

Review Article

David Elia, Marco Gambiacciani, Jean-Marc Ayoubi, Nicolas Berreni, Jean Marc Bohbot, Philippe Descamps, Rene Druckmann, Hugues Geoffrion, François Haab, Niko Heiss*, Nicolas Rygaloff and Eleonora Russo

Female urine incontinence: *vaginal erbium laser (VEL)* effectiveness and safety

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Abstract: Urinary incontinence is a common health problem that impacts the quality of life of women at different ages. Its physiopathology is not unequivocal, and it is necessary to consider the stress urinary incontinence (SUI), the overactive bladder syndrome and the mixed incontinence (MUI). According to the type of incontinence, its impact on the quality of life and age of the patients, therapeutic strategies are currently summarized in physiotherapy, surgery and drug treatments. We already know the benefit/risk ratio of each of these strategies. Our objective is to evaluate the potential effectiveness and safety of the VEL, an innovative vaginal laser technique (VEL – Vaginal Erbium Laser, erbium yttrium-aluminum-garnet -Er: YAG) a non-invasive laser proposed as a treatment for SUI, overactive bladder syndrome and MUI. The mechanisms of action of lasers are discussed in general and those of VEL in particular with the description of the Smooth® mode. To do this, we have collected the 21 published studies including the first randomized vs. placebo and two pilot studies of intra-urethral VEL. In conclusion: VEL procedures already have their place between the rehabilitation of the perineal floor and surgery. Further properly sized, randomized studies are needed to evaluate the laser treatments in comparison with other therapies, as well as to assess the duration of the therapeutic effects and the safety of repeated applications.

***Corresponding author: Niko Heiss**, Vaginal Erbium Laser Academy France, Elsan, Polyclinique Kenval, Nîmes, France, E-mail: docteur.heiss@orange.fr

David Elia, Jean-Marc Ayoubi, Nicolas Berreni, Jean Marc Bohbot, Philippe Descamps, Rene Druckmann, Hugues Geoffrion, François Haab and Nicolas Rygaloff, Vaginal Erbium Laser Academy France, Paris, France

Marco Gambiacciani and Eleonora Russo, Vaginal Erbium Laser Academy Italia, Livorno, Italy

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- I. Overactive bladder syndrome (OAB) is mainly characterized by a urinary urgency complaint often accompanied by frequent urination, nocturia and occasional urinary incontinence [9, 10]. The overactive bladder is either neurogenic (neurological conditions) or non-neurogenic, the main causes of which are aging and pelvic prolapse [11]. Drug treatments are the main modalities used to treat this syndrome. There are two types of molecules:
 - anticholinergics [11]
 - β 3-adrenergic receptor agonists [12].

However, these molecules exhibit a number of side effects [13, 14]. As for β 3-adrenergic receptor agonists, they may be contraindicated in patients with severe uncontrolled hypertension as they can worsen it [12].

- II. Stress urinary incontinence (SUI) is defined as urinary leakage caused by increased abdominal pressure for example such as coughing [1]. These leaks are the result of the alteration of the support structures of the bladder and urethra. This condition affects up to 49% of women. Current treatments for SUI include either non-invasive treatment or surgery if the first fails. Although pelvic floor rehabilitation therapy may work very well, many patients experience poor outcomes due to bad persistence and inadequate practice [3, 4]. Among the various surgical techniques effective in the treatment of SUI, the procedure for placing a prolene urethral strip is effective [1]. The tension-free vaginal band (TVT) allows replacement of defective support structures by supporting the bladder neck and urethra with synthetic material [5–7]. Today, a TVT or a transobturator band (TOT) is generally used [1]. These procedures have worked. However, in the long term, a risk of complications may arise due to the synthetic nature

of the bands and patients may be reluctant to undergo surgery due to possible complications [8, 15–18].

III. Mixed urinary incontinence (MUI) is a combination of SUI and urge incontinence that affects 29% of women [2]

In addition, the United States Food and Drug Administration (FDA) have issued warnings regarding their use. Consequently, the risks of these devices must continue to be assessed and patients must be informed before making their decision [19]. It is in this context that a new strategy has emerged in recent years: that of technologies laser applied to the vaginal mucosa in general and that of the Erbium: YAG Smooth® laser in particular (VEL in this article). This review of the literature aims to summarize the main results available to date on the efficacy and safety of the VEL in the female indications of SIU and mixed urinary incontinence.

Main features of VEL: vaginal erbium laser

It was Gordon Gould who created [21] in 1959 the word LASER (amplification of light by stimulated emission of radiation). Since then, medical indications have multiplied: dental and ophthalmological interventions (refractive eye surgery, removal of tumors and cataracts), cosmetic surgery, genitourinary surgery, ORL surgery. Today, the non-ablative vaginal erbium laser (VEL) and fractional micro-ablative CO₂ lasers are increasingly being considered as a therapeutic option that allows women to treat their symptoms of SGM without hormonal absorption. Another non-ablative electromagnetic energy, radio frequency, is also currently considered in this particular indication [22]. The Smooth® mode of the Erbium YAG Fotona® laser (VEL = vaginal erbium laser) is non-invasive (Figure 1) because it acts by pure heating without ablation: it uses the photo thermal effect of the laser beam on the water present at the mucosal tissue surface [20, 23]. The laser pulses, whose wavelength (2,940 nm) corresponds exactly to the vibrational frequency of the water molecules (3,400 cm⁻¹), lead to their rupture; this phenomenon generates the synthesis of reactive oxygen derivatives (ROS), which themselves induce secretion of heat shock proteins (HSP) at the origin of the cell repair process. The heat provided to the tissues also causes contraction of the collagen fibers, with fibroblastic stimulation and intense neo-collagenesis. The result is an overall improvement in tone and elasticity of the treated tissue. The thickness of the vaginal mucosa varies, but it generally measures several

hundred microns. For controlled heat deposition at its level, an efficient and safe heat source is required. Smooth® technology is capable of providing effective stimulating heat over 400 microns deep without damaging the surface of the mucosa or deeper surrounding tissue. The IntimaLase®, IncontiLase®, RenovaLase® and ProLapLase® applications are based on the non-ablative Smooth® mode of Fotona®. A Smooth® pulse consists of a burst of six low-fluence laser micro-pulses separated by short intervals to refresh the affected surface, thus avoiding its ablation (Figures 1 and 2).

Different LASER technologies in general and VEL Smooth® technology in particular

The acronym L.A.S.E.R stands for Amplification of light by stimulated emission of radiation. Medical laser light travels along an articulated arm or an optical fiber, then through a handpiece to reach the target tissue. The parameters of the medical laser beam are controlled by the practitioner via an interface depending on the target to be treated, the type of effect sought on the target and the speed at which the beam must act on the tissue.

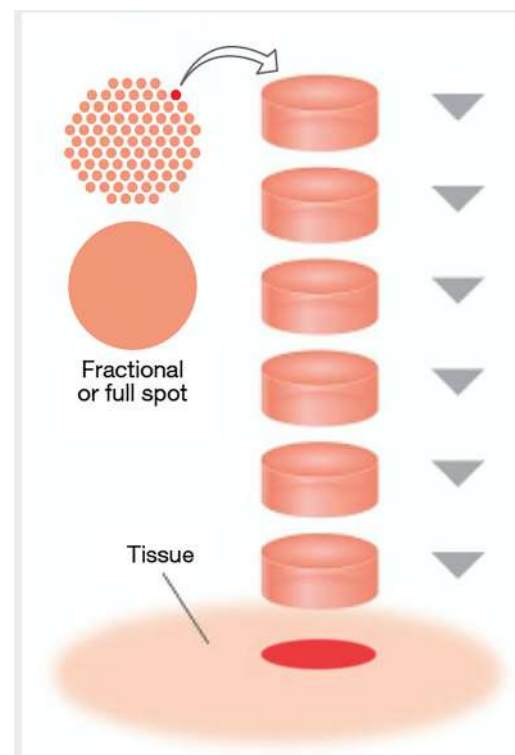


Figure 1: Smooth mode.

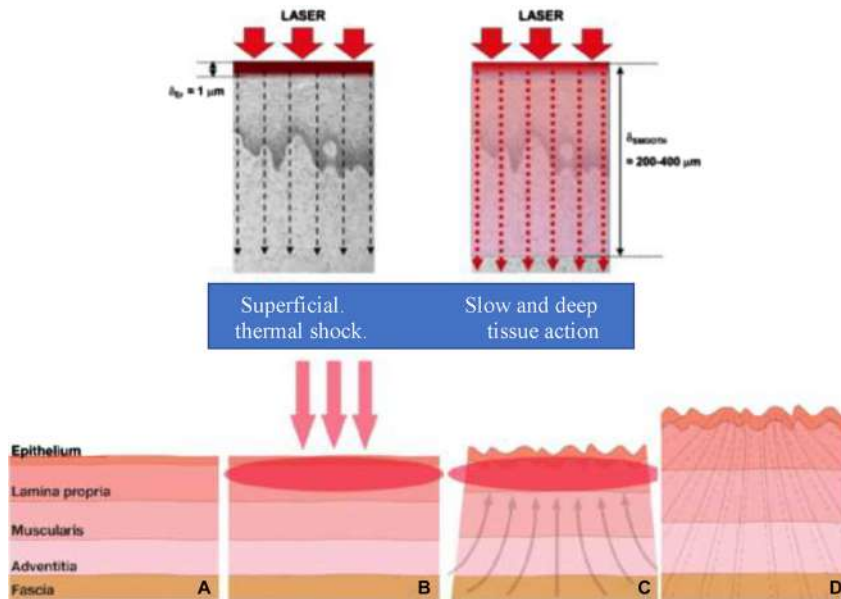


Figure 2: Tissue action of smooth mode. Mechanism of action of non-ablative SMOOTH-mode erbium laser on the vaginal mucosa: (A) the structure of vaginal mucosa consisting of the epithelium, lamina propria, muscularis, adventitia and fascia; (B) irradiation by special SMOOTH-mode pulsing sequence of erbium: YAG laser produces collagen hyperthermia in the epithelium and lamina propria; (C) temperature increase to around 65° C on the mucosa surface causes immediate shrinkage of the upper layers of the vaginal wall as well as mechanical pull of the lower lying structures; and (D) 6 months after the treatment there is a significant thickening of the vaginal wall due to new collagen synthesis.

Medical lasers include four groups:

- (1) Solid crystal lasers (Er: YAG, Nd: YAG, KTP etc.)
- (2) Diode lasers (semiconductor)
- (3) Liquid lasers (dye)
- (4) Gas lasers (CO₂, Argon, HeNe, etc.)

Laser action mechanisms

Laser therapies improve the vascularity of the vaginal mucosa by increasing angiogenesis and stimulating the synthesis of new collagens—fundamental substances of the extracellular matrix in the vaginal connective tissue—by thickening the vaginal epithelium with the formation of new taste buds, restoring the glycogen in the vaginal epithelium as well as the mucosal microbiota and its PH, increasing the hydration of the vaginal mucosa (Figure 3), thereby reducing the symptoms of vulvovaginal atrophy and the signs urinary tract from SGM. Data from the current literature suggest that inducing morphological changes in vaginal tissue induced by laser intervention may relieve the symptoms of vaginal dryness accompanying SGM [22, 24–27]. It is a fully ambulatory procedure that is done in a consultation room.

Urinary incontinence: 2 VEL laser procedures

- Incontilase® procedure

This is the one most often used in the indication “urinary incontinence”. According to studies 1 or more sessions are required at 1-month intervals. Today it seems that the

practice of three sessions would be one to optimize the sustainability of the results.

The protocol usually includes three steps:

- The first step, (shown on the machine screen: Incontilase 1), irradiates the anterior vaginal wall in a single pass using a patented handpiece introduced into a speculum today mostly glass and autoclavable (two diameters available) that allows the laser beam to be directed only to the anterior wall beneath urethra: it sweeps it and its right and left side of the vaginal bottom to the introitus. The parameters used: the energy (fluence), the number of pulses per burst, the frequency (Hz) are preset optimally on the machine.
- The second step (shown on the screen of the machine: Incontilase 2) irradiates the entire vaginal wall in two passes through 360° using a full-beam handpiece.
- The last step (Incontilase 3) irradiates the vestibule and the vaginal introitus with a handpiece using a straight shot and most often a fluence of 10 J/cm².

Reminder: the parameters used for Incontilase 1, 2 and 3 are pre-set on the machine and no anesthesia is needed during the treatment. When approaching the introitus, it is often appreciated by the patient to reduce the fluence for example by 30% so that its comfort remains total. There is no pre or post protocol medication needed.

Patients are advised to avoid sex for at least three days after treatment. This is a fully outpatient procedure that is practiced in a consulting room.

- Renovalase® procedure

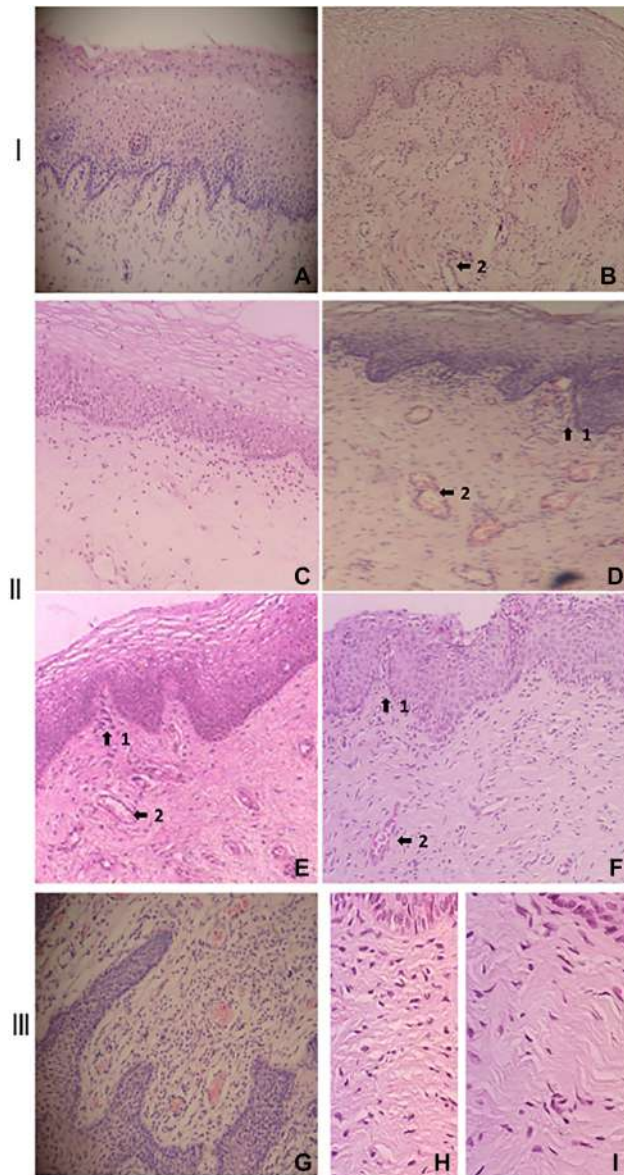


Figure 3: Histological examination (hematoxylin-eosin staining) of the vaginal mucosa of patients with SGM symptoms before and after Er:YAG laser treatment. Panel I show images before treatment (A) and 1 month after laser treatment (B). New vessel formation can be observed [2]. Panel II shows images before treatment (C) and 3, 6, and 12 months after laser treatment (D–F, respectively). Increased cellularity and neo-angiogenesis can be observed [2] after Er:YAG laser treatment, increase in papillomatosis [1], basal cells hyperplasia, and a complete restorative reaction at the level of the lamina propria. Panel III shows images at 6 months after laser treatment, displaying increased angiogenesis (G) and restorative reaction at the level of the extracellular matrix (H and I). Photomicrographs at 4 (A–G) and 10 (H and I) magnification are presented.

Although this is the usual procedure used to treat the atrophic component of the vaginal mucosa of the GMS, a number of studies presented in this review have shown significant efficacy in the context of urinary incontinence

as well. It usually includes two repeated steps three times during the same session.

- The first step, (shown on the machine screen: Renovalase 1), irradiates the vaginal wall 360° from the vaginal bottom to the introitus in a single pass using a patented handpiece introduced into a speculum today. Most often made of glass and autoclavable which allows the laser beam to irradiate all the vaginal walls. The parameters used: the energy (fluence), the number of pulses per burst, the frequency (Hz) are preset optimally on the machine.
- The second step (Renovalase 2) irradiates the vestibule and the vaginal introitus with a handpiece with a straight shot pattern and most often a fluence of 10 J/cm².

When approaching the introitus, it is often appreciated by the patient to reduce the fluence for example by 30% so that its comfort remains total. There is no pre or post protocol medication needed. The end of the procedure is in no way different from that of Incontilase®.

Fotona-Smooth® Er: YAG and urinary incontinences: to date available data

- (1) It was Vizintin and his collaborators who published the first study describing almost 8 years ago the first research study presenting this Er: YAG Smooth® non-ablative laser technology [52]. The pioneering authors demonstrate here how the ErYAG Smooth® treatment studying the photo-thermal effect of a laser beam on the tissue of the vaginal mucosa is capable of causing its retraction without tissue ablation.
- (2) Fistonc et al. presented in 2012 [53] the first pilot study demonstrating the effectiveness of the Incontilase procedure in the treatment of stress urinary incontinence (SUI). They also noted a significant improvement in the sexual satisfaction of women treated. These results show that Er: YAG Smooth® non-ablative laser therapy may be a noninvasiveness effective treatment option without significant pain and without significant side effects for mild or moderate SUI (Figure 4).
- (3) Three years after this first study, Urska B. Ogrinc and her collaborators publish [54] a study including 175 women (aged 49.7 ± 10 years) of which 66% suffer from stress incontinence (SUI) and 34% These women are examined and classified by types of incontinence and by severity as mild, moderate, severe and very severe using the ICIQ [31] (International Incontinence Questionnaire) and 'ISI [33] (evaluation of the incontinence severity index). This time, the authors perform an

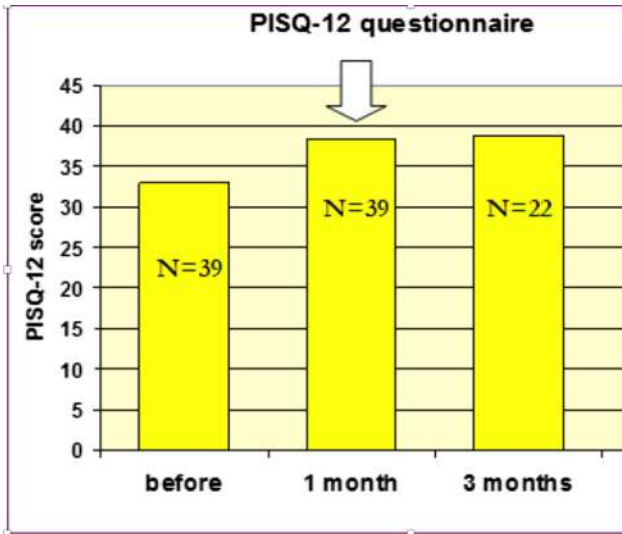


Figure 4: Patients’ assessment of improved sexual gratification measured with PISQ-12 Questionnaires before the treatment and after 1-, 3- and 6-month follow-ups. The improvement after IncontiLase TM treatment after 6 months was more than 6 score points.

average of 2.5 ± 0.5 Er: YAG Smooth Incontilase procedures instead of a session separated by a period of 2 months. During each session a clinical examination is carried out and the treatment is evaluated using the ICIQ [31] and ISI [33] tools. Adverse reactions and patient satisfaction are assessed using the Visual Analog Scale (VAS). Women are followed 2, 6 and 12 months after treatment.

After treatment, the ISI [33] decreased vs. the pretreatment (Figure 5):

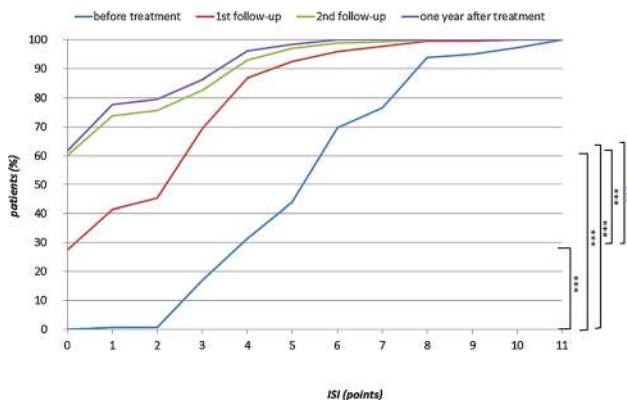


Figure 5: The effect of the Er:YAG laser therapy on the improvement of incontinence severity index [33] (ISI). The distribution of patients (in %) regarding ISI (expressed in points) before the treatment (blue line), at the first follow-up (2 months after the first procedure, red line), at the second follow-up (6 months after the first procedure, green line) and one year after the laser treatment (violet line) is presented. $p < 0.001$, ANOVA with Bonferroni test.

- 2.6 ± 1.0 points in light SUIs
- by 3.6 ± 1.4 points in moderate SUI,
- 5.7 ± 1.8 points in severe SUI
- and 8.4 ± 2.6 in very severe SUI ($p < 0.001$).

77% of SUI women consider themselves to be very improved, but only 34% of women with MUI remain continuous after one year of follow-up. Age did not have any influence on the results. No woman has side effects or complications

Three years have passed since the first pilot study. Fistonic et collaborateurs study in a prospective monocentric cohort study the impact of non-ablative laser treatment on mild to severe stress urinary incontinence. Seventy-three patients are offered a unique Er: YAG laser procedure at 2940 nm designed to heat the mucosa to around 60°C , 500 to a depth of $700 \mu\text{m}$. Women are followed for 6 months. The assessment tool is the ICIQ-IU quality of life scale [31] (Questionnaire International Consultation on Incontinence Questionnaire-Urinary Incontinence)

The results (Figure 6) note an ICIQ-IU score reduced by 46% ($p < 0.001$). The reduction is significantly greater in women with a normal BMI (67%) vs. those who are overweight (25%). The reduction in score is 100% in women under 39 years of age vs. one over 60 (8%) ($p < 0.001$). There were no serious side effects.

- (4) In Kuwait, Khalafalla and colleagues [55] included 50 women with SUI. The duration of follow-up was 1 year. Urodynamic assessment is carried out before treatment and 6 months later. The Erbium Yag Smooth® Incontilase® 1 and 2 procedure is performed only once. No serious side effect is noted, neither during nor after the realization of the session.

The results show a significant improvement in all the items of the urodynamic assessment (Table 1):

- Increase in the average flow from 3 mL/s before treatment to 11 mL/s after treatment.
- Increase in urination time from 9 s before treatment to 24 s after treatment.

TABLE 3. Robust Regression on ICIQ-UI Result 2-6 Months After the Intervention (n = 84)

	Bivariate		Multivariate			
	β_{bi}	P_{bi}	B	β_{mult}	t	P
Age (years)	0.27	0.009*	0.18	0.34	2.52	0.014
Parity, n (%)	0.04	0.670				
Average birth weight (kg)	-0.06	0.550				
Last birth weight (kg)	-0.02	0.833				
BMI (kg/m^2)	0.23	0.022*	0.26	0.16	1.65	0.104
Menopause	0.14	0.183	-1.79	-0.15	-1.13	0.263
Perineometry						
Average (mmHg)	0.03	0.789				
Maximum (mmHg)	0.00	0.987				
Duration (seconds)	-0.08	0.411				
Q-tip test (degrees)						
Rest	0.16	0.118*	0.05	0.15	1.58	0.118
Valsalva manoeuvre	0.05	0.610				
ICIQ-UI before the intervention	0.59	<0.001*	0.60	0.50	5.19	<0.001

Figure 6: Kloving’s categories of ICIQ-UI SF score severity. ICIQ-UI, Consultation on Incontinence Questionnaire Urinary Incontinence-Short Form; UI, urinary incontinence.

Table 1: Standardized regression coefficient in bivariate analysis adjusted for ICIQ-UI [35] value before the intervention; P bi, two-tail test statistical significance of bivariate regression coefficient; B, unstandardized multivariate regression coefficient; b multi, standardized multivariate (adjusted for all included variables) regression coefficient. t, t-test statistic with n-p-1 degrees of freedom where p is total number of parameters in the model; P, two-tail test statistical significance of multivariate regression coefficient. Variables included into the multivariate model based on bivariate criterion P 0.25 [55].

Urethral pressure profile parameters	6 months after laser treatment	Before treatment	p-Value, significance, test used for statistical analysis
MUP (cm HO) ₂	32	19	p=0.1 (>0.5), non-significant, X ₂ test
MUCP (cm HO) ₂	35	16	p=0.02 (<0.5), significant, X ₂ test
FUL (cm)	4	1	p=0.1 (>0.5), non-significant, X ₂ test
CL (cm)	1.76	0.6	p=0.4 (>0.5), non-significant, X ₂ test
UCPA (cm ₂ HO) ₂	53	38	p=0.2 (>0.5), non-significant, X ₂ test
CA (cm HO) ₂	26	22	p=0.6 (>0.5), non-significant, X ₂ test

MUP, Maximal Urethral Pressure; MUCP, Maximal Urethral Closure Pressure; FUL, Functional Urethral Length; CL, Continence Length; UCPA, Urethral Closure Pressure Area; CA, Continence Area; X₂ test, Chi-square test.

- Increase in residual urine volume from 17 mL before treatment to 38 mL after treatment.
 - Increase in the first sensation from 54 mL before treatment to 122 mL after treatment.
 - Increase in the first need to urinate from 75 mL before treatment to 180 mL after treatment.
 - Increase in the urgent need from 150 mL before treatment to 250 mL after treatment.
 - Increase in maximum urethral closure pressure from 16 cm H₂O before treatment to 34 cm H₂O after treatment.
- (5) In Italy, Gambacciani et al. [56] study the results of erbium vaginal laser treatment (VEL) in 45 GSM women treated by three laser applications separated by an interval of 30 days by comparing them with those obtained in 25 women receiving “standard” hormone therapy from GSM.

The VEL procedures used here are the Renovalase Phase 1 and 2 procedures (and not Incontilase® in this study): each session includes three consecutive circular irradiations of the vaginal wall (phase 1) from the vaginal fundus to the introitus with finally irradiation of the

vestibule and introitus with a different handpiece (phase 2). Patients are included 2–4 weeks before the first laser session and are seen 4, 12 and 24 weeks after the last laser session.

Non-VEL patients receive 1 g of vaginal gel containing 50 mg estriol twice a week for 3 months. GSM symptoms are assessed using subjective (VAS visual analog scale) [49] and objective (VHIS Vaginal Health Index score) [50, 51] tools. The degree of incontinence is assessed using the abridged version of the International Consultation Questionnaire on Incontinence (Urinary Incontinence) [31, 32] (ICIQ-UI SF) before and after treatment for VEL in 19 of menopausal women with of stress urinary incontinence. In VEL women there is a significant improvement (p <0.01) in the ICIQ-SF scores [32] which lasts until the 24th week of the period of observation in postmenopausal women with mild to moderate SUI. VEL treatment also induces a significant decrease in VAS scores [49] for symptoms of vaginal dryness and dyspareunia (p <0.01), with a significant increase (p <0.01) SISV (Figures 7 and 8) [50, 51]. The VEL treatment is well tolerated: only 3% of women stopped treatment due to adverse effects.

- (6) In 2015, Gambacciani have designed the project for a large study [57] to evaluate VEL treatment. Laser treatment and in particular vaginal laser erbium (VEL) may be a new, non-invasive treatment for GSM and SUI. However, estimating the results of different laser treatments can be difficult due to different issues: patient selection, concomitant treatments and the long-term effect of vaginal laser therapy. The authors present here the project for a large multicenter VELAS study (study by the Laser Erbium Vaginal Academy), the aim of which is to assess the efficacy and safety of VEL for the treatment of GSM and SIU. This study will assess the effects of three laser applications in 1500 postmenopausal women. Subjective and objective tools will be used to measure improvement in symptoms. Evaluations will be carried out before the first treatment during follow-up visits 4 weeks after the last laser treatment, then every 3 months for 1 year. The results of VELAS aim to clarify the practice of clinical care and the health decisions of millions of women worldwide for a non-hormonal treatment concerning the treatment of GSM and for the non-invasive treatment SUI.
- (7) A year later, this prospective longitudinal study by Pardo [58] assesses the effectiveness of non-ablative Er: YAG laser for 1 year (July 2014/October 2015) within a group of 42 women with mild to severe SUI. The effectiveness of the treatment is evaluated by the visual evaluation scale and the scores obtained with

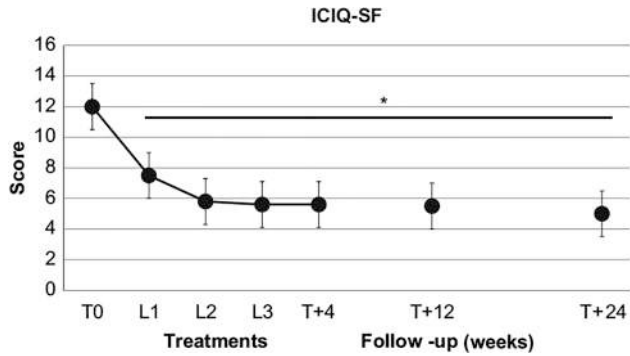


Figure 7: Effect of second-generation laser thermotherapy on International Consultation on Incontinence Questionnaire (ICIQ-SF) score in 19 postmenopausal women suffering from stress urinary incontinence. *p <0.01 vs. corresponding basal values.

the urinary quality of life scale ICIQ-SF [32] (Incontinence questionnaire – Urinary treatment, abbreviated form incontinent), with a 95% confidence level.

Results (Figures 9 and 10): The median ICIQ-SF score of 11 before treatment drops to 3 after 6 months (p <0.001).

78.6% of women (n=33) have improved while 38.1% (n=16) attest to complete healing of their IUS during follow-up. As for the quality of their sexual life, 66.7% (n=28) report high satisfaction and 81.8% (n=27) of sexually active women also report an improvement. No significant side effects during and after the study except moderate pain during the session.

(7) In 2016, the Spanish Barber team [59] published a prospective study of their first 40 cases treated

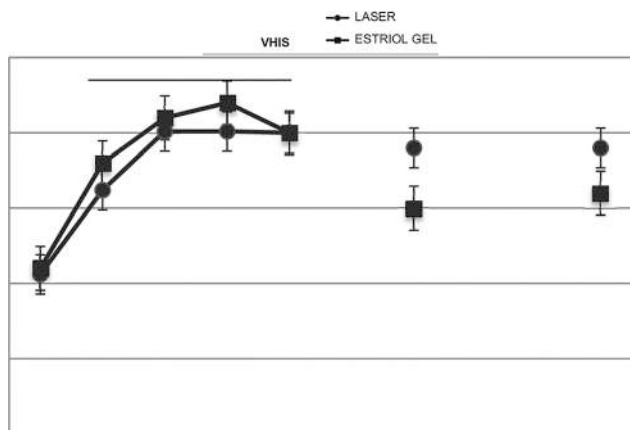


Figure 8: Effect of second-generation laser thermotherapy on the Vaginal Health Score Index (VHS) for the women receiving laser treatment (n=43) and the women receiving estriol (n=19). See text for details. *p <0.01 vs. corresponding basal values in both groups; **p <0.05 vs. estriol basal values and corresponding laser group values.

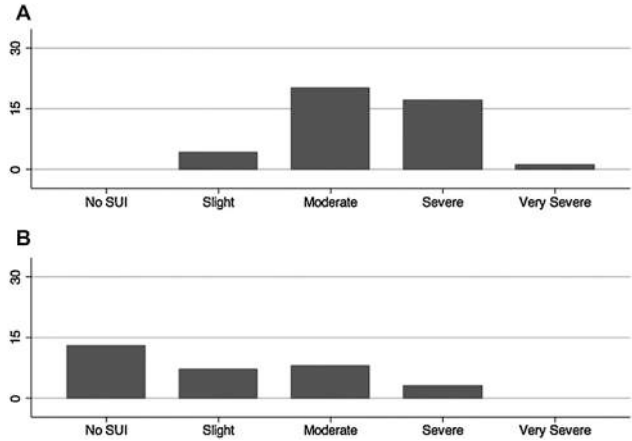


Figure 9: SUI severity, according to ICIQ-UI SF scores: before (a) and after (b) Er:YAG laser treatment.

consecutively with an erbium laser at 2940 nm. The Sandvik test [47, 48] assesses the degree of SUI of the patients. Among these 40 patients, 27% (n=11) have vaginal relaxation syndrome, 52% (n=21) have mild to moderate urinary incontinence, and 20% (n=8) have GSM. Their average age is 47.6 years (30–61 years). 92% had a vaginal birth and 50% gave birth two or more times. The Fotona® protocols used are Intimalase® for vaginal relaxation syndrome and incontilase® for SIU. Two treatment sessions separated by an interval of 30 days are performed. A four-month follow-up assessment is performed, and satisfaction assessment questionnaires are provided to patients. After treatment (Figure 11):

- Among the patients affected by SIU, 75% of women attesting to an improvement (n=15/21) and 86% (n=13/15) indicate a significant improvement.

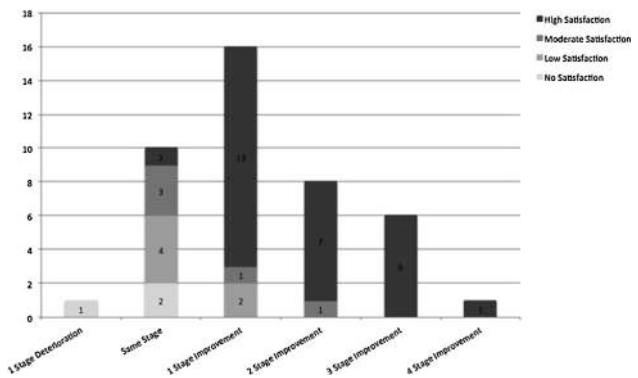


Figure 10: Stage of improvement according to ICIQ-SF at follow up compared to patient’s satisfaction with the results of the treatment.

- 80% of patients with vaginal dryness are improved (85% of those who finished the sessions).
 - 80% of women with vaginal relaxation syndrome (n=8/11) report an improvement and 70% consider their improvement “significant” (82% of partners questioned). 20% of women report an increase in their sexual desire.
- (8) The objective of this prospective study [60] published in 2016 is to assess the effects of the IncontiLase® procedure in 35 women suffering from stress urinary incontinence (SUI). The evaluation tools used in this study are particularly numerous and varied in order to obtain the maximum amount of information. For example, the Chinese versions of the Perception Patient Bladder Condition (PPBC) [34, 35], the USS [36] (Emergency Severity Scale Questionnaire) and the Overactive Bladder Symptom Questionnaire (SAAH) Score, the IDU6 [38] (inventory of urogenital distress), IIQ-7 [39, 40] (incontinence impact questionnaire), KHQ [77] (King’s health questionnaire), FSFI [41–43] (questionnaire on female sexual function). All questionnaires are administered before, 3 and 6 months after the laser procedure. A questionnaire [44] evaluating the modification of male sexuality was also administered. In addition, the Pad 20 min test [28, 29], an urination program and an urodynamic assessment are carried out before, 3 and 6 months after treatment.

Results (Figure 12): Of the 28 women whose weight of the pad is greater than 1 g before treatment, 11 (39.3%) are objectively cured and 11 (39.3%) are improved. Of the 18 women with mild SUI (i.e., Pad test = 1–10 g), 9 (50%) were cured and 5 (27.8%) improved. Of the 10 women with a test tampon >10 g, 2 (20%) are cured and 6 (60%) are improved. Of the 32 women who completed all the questionnaire data

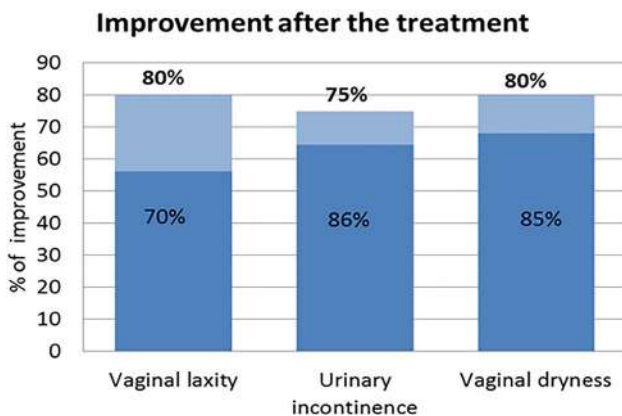


Figure 11: Improvement Results. Group 1: Vaginal laxity; Group 2: Urinary incontinence; Group 3: Vaginal dryness.

at 6 months, 7 (21.9%) were subjectively cured and 4 (12.5%) were improved. When it comes to LUTS (lower urinary tract symptoms), the majority of King’s Health question areas and questionnaires exploring the quality of female sex shows significant improvements. Forty percent (12/30) of patients’ partners experience an improvement in their sexuality at 6 months. However, the urodynamic values remain stable before and after treatment.

(9) 2017 is the year of publication of the first intra-urethral laser procedure ever performed before. Gaspar et al. [61] hypothesize that by targeting the mucosa of the urethral sphincter this could induce angiogenesis and restore the properties of the lamina propria and ultimately lead to the restoration of the urethral mucosa. This is the first published study to report the effects of intra-urethral (and not vaginal) treatment with an Er: Yag-Smooth laser. The inclusion criteria are type III urinary stress incontinence or ISD (intrinsic deficiency of the urinary sphincter). Twenty-two patients with Valsalva vanishing point pressure (VLPP) below 60 cm H₂O are recruited and treated with a non-ablative erbium laser delivering pulses of low fluence over the entire length of the urethra using a specially designed cannula (4 mm in diameter). The treatment consists of two treatment sessions spaced 3 weeks apart. The therapeutic efficacy is evaluated by the ICI-UI SF [31, 32] and the 1-h test pad [28, 29] (Figures 13 and 14). These two assessment methods show 3 and 6 months after the procedure a significant improvement in type III stress urinary incontinence as well as an improvement in the quality of life. The side effects were mild and transient and there were no complications.

(10) This Russian study published in 2017 [62] is carried out on 98 women aged 37–62 years (median 49.0 ± 12.5 years) with SUI and prolapse (degree 0-1-2, POP- system Q). The authors study the impact of VEL on the characteristics of the vaginal mucosa of women with SUI.

Patients receive VEL (Incontilase) treatment consisting of two sessions separated by an interval of 1–1.5 months.

Biopsies of the anterior vaginal wall are performed before and after 1.5–2 months after the last session in 18 women.

Exposure to the YAG laser induces (Figure 15 and Table 2) signs of neo-collagenesis, elastogenesis and neo-angiogenesis, a reduction in atrophy and an increase in the fibroblast population. The morphometry shows that the density of the blood capillaries and the thickness of the epithelial layer increased by 61.1 and 64.5% respectively.

(11) This Taiwanese retrospective study [63] aims to study the effects of the non-ablative laser in 30 women (mean

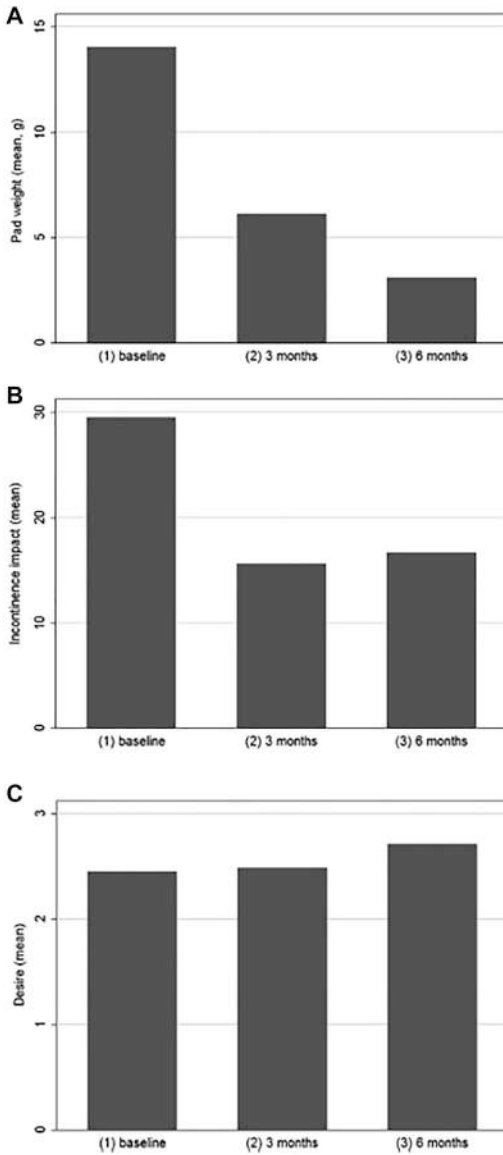


Figure 12: (A) Pad weights; (B) incontinence impact scores from the King’s Health Questionnaire; and (C) sexual desire scores from the Female Sexual Function Index (FSFI) at baseline and 3 and 6 months after therapy.

age 52.6 ± 8.8 years) suffering from SUI/emergency syndromes after two treatment sessions with Erbium laser: YAG

The evaluation of the results is done using:

- 6 validated urological questionnaires [32, 37–40, 45] and a sexual quality of life questionnaire [30] completed at inclusion and 12 months after laser by telephone consultation.
- Urodynamic evaluation
- A clinical examination
- Pad test at 1 h [28, 29]
- Perinometric measurement of vaginal pressure before, 1 and 3 months after laser
- The analog scale VAS [49] assesses pain sensations during laser sessions

Results (Figure 16):

- 12 months after the two sessions in SUI women, 2 patients (6.8%) are very satisfied, 16 (55.2%) are satisfied, 8 (26%) have not improved and 4 (13.8%) are dissatisfied.
- There are significant improvements in overactive bladder symptoms in 4 of 6 questionnaires 3 months after treatment, but this improvement does not persist after 12 months for two of them.
- The Pad test [28, 29] decreases significantly ($p=0.039$).
- Three months after treatment, the mean vaginal pressure improved ($p=0.009$)
- At 3 months, among 24 women (82.7%) sexually active, 62.5% (15/24) report an improvement in their sex life and 54.2% (13/24) of their partner also note. The study does not report any major side effects.

- (12) One year after their first publication concerning the application of intraurethral VEL in the indication of intrinsic damage to the urinary sphincter or DSI [61], Gaspar et al. explore [64] this new procedure in the context of urinary symptoms of GSM. They included 29 patients with less than 5% of vaginal surface cells in cytology, a vaginal pH >5 and presenting urinary symptoms of GSM: dysuria, increased frequency of

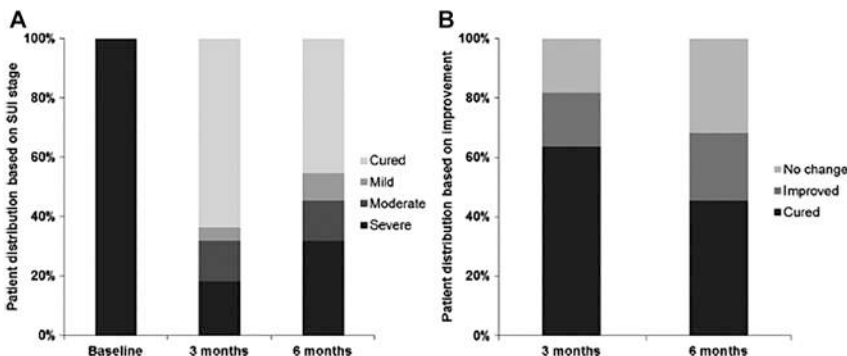


Figure 13: ICIQ-UI SF evaluation of SUI after intraurethral Er:YAG laser treatment; plots represent patient distribution (in %) based on SUI stage before treatment (baseline), at 3 and at 6 months following treatment (a) and patient distribution (in %) based on improvement rates at 3 and 6 months following treatment (b).

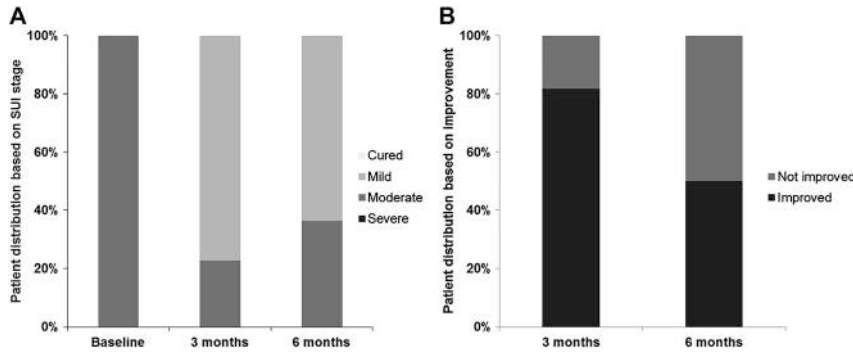


Figure 14: 1-h pad test evaluation of SUI after intraurethral Er:YAG laser treatment; plots represent patient distribution (in %) based on SUI stage before treatment (baseline), at 3 and at 6 months following treatment (A) and patient distribution (in %) based on improvement rates at 3- and 6-months following treatment (B).

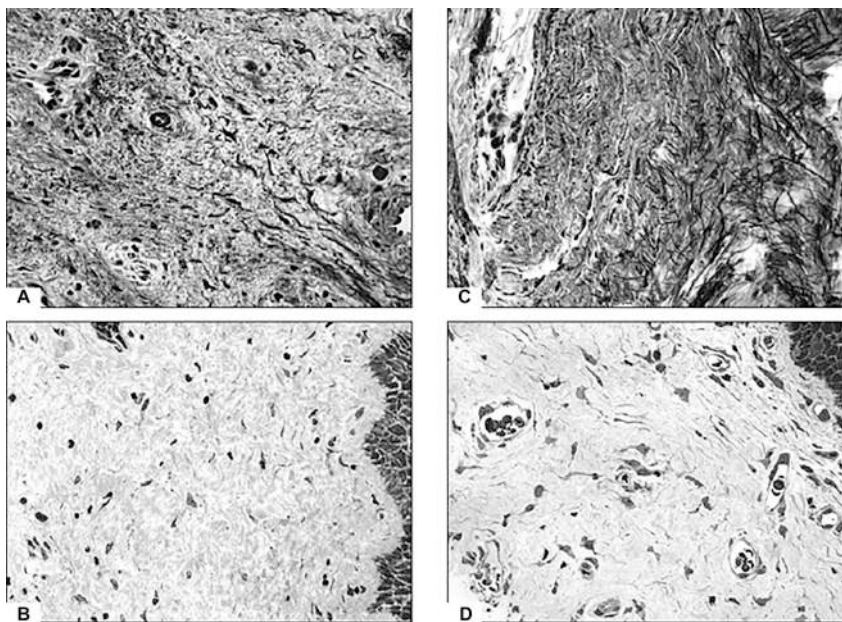


Figure 15: Structural characteristics of the vaginal mucosa in stress urinary incontinence before (A, B) and after (C, D) exposure to Er:YAG laser; van Gieson staining (A, C), semithin section, azure II staining (B, D), $\times 400$. (A) Reduction and fragmentation of elastic fibers, focal disintegration of collagen fiber network; (B) scanty connective tissue cells and solitary capillaries between thick fragmented bundles of collagen fibers; (C) pronounced growth of elastic fibers in vaginal mucosa; and (D) numerous blood capillaries and fibroblasts with signs of synthetic activity in vaginal stroma.

urination, urgency, incontinence. Each woman receives two Er: YAG intra-urethral laser sessions separated by 3 weeks. The laser is delivered without ablation using Erbium SMOOTH mode technology and a 4 mm thick intra-urethral cannula. Therapeutic efficacy is evaluated at each consultation and then at 3 and 6 months using ICIQ-SF [32], the 1 h test

pad [28, 29] and scores obtained on the VAS analog scale [49] (Figure 17). Significant improvement was observed for all the parameters measured during the two follow-ups at 3 and 6 months. The elements of ICIQ-SF (Figure 18) are improved by 64% on average at 3 months and by 40% at 6 months. The 1-h Pad test [28, 29] shows a 59% reduction in the amount of urine lost at 3 months and a 42% reduction at 6 months. All urinary symptoms of GSM are improved (Figure 17). Dysuria decreases by 13 and 31% vs. the baseline values at 3 and 6 months respectively, the urinary urgency decreases to 23 and 47% and the frequency to 22 and 43% respectively after 3 and 6 months. The side effects were mild and transient.

Table 2: Morphometric analysis of vaginal mucosa in stress incontinence under conditions of Er:YAG Laser Exposure ($M \pm m$) [67].

Parameter	Before exposure	After exposure
Thickness of epithelium, μ	114.19 \pm 17.31	187.83 \pm 15.35*
Volume density of capillaries, %	1.8 \pm 0.2	2.9 \pm 0.3**
Number of capillary profiles in test area	8.5 \pm 0.63	12.10 \pm 1.07*
Vessel diameter, μ	6.43 \pm 0.33	7.14 \pm 0.35

* $p \leq 0.05$, ** $p \leq 0.01$.

(13) The aim of this randomized, placebo-blind study [65], the first of its kind, is to assess the efficacy and safety of the VEL IncontiLase® program for the treatment of SUI as well as for the improvement of the quality of sexual life. 114 premenopausal women

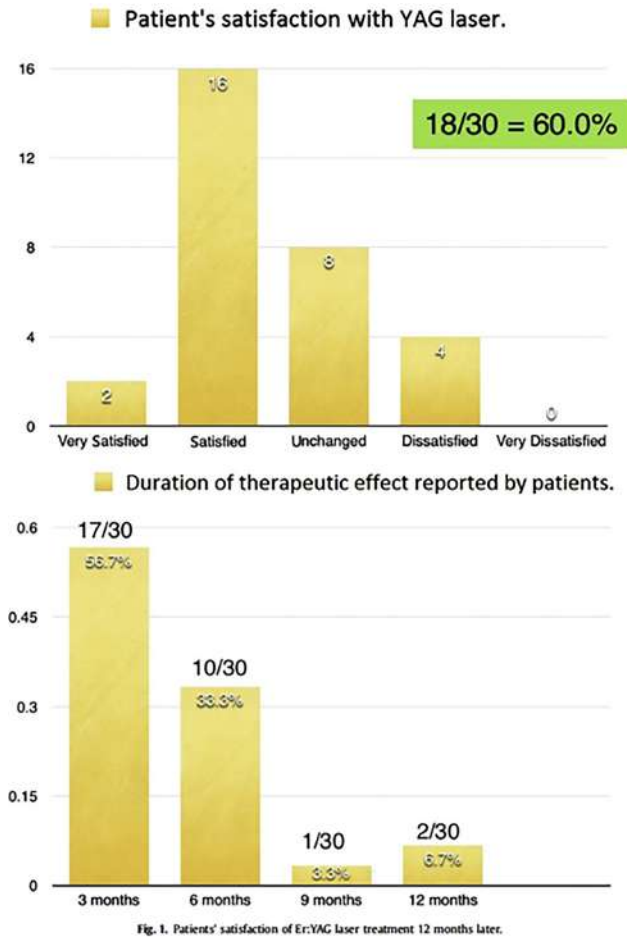


Figure 16: Patient's satisfaction.

with at least one natural birth, sexually active and with SUI are recruited between August 2012 and May 2013. They are randomized into two groups of 57 women:

- A laser intervention group
- A placebo group for which the laser intervention is simulated.

They complete the ICIQ-UI SF questionnaire [31, 32] for urinary incontinence as the main evaluation criterion and the two FSFI quality of sexual life questionnaires [41-43] and PISQ-12 [30] respectively the index of sexual function and the shortened form of the sexual questionnaire on urinary incontinence of pelvic organ prolapse.

They are examined clinically and the quality of their pelvic floor and their muscle function (PFM) is assessed by perineometry.

Results:

- Three months after treatment, the ICIQ-UI SF ($p < 0.001$), PISQ-12 ($p = 0.014$) and FSFI ($p = 0.025$) scores were significantly improved in the laser group compared to the placebo group (Figure 19).
- All the variables of the perineum (Figure 20) are improved in the laser group: the duration and the maximum pressure are statistically significantly improved compared to the control group but note that the average pressure is not.
- Twenty-one percent of patients treated with laser are continuous (ICIQUISF=0) after 3 months against only

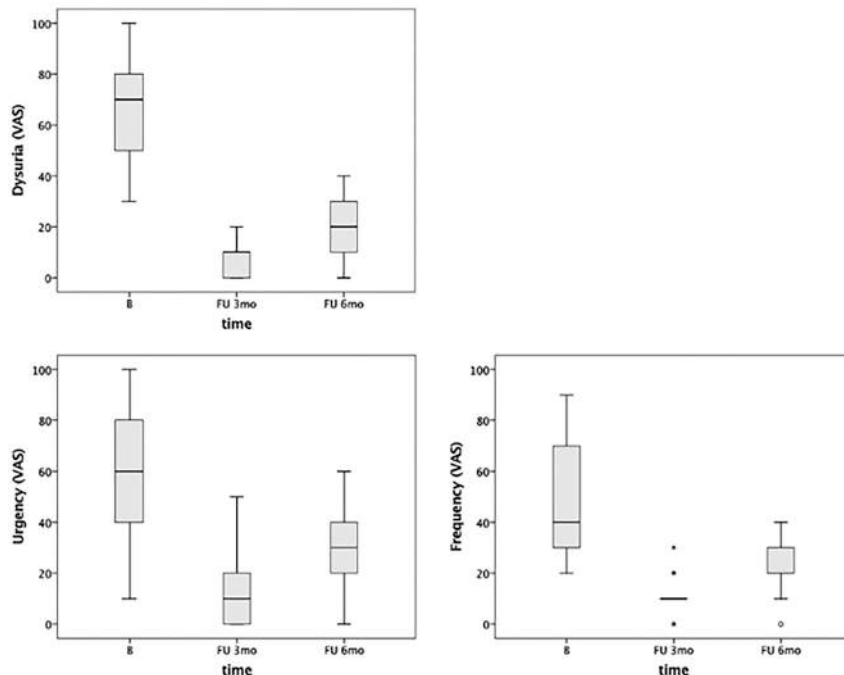


Figure 17: Effect of intraurethral laser treatment on three urinary symptoms of GSM: dysuria (A), urgency (B), and frequency (C). The horizontal line within the box indicates a median, boundaries of the box indicates the 1st and 3rd quartile, and whiskers indicate the minimum and maximum values. Empty circles indicate outliers with values 1.5 IQR above and below the marked quartiles (Q1 and Q3) and asterisks indicate outliers with values 3QR above and below the Q1 and Q3.

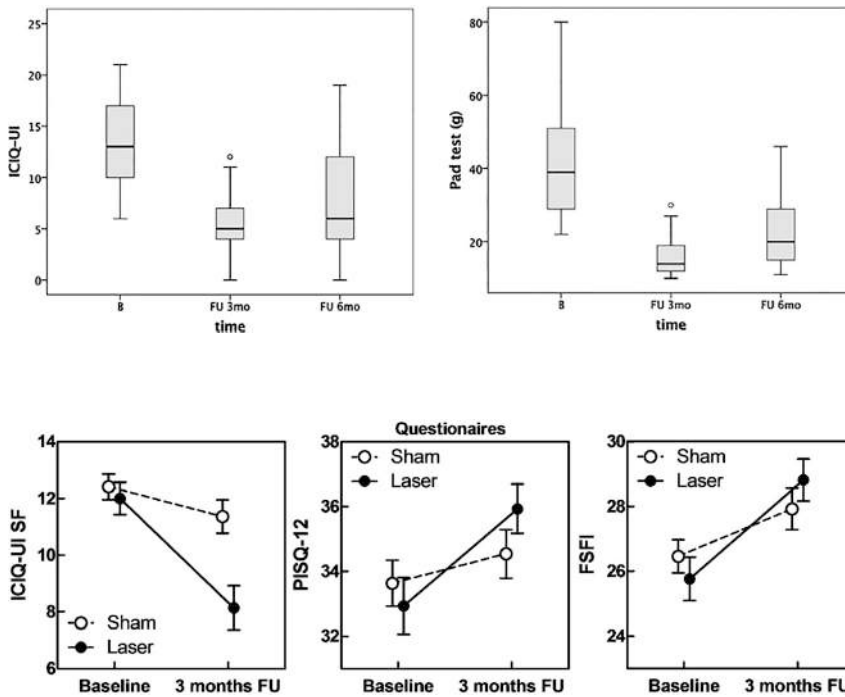


Figure 18: Effect of intraurethral laser treatment on UI, determined by ICIQ-UI SF [31, 32] (A) and 1-h pad test (B). The horizontal line within the box indicates a median, boundaries of the box indicate the 1st and 3rd quartile, and whiskers indicate the minimum and maximum values. Empty circles indicate outliers with values 1.5_IQR above and below the marked quartiles (Q1 and Q3) and asterisks indicate outliers with values 3_IQR above and below the Q1 and Q3.

Figure 19: ICIQ-UI SF sum score (left), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) sum score (centre), and Female Sexual Function Index (FSFI) sum score (right) in the laser and sham control groups at baseline and 3 months after treatment (mean SE, n=56 in each group except FSFI where n=54 in laser group and n=52 in sham group). Score range: ICIQ-UI SF: 0 (best) 21 (worst); PISQ-12: 0 (worst) 48 (best); FSFI: 2 (worst) 36 (best). ICIQ-UI SF sum score (left), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) sum score (centre), and Female Sexual Function Index (FSFI) sum score (right) in the laser and sham control groups at baseline and 3 months after treatment (mean SE, n=56 in each group except FSFI where n=54 in laser group and n=52 in sham group). Score range: ICIQ-UI SF: 0 (best) 21 (worst); PISQ-12: 0 (worst) 48 (best); FSFI: 2 (worst) 36 (best).

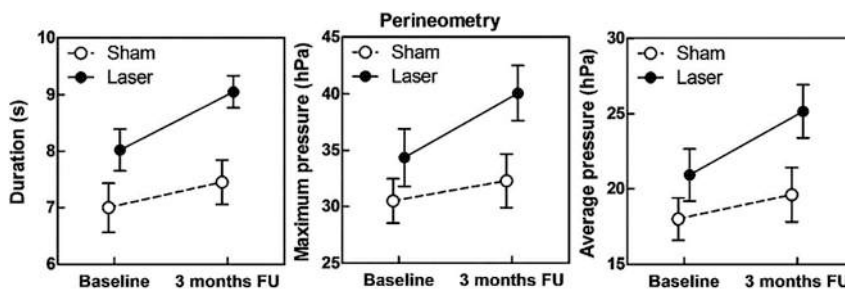


Figure 20: Perineometry: duration (s) of contraction (left), maximal (centre) and average (right) pelvic floor muscle contraction pressure (hPa) in the laser and sham control groups at baseline and 3 months after treatment (mean SE, n=56 in each group).

4% of women in the placebo group. No serious side effects were noted during the study.

- (14) The main objective of this prospective study published in 2018 by Fistonc [66] is to identify the characteristics of patients likely to predict the short-term results of VEL. Its secondary objective is to identify which patients might be expected to achieve the best short-term results after VEL treatment. A prospective cohort study is being conducted in. The predictive elements selected for the analysis are age of the patient, body mass index, number of births,

- average birth weight of children, birth weight of the last child, menopausal status, state of the pelvic floor.
- Muscular strength (PFMS) of the pelvic diaphragm is measured with an Apimedis Perinometer1 (EXTT-101, Korea) and recorded for four consecutive contractions of the pelvic floor muscles: the maximum contraction (in mm-Hg), the average contraction (in mm-Hg), and the duration of contraction (in seconds) are recorded.
- The adequacy of the anatomic support to the neck of the bladder and the uretro-vesical angle measured by the elevation of the tip Q.

- The basic value of ICIQ-UI [31, 32] before the intervention

The study recruits 85 women with SUI. Three times VEL Incontilase® Protocol are performed with an interval of 30 days between each session. The laser irradiation is first directed to the anterior wall (1 pass), then to the entire circumference of the vaginal canal (2 passes) and to the vestibule. The results (Table 3): we can hope for a significant decrease in ICIQ-UI (minimum of 30%) by considering the following predictors: age, BMI, mean birth weight, values indicated by the perineometer and ICIQ scores before the intervention. Finally, the best results can be expected in young women whose BMI ≤ 23.3 , with a mean birth weight of children > 3.6 kg, a baseline value ≤ 10 at ICIQ-IU and a basic compression duration ≥ 3.51 s perinometer.

(16) This study by Gambacciani et al. aims to assess the long-term effects of a vaginal laser on the symptoms of menopausal genitourinary syndrome [67]. 205 postmenopausal women are treated with three Renovalase VEL laser applications 30 days apart. Symptoms are assessed before and after treatment for 24 months using the subjective analog visual scale [49] (VAS) and the objective vaginal health index score (VHIS) [50, 51]. Postmenopausal women suffering from stress urinary incontinence are evaluated by the ICI-UI SF [31, 32] (short questionnaire on urinary incontinence).

Among the 114 patients with SUI (mean age 64.6 ± 4.4 years, menopausal 49.6 ± 3.6 years), VEL treatment induced a significant decrease ($p < 0.05$) in ICIQ-SF scores

(Figure 21). The ICIQSF scores remained significantly ($p < 0.01$) below the baseline after 1 month after the last application of VEL. However, at 18 months from the last application of VEL, the values found are no longer significantly different from the basal values. 96 SUI patients then requested a repeat of the VEL procedure: among them, 51 patients after the 12th month, 30 after the 18th and 15 patients after the 24th month of the first procedure:

- In total, nine patients were still satisfied 24 months after the last VEL intervention.
- Only 10 patients (7.2%) had to undergo surgery
- 23 patients (16.6%) were lost to follow-up.

Less than 3% of patients stopped treatment due to side effects.

(17) This Taiwanese study published in 2019 [68] assesses the effectiveness of a non-ablative laser to treat stress urinary incontinence (SUI): 41 women with SUI are treated vaginally with an Er: YAG laser (Fotona Smooth™ XS, 2940 nm) Women are classified into three categories according to the severity of their symptoms:

- Grade I: urinary incontinence when coughing or sneezing.
- Grade II: urinary incontinence when running or grabbing objects on the floor.
- Grade III: urinary incontinence when walking or climbing stairs.

They are followed for 6 months and the post-treatment evaluation includes a perineal ultrasound and an

Table 3: Patients' clinical characteristics before and 2–6 months alter the intervention (n=1/4 84) [66].

	Before the intervention		After the intervention		Absolute change	Relative change (%)	p-Value
Perineometry							
Average (mm-Hg)	5.3	(4.2–7.3)	6.4	(4.8–11.1)	1.75	(–0.13–3.75)	0.018
Maximum (mm-Hg)	10.5	(8.0–14.0)	11.3	(8.4–17.8)	1.75	(–1.00–6.00)	0.001
Duration (s)	8.5	(5.0–14.3)	12.1	(6.1–18.3)	2.63	(–1.50–8.50)	0.001
Residual urine (mL)	2.9	(0.8–9.4)	0.5	(0.0–1.7)	–0.91	(–6.01–0.01)	<0.001
Q-tip test (degrees)							
Rest	10.0	(0.0–20.0)	10	(0.0–20.0)	0.00	(0.00–0.00)	0.052
Valsalva manoeuvre	72.5	(48.8–80.0)	50.0	(30.0–70.0)	–15.0	(–20.00–0.00)	<0.001
ICIQ-UI	12.0	(7.5–16.0)	6	(0.0–11.0)	–5.00	(–10.00–2.00)	<0.001
ICIQ-UI, n (%)							
No urinary incontinence	0	(0.0)	29	(34.1)	34.1		<0.001
Mild (1–5)	8	(9.5)	12	(14.1)	4.6	48	
Moderate (6–12)	36	(42.9)	29	(34.1)	–8.8	–21	
Severe (13–18)	35	(41.7)	13	(15.3)	–26.4	–63	
Very severe (19–21)	5	(6.0)	1	(1.2)	–4.8	–80	

Data are presented as median (interquartile range) if not stated otherwise; Relative change, $([value_after - value_before]/value_before)$; P , two sided Wilcoxon signed ranks test for all variables except ICIQ-UI categories, where a Marginal homogeneity test was used.

evaluation of the symptoms of the lower urinary tract. Six months after the laser treatment, there is a significant improvement vs. the baseline values ($p < 0.001$) of urinary frequency and incontinence. The patient questionnaires, UDI-6 [38], IIQ-7 [39, 40], OABSS [37, 38] and POPDI-6 [45], all show a significant improvement after treatment ($p < 0.001$). The SUI efficacy of the Er: YAG vaginal laser treatment is 75.5% (31/41) at 6 months. The mobility of the bladder measured by perineal ultrasound (Figure 22) decreased significantly after treatment ($p=0.039$) (Tables 4 and 5). No unwanted events are noted.

(18) This prospective study is conducted at the Kaohsiung Veterans General Hospital in Taiwan and published in 2018 [69] and its results are disappointing and contrast with those of most other studies. The inclusion criteria are SUI and sexual dysfunction. Thirty-one participants are treated with either Er: YAG Smooth or fractional micro-carbonic laser (CO₂). Twenty-one patients are treated with the Erbium laser: YAG and 10 with the CO₂ laser. For the 2 groups groups the ICIQ-SF scores [32] improved (respectively $p=0.007$ and $p=0.035$). The overall decrease in ICIQ-SF scores for the 31 patients was from 9.14

(± 6.08) to 5.45 (± 4.05) ($p=0.001$). However, the objective measurement using the Pad test [28, 29] does not show any significant difference after treatment compared to the baseline values. sexual improvement was noted in 13 patients (44.83%), but the FSFI scores were not different before and after the laser treatment (Figure 23).

(19) OKUI N. et al. In Japan contributed a lot in 2019 to the advancement of knowledge of VEL by comparing in a first study the results of VEL with those of TVT/TOT [70], then in a second study with those of the drugs conventionally used for urinary urgency [71].

(1) The first study [70] included 150 women with SUI or mixed incontinence (MIU): 50 underwent a TVT procedure, 50 a TOT procedure and 50 a VEL procedure comprising 3 VEL sessions spaced one month apart (Incontilase 1, 2 and 3). The results are evaluated for each of the 3 techniques after 12 months using the Pad test (1 h) [28, 29], the ICIQ-SF [32] and the score for the symptom of overactive bladder (OABSS). The improvement in SUI symptoms was comparable in the 3 groups (Figures 24 and 25). For women with mixed

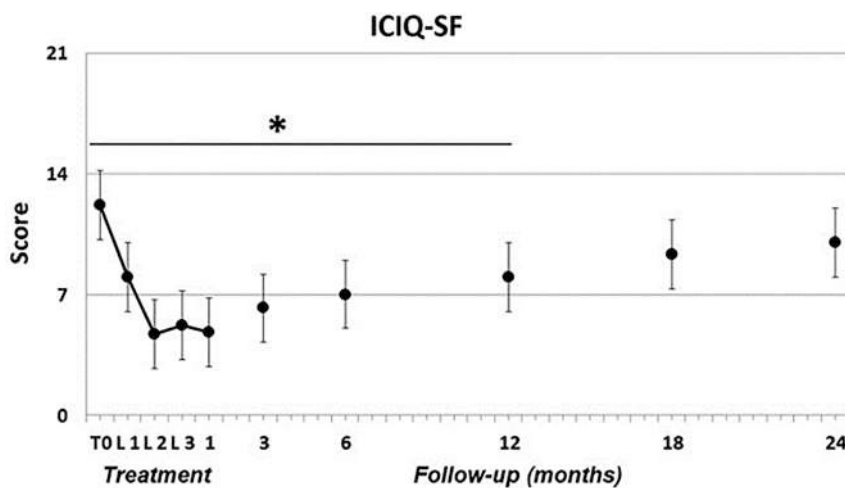


Figure 21: Effect of second-generation laser thermotherapy on International Consultation on Incontinence Questionnaire (ICIQ-SF) score in 114 postmenopausal women suffering from stress urinary incontinence. $p < 0.01$ vs. corresponding basal values.

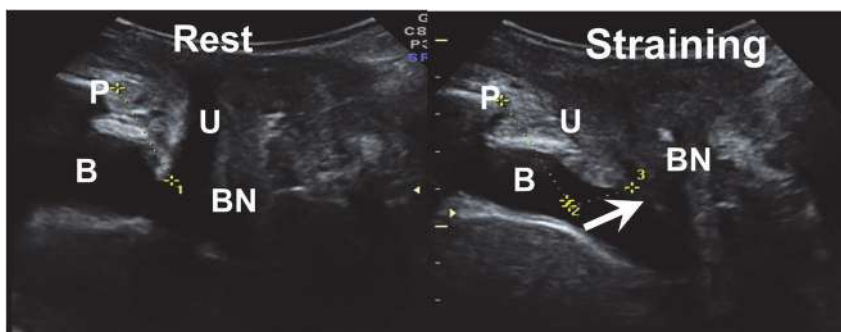


Figure 22: The effect of laser therapy on the improvement in female stress urinary incontinence. (A) Plots show the distribution of patients (in %) by grade of incontinence (mild, moderate, severe, very severe) before treatment and at follow-up. (B) The International Consultation on Incontinence Questionnaire e Urinary Incontinence Short Form (ICIQ-SF) results and (C) 1-h pad weight test decrease following therapy. Data are presented as the means and SD. *** $p < 0.001$.

Table 4: Resting urethral topography at baseline and 6 months after treatment [70].

Rest	Baseline	6 months post laser	p-Value*
Proximal (area)(mm ²)	122.3 ± 54.2	95 ± 52.4	0.099
A (mm)	5.6 ± 1.9	4.7 ± 1.5	0.028*
B (mm)	6.8 ± 1.7	6.1 ± 1.5	0.965
Middle (area)(mm ²)	130.6 ± 58	93.5 ± 42.7	0.001*
A (mm)	5.4 ± 1.2	4.7 ± 1.0	0.033*
B (mm)	7.4 ± 2.1	6.4 ± 1.7	0.024*
Distal (area)(mm ²)	107.2 ± 52.2	78.9 ± 61.8	0.003*
A (mm)	4.7 ± 1.2	4.0 ± 1.2	0.152
B (mm)	7.0 ± 2.0	5.8 ± 2.0	0.001*

Values are expressed as mean ± standard deviation or numbers.
* Statistical significance; paired t-test.

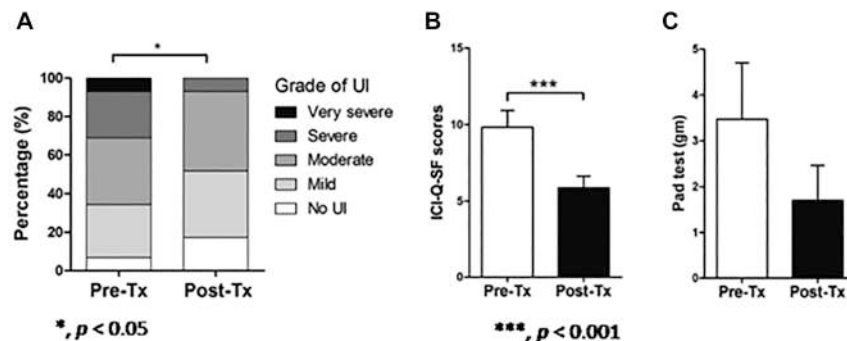
Table 5: Straining urethral topography at baseline and 6 months after treatment [68].

Straining	Baseline	6 months post laser	p-Value*
Proximal (area)(mm ²)	102.4 ± 47.1	95.0 ± 55.9	0.553
A (mm)	4.8 ± 1.3	4.0 ± 3.8	0.319
B (mm)	6.5 ± 1.6	5.5 ± 4.7	0.208
Middle (area)(mm ²)	90.0 ± 57.4	80.0 ± 30.9	0.048*
A (mm)	2.2 ± 3.3	2.3 ± 3.4	0.006*
B (mm)	7.6 ± 4.2	6.5 ± 4.3	0.065
Distal (area)(mm ²)	76.0 ± 59.6	78.0 ± 44.1	0.001*
A (mm)	2.5 ± 3.7	1.2 ± 2.6	0.137
B (mm)	5.5 ± 4.7	6.4 ± 4.7	0.301
Bladder neck mobility (mm)	16.1 ± 6.4	10.5 ± 4.6	0.039*

Values are expressed as mean ± standard deviation or numbers.
*Statistical significance; paired t-test.

incontinence, a few women showed exacerbation of symptoms with TVT and TOT while VEL women all showed improvement.

- In the laser group, no undesirable effects were observed in the short or long term.
- In the short-term authors note hyperalgesic manifestations in one patient



and two infectious syndromes in the TVT group and severe femoral pain in one patient and an infectious syndrome in the TOT group.

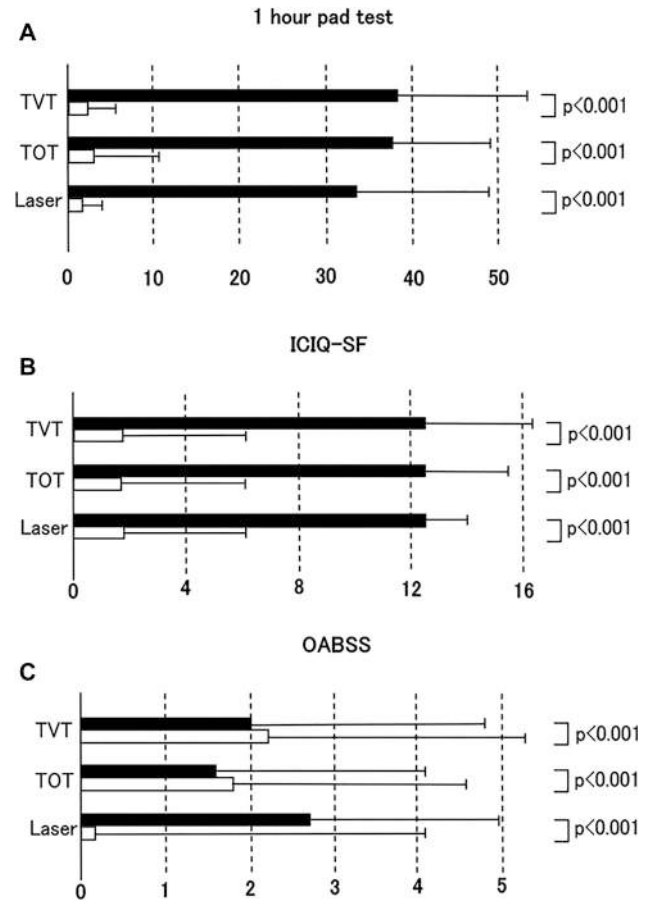


Figure 24: Results of the 1-h pad test 12 months after treatment for the TVT, TOT, and laser therapy groups. (A) TVT, TOT, and laser on vertical axis represent the corresponding groups. The horizontal axis indicates the quantity of incontinence (g) ± SD. (B) Results of the ICIQ-SF [32] 12 months after treatment for the three groups. TVT, TOT, and laser on vertical axis represent the corresponding groups. The horizontal axis indicates the scores ± SD. (C) Results of the OABSS [37, 38] 12 months after treatment for the three groups. TVT, TOT, and laser on vertical axis represent the corresponding groups. The horizontal axis indicates score ± SD.

Figure 23: Effect of Er:YAG and CO2 laser therapy on stress urinary incontinence and sexual satisfaction using ICI-Q-SF scores, the pad test and FSFI scores. Data are presented as the means and SD. **, p < 0.01; *, p < 0.05.

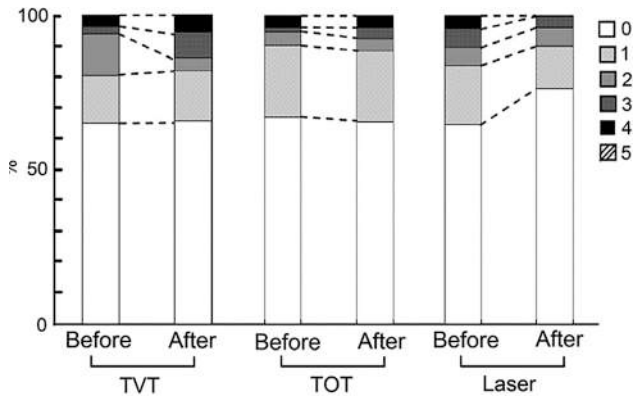


Figure 25: OABSS results of Q4 before and after 12 months of treatment for the TVT, TOT, and laser therapy groups. Vertical axis indicates the percentage of patients (%) grouped according to scores of 0, 1, 2, 3, 4, or 5 points. TVT, TOT, and laser on the horizontal axis represent the corresponding groups.

- In the long term after 12 months, persistent femoral pain is noted in a patient in the TOT group.

This comparative study with a large number of patients is interesting: it seems to indicate that VEL can produce the same positive results as surgery without exposing women to undesirable effects or complications.

(2) The second study by OKUI N. [71] compares the effectiveness of two known drug treatments to that of VEL: 150 women aged 60–69 years with symptoms of

overactive bladder are divided into 3 groups of 50 women receiving:

- 4 mg of (anticholinergic -Toviaz® in France).
- 25 mg of mirabegron (beta 3 adrenoceptor-Betmiga® agonist in France)
- VEL: 3 sessions spaced one month apart (Incontilase 1, 2 and 3)

The results (Figure 26) are evaluated using the OABSS score [37, 38] and the VHIS index [50, 51].

- Overall, the OABSS improved significantly in all groups ($p < 0.001$).
- In the VEL, anticholinergic and $\beta 3$ groups, the scores improved (Figure 26a).
- For Q1 indicating frequent urination, the OABSS improved significantly in all groups ($p < 0.001$). The scores of the 3 groups also improved (Figure 26b).
- For Q2 indicating nocturia, OABSS significantly improved in all groups ($p < 0.001$). The scores of the 3 groups also improved (Figure 26c).
- For Q3 indicating urinary urgency, the OABSS significantly improved in all groups ($p < 0.001$). The scores of the 3 groups also improved (Figure 26d).
- For Q4 indicating emergency urinary incontinence, the OABSS significantly improved in all groups ($p < 0.001$). The scores of the 3 groups also improved (Figure 26e).

Vaginal Health Index score (VHIS) scores was improved after treatment for the 3 groups, but a significant improvement was only observed in the VEL group ($p < 0.001$).

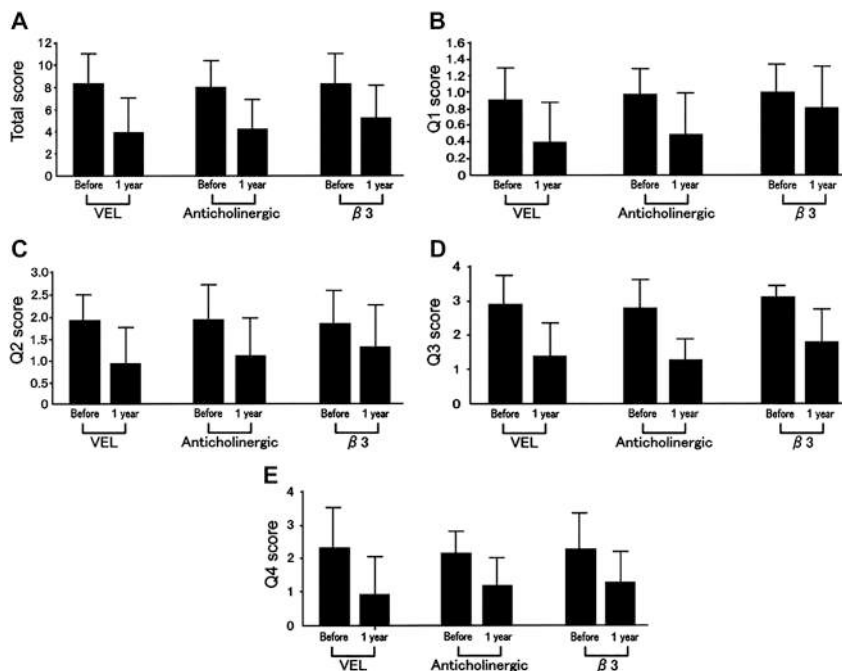


Figure 26: The OABSS results of the three groups. (A) The total OABSS scores are shown. The patients were classified into three groups; (B) Scores for Q1 of the OABSS; (C) Scores for Q2; (D) Scores for Q3; (E) Scores for Q4.

Side effects or complications are noted up to 1 year after the start of treatment. In the VEL group, there were no adverse events while the 2 drug groups a number of patients showed the known side effects of these (constipation and dry mouth) [46].

This comparative study shows that the VEL Incontilase procedure would be able to improve symptoms of overactive bladder just like known drug treatments, without exposing patients to their side effects and to the constraint of daily absorption of tablets.

Two very recent studies confirm the previous data

- 1: It is a cohort study [74]. Eighty-two women suffering from urinary incontinence: 42 SUI (51%) and 40 MUI (49%) are treated with Er: YAG laser and monitored between 2014 and 2018. A Q-tip [75] test angle of more than 40° was a positive factor in establishing the diagnosis of SUI. Women with cystocele of grade greater than 3–4 are excluded. 40% had normal BMI, 43%, 43% were overweight and 17% were obese. Pelvic exams are repeated every 6 months.
 - The ICIQ-SF scores show 26.8% of women without improvement 26.8% with slight improvement, 22% with moderate improvement and 24.4% with high improvement.
 - The SUI group improved overall for 78.6% of women (mild, moderate and high) while in the MUI group the overall improvement was found for 67.5%. Improvement of SUI after VEL continued for up to 15 months.

Some elements of a positive prognosis are noted:

- Age: the youngest show a better response
 - Status in relation to menopause: premenopausal women show better improvement than menopausal women.
 - BMI: the average BMI of patients with high improvement = 25 kg/m². The patients who responded best to Er: YAG laser treatment had a BMI 3.6 kg/m² lower than those who did not respond to treatment: Fistic [54, 66] had already noted this point.
 - Higher total energy provided greater improvement
- 2: The objective of this prospective study [76] is to try to define a prognosis for the effectiveness of 5 VEL Incontilase procedures separated by 1 month each one according to the severity of SIU: SIU I = mild, SIU II = moderate, SIU III = severe.

The authors also assess the duration of the effect of VEL 6 and 24 months after the last session of VEL.

Fifty-nine SIU women were enrolled in the study: 32 SIU I, 16 SIU II, 11 SIU III.

The results:

- SIU I: respectively after 2, 4 and 5 sessions and during the 6 and 24 months following the sessions:
 - The tampon test (1 h) shows an improvement of 69, 78, 91 and 78%
 - The subjective impression rates of subjective healing measured with ICIQ-UI SF are 53, 69, 72 and 66%.
 - Sexual function (PISQ-12) is also improved.
- SIU II: the authors also note an improvement which is maintained at 50% for the test pad (1 h) at 24 months but the subjective recovery rate drops to 13% at 24 months
- Finally, for SIU III, only one of the 11 women included notes a subjective feeling of healing after 2 and 4 sessions of VEL.

So only mild to moderate SIUs find a solution to their incontinence symptom here. The results remain significant until the end of the 24 months of observation (see Figure 27).

Discussion

The number of studies on VEL outcomes and safety is beginning to accumulate and results are consistent. VEL now has more than 50 clinical studies and articles published in peer-reviewed journals. The vast majority of these studies are observational prospective studies. Currently only Blaganje's [65] VEL study conducted in 114 women is a randomized sham-controlled study. Although other randomized studies will be available in the near future, long term [22] and comparative studies [70, 71] with the absence of serious adverse events confirm that VEL as non-ablative thermotherapy is an effective and safe technique for the treatment of urinary incontinence.

Many questions remain to explore in order to optimize the results

- VEL and the grade of SUI

Estimating VEL treatment outcomes is still difficult to define because of the variable characteristics of the women

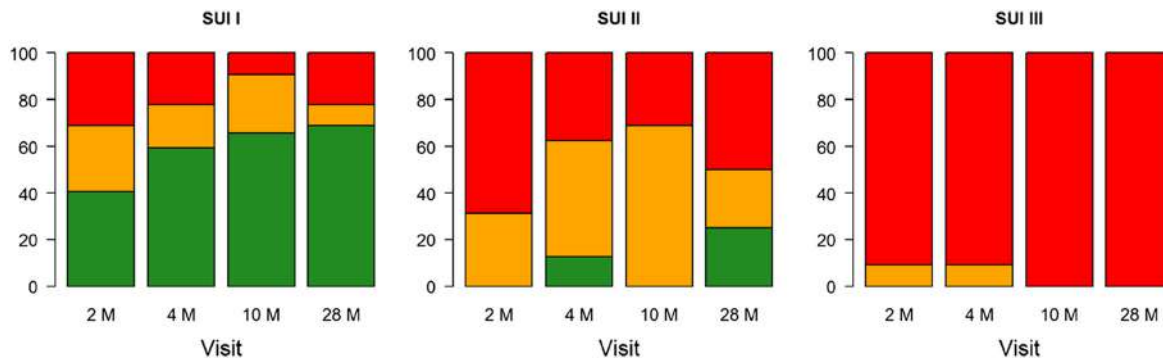


Figure 27: One-hour pad test. Objective cure rates (%) are shown for patients with initial stress urinary incontinence (SUI) I, SUI II or SUI III at the following time points: 1 month after two laser sessions (2 M), 1 month after four laser sessions (4 M), and 6 months and 2 years after the fifth laser session (10 and 28 M). M month, green cured (pad weight ≤ 2 g), orange improved (pad weight reduction of $>50\%$ compared with baseline), red not cured (pad weight reduction of $\leq 50\%$ compared with baseline).

included and the different protocols used in the studies. To answer this question Gambacciani [57] is evaluating 1500 postmenopausal women with 3 consecutive Incontilase sessions with 1-year follow-up after the 3rd VEL session.

- The durability and the effectiveness of the results:

It is also difficult today to get a clear idea about the disparity of protocols implemented: some studies have tested Renovalase®, while others have preferred Incontilase®. In the first case the vaginal walls are exposed to the VEL uniformly at 360° while in the second case the anterior vaginal wall beneath the bladder and urethra is specifically exposed with a VEL with 3 times higher fluence. The protocols (Renovalase, Incontilase ...) must benefit from comparative studies. For the same protocol, depending on the severity of the incontinence and its physiopathology:

- How many sessions?
- How many passages from the vaginal bottom to the introitus?
- Optimum intervals between each session?
- Average time to need iterative session (s) over time?
- How effective it is for urge incontinence?

Thus, the overactive bladder syndrome study of Lin, Y. [63] shows an effectiveness but limited to a few months with 2 sessions of a protocol approaching Renovalase®. Conversely, Okui [71] shows an effectiveness comparable to medical treatment with 3 sessions of 20 min of Incontilase® 1 month apart with a follow-up of 1 year (whatever the indication: SUI, MUI, OAB).

- The incidence of complications

All published VEL studies report the absence of serious side effects and complications. However, it would be

utopian to think that we are here in the presence of a “zero risk” technology.

The recent article by Jusleen Ahluwalia [73] collects 45 distinct events between October 2015 and January 2019 that describe 46 patients on the FDA’s MAUDE incident logbook. The most commonly reported adverse event ($n=19$) is pain (vulva, bladder, urethra, or unspecified). Thirty-three patients indicated a transition to the chronicity of their problem (radiofrequency = 12, CO2 = 17, Er: YAG = 2, Er YAG non-ablative = 1, DM unknown = 1) including long-term pain, numbness, burning sensation, bladder disorders, dyspareunia, worsening of symptoms, worsening of multiple sclerosis, scar problems. Note that these figures are more than 3 years old: they remain particularly weak in a country particularly well equipped with energy machinery and having a population of 330 million inhabitants. The most frequently implicated machines were radio frequencies and CO2 lasers. But beware this is an obvious bias because they are the more numerous energy machines in the US. In addition, we must not forget that it takes sometimes many years and millions of patients treated by a given therapy to unmask one or more complications proving to be very long term and ignored until then. Nevertheless, the medium-term evidence of safety that is attested by the existing studies makes us assume that EBD are safe. This study reinforces the contention of a largely clearly positive benefit-to-risk ratio for women treated with EBDs. It is also necessary to consider the technical failures of the machines, certainly exceptional but always possible: it is therefore necessary to ensure a rigorous maintenance. Finally, and above all, it must be understood that all EBDs are different in terms of risk: the non-ablative Smooth® technology of VEL is an additional guarantee of “primum non nocere”.

- What about FDA Warning (Food in Drug Administration) of July 2018 updated on November 20, 2018?

In July 2018 the Food and Drug Administration (FDA) points out to companies marketing that energy-based medical devices in the USA are validated by the Agency for indications of conization or removal of condyloma for example but that they never asked them—as is the law—their approval and authorization for the indications “*vaginal laxity, vaginal atrophy, dryness or itching, pain during intercourse and/or during urination, decreased sexual sensations. To date, we have not approved or authorized the marketing of energy-based devices to treat these symptoms or any symptoms related to menopause, urinary incontinence or sexual function*”. And the FDA points out that these energy-based vaginal treatments can cause serious side effects, including vaginal burns, scarring, pain during intercourse, and recurrent, chronic pain. So surprising that it may appear in a country as attentive to legal procedures as the US, we understand that the various vaginal procedures based on energy developed in the US until July 2018 outside any legal framework: the therapeutic claims of some companies have spread not only without having produced sufficient evidence of efficacy and safety but also without having even asked the Health Authorities for their approval and authorization Following this warning, the FDA promptly sent a letter (with a written response time required within 30 days of receipt of this letter) to 7 companies of energy-based medical equipment (4 radio frequency equipment, 2 fractionated CO₂, Erbium: YAG). It asks each of the 7 companies for their FDA approval or approval number for their material in these specific indications. The FDA promises to continue to actively monitor promotional messages and claims as well as complaints and adverse reaction reporting from patients, health care providers and industry. Fotona® (manufacturer of Erbium YAG Smooth®) has not received any letter from the FDA and for good reason because it has never claimed the vaginal indications currently in the hot seat in the US. Fotona® is a European Company (Slovenia) and it was logical that it is first to Europe that it has submitted its application for approval (European Community label CE label *) that it has obtained for its four indications under the names Incontilase® in 2012 (stress urinary incontinence), Intimalase® (vaginal relaxation) in 2012, Renovalase® in 2016 (GSM atrophy) and Prolaplast® recently in 2018 (pelvic organ prolapse) The Fotona/FDA dossier is now in progress and until it succeeds Fotona® is not promoting these indications in the USA.

FDA’s warning seems to us totally justified: The FDA, “policeman” guarantor of the American health safety, could not let develop this technology further without

imposing a legal framework. FDA’s warning should be interpreted not as a definitive stopping point for EBDs, but rather as a constructive warning to the producers and care givers to rely to scientific and published data, avoiding enthusiastic “laissez-faire” of claims and practices. Doctors practicing these new techniques are strongly advised not to succumb to the temptation of amateurism: it is important not to become “amateurs” gynecologist or urologist. They need to get an appropriate training dealing with these innovative techniques. We hope that this controversy might be an opportunity to shed more light upon EBDs and clarify the differences among the technologies marketed for SUI. In this view, a vast clinical experience and scientific evidences indicate that VEL-Smooth® can really be seen as an effective, non-invasive ambulatory procedure.

In Europe and France in particular the CE marking (European Community marking) on a medical device (MD) means that it complies with the legal requirements of the European Union directives on health and safety involve three actors, the manufacturer, the notified body (except for classes I) and the competent authority (in France, the ANSM). In order to benefit from the affixing of CE marking, the company must demonstrate that its product complies with the requirements of quality and safety. Once affixed it allows the placing on the market of the medical device in all member states of the European Union and the European Economic Area. It constitutes a mutual recognition of harmonized legislation between the Member States. In terms of promotion and marketing of a medical device to patients and the medical profession “claims/results or properties claimed for promotional purposes must be supported by data that objectively justify these claims”. In addition, these data must be relevant to the French medical practice claims/properties/clinical results specific to the medical device promoted must be supported by clinical data [72].

Conclusion

Although large randomized trials have not been reported to date, the vast clinical experience and scientific evidences indicate that VEL-Smooth® can really be seen as an effective, non-invasive ambulatory procedure. VEL-Smooth® can offer a new, long term therapeutic option to improve women quality of life, considering the limits and the balance between benefits and risks associated with each therapeutic approach.

The preference of our patients towards “non-invasive” procedure is here strongly reinforced with VEL: its procedures don’t require pre or post medications, anesthesia,

and are associated with very low number of just mild and transient adverse effects. Although TVT/TOT can be considered as mini-invasive surgical procedures VEL treatment could be suggested before surgery when perineal floor rehabilitation fails or do not satisfy the patient's expectations.

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