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ORIGINAL RESEARCH

Mechanically Supporting Uterosacral Ligaments for the Relief of Provoked Vulvodynia: A Randomized Pilot Trial

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Purpose: Provoked vulvodynia (PV) is the most common cause of vulvar pain and dyspareunia. Although its etiology is unknown, it has been associated with musculoskeletal dysfunction. The inability of the lax uterosacral ligaments (USLs) to support the adjoining T11/L2 and S2-4 nerve plexuses is considered to cause PV. This study aimed to determine whether providing mechanical support to the USLs would improve PV.

Patients and Methods: PV patients were randomly divided into two groups. The participants in each group underwent sham manipulation (inserting a wide swab in the vagina without applying pressure) and trial manipulation (supporting the posterior fornix with a wide swab sufficiently broad to mechanically support the USLs). This was a cross-over trial, and the participants alternated between the sham and trial manipulation. Using a 0–10 visual analog pain scale (VAS), PV-associated pain levels experienced by participants were recorded during each manipulation, and the results were compared with baseline levels.

Results: The pain level significantly reduced with USL support compared with the baseline value and the sham manipulation pain level ($P = 0.003$). Pain during sham manipulation was not significantly different from that recorded at baseline. The average reduction in pain with USL support was 18.4% ± 2.2%. The manipulation order did not affect changes in the pain level during trial manipulation ($P = 0.512$).

Conclusion: Applying mechanical support to the posterior fornix temporarily alleviates provoked vulvar pain in some women.

Keywords: vestibulodynia, support structures, referred pain, dyspareunia, vulvar pain, pelvic floor dysfunction

Introduction

Provoked vulvodynia (PV) is a condition of chronic vestibular allodynia with superficial pain, entry dyspareunia, and sexual dysfunction.[1] It significantly reduces patients' quality of life, with a prevalence of approximately 10% in young women.[2] Vulvodynia has no clear identifiable cause;[1] however, a recent consensus recognized that vulvodynia might be associated with several factors.[1]

Neuroproliferation has been associated with PV,[3] as well as musculoskeletal pelvic floor dysfunction, and physical therapy aimed at pelvic floor rehabilitation has been effective.[4] However, the accurate pathogenesis of pelvic floor instability and its association with the development of vulvodynia has not yet been elucidated. We hypothesized that laxity of the uterosacral ligaments (USLs) in pelvic floor disorder in vulvodynia occurring without overt pelvic organ prolapse triggers the

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development of PV. USLs normally support the T10-L1-2 Frankenhauser sympathetic plexus or sacral S2-4 parasympathetic plexus (Figure 1).[5] Loss of USL support of the Frankenhauser plexus has been associated with chronic pelvic pain of unknown origin (CPPU).[5,6] Our hypothesis that PV, like CPPU, may refer to pain from unsupported nerve plexuses was based on our observation of three women with CPPU and vulvodynia who were cured by a posterior sling procedure.[7,8] This was also based on a study of 10 women with PV who were injected with 2 mL of local anesthetic in the USLs at their insertion points to the cervix, which were the determined anatomical sites of the nerve plexuses.[9] PV was completely relieved for 30 minutes. Among these women, the pain disappeared completely on both sides in eight patients; however, in two women, the pain disappeared on one side only.[9]

These findings are interesting because the sensory nerve fibers to the vestibule have been reported to exit from the pudendal nerve, mainly through its perineal branch. The route of this nerve from its origin in S2-4 through the pelvis to the vestibule is not associated with or supported by the USL.[7] Nevertheless, nerve fibers originating from the Frankenhauser plexus terminate at regions very close to the vestibule, clitoris, Bartholin's gland, and distal vagina;[7] therefore, they may be involved in the allodynia and hypersensitivity associated with PV. This pilot study aimed to provide temporary mechanical support to the USLs to further test our hypothesis that the cause of PV is the inability of the lax USLs to support the Frankenhauser and sacral plexuses stimulated by gravity to cause pain.

Patients and Methods

This study was a prospective, single-blind, randomized, controlled pilot trial using a within-participant cross-over design. The study was conducted in accordance with the Declaration of Helsinki. It was approved by the institutional review board of the Galilee Medical Center of the Israeli Health Ministry on July 23, 2017 (authorization number, 0043–17-NHR; ClinicalTrials.gov Identifier, NCT03197337). Written informed consent was obtained from all participants.

Participants were women aged 18–35 years who met Friedrich's first two criteria[10] for vulvar vestibular syndrome (referred to as PV in this study): severe pain in the vulvar vestibule on touch or attempted vaginal entry and tenderness to pressure (ie, with a Q-tip applicator) localized within the vulvar vestibule. The pain was assessed using a 0–10 visual analog scale (VAS). This age group (18–35 years) typically consists of almost all

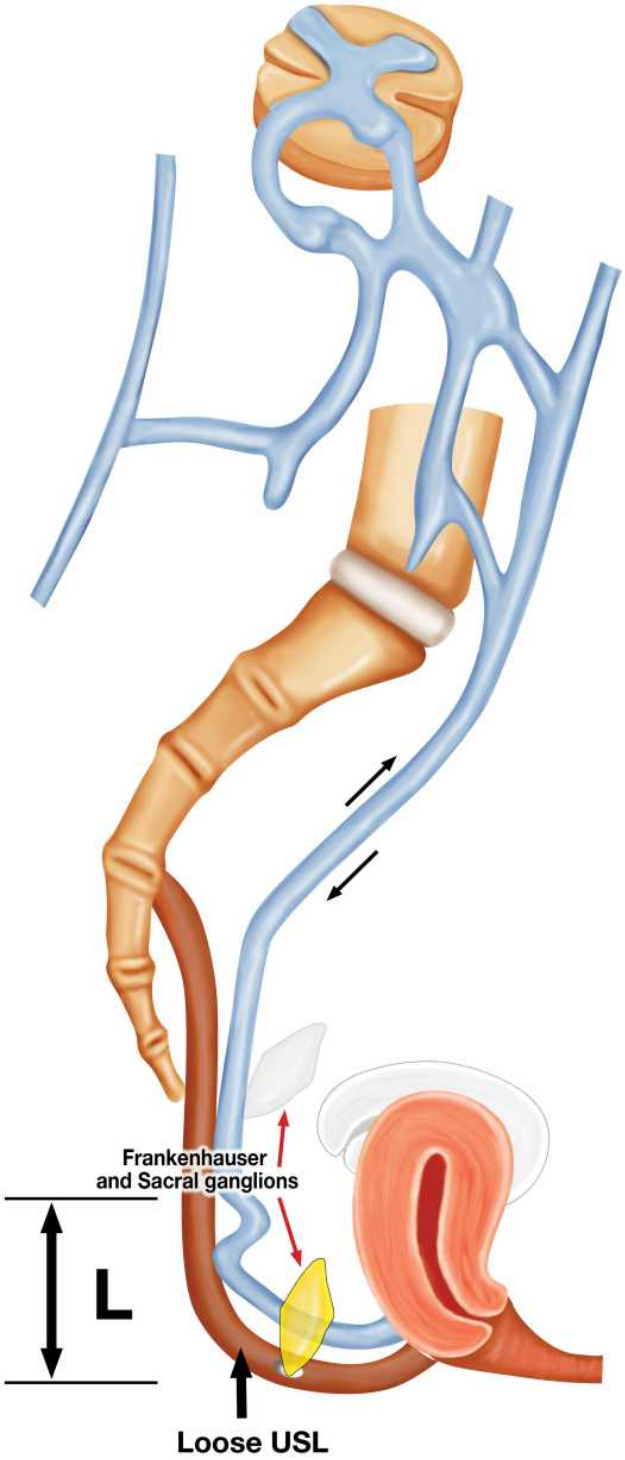

Figure 1 The ganglia of the Frankenhauser and sacral plexuses are supported by uterosacral ligaments (USLs) at their uterine end. The nerves may be stimulated by gravity or by pelvic organ prolapse, which can be perceived as pain by the cortex. Supporting ligament laxity with a wide swab tensions the USLs sufficiently to support the nerve plexuses, thereby relieving vulvodynia pain.
Abbreviation: L, ligament laxity.

those with PV. We included only women diagnosed with either moderate or severe PV (able to have sexual intercourse but with immense pain or unable to have sexual intercourse at all),[11] because women with mild PV experienced spontaneous remissions. In addition, the moderate and severe PVs present more difficult conditions and harder to heal. Patients were excluded if they had vulvar pain caused by a specific disorder (such as that defined by the 2015 consensus terminology),[1] had been diagnosed with generalized vulvodynia, had been previously treated surgically for vulvodynia, had an acute genital infection or inflammation during the trial period or recovered from such an episode within 14 days, had pelvic pain or sensitivity on bimanual examination, had been diagnosed with pelvic organ prolapse of any degree, had any significant medical condition, or had a history of abnormal cervix cytology.

A total of 20 participants were enrolled (Figure 2). Each patient was examined by the same vulvar disease specialist who ruled out other causes of dyspareunia and verified the diagnosis of PV using the Q-tip test and Friedrich's criteria[10] (extreme pain elicited by applying light pressure with a cotton swab on seven fixed points at the introitus).

During this test, patients were asked to rank their pain intensity on the VAS from 0 to 10 (0, experiencing no pain; 10, experiencing maximum pain) to document their baseline pain level.[12]

Subsequently, all patients underwent trial manipulation, which involved applying pressure with a swab stick

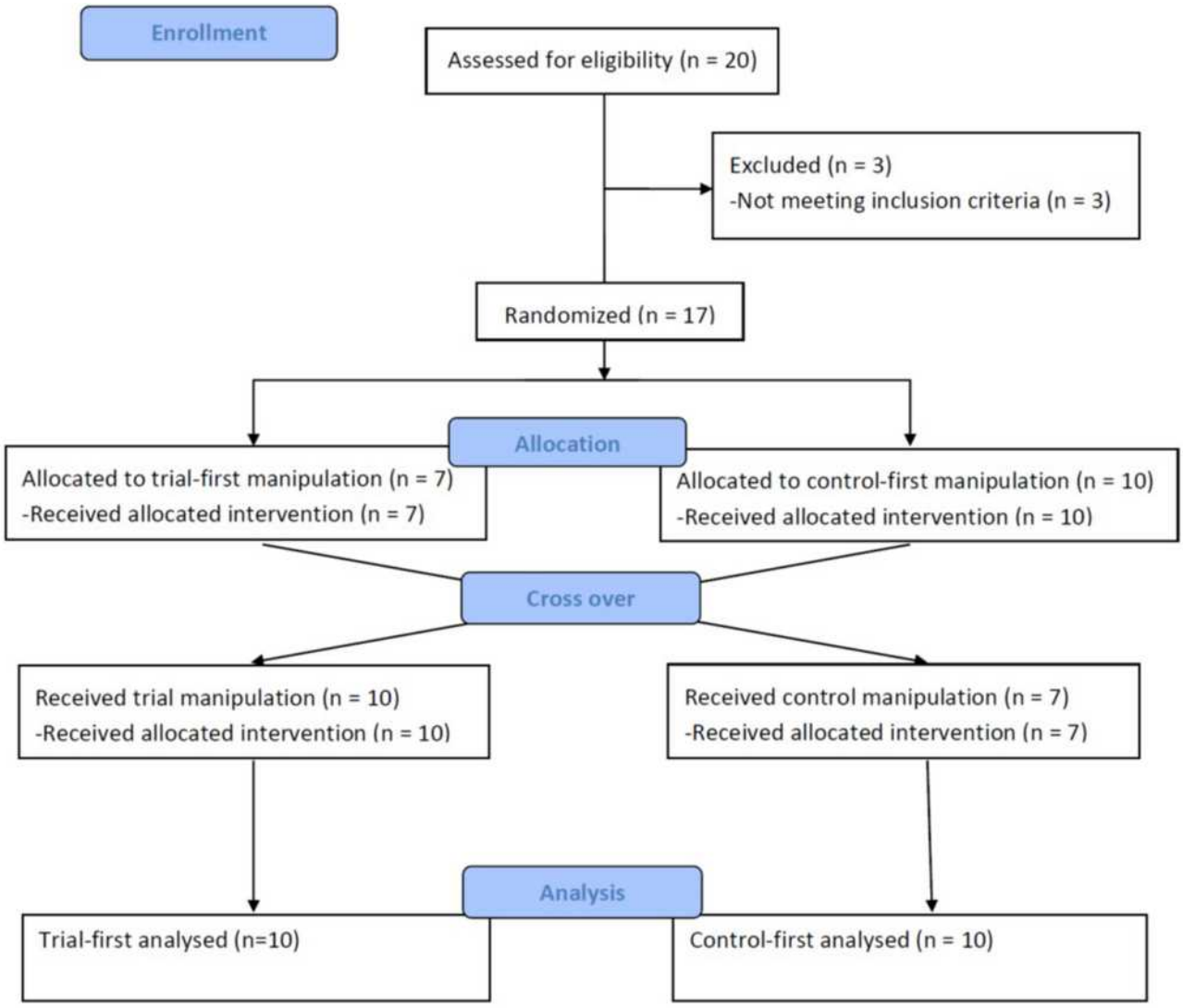

Figure 2 Study flow diagram.

sufficiently wide to stretch the posterior fornix without overstretching it, thereby temporarily providing support to the USL. To identify the posterior fornix, a lubricated narrow speculum was used, and a swab sufficiently wide to support the USLs was inserted through it (Figure 3). After placing the wide swab stick in the posterior fornix, the speculum was immediately removed, leaving the wide swab in its place for 1 minute (Figure 4). Then, after a "wash out" period of 2 minutes, we crossed over to perform sham manipulation (insertion of the device to the posterior fornix without applying pressure). Every patient received both sham and trial manipulation.

During each manipulation, while the wide swab stick was in the posterior fornix, the Q-tip test was re-performed (Figure 5), and patients were again asked to rank their vestibular foci pain intensity.

To determine whether the results were affected by the manipulation order, participants were computer-randomized into two groups before manipulation. The participants in the first group (trial-first group) underwent trial manipulation first, followed by sham manipulation, whereas those in the second group (sham-first group) underwent sham manipulation first, followed by trial manipulation.

Sample Size Calculation and Statistical Methods

After collecting all data, the average pain intensity levels during the different scenarios were calculated for each group. We used a Wilcoxon rank-sum test to determine whether the manipulation order affected the differences in pain intensity compared with the baseline pain level. The average pain levels under the different conditions were determined using a paired sample *t*-test for the following pairs: baseline pain level and trial manipulation pain level

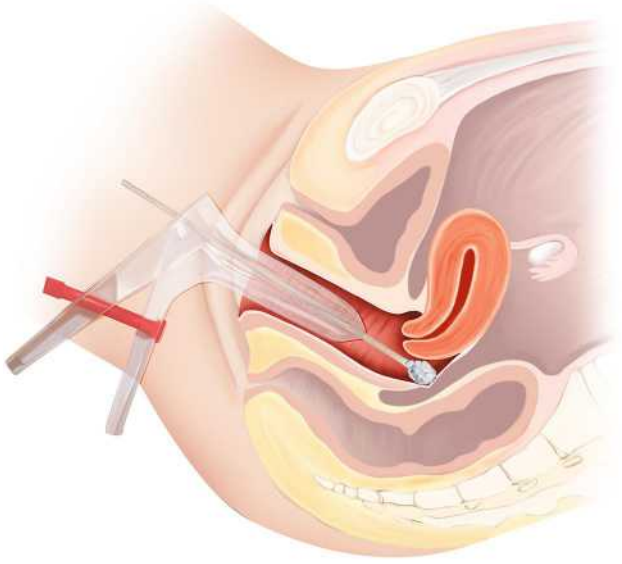

Figure 3 A lubricated narrow speculum was used to identify the posterior fornix, and a wide swab stick was inserted through it.

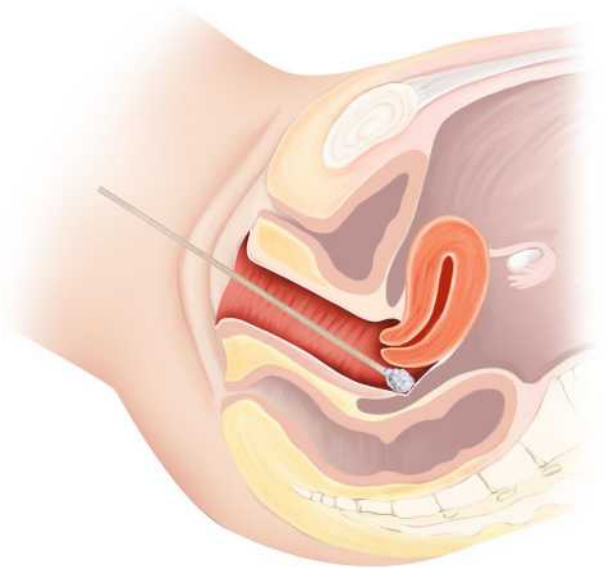

Figure 4 The speculum was removed, and the wide swab stick was left in the posterior fornix. During trial manipulation, the examiner applied pressure with a swab sufficiently wide to support the posterior fornix, thereby temporarily providing support to the uterosacral ligaments. During sham manipulation, the examiner inserted the wide swab stick to the posterior fornix without touching it.

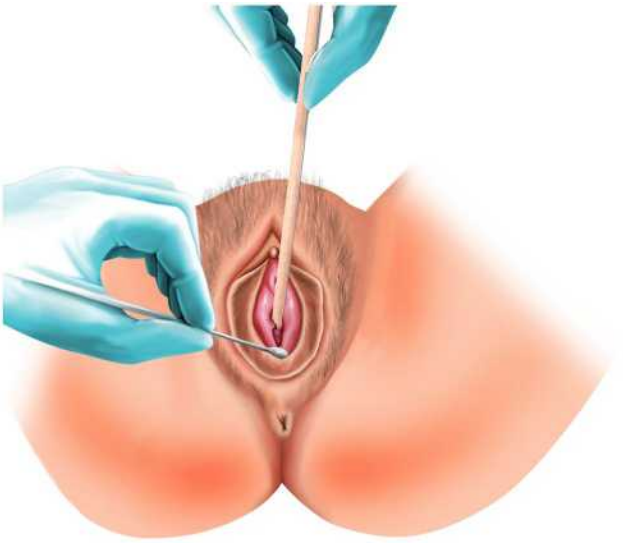

Figure 5 With the wide swab stick in the posterior fornix, the Q-tip test for diagnosing provoked vulvodynia was performed by applying light pressure with a wet Q-tip applicator on seven vestibular foci corresponding with the 1, 3, 5, 6, 7, 9, and 11 o'clock positions. Subjective elicited pain was recorded using a numeric rating scale of 0 to 10.

(baseline-trial); baseline pain level and sham manipulation pain level (baseline-sham); and trial manipulation pain level and sham manipulation pain level (trial-sham).

Because of multiple comparisons, we applied the Bonferroni correction. Statistical significance was set at 1.67% ($\alpha = 0.0167$). We expected significant differences to result from the baseline-trial and trial-control comparisons and no difference resulting from the baseline-control comparison. A difference between the two conditions was viewed as clinically significant if it reflected a change of at least 30% in the pain level. Fifteen patients were required for this crossover study. All calculations were performed using IBM SPSS Statistics, version 25.

Results

Women were enrolled at the colposcopy clinic between August 1, 2017 and January 30, 2018. Of the 20 patients who agreed to participate in the study, three did not meet the inclusion criteria. There were no differences in the background variables (Table 1) or baseline pain levels (6.7±2.2 units versus 6.4±3.0 units, respectively; two-tailed Wilcoxon rank test, p = 0.686; data not tabulated) between the sham-first group and the trial-first group. We used Cronbach's alpha test to confirm the statistical validity of calculating the average pain intensity from the various foci under each condition (Table 2). Then, we tested whether the manipulation order affected the difference between the baseline pain level and the trial manipulation pain level. For the seven women in the trial-first group, the average change in pain intensity was 0.86. Whereas, for the 10 women in the sham-first group, the average change was 1.5 (P < 0.512). Therefore, the manipulation order did not have a significant effect on the change in pain levels. Following these results, data from all participants were gathered in one group. Then, we compared the average pain levels (Table 3) and showed that posterior fornix pressure led to a significant decrease in the average pain level elicited in the vestibular Q-tip test compared with the sham manipulation pain level and baseline pain level (decreases of 1.12 and 1.13 units in pain intensity, respectively; P = 0.003). No significant difference was observed between the average baseline

Table 1 Background Variables

	Trial First n=7	Sham First n=10	P (Two-Sided)
Age (years)			
Average±SD	24.14±4.0	26.2±5.7	0.583*
Median (range)	25 (18–29)	25 (20–35)	
Age at the first menstrual period (years)			
Average±SD	13.3±0.8	12±1.6	0.112*
Median (range)	13 (12–14)	12 (9–14)	
Use of oral contraception			
N (%)	5 (71.4%)	5 (50%)	0.622**
Smoking			
N (%)	1 (14.3%)	1 (10%)	1.0**
PV, N (%)			
Primary	4 (57.1%)	2 (20%)	0.162**
Secondary	3 (42.9%)	8 (80%)	
Symptom severity N (%)			
Moderate	2 (29%)	5 (50%)	0.434**
Severe	5 (71%)	5 (50%)	

Note: *Wilcoxon rank-sum test. **Fisher's exact test.
Abbreviations: PV, provoked vulvodynia; SD, standard deviation.

Table 2 Average Pain Level Experienced at Different Foci (n = 17)

	1	3	5	6	7	9	11	Cronbach's Alpha
Basal level (units)								
Average	5.2	6.4	7.9	6.1	7.9	6.9	5.4	0.88
Sham manipulation (units)								
Average	5.2	6.4	7.9	6.1	7.9	6.9	5.4	0.87
Trial manipulation (units)								
Average	4.1	5	6.9	5.3	7.2	5.6	3.9	0.89

Table 3 Differences in Pain Levels Under Different Conditions Across All Subjects

	n = 17	P (Two-Sided) *
Difference between trial manipulation and basal pain level (units), average±SD	1.13±1.34	0.003
Difference between trial manipulation and sham manipulation, average±SD	1.12±1.34	0.003
Difference between sham manipulation and basal pain level, average±SD	0.01±0.04	0.332

Note: *Paired-samples *t*-test.
Abbreviation: SD, standard deviation.

Table 4 Overall Decrease in Pain Level with Trial Manipulation

	All Subjects (n=17)	Subjects with Any Decrease in Pain Level (n=11)	Subjects with a Clinically Significant Decrease in Pain Level[§] (n=5)	Subjects Reporting no Decrease in Pain Level (n=6)
Decrease in pain level (%)				
Average±SD	18.4%±2.2%	28.4%±2.2%	48.5%±16.7%	0%
Median (range)	12.5% (0–78%)	16.7% (6–78%)	42.9% (36–78%)	0%

Notes: [§]A clinically significant decrease in pain level was defined as a difference of at least 30% in the average pain level of the trial manipulation pain level compared to the baseline pain level.

pain level and the sham manipulation pain level (P = 0.332), as anticipated. However, the overall decrease in the average pain level during trial manipulation was 18.4% ± 2.2%, which was below the 30% threshold that we considered clinically significant (Table 4). Further examinations of the data revealed that the decrease in the average pain level ranged between 0% and 78%, indicating that there was at least one participant who experienced no influence of trial manipulation and some participants who experienced significant influence. Then, we calculated the overall decrease in the average pain level for the 11 patients who reported any improvement during trial manipulation, resulting in an average change of 28.4% ± 2.2%. Five patients experienced more than 30% improvement in their pain level.

Discussion

By mechanically supporting the USL, we were able to temporarily alleviate provoked vulvar pain in some women. These results support our hypothesis and possibly create a new field in the study of PV.

During trial manipulation for USL support, patients reported a significant reduction in pain intensity compared with their baseline pain level. The wide swab probably sufficiently supported the USL to restore its ability to mechanically support the nerve plexuses, thereby relieving the pain (Figure 1).

Although the improvement with USL mechanical support was impressive, several patients described no improvement in their pain level. These findings are in accordance with the current consensus, suggesting that vulvodynia is associated with different contributing factors.[1]

In line with this consensus, it is reasonable to suggest that the participants who reported pain alleviation experienced USL laxity-associated PV.

Our hypothesis was based not only on our previous experimental studies[8,9] but also on a general hypothesis of CPPU caused by weakened USLs,[6] with CPPU found to be curable either by USL plication[11] or by a posterior sling during a randomized trial involving 1420 women.[13] The same concept of the role of the USLs was first published in a German study in 1938 by one of the most famous German gynecologists of the twentieth century, Heinrich Martius.[14] Martius revealed that in 30% of cases, backaches and pelvic pain were provoked by damage to the paired "ligamenta sacro-uterina" (USL) and that the Frankenhauser and sacral ganglia were involved in causing chronic pelvic pain because of the inability of weakened USLs to support them.[14]

The mechanism by which strengthening the USLs in women without overt pelvic organ prolapse alleviates vestibular sensitivity is consistent with that previously proposed (Figure 1). [5,6,8,9,14] Lax USLs cannot mechanically support the nerve plexuses. Furthermore, vulvodynia may be only one phenotype of T10-L2 and S2-4 referred nerve pain. Nevertheless, it remains unknown why some patients did not experience pain relief from USL mechanical support with a swab. A method that provides broader support to include both USLs (such as the lower blade of a bivalve speculum) may, in fact, alleviate pain in more women.[14] This was not an option during our study, however, because the handle of the speculum covered the vestibule and prevented Q-tip testing, the device had to be sufficiently narrow to be inserted through the allodynic vulvar vestibule.

Our method of USL support may further support an already established associated factor of PV, namely, musculoskeletal dysfunction, such as pelvic muscle overactivity, myofascial changes, and biomechanical changes.[1,4] It has been repeatedly shown that physical therapy is helpful for improving some cases of PV.[4] Musculoskeletal

dysfunction of the pelvic muscles can be caused by USL laxity. It has been demonstrated by videos, radiography, myogram, and electromyography[15,16] that three oppositely acting directional forces, namely, forces in the forward, backward, and downward directions, act against pubourethral ligaments anteriorly and USLs posteriorly to control bladder continence and evacuation. These forces are equally balanced in the region of the bladder neck.[17] If USLs are loose, then the posterior forces weaken, and the system becomes unbalanced; the forward force (the anterior portion of pubococcygeus muscles) overcompensates by contracting harder to the extent that it can narrow the urethra.[17] These are the "overactive" muscles addressed by physical therapy.[4] These findings[17,18] adequately explain the link between our hypothesis and pelvic muscle dysfunction.[1,4] USL laxity has also been shown to be associated with painful bladder syndrome, previously known as interstitial cystitis.[19] Injection of 1% xylocaine into the USLs resulted in the immediate, significant disappearance of the abdominal, urethral, introital, and cervical tenderness and pain demonstrated prior.[19] Furthermore, USL laxity may also be associated with generalized vulvodynia or chronic pelvic pain syndrome.

The strength of this study was that it explored the background etiology of an enigmatous condition. Conversely, this study was limited by the small number of patients who agreed to participate in this study. We have planned to start a larger trial with more participants.

We propose that our procedure of mechanically supporting the USLs with a wide swab be used as a readily available clinical test for the existence of USL laxity, not only for patients with vulvodynia but also for those with chronic pelvic pain of unknown origin.[14] However, this association requires further examination.

Conclusions

Our findings from this randomized, controlled pilot trial support the hypothesis that USL laxity causes pelvic floor dysfunction leading to PV. These results encourage further studies because of their potential therapeutic implications.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. It was approved by the institutional review board of the Galilee Medical Center of the Israeli Health Ministry on July 23, 2017 (authorization number, 0043-17-NHR; ClinicalTrials.gov Identifier, NCT03197337). Written informed consent was obtained from all participants.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare.

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