Obstetrics and Gynecology Reports

Research Article ISSN: 2515-2955

# Vulvar rejuvenation with polynucleotides HPT® and benefits on postmenopausal sexual life disruption

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## Abstract

**Introduction:** *M*enopausal atrophy severely compromises *vulvar structures and sexual function*. W*ould limiting "rejuvenating" strategies to the areas before the hymenal ring benefit the sexual function in middle-aged women without the difficulties of vaginal procedures? An exploratory study with intradermal Polynucleotides Highly Purified Technology (PN-HPT®) as pivot* vulvar *rejuvenating agent probed the issue.*

**Methods:** Observational cohort of 47 menopausal, sexually ungratified women treated intradermally with *PN-HPT® (10 mg/mL), hyaluronic acid (10 mg/mL) and mannitol (220 mM/L)* in prefilled syringes (*Class III* CE0373 medical device*)*. Vulvar "*rejuvenation" ambulatory* technique: five injections *in labia and vestibular areas every fifteen days*. Assessments: "Personal Assessment of Intimacy in Relationships" (PAIR) scale self-administered 15 and 30 days after the last vulvar injection. Internal consistency controls: impromptu atrophy symptom scoring.

**Results:** All atrophy scores significantly decreased, suggesting PAIR outcomes were robust. The thirty PAIR items probing the day-by-day non-sexual couple relationship showed no change. Conversely, five out of the six PAIR items probing the woman's sexual satisfaction and couple's sexuality improved significantly (e.g., "I am satisfied with our sex life": 1.6 ± 0.50 at baseline, 2.3 ± 0.59 at follow-up, p <0.01).

**Conclusions:** When injected intradermally for menopausal vulvar rejuvenation, the combination PN-HPT®/HA/mannitol significantly benefits the woman's sexual gratification and the couple's sexual closeness.

## Highlights

- Would limiting "rejuvenation" to the vulva benefit menopausal sexual problems?
- Vulvar rejuvenating agent: intradermal Polynucleotides Highly Purified Technology.
- Assessment: validated "Personal Assessment of Intimacy in Relationships" scale.
- Five of the six PAIR items related to sexual gratification improved significantly.
- Vulvar-only rejuvenation improves the sexual life of menopausal women and couples.

## Introduction

As recently as early 2022, the Clinical Practice Guideline no. 423 of The Society of Obstetricians and Gynaecologists of Canada seemed to leave few doubts: "There is insufficient evidence to support any female genitalia surgery or procedure to improve sexual satisfaction and/or self-image" [1]. According to the American College of Obstetricians and Gynecologists, the lack of high-quality data is especially severe for genital cosmetic surgical procedures [2]. However, in all cultural environments, worldwide surveys show that most women believe sexuality and a gratifying sexual activity are meaningful contributors to their emotional satisfaction, including in perimenopausal years [3,4]. Surveys also show that physical pleasure in sexual life and emotional satisfaction are intertwined [5]. Consequently, the lively clinical research effort on female genitalia surgical and non-surgical procedures to improve sexual satisfaction should not be a surprise [6-8].

In the vulvovaginal skin and mucosa, the progressive estrogen deficiency goes hand in hand with the depletion of collagen and elastin fibers in sub-epithelial connective tissues. The consequences are weaker tissue elasticity and tension, loss of blood vessels in the dermis and lamina propria of the vulvar skin and mucosae, decreased superficial squamous cells with increased parabasal cells and flattening of mucosal rugae [9].

### The energy-based techniques - benefits and liabilities

By heating the vaginal wall connectives to 40°C to 42°C, energy-based, fractional ablative laser and radiofrequency devices aim to induce collagen contraction and neocollagenesis, tissue remodeling with fibroblast activation and novel synthesis of extracellular matrix. The outcomes and benefits - improved tissue elasticity and increased local blood flow, engorgement and lubrication - extend to the middle-

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***Key words:*** *Genitourinary syndrome of menopause, hyaluronic acid, Polynucleotides Highly Purified Technology, vulvar atrophy, vulvar rejuvenation*

**Received:** October 19, 2022; **Accepted:** October 24, 2022; **Published:** October 31, 2022

aged woman's sexual function and gratification [10,11]. The liabilities of those energy-based, high-technology devices are costs, including the need for specialized handpieces and training and the technical difficulties of any procedure beyond the hymenal ring - e.g., the need for a speculum when performing injections.

### The Polynucleotides Highly Purified Technology option

Polynucleotides Highly Purified Technology (PN-HPT®) are DNA polymers extracted from male salmon trout gonads thanks to advanced purification and high-temperature sterilization procedures. Exposure to PN-HPT® is associated with enhanced fibroblast growth and vitality, increased tissue hydration, and production of collagen and extracellular matrix proteins [12,13]. By replenishing the local pool of nucleotides, nucleosides and nitrogen bases, PN-HPT® indirectly support the production of new matrix glycosaminoglycans and new collagen and elastin fibers by vulvar fibroblasts [12]. An accumulating body of evidence points to PN-HPT®, combined with hyaluronic acid, as an effective vulvovaginal rejuvenating strategy in peri- and postmenopausal women [13-15].

### Vulvar vs. vulvovaginal "rejuvenating" strategies

An exciting field of research is whether concentrating or limiting the rejuvenating strategy to the vulvar skin and mucosa may benefit the peri- and postmenopausal sexual function. Avoiding all structures beyond the hymenal ring would simplify procedures, shorten operative times, and reduce costs.

A sound rationale supports this strategy, based on the strong association between women's sexual pleasure and gratification and vulvar trophism. The rich labia minora innervation reaches a zenith in the clitoral glans embryologically pertaining to the vulva. The estimated number of sensory terminations and genital corpuscles in the clitoral glans and penile glans is similar (about 8,000), although with a volume density 50 times higher in the woman, meaning a lot higher sensitivity for the clitoral glans compared with the male glans [16].

The striking changes in the depth of the peri- and postmenopausal atrophic vulva - thin and pale mucosa of introitus and labia minora, decreased transudates and secretions leading to dry skin and mucosa, fused and hyalinized collagen and fragmented elastic fibers, reduced matrix mucopolysaccharides - are associated with the demonstrated loss of trophism and sensitivity of genital corpuscles due to decreased blood flow [17].

Would limiting the rejuvenating strategy to the vulvar structures before the hymenal ring mean more straightforward procedures with less training and reduced costs while still benefiting the peri- and postmenopausal women's sexual function and gratification? This exploratory study aimed to address and possibly substantiate the inter-relationship between vulvar rejuvenation and the impact on the sexual function of middle-aged women. Intradermally injected Polynucleotides Highly Purified Technology (PN-HPT®) combined with hyaluronic acid (HA) and mannitol, an inhibitor of HA degradation, were the vulvar rejuvenating formulation chosen for the study.

## Methods

### Study protocol and vulvar "rejuvenating" technique

Candidate subjects: a prospective cohort of ambulatory women with ungratifying personal and couple sexual experience due to menopausal vulvovaginal atrophy spontaneously looking for vulvar "rejuvenation" procedures to alleviate their atrophy symptoms, including dyspareunia and sexual dissatisfaction, thus qualifying the study as observational. The women underwent vulvar "rejuvenation" with injections of isotonic viscoelastic gel in prefilled, 2-mL single-use sterile apyrogenic syringes containing 10 mg/mL PN-HPT®, 10 mg/mL HA (molecular weight, 1000-1500 kDa) and 220 mM/L mannitol as an inhibitor of enzymatic and oxidative HA degradation (NewGyn®, Class III CE0373 medical device dispensed with two 30G ½, 13-mm needles, Mastelli S.r.l., Sanremo, Italy). Vulvar "rejuvenation" protocol: five PN-HPT®/HA injections every fifteen days in the vulvar skin dermis and mucosal lamina propria.

Injections were usually by the linear retrograde technique over labia majora and the micro-wheal technique over labia minora and around the vaginal meatus and peri-clitoral areas (0.1 mL per wheal; distance between wheals, 0.5-1 cm; needle inserted with a 30-45 degrees inclination to a depth of about three mm below the vulvar surface). The usual procedure involved no more than two injections below the posterior labial commissure overlying the perineal body and one or two injections at the anterior labial commissure below the mons pubis. The residual syringe content was usually injected in several small hives on the labia minora at the side of the vestibule and up to the prepuce. Other injection techniques (fan-like pattern, reticular pattern, mixed) were occasionally helpful in individual cases. The first author performed all injections after getting informed consent. All sessions ended with a prolonged massage of the treated areas to help the local gel diffusion.

Preliminary preparation before each rejuvenation session: standard local disinfection followed, if needed, by a galenic (e.g., 30% lidocaine gel) or proprietary anesthetic cream (smallest amount sufficient to numb the target vulvar area 30 minutes before the injection, usually about 1 cm).

The protocol suggested the at-home application of a polynucleotide vaginal cream but did not strictly require it and recommended avoiding sexual intercourse and other activities involving rubbing or pressure on treated areas for some days.

### Efficacy assessments

PAIR scoring and internal consistency controls: performed 15 and 30 days after the last vulvar injection—assessment tool: 36-item PAIR scale ("Personal Assessment of Intimacy in Relationships"). PAIR is a five-point multi-item validated scale that investigates many perspectives of the couple's relationship and quality of life, such as overall harmony, psychological intimacy, willingness to share interests, and feelings of being criticized by the partner. Six PAIR items investigate the woman's sexual function and gratification and the overall emotional closeness and harmony in the couple's sexual relationship. In 1981, Schaefer & Olson described the PAIR development and validation process [18]. Figure 1 illustrates the easy PAIR scoring procedure.

The authors also devised five impromptu non-validated scales, with scores ranging between 0 and 3, to assess the woman's physical discomfort and troubles during sexual activity and, generally, the evolution of representative atrophy symptoms - dyspareunia, vaginal loss during intercourse, vaginal dryness, vulvovaginal itching and irritation, dysuria. The non-validated five scales had no ambition but the limited purpose of acting as internal confirmatory controls of the credibility and strength of any PAIR change.

Photographic documentation: before the first treatment session and at the last treatment session.

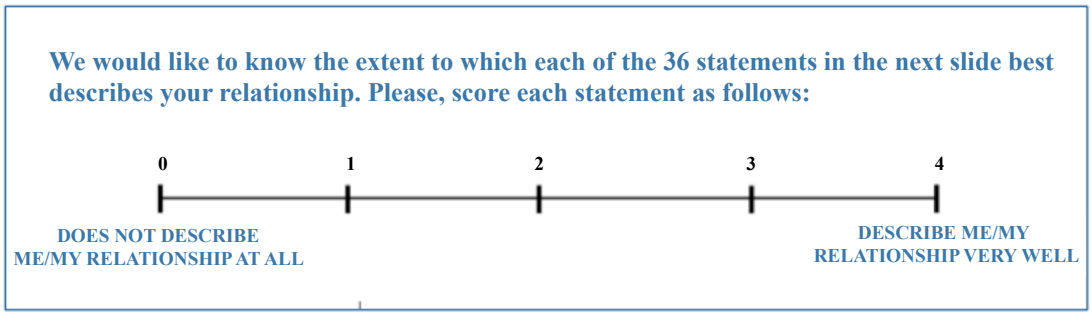


**Figure 1.** Multi-item PAIR scale, scoring instructions [18]

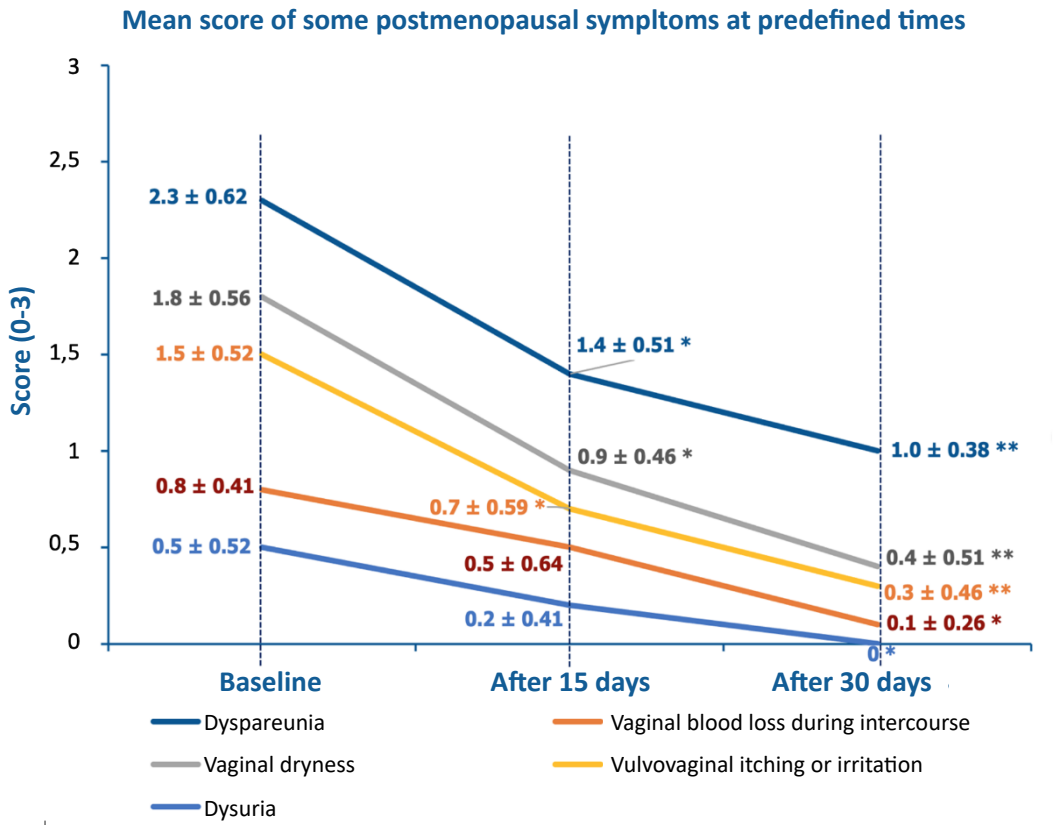


**Figure 2.** Mean impromptu scores of atrophy symptoms (± SEM) as reported by the 47 cohort women 15 and 30 days after the last vulvar PN-HPT®/HA rejuvenation session

## Safety assessment

Direct assessment by the investigator of objective side effects like swelling, erythema or vulvar color changes; women were also routinely questioned about minor or significant adverse events they experienced before each treatment session.

## Statistics

Due to the purely exploratory nature of the study with ambitions limited to a first orientation and concept building, the authors decided to perform no formal sample size estimation and deliberately risk incurring "beta" false-negative errors. Only looking for trends and overlooking statistical significance was a compromise justified by the study's exploratory nature.

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA), version 13.0. Descriptive data were tabulated as means ± standard errors of the mean (SEM). For the end-of-treatment vs. baseline PAIR outcomes, the low number of cohort subjects required a cautious non-parametric approach (Wilcoxon matched-paired signed-rank test, later confirmed by a more conservative pairwise multiple-comparisons Tukey procedure).

Regarding the results of the impromptu parameters related to atrophy and considered internal controls of the primary PAIR outcomes, although the variances appeared homogeneous (Levene's test), the non-validated nature of the outcome data once again solicited a non-parametric approach. The analysis applied the general linear model for repeated measures (Kruskal-Wallis test for independent samples or non-parametric one-way ANOVA) to assess how the treatments influenced the follow-up curves. After detecting a significant treatment effect, pairwise post-hoc Šidák multiple comparisons identified the exact time points of divergence of the curves during the follow-

up period. All statistical tests were two-sided with 95% confidence intervals (5% significance level).

## Results

As previously outlined, the prospective exploratory cohort was deliberately limited to 47 postmenopausal women that satisfied the inclusion and exclusion criteria. The mean age of enrolled women was 60.0 ± 4.15 years old (minimum 51, maximum 69 years old). On average, women were slightly overweight (mean body weight, 64.7 ± 6.76 kg); twenty-four were smokers.

Figure 2 illustrates the results of the internal control of consistency: the favorable evolution of the impromptu scores for dyspareunia, vaginal dryness, and vulvovaginal itch/irritation supported the possibility that any favorable PAIR outcome would be robust and authentic.

Regarding PAIR, the primary assessment parameter targeting personal and couple satisfaction, including the impact on sexual function, Table 1 gives an overall view of the end-of-treatment (day 30 after the last PN-HPT®/HA vulvar injection) vs. baseline outcomes for all the thirty-six PAIR items.

The thirty items probing the woman's sexual experience and the day-by-day non-sexual couple relationship showed no change, not even as non-significant trends. Conversely, five of the six PAIR items investigating the woman's sexual function and experience showed significant and highly significant improvements, most impressive for the two items "I am satisfied with our sex life" (1.6 ± 0.50 at baseline vs. 2.3 ± 0.59 at follow-up, $p < 0.01$) and the item "I feel our sexual activity is just routine" (2.4 ± 0.74 at baseline vs. 1.6 ± 0.61 at follow-up, $p < 0.01$). The highly significant improvement (score decreasing) for the item "I 'hold back' my sexual interest because my partner makes me feel uncomfortable" is especially revealing of greater harmony and complicity in the couple's sexual relationship (2.2 ± 0.69 at baseline vs. 1.5 ± 0.62 at follow-up, $p < 0.01$).

Of the six items related to the woman's sexual experience, only "Sexual expression is an essential part of our relationship" showed only a non-significant trend towards improvement (Figure 3); the end-of-treatment vs. baseline outcomes for all other items were significant or even highly significant.

Figure 4 illustrates the improvement in labial and vestibular atrophy between baseline and end of treatment in two representative

| PAIR ITEMS | Baseline mean score | Final mean score |
|---|---|---|
| 1. My partner listens to me when I need someone to talk to. | 2.3 ± 0.65 | 2.3 ± 0.62 |
| 2. We enjoy spending time with other couples. | 2.5 ± 0.75 | 2.6 ± 0.79 |
| 3. I am satisfied with our sex life. | 1.6 ± 0.50 | 2.5 ± 0.59 ** |
| 4. My partner helps me clarify my thoughts. | 2.0 ± 0.68 | 2.2 ± 0.73 |
| 5. We enjoy the same recreational activities. | 2.3 ± 0.78 | 2.6 ± 0.75 |
| 6. My partner has all the qualities I've ever wanted in a mate. | 1.8 ± 0.43 | 2.0 ± 0.66 |
| 7. I can state me feelings without him/her getting defensive. | 1.9 ± 0.61 | 1.9 ± 0.65 |
| 8. We usually "keep to ourselves". | 2.4 ± 0.64 | 2.5 ± 0.65 |
| 9. I feel our sexual activity is just routine. | 2.4 ± 0.74 | 1.6 ± 0.61 ** |
| 10. When it comes to having a serious discussion, it seems that we have little in common. | 1.9 ± 0.73 | 1.7 ± 0.69 |
| 11. I share very few of my partners' interests. | 1.6 ± 0.67 | 1.6 ± 0.68 |
| 12. There are times when I do not feel a great deal of love and affection for my partner. | 1.9 ± 0.70 | 1.7 ± 0.62 |
| 13. I often feel distant from my partner. | 1.7 ± 0.81 | 1.5 ± 0.66 |
| 14. We have very few friends in common. | 1.7 ± 0.75 | 1.7 ± 0.81 |
| 15. I am able to tell my partner when I want sexual intercourse. | 1.6 ± 0.58 | 2.2 ± 0.72 ** |
| 16. I feel "put down" in a serious conversation with my partner. | 1.6 ± 0.68 | 1.5 ± 0.59 |
| 17. We like playing together. | 2.1 ± 0.72 | 2.3 ± 0.73 |
| 18. Every new thing that I have learned about my partner has pleased me. | 1.8 ± 0.59 | 2.0 ± 0.57 |
| 19. My partner can really understand my hurts and joys. | 2.0 ± 0.63 | 2.0 ± 0.66 |
| 20. Having time together with friends is an important part of our shared activities. | 2.6 ± 0.80 | 2.6 ± 0.85 |
| 21. I "hold back" my sexual interest because my partner makes me feel uncomfortable. | 2.2 ± 0.69 | 1.5 ± 0.62 ** |
| 22. I feel it is useless to discuss some things with my partner. | 1.9 ± 0.73 | 2.0 ± 0.75 |
| 23. We enjoy the out-of-doors together. | 2.6 ± 0.77 | 2.7 ± 0.78 |
| 24. My partner and I understand each other completely. | 1.9 ± 0.60 | 2.0 ± 0.63 |
| 25. I feel neglected at times by my partner. | 2.1 ± 0.70 | 1.9 ± 0.71 |
| 26. Many of my partner's closest friends are also my closest friends. | 2.2 ± 0.69 | 2.2 ± 0.69 |
| 27. Sexual expression is an essential part of our relationship. | 1.4 ± 0.61 | 1.7 ± 0.59 (NS) |
| 28. My partner frequently tries to change my ideas. | 1.7 ± 0.74 | 1.6 ± 0.64 |
| 29. We seldom find time to do fun things together. | 1.7± 0.75 | 1.6 ± 0.68 |
| 30. I don't think anyone could possibly be happier than my partner and I when we are with one another. | 2.1 ± 0.66 | 2.2 ± 0.70 |
| 31. I sometimes feel lonely when we're together | 2.1 ± 0.80 | 1.9 ± 0.72 |
| 32. My partner disapproves of some of my friends. | 1.8 ± 0.93 | 1.7 ± 0.90 |
| 33. My partner seems disinterested in sex. | 1.8 ± 0.76 | 1.4 ± 0.58 * |
| 34. We have an endless number of things to talk about. | 2.1 ± 0.80 | 2.2 ± 0.77 |
| 35. I think that we share some of the same interests. | 2.3 ± 0.64 | 2.4 ± 0.58 |
| 36. I have some needs that are not being met by my relationship. | 2.3 ± 0.60 | 2.2 ± 0.55 |

**Table 1.** Overall PAIR items [18]: score changes between pre-treatment baseline and post-treatment follow-up (30 days after the last PN-HPT®/HA vulvar infiltration session). Only the PAIR items investigating the woman's sexual function, evidenced in red (five out of six), showed statistically significant items. * $p < 0.05$; ** $p < 0.01$; NS: not significant

PAI questionnaire: baseline and end-of-treatment scores

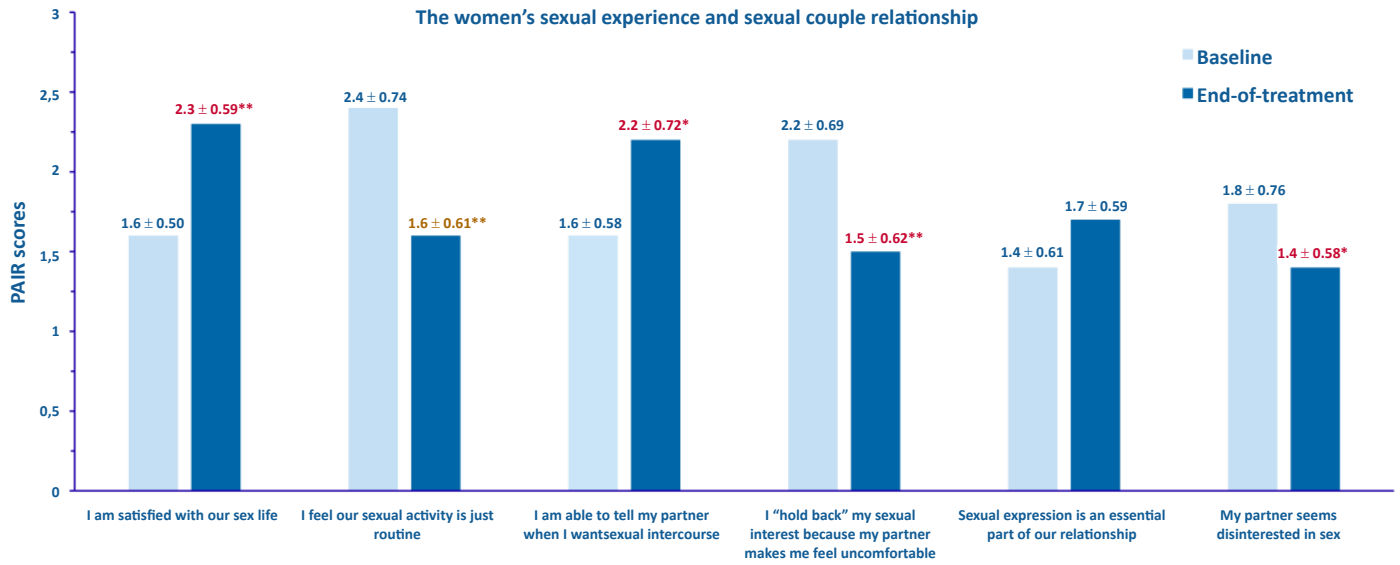


**Figure 3.** Baseline vs. end-of-treatment outcomes (mean scores ± SEM) in the six PAIR items investigating the quality of the woman's sexual experience in terms of individual satisfaction and gratifying intimate relationship with her partner. Improvements: score reductions for the second, fourth and sixth items; score increase for the first, third and fifth items. Significant differences (five items out of six: * p <0.05, ** p <0.01) in red

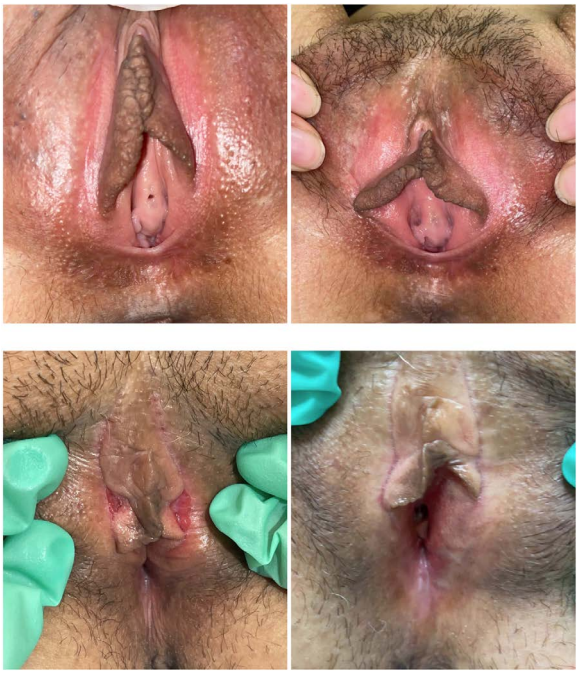

**Figure 4.** Vulvar atrophy in two middle-aged women before the first vulvar rejuvenating session with the PN-HPT®/HA/mannitol combination (photographs on the left) and improvements at the end of the five-session vulvar rejuvenating cycle (photographs on the right)

middle-aged women. Photographs documented an appreciable vulvar atrophy improvement in almost all cohort women.

Some occasional mild burning in six women (12.8%) at the site of vulvar injections was the procedure's only rapidly transient and untroublesome side effect.

## Discussion

All surveys highlight how, in women, emotional dissatisfaction and poor self-esteem intertwine with sexual dysfunction [19]. All misalignment between the sexual needs and desires expressed by the woman and her partner leads to lower satisfaction in the relationship and even affects the non-sexual aspects of the couple's life [20]. Surveys also show that the two partners enjoy less marital happiness in sexually inactive marriages [5]. Unsurprisingly, the peri-and postmenopausal changes mean that about 10 to 15% of middle-aged women report no sexual desire while about 20% of perimenopausal women report more or less frequent dyspareunia; moreover, arousal is always, or almost always, a mirage for about 5% of perimenopausal women [21]. Sexual function disorders and all problems related to the estrogen fall appear

independent of the iatrogenic or spontaneous nature of menopause [22]. Within this framework, the results of this exploratory study, mainly focused on the sexual problems the woman and the couple experience in peri- and post-menopause, deserve attention.

The combination of natural-origin PN-HPT® with HA and mannitol is associated with histochemically demonstrated enhanced fibroblast vitality. The intradermal vulvar injection of the PN-HPT®-based combination, a technically simple and safe procedure, leads to visually evident restructuration of local connectives and correction of genital atrophy, as documented in most cohort women [12,13]. Although preliminary before well-designed investigations, the study outcomes show that a short cycle of intradermal vulvar injections of PN-HPT®/HA/mannitol leads to significant improvements in the unsatisfactory sexual experience of middle-aged women. Avoiding more technically challenging vaginal injections beyond the hymenal ring or expensive procedures with high-technology energy-based devices is a further benefit.

The study can be no more than exploratory due to its liabilities - uncontrolled cohort design, relatively few treated women, easy-to-use but non-validated Likert-like scales for atrophy-related symptoms, including problems related to sexual activity. However, several strong points give solid foundations to the favorable outcomes observed in sexual gratification, the study's main area of interest.

Unlike a previous symptom-focused study with the same combination [14], evaluating the effects of the PN-HPT®/HA combination on menopausal vulvovaginal symptoms was not the primary purpose. The authors resorted to the same five impromptu scales they used in their former study to assess atrophy-related symptoms; however, they intended the scores for vaginal dryness and other symptoms only as an internal consistency tool. The atrophy-related symptoms evaluation only aimed to assess how solid and reliable the principal PAIR sexual function outcomes were. The satisfactory results on atrophy symptoms agreed with the previous 2019 evidence [14] and suggested that the primary focus of interest, the sexual-area outcomes, were indeed robust.

The second strong point of the exploratory study was choosing the PAIR scale, an internationally validated assessment tool, to assess the overall couple's harmony. With one-sixth of the validated PAIR items addressing specifically the woman's sexual experience and the couple's sexual relationship, the PAIR tool was most helpful to substantiate, at least tentatively waiting for more in-depth future studies, the relationship between vulvar rejuvenation and the impact on the sexual function of middle-aged women.

The observed PAIR outcomes are outstanding - five of the six PAIR items devoted to sexuality showed significant and highly significant improvements with no remarkable effect on the thirty PAIR items devoted to the non-sexual aspects of the day-by-day couple relationship.

Regarding the study's weak points, the authors believe its exploratory, hypothesis-building design may justify them and its strong points more than compensate for its acknowledged liabilities.

## Conclusions

Intradermally injected 10 mg/mL PN-HPT® combined in a viscoelastic Class III CE0373 gel medical device with 10 mg/mL HA and mannitol to inhibit the HA degradation is an efficient vulvar rejuvenating formulation. Performing rejuvenating injections limited to the vulvar structures before the hymenal ring simplifies technical difficulties and requires less training. At the same time, vulvar rejuvenation still allows highly significant benefits for sexual function as subjectively perceived by peri- and postmenopausal women and for the couple's sexual harmony and closeness.

## Statements

### Conflicts of interest statement

The authors have been R&D consultants to Mastelli S.r.l., Sanremo, Italy, the PN-HPT® patent holder and producer. However, they have no current conflict of interest related to the study, received no funds, and have no paid or unpaid relation with industry manufacturers, publishers, or other companies related to their research.

### Ethical statement

The authors performed the study in agreement with the Declaration of Helsinki and its modifications over time. All screened and enrolled women could expect no unusual risk other than those associated with routine non-surgical vulvar aesthetic procedures like ambulatory PN-HPT®/hyaluronate infiltrations, an extensively documented aesthetic gynecology procedure in menopausal women. The lack of unexpected risks and the exploratory, hypothesis-generating nature of an observational study carried out under everyday ambulatory practice allowed waiving the need for formal approval by an Ethical Committee. The authors confirm they are accountable for the manuscript's accuracy and integrity, including all clinical interpretations and commentaries, and are responsible for its submission to the journal.

### Authors' contribution statement

The first and principal author sought and got informed consent from all women subjects seeking a vulvar rejuvenation treatment and enrolled in the study. The co-author was responsible for the study design, statistical considerations and analysis, and manuscript writing.

### Funding information

The authors declare that their study was spontaneous and self-financed. The authors also acknowledge that support with any possible article processing charges will be the only funding they agreed to receive (corporate sponsor: Mastelli S.r.l., Sanremo, Italy).

### Data availability statement

The datasets generated during the study are not publicly available. After conversion in an anonymous form, all datasets are available on reasonable request from the principal author, who currently archives all details of participating subjects according to current regulations.

### Photo consent statement

All photographs were taken by and belong to the principal author, who agrees to their submission. The women participating in the study also agreed in writing to the photographs' publication, provided all were made unrecognizable.

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