rotation of the vaginal device (Angle).

As mentioned above, the prototype of this energy-delivery mechanism was used in oncology and benign gynecological and urological pathology [37,38]. However, the technology was promptly taken to aesthetics, with the first HIFU equipment for facial lifting appearing almost ten years ago (2009 Ultherapy®; Ulthera Inc., Mesa, AZ, USA). Such equipment used these thermal energy points to produce regenerative controlled micro-burns and lift the SMAS. As the technology evolved, we saw the first machines for body lipolysis and contouring, and vaginal devices were finally developed to regenerate genital tissue at depths that cannot be reached with the photonics technology we have been using for more than a decade.

The vaginal devices are made with the same type of transducer (**Figure 1b**) used in aesthetic equipment, including a 25 mm-long and ten mm-wide contact plate for emission — only, in this case, its shape is cylindrical to enable intravaginal treatment. The vaginal device (**Figure 1d**) allows the transducer to reach the interior of the vagina and treat its whole length and circumference by automatically shooting dotted treatment lines while rotating up to 360°.

The study aimed to test this regeneration technology in the mucosa, fascias, and deeper muscle tissue to assess its effects in GSM and SUI simultaneously. **Our results are conclusive regarding HIFU's positive effect on patients with GSM and SUI.**

Based on our knowledge of the physics of light and energy equipment, HIFU systems are the

ones that can produce the deepest regenerative thermal effect in a safe, known, and programmable manner.

The regeneration mechanism is explained in **Figure 21**. The mechanical vibration produced by the convergent waves emitted by the transducer (2) causes a regenerative thermal effect on their way to the focal point (3), where the temperature reaches 60-70 °C and produces the cavitation point. Then, by thermal diffusion, heat is irradiated again on the primary treatment zone that received the sound waves (arrow marked with number 4).

**The epithelial changes in the mucosa (stratification and increased glycogen in the superficial keratinocytes) fully explain the pH variation** shown in the study and the improvement in the microbiota and vaginal condition. This change is related to many of the positive effects achieved in GSM due to the thermal effect that, as we already know, produces an even higher stimulus in the epithelium than topical estrogens [39,40]

**The sexuality of all patients improved significantly.** The assessment of the questionnaires (PISQ-12 and FSFI) is indisputable, and the patients of the group expressed an extraordinary degree of satisfaction in their medical visit, interview, and feedback. The fact that many of them recovered orgasm and sexual satisfaction is another sign that many patients do not lose their libido, but withdraw from sex as a consequence of pain and the resulting inability to feel satisfaction. The mucosal tissue recovery and the restoration of vaginal lubrication, elasticity, and compliance by neocollagenesis and angiogenesis, which are

characteristic of the thermal effect, added to the anatomical restoration, improve the patient's confidence and self-esteem.

The histological changes we were able to demonstrate do not differ in any way from those that were already published about other thermal technologies such as lasers. The higher number of hormone receptors we found in the treated tissue leads us to suggest the use of intermittent local stimulation with estriol to maintain the tissue regeneration achieved.

**Vaginal and vulvar mucosa regeneration with the use of HIFU is visually evident and is supported by the Vaginal Health Index (VHI)**, which is clearly and significantly improved from a statistical point of view.

The pictures of one of the cases from this sample (before and after the treatment) speak for themselves. The regenerative effect is remarkable, and only after two treatment sessions (**Figure 22**).

The study focus of this technology was to produce a regenerative thermal effect at depths that could not be reached with lasers such as CO<sub>2</sub> and Erbium, i.e., **BEYOND THE MUCOSA**, where we find the supporting elements that determine the pelvic floor health and are affected by a pregnancy, childbirth and hormonal deficiency. This, in turn, enabled the assessment of effects on SUI and Prolapses, as well as Vaginal Hyperlaxity results.

**The questionnaires focusing on incontinence showed a statistical improvement of the symptom.** Patients reported healing or leakage reduction, therefore using fewer liners, and perceiving an improvement in their quality of life. The PAD test confirmed the clinical tales and the analyses of the patients' ICIQ-SF questionnaire. **All patients diagnosed with**

**mild SUI using the PAD Test (-10 ml leakage as per the test) healed**, which was a very important finding given the predictive value implied by this concept. Only three patients (17%) reported no favorable changes with the therapy, leaving a favorable impact (healing or improvement) rate of over 80%. Such a percentage makes it interesting to continue with the development of this study, involving more patients and evaluating the persistence of the symptom correction over time.

Regarding **dystopia**, the clinical examination revealed a **clear descent improvement**, 50% of the patients moving from Blaivas II to Blaivas I. This relates to the improved elasticity of the submucosal tissues that were treated.

The whole new topographic and surgical anatomy description made by John DeLancey sets a new course for all pelvic floor therapies and pathologies [18, 41, 42]. The apical level (Level I in DeLancey's classification) cannot be treated with HIFU technology, but **the most central bundles of the pubococcygeus and puborectal muscles (Level II) in the urogenital hiatus can be reached with the 4.5 mm-depth transducer and thus regenerated and retracted, which explains the improvement of some prolapses and incontinence due to a reduced urethral hypermobility.** In the case of grade I-II prolapses or mild to moderate SUI, this can improve or eliminate the symptoms, but it does not replace surgery in severe cases or prolapses higher than grade II. However, we saw and treated four prolapse cases that were more severe than Blaivas II (out of this series), achieving a significant support improvement

as a consequence of the inflammatory response to the therapy. This procedure does not cure the prolapse but reduces its exposure, providing a new option in the case of patients that cannot or do not want to be operated on; the collagen, vascularization and elasticity improvements can help the patient perceive the problem and could avoid taking her to the operating room. **Figure 23** illustrates one of the cases described here: the image on the left shows the total prolapse condition before the first HIFU therapy session, whereas the image on the right clearly shows the improved condition before the second session 45 days later. These prolapses **DO NOT HEAL**, but the patients we treated showed clinical improvement, and only one of them eventually decided to undergo surgery. We maintain that previous therapy with HIFU can be very useful for the outcome of the suspension surgery because even when the pathology is not cured, the functional trophic regeneration of deep tissue leaves the patient in the best possible condition for the operation.

In our extensive experience (more than 100 cases), we did not have significant complications or adverse effects, which is in line with the studies that have been published so far about the facial and body therapies using HIFU [43]. All participants showed a steadfast adherence to the treatment and its continuity, and most of them are still in follow-up and evolutionary control of the therapy.

**The follow-up six months after the treatment** enabled an exhaustive evolutionary assessment of 27 patients that answered to the call and kept their appointment for a physical examination. **The 17 patients with SUI and**

**the six patients with Vaginal Hyperlaxity were all present in the follow-up visit. The improvement achieved after the therapy persisted in all of them** Metformin treatment for longer durations or higher doses might have caused a significant decrease in the BMI. These results are supported by the conclusion of one meta-analysis studying the effect of Metformin therapy on CRP and interleukin-6 (IL-6) levels in PCOS women, this meta-analysis found that the effect of Metformin therapy on CRP levels was both dose and duration dependent; also it noted a more beneficial effect in obese PCOS, a finding that is consistent with the results of this study [31]. Being a randomized and blinded controlled trial, this study gives a good evidence that the use of Metformin has a beneficial role in lowering serum CRP levels in PCOS women, especially in obese PCOS, thus decreasing the chronic low-inflammatory condition associated with these women which might have an important role in the prevention of long-term sequelae of PCOS like diabetes and cardiovascular insults. Still, it is one of the drawbacks of this study that it did not address the relation between CRP and insulin resistance, neither did it investigate the effect of Metformin therapy on other related inflammatory markers as IL-6. Further studies are needed to investigate the optimal dose and duration of Metformin therapy for prevention of PCOS long-term complications and to investigate whether its role is confined only to obese PCOS or also lean PCOS. Also, long-term follow up studies are needed to study the actual beneficial role of Metformin therapy on reducing the risk of long-term complications of PCOS and not only the theoretical role

assumed by decreasing the chronic inflammatory markers associated with PCOS.

## V. CONCLUSION

HIFU therapy is effective in stimulating tissue regeneration processes aimed at solving pathologies related to mucosal atrophy (GSM) and pelvic-support defects (SUI and Vaginal Hyperlaxity). The results in GSM patients put HIFU on a par with laser and other undisputed therapies for mucosal regeneration. The effects on deep tissue and the resulting solutions or significant improvements achieved in SUI and Vaginal Hyperlaxity make us continue to study HIFU therapy as we believe that it can exceed the indisputable benefits of photonic therapy.

**We understand follow-up is still short, but the results obtained so far with this pilot study and the persistence of the beneficial effect cannot be ignored, and we are adding patients and follow-up to confirm our primary impression and encourage more prospective studies.**

## VI. References

- [1] Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. *Menopause* 2013;20(9):888–902; quiz 903–904.
- [2] Portman DJ, Gass ML. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women’s Sexual Health and the North American Menopause Society. *Vulvovaginal Atrophy Terminology Consensus Conference Panel*. *Menopause* 2014;21(10):1063–1068.
- [3] Gaspar A, Addamo G, Brandi H. Vaginal Fractional CO<sub>2</sub> Laser: A minimally invasive option for vaginal rejuvenation. *American Journal of Cosmetic Surgery* 2011;28(3):156–162.
- [4] Salvatore S, Pitsouni E, Del Deo F, et al. Sexual function in women suffering from genitourinary syndrome of menopause treated with fractionated CO<sub>2</sub> laser. *Sexual Medicine Reviews* 2017;5:486–492.
- [5] Salvatore S, Maggiore U, Zerbinati N, et al. Microablative fractional CO<sub>2</sub> laser improves dyspareunia related to vulvovaginal atrophy: a pilot study. *Journal of Endometriosis* 2014;6:150–6.
- [6] Salvatore S, Nappi RE, Parma M, et al. Sexual function after fractional microablative CO<sub>2</sub> laser in women with vulvovaginal atrophy. *Climacteric* 2015;18:219-25.
- [7] Zerbinati N, Serati M, Origoni M, et al. Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. *Lasers in Medical Science* 2015;30:429–24.
- [8] Gambacciani M, Palacios S. Laser therapy for the restoration of vaginal function. *Maturitas* 2017;99:10–15.
- [9] Vizintin Z, Rivera M, Fistončić I, Saraçoğlu F, Guimares P, Gaviria J, Garcia V, Lukac M, Perhavec T, Marini L. Novel minimally invasive VSP Er:YAG laser treatments in gynecology. *Journal of the Laser and Health Academy* 2012;1:46–58.
- [10] Streicher Lauren MD. NAMS (North American Menopause Society). Practice Pearl. “Vulvar and vaginal fractional CO<sub>2</sub> laser treatments for GSM”. October 31-2017. Chicago, Illinois. USA.
- [11] FDA News release – Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women’s health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for “vaginal rejuvenation”.



<https://www.fda.gov/news-events/comunicados-de-prensa/declaracion-del-dr-scott-gottlieb-comisionado-de-la-fda-sobre-los-esfuerzos-por-protger-la-salud-de>

[12] Tadir Y, Gaspar A, Lev-Sagie A, Elias JA, et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. *Lasers in surgery and medicine* 2017;49:137-59.

[13] Pitsouni E, Grigoriadis T, Falagas ME, et al. Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis. *Maturitas* 2017;103:78-88.

[14] Petros P. The integral system. *Central European Journal of Urology* 2011;64:110-19.

[15] DeLancey JO. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. [Comment in] *American Journal of Obstetrics and Gynecology*. 1994;170:1713.

[16] DeLancey JO. Structural anatomy of the posterior pelvic compartment as it relates to rectocele. [Comment in] *American Journal of Obstetrics and Gynecology*. 1999;180:815.

[17] DeLancey JO, Kearney R, Chou Q, et al. The appearance of levator ani muscle abnormalities in magnetic resonance images after vaginal delivery. *Obstetrics and Gynecology*. 2003;101:46-53

[18] DeLancey JO. Functional Anatomy of the Pelvic Floor and Lower Urinary Tract. Available from: [https://www.researchgate.net/publication/225910365\\_Functional\\_Anatomy\\_of\\_the\\_Pelvic\\_Floor\\_and\\_Lower\\_Urinary\\_Tract](https://www.researchgate.net/publication/225910365_Functional_Anatomy_of_the_Pelvic_Floor_and_Lower_Urinary_Tract) [accessed Oct 08 2018].

[19] Magon N, Alinsod R. ThermiVa: The Revolutionary Technology for Vulvovaginal Rejuvenation and Noninvasive Management of Female SUI. *Journal of Obstetrics and Gynecology of India*. 2016;66:300-2

[20] Sadick N, Rothaus KO. Aesthetic Applications of Radiofrequency Devices. *Clinics in Plastic Surgery*. 2016;43:557-65.

[21] Dillon B, Dmochowski R. Radiofrequency for the treatment of stress urinary incontinence in women. *Current Urology Reports*. 2009;10:369-74. 22. Krychman M, Rowan CG, Allan BB, et al. Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controlled Trial. *The Journal of Sexual Medicine*. 2017;14:215-25.

[22] Krychman M, Rowan CG, Allan BB, et al. Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controlled Trial. *The Journal of Sexual Medicine*. 2017;14:215-25.

[23] Chilukuri S, Lupton J. "Deep Heating" Noninvasive Skin Tightening

Devices: Review of Effectiveness and Patient Satisfaction. *Journal of Drugs in Dermatology*. 2017 Dec 1;16(12):1262-1266

[24] Fabi SG. Noninvasive skin tightening: Focus on new ultrasound techniques. *Clinical, Cosmetic and Investigational Dermatology*. 2015 Feb 5;8:467-52

[25] Hyunchul Park, Eunjin Kim, et al. High-Intensity Focused Ultrasound for the Treatment of Wrinkles and Skin Laxity in Seven Different Facial Areas. *Journal of Cosmetic and Laser Therapy*. 2012 Dec;14(6):290-5

[26] Lee HS, Jang WS, et al. Multiple pass ultrasound tightening of skin laxity of the lower face and neck. *Dermatologic Surgery*. 2012 Jan;38(1):20-7

[27] O'Sullivan R, Karantanis E, Stevermuer TL, et al. Definition of mild, moderate and severe incontinence on the 24-hour pad test. *BJOG* 2004; 111: 859-862

[28] Blaivas JG. Classification of stress urinary incontinence. *Neurourology and Urodynamics* 1983; 2:103-104

[29] Blaivas JG, Olsson CA. Classification of stress urinary incontinence. *Journal of Urology* 1988; 139:727-731

[30] Palacios S. Vaginal hyperlaxity syndrome: a new concept and challenge. *Gynecological Endocrinology*. Dec 2017. Editorial

[31] España Pons M, Rebollo Alvarez P, et al. *Medicina Clínica*. Elsevier.

Validation of the Spanish version of the International Consultation on Incontinence Questionnaire-Short Form. A questionnaire for assessing the urinary incontinence (ICIQ-SF). *Vol.122 No.8 March 2004;310-320*.

[32] España Pons M, Puig Clota M, et al. Questionnaire for evaluation of sexual function in women with genital prolapse and/or incontinence. Validation of the Spanish version of "Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12)". *Actas Urológicas Españolas*. Vol.32 No.2 Feb 2008.

[33] Blümel JE, Binfa L, et al. Índice de función sexual femenina: Un test para valorar la sexualidad de la mujer (FSFI). *Revista Chilena de Obstetricia y Ginecología* 2004; 69(2):118-125

[34] Bachmann G. Urogenital ageing: an old problem newly recognized. *Maturitas*. 1995 Dec;22 Suppl:S1-S5.

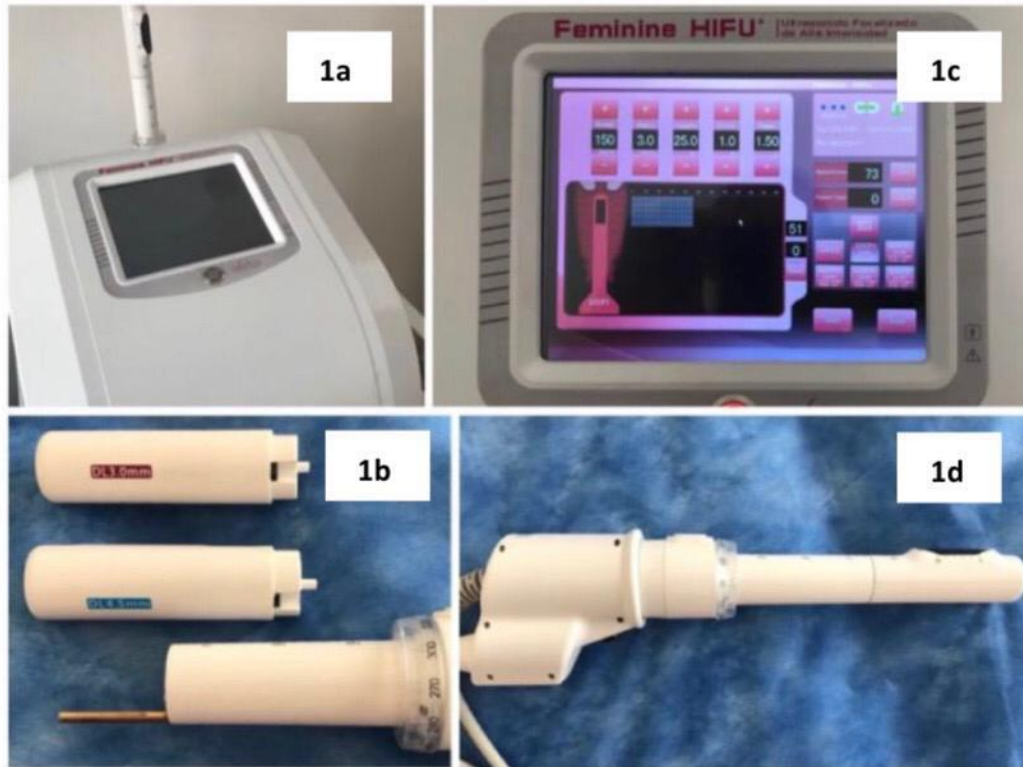
[35] Haar GT, Coussios C. High Intensity Focused Ultrasound: Past, present and future. *International Journal of Hyperthermia*. 2007 Mar;23(2):85-7

[36] Haar GT, Coussios C. High Intensity Focused Ultrasound: Physical principles and devices. *International Journal of Hyperthermia* 2007; 23(2):89-104

[37] He M, Jacobson H, Zhang C, Setzen R, Zhang L. A retrospective study of ultrasound-guided high intensity focused ultrasound ablation for multiple uterine fibroids. *International Journal of Hyperthermia*. 2018 Dec;34(8):1304-1310.

- DOI: 10.1080/02656736.2017.1421323. Epub 2018 Jan 5.
- [38] Hübner N, Shariat SF, Remzi M. Focal therapy of prostate cancer. *Current Opinion in Urology*. 2018 Nov;28(6):550-554.
- [39] Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause*. 2010 Jan-Feb;17(1):194-203
- [40] Gaspar A, Brandi H et al. Efficacy of Erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. *Lasers in surgery and medicine*. 2017 Feb;49(2):160-168.
- [41] DeLancey JO. Correlative study of paraurethral anatomy. *Obstetrics and Gynecology*. 1986;68:91-97.
- [42] DeLancey JO. Structural aspects of the extrinsic continence mechanism. *Obstetrics and Gynecology*. 1988;72:296-301
- [43] Friedmann DP, Bourgeois GP, et al. Complications from microfocused transcutaneous ultrasound: Case series and review of the literature. *Lasers in surgery and medicine*. 2018 Jan;50(1):13-19

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**Figure 1. Feminine HIFU Equipment.**

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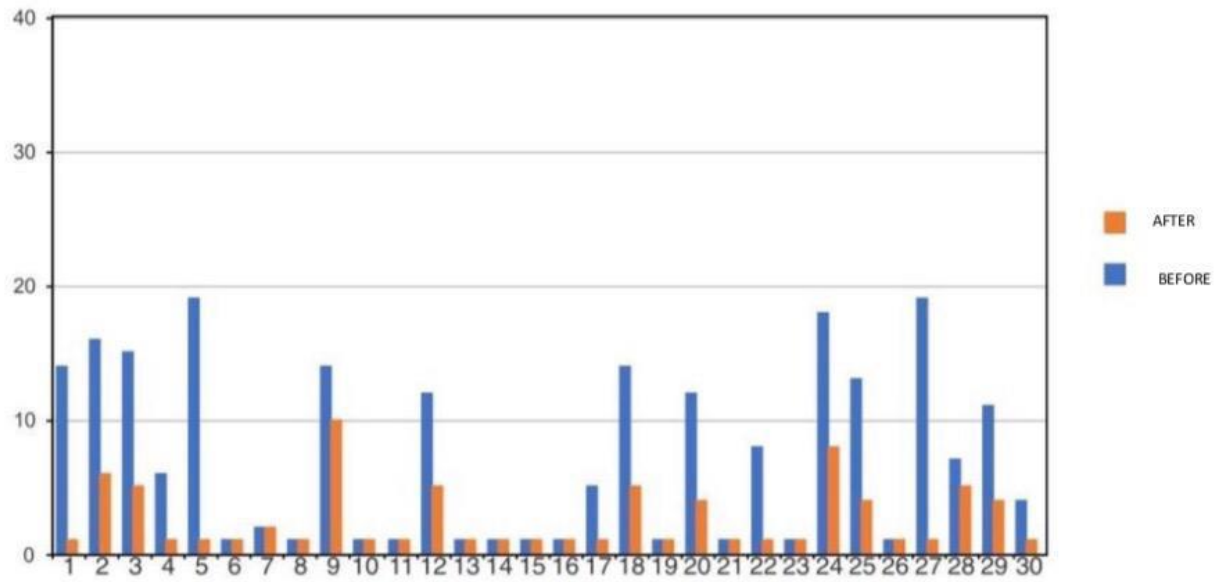


Figure 2. ICIQ-SF Questionnaire. Before and After HIFU (n:30)

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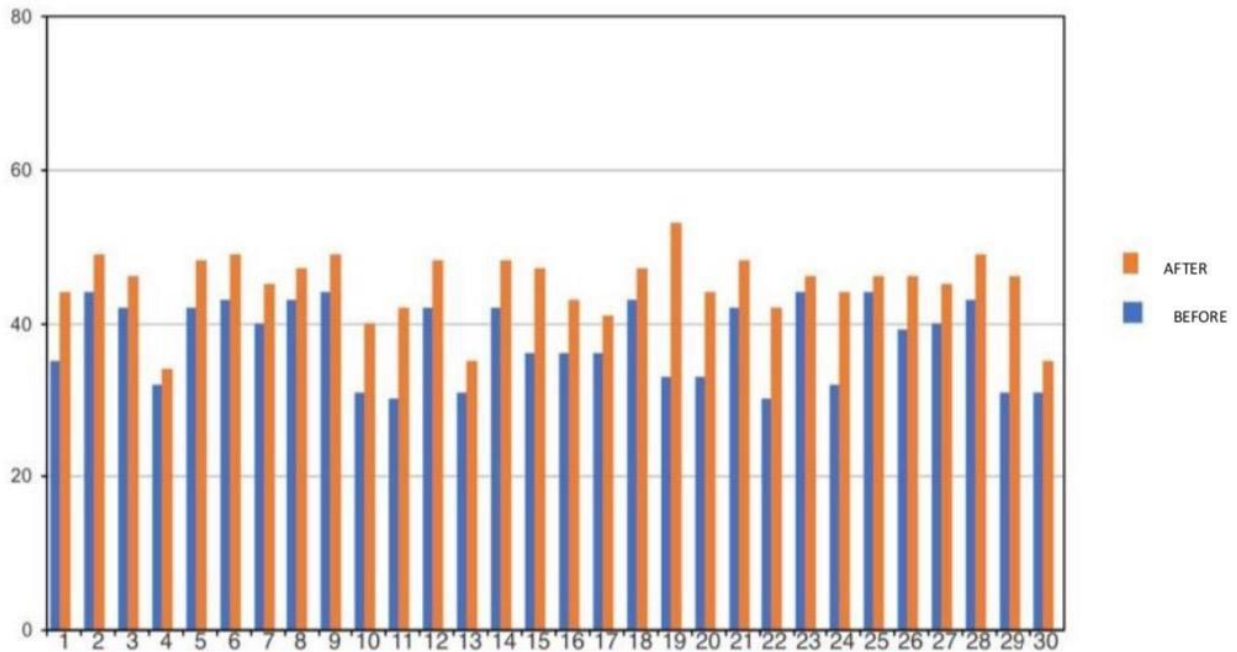


Figure 3. PISQ-12 Questionnaire. Before and After HIFU (n:30)

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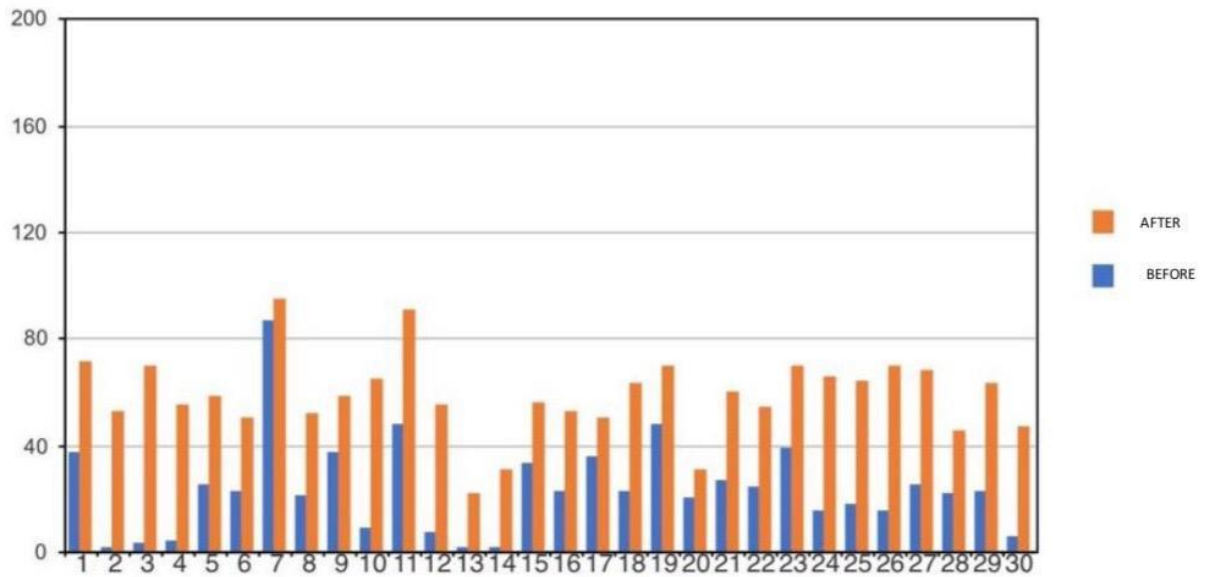
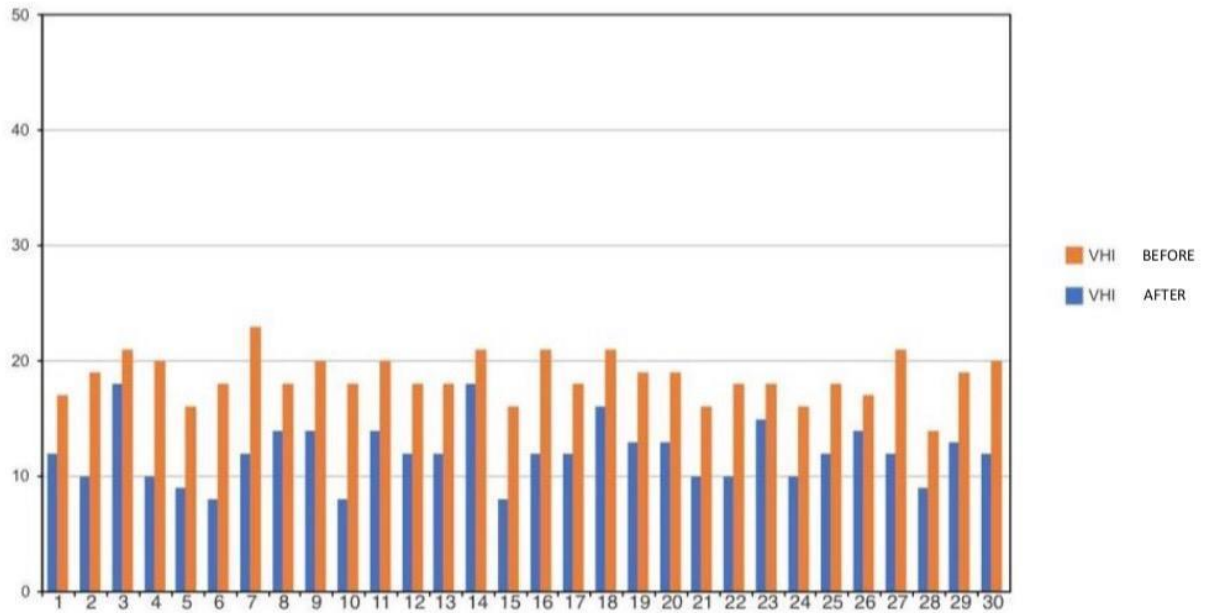


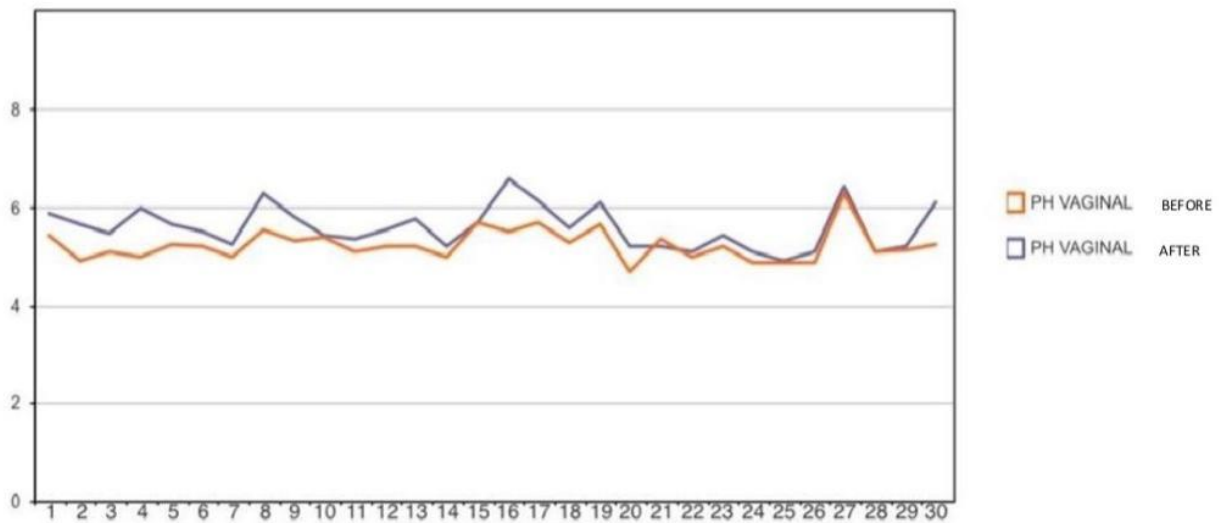
Figure 4. FSFI Global Questionnaire. Before and After HIFU (n:30)

	MEDIAN		MEAN		p
	BEFORE	AFTER	BEFORE	AFTER	
DESIRE	1	2	1,5 +/-0,86	2,63 +/- 1,16	<0,001
PAIN	1	4	1,33 +/-1,21	3,7 +/-0,99	<0,001
AROUSAL	1	2	1,17 +/-1,18	2,53+/-1,22	<0,001
LUBRICATION	1	4	1,43 +/-1,3	3,8 +/-0,55	<0,001
ORGASM	1	4	0,87 +/-1,07	2,47 +/-1,38	<0,001
SATISFACTION	1	2,5	1,07 +/-0,78	2,63 +/-1,19	<0,001

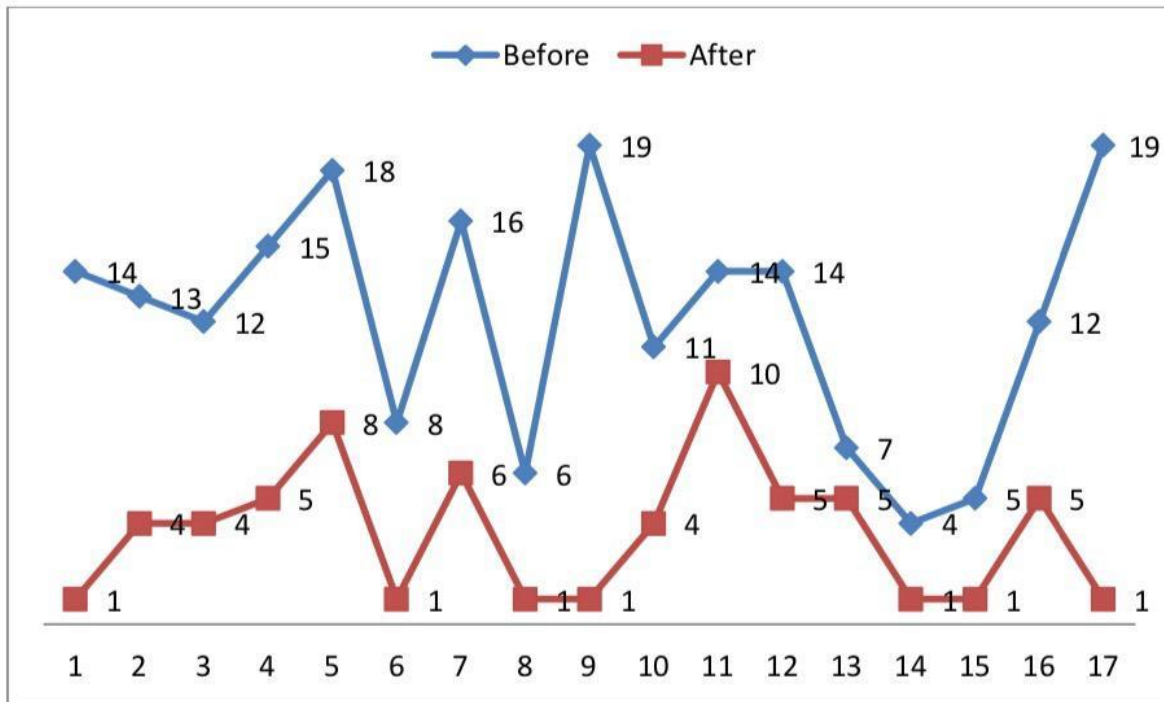
Figure 5. FSFI Domain Questionnaire. Before and After HIFU (n:30)



**Figure 6 .** VHI Score. Before and After HIFU (n:30)



**Figure 7 .** PH Measurement. Before and After HIFU (n:30)



**Figure 8.** ICIQ-SF Questionnaire patients with SUI before and after HIFU

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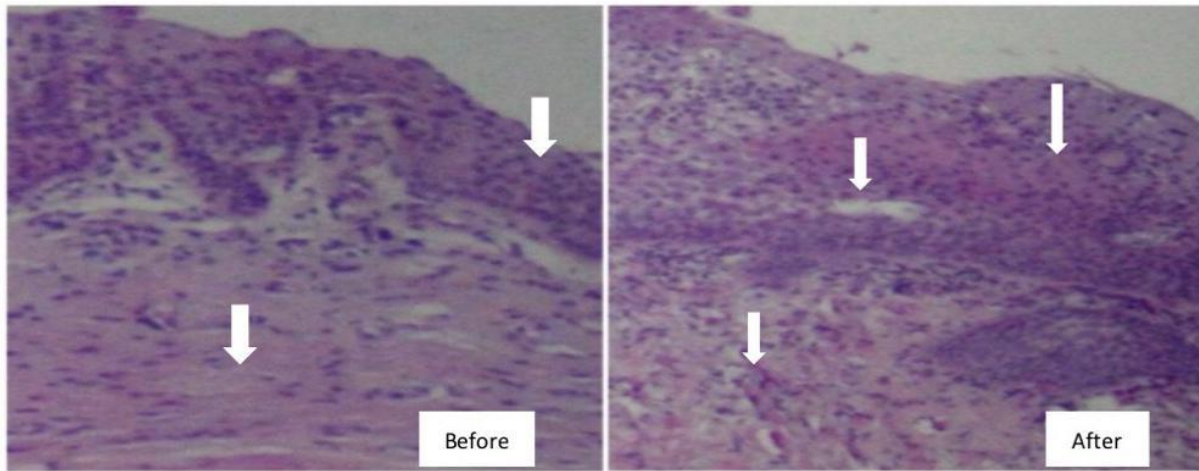
	PAD TEST weight 1 Hour			ml 1 hour	
	BEFORE	AFTER	Degree of improvement	BEFORE	AFTER
1	10	10		0	0
2	42	51	-22%	48,5	62
3	15	10	100%	7,6	0
4	30	20	33%	30	16,6
5	16	10	100%	9,1	0
6	13	10	100%	4,5	0
7	32	24	25%	33,3	21
8	10	10		0	0
9	25	16	38%	22,7	9
10	32	16	49%	33	9
11	10	10		0	0
12	16	10	100%	9,1	0
13	15	10	100%	7,6	0
14	10	10		0	0
15	40	20	60%	45,45	15
16	10	10		0	0
17	14	10	100%	6,1	0

Mild: -10 ml Moderate: +11 - 50 ml Severe: +50 ml  
1 ml: 25 drops: 0,66 gr Pad weight: 10 gr

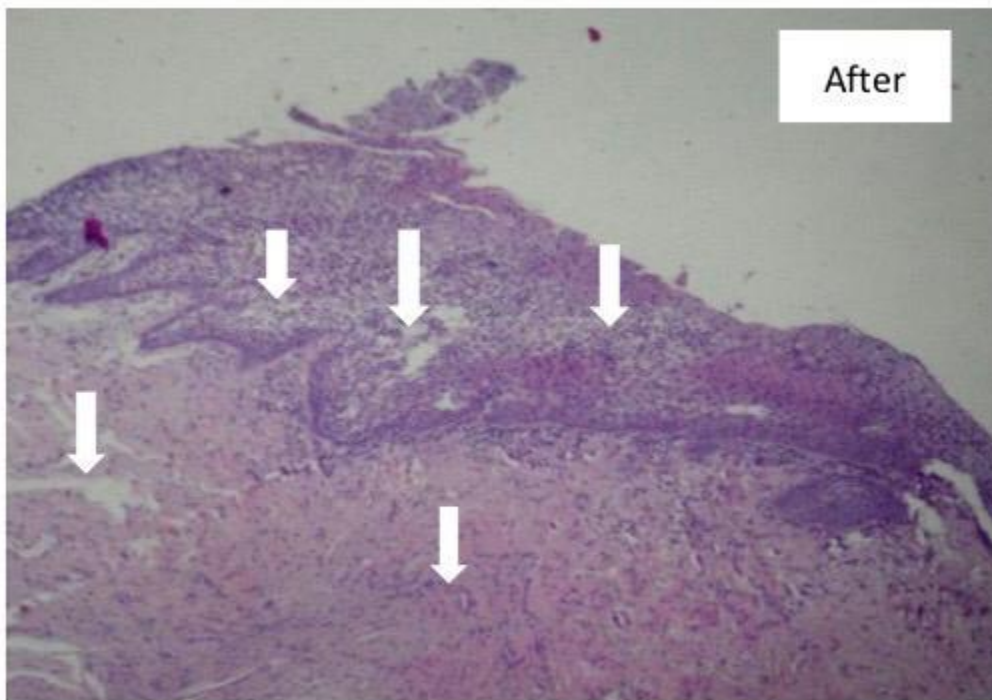
Figure 9. Analisis 1 Hour PAD Test

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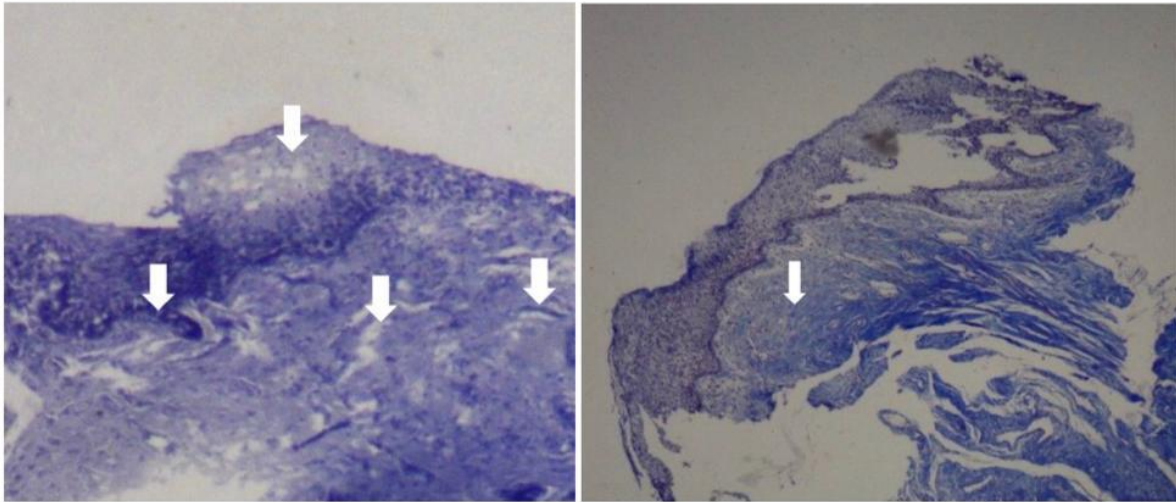




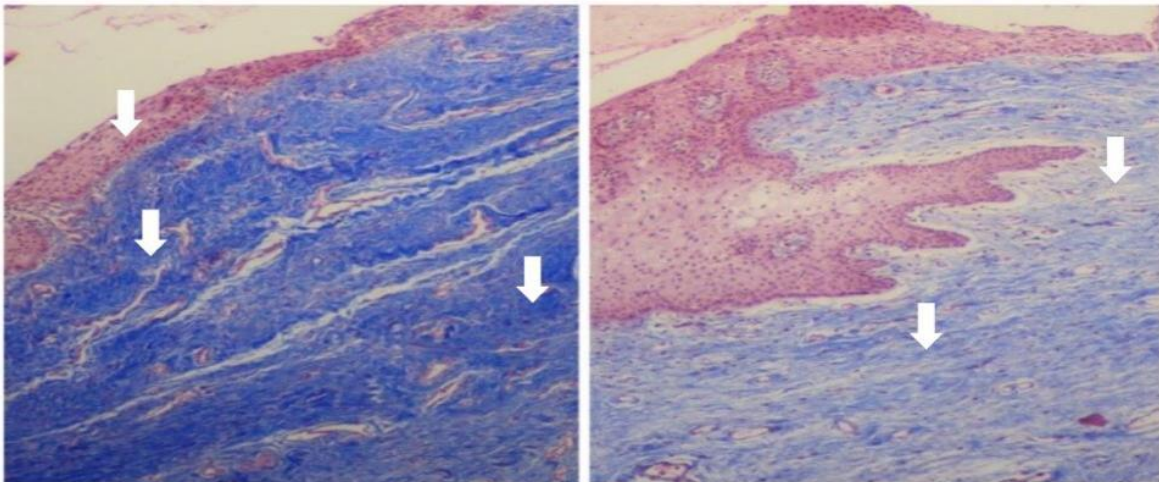
**Figure 10-11.** H-E Technique, Before and After HIFU



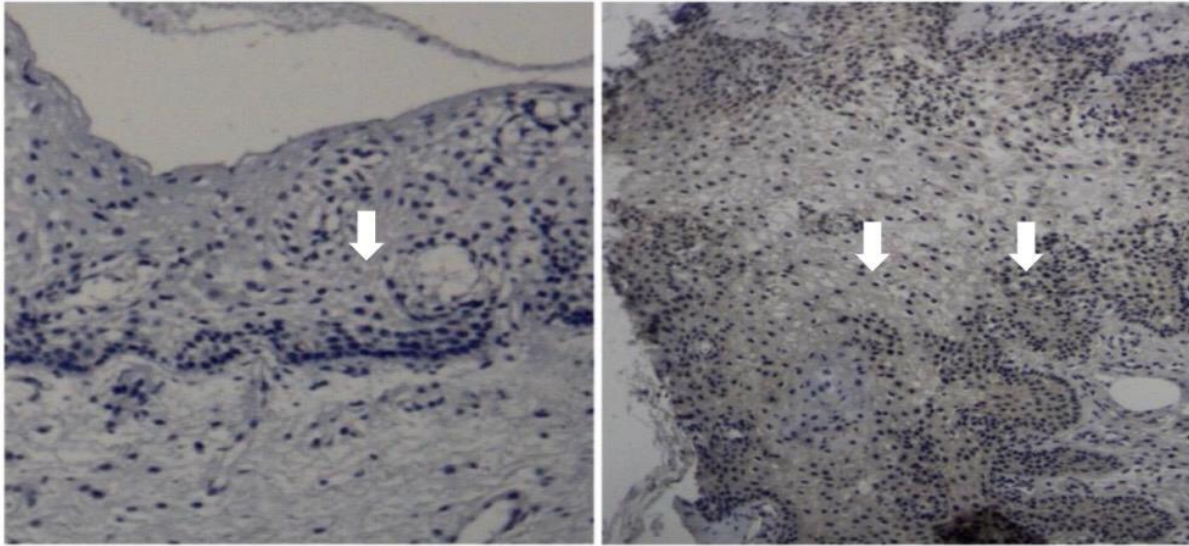
**Figure 12.** H-E Technique. After HIFU



**Figure 13-14.** Masson Technique. After HIFU

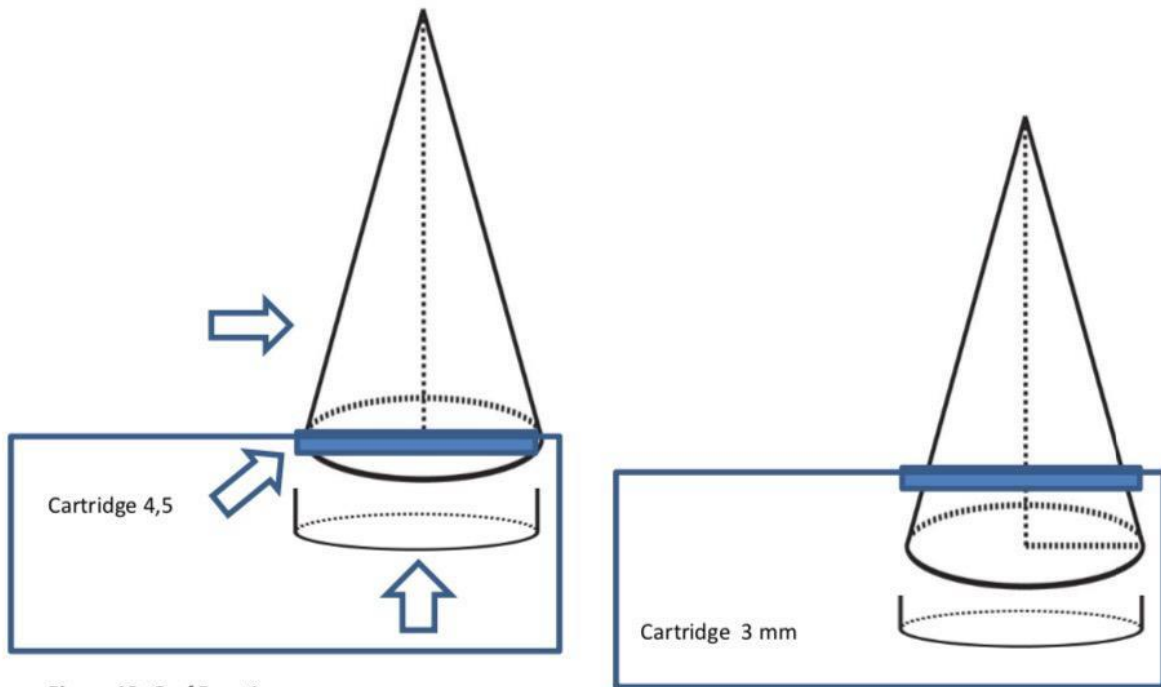


**Figure 15-16.** Masson Trichrome before and after HIFU.



**Figures 17-18.** Novacastra Technique estrogen receptors. Before and After HIFU





**Figure 19.** Graf Function

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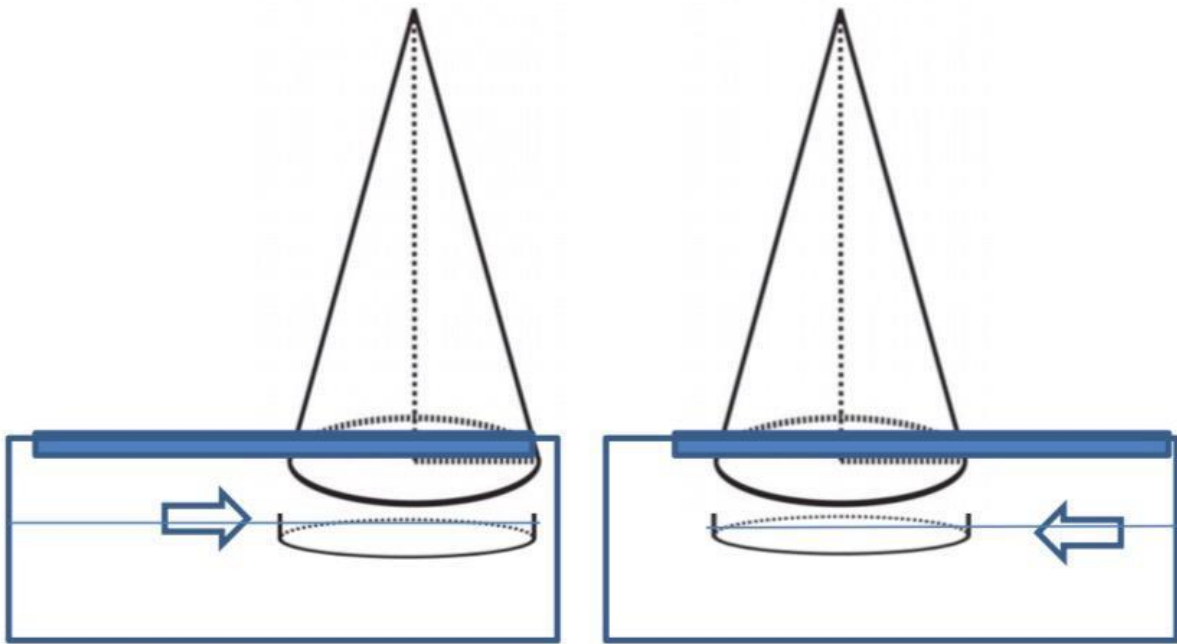
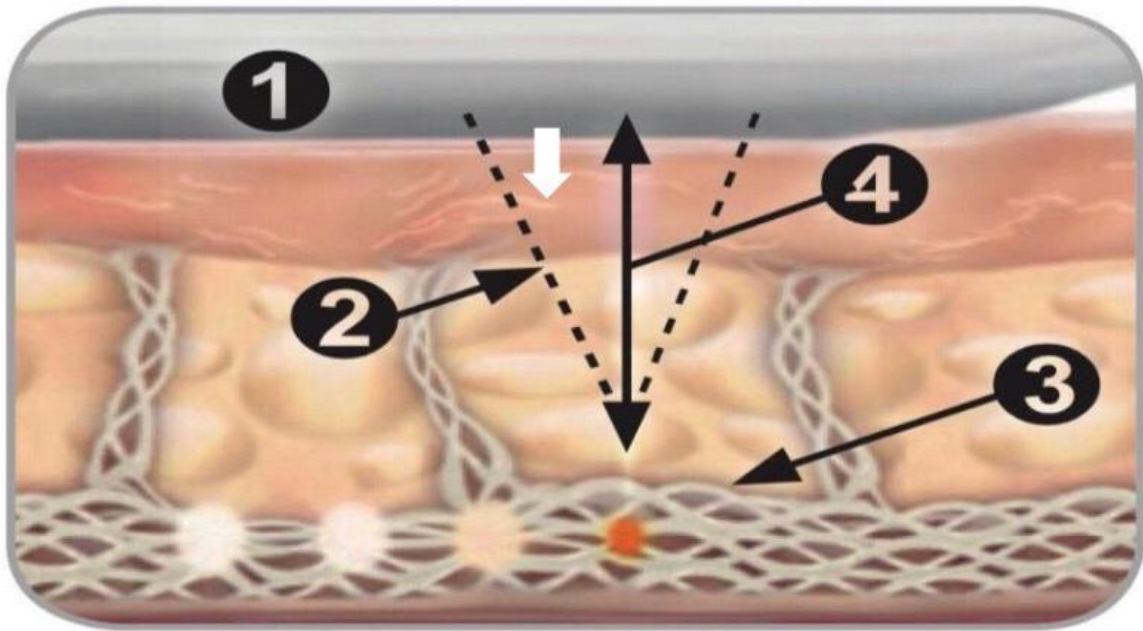


Figure 20. Graf function b

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**Figure 21.** Graf action HIFU energy

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**Figure 22.** Patient before and after treatment

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**Figure 23.** Patient with Prolapse before and after treatment

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