Rivista Italiana di Colon-Proctologia Founded in 1982

PELVIPERINEOLOGY

A Multidisciplinary Pelvic Floor Journal

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2020
Volume: 39
Issue: 3
September

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ISSN: 1973-4905 E-ISSN: 1973-4913

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Quarterly journal of scientific information registered at the Tribunale di Padova, Italy n. 741 dated 23-10-1982 and 26-05-2004 Editorial Director: Giuseppe Dodi. The journal is property of the International Society for Pelviperineology

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25
Fax: +90 (212) 621 99 27
E-mail: info@galenos.com.tr/ yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printer: "Centro Copie" Via Cavallotti 383 Chioggia (Ve)
E-mail: centrocopie.rb@libero.it
Printing Date: September 2020
ISSN: 1973-4905 E-ISSN: 1973-4913

International scientific journal published quarterly.

Official Journal of the: International Society for Pelviperineology (www.pelviperineology.com)
Associaciòn LatinoAmericana de Piso Pelvico
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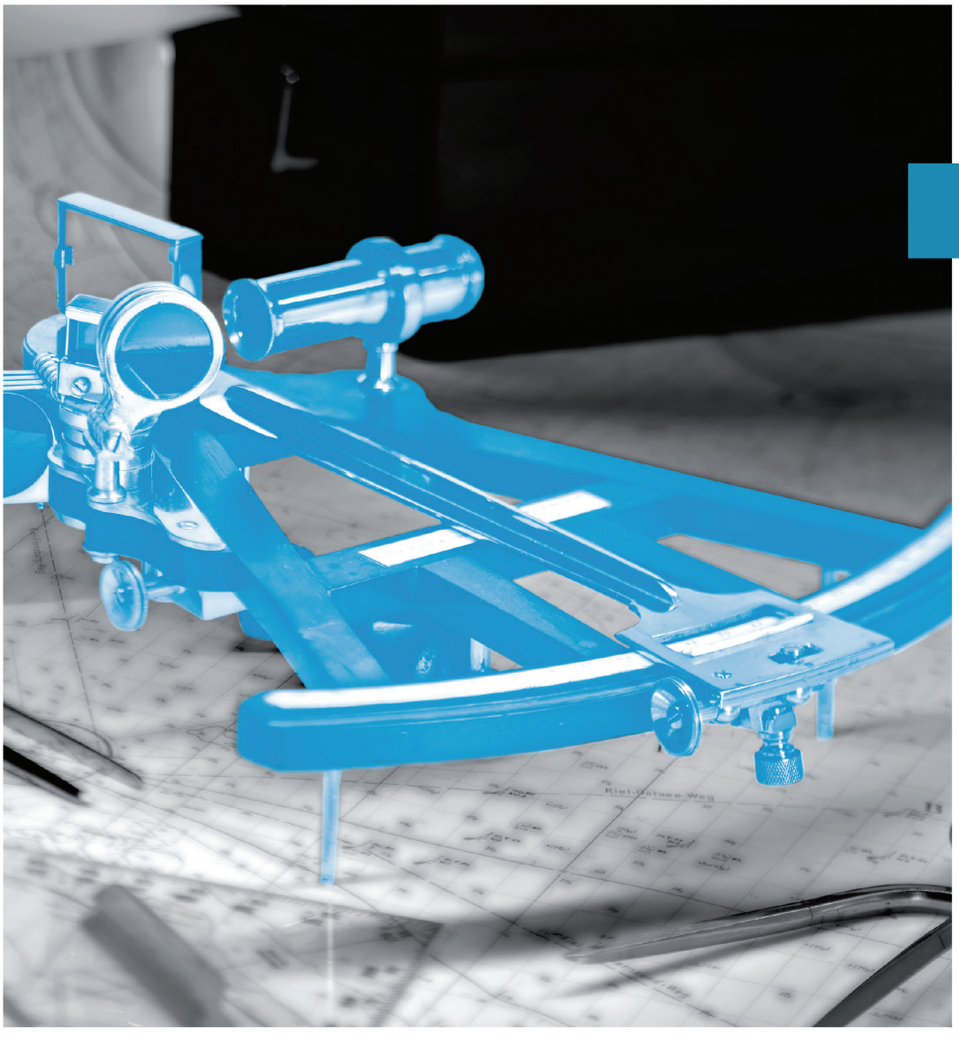

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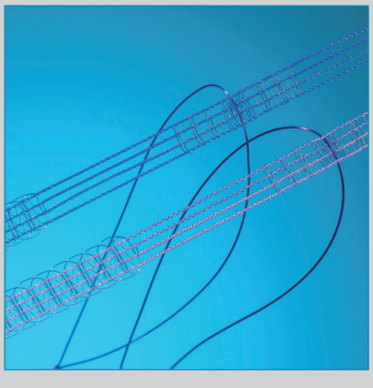

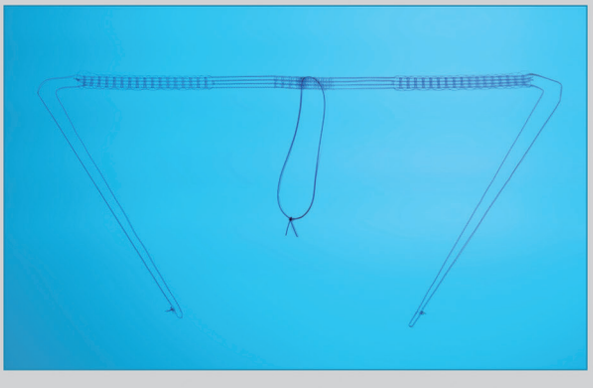

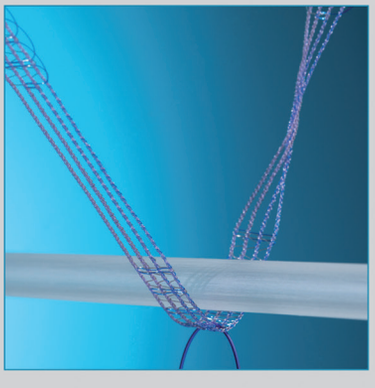

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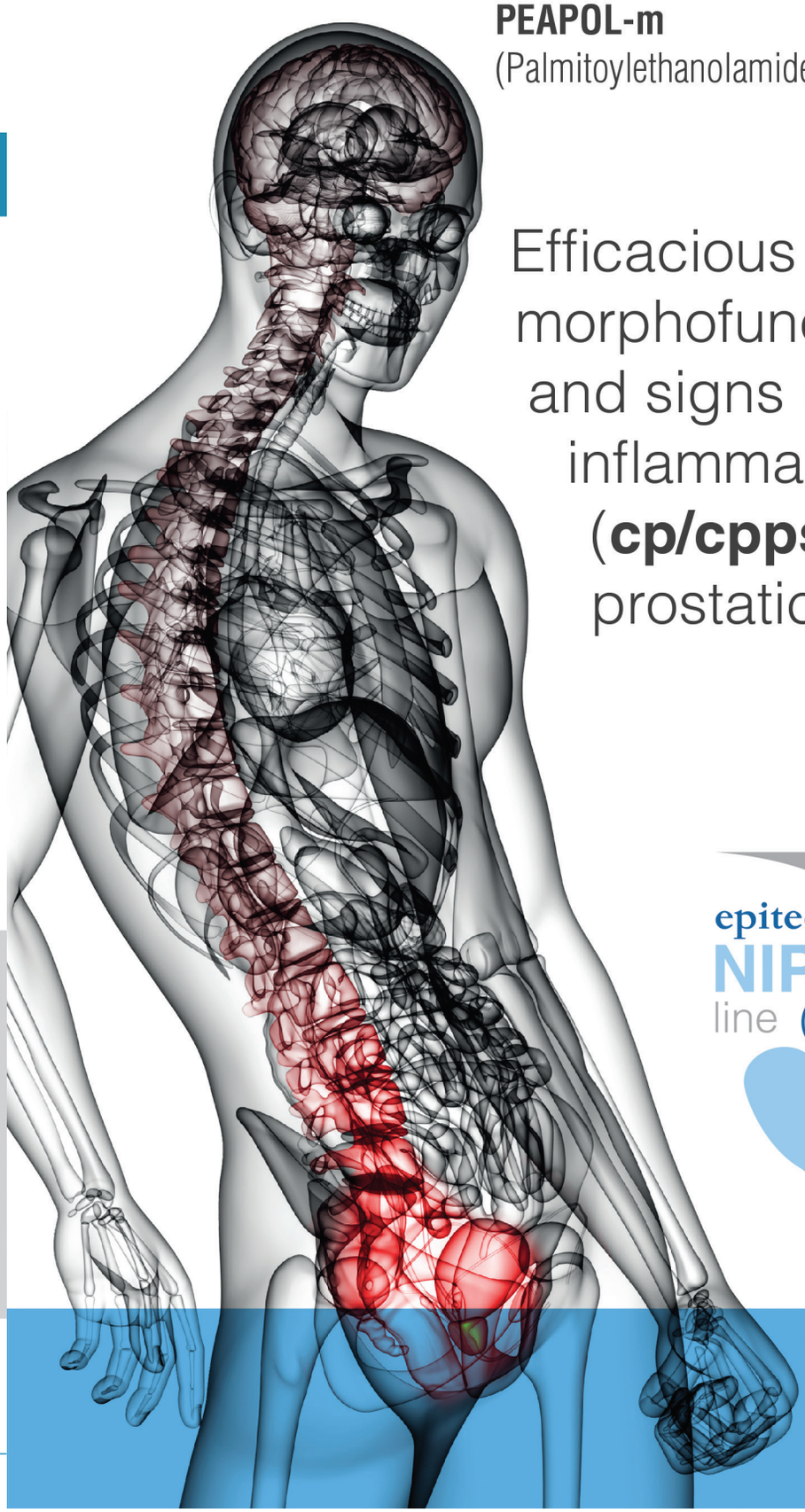

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REVIEW

DOI: 10.34057/PPj.2020.39.03.001
Pelviperineology 2020;39(3):68-76

Provoked vulvodynia: A peripheral neurological pain syndrome

JACOB BORNSTEIN[1], EILAM PALZUR[2]

[1]Department of Obstetrics and Gynaecology, Galilee Medical Center and Azrieli Faculty of Medicine, Bar-Ilan University, Nahariya, Israel
[2]The Research Institute of Galilee Medical Center and Azrieli Faculty of Medicine, Bar-Ilan University, Nahariya, Israel

ABSTRACT

The main cause of vulvar pain and dyspareunia is provoked vulvodynia (PV), also known as vestibulodynia, and formerly termed "vulvar vestibulitis". It affects 8-10% of women of all ages. Although the etiology remains an enigma, peripheral neurologic mechanism has recently been identified as a factor associated with vulvodynia. The aim of the present review is to present and discuss neuroproliferation as a main cause of PV.

Studies comparing Immunohistochemical staining of specimens from women with PV to controls, and animal models of PV, have been analysed for evidence of inflammation and neuroproliferation.

The density of nerve fibres in the vestibular stroma of women with PV was 10 times greater than that in the vestibular stroma of non-affected women controls. Moreover, the fibres penetrated the basal membrane and continued vertically, reaching close to the surface of the epithelial surface. An increase in the number of stromal mast cells has also been demonstrated in women with PV. Heparanase, discharged from mast cells, degrades the connective tissue and epithelial basement membrane, allowing the proliferating nerve fibres to penetrate the degraded epithelial basement membrane into the epithelium. This intraepithelial hyperinnervation results in local hyperesthesia characteristic of PV. In a mouse model a significant increase has been depicted in the density of nerve fibres in 40% of the mice repeatedly infected with fungal antigen. An increase in mast cells number has been depicted in a mouse model as well.

A peripheral neurologic mechanism leading to neuroproliferation has been recognised in women with PV and animal models. Future research should consider this pathogenesis.

Keywords: Provoked vulvodynia; neuroproliferation; hyperinnervation; mast cell; heparanase; vestibulectomy

INTRODUCTION

Provoked vulvodynia (PV), also called "vestibulodynia" and formerly termed "vulvar vestibulitis", is the primary cause of vulvar pain and dyspareunia.[1] It affects 8-10% of women of all ages and significantly impairs their quality of life. Its most recognizable symptom is dyspareunia, and it is characterized by extreme symmetric sensitivity at the vestibule, close to the hymenal base. This concealed location of sensitivity has made diagnosis difficult and has led to myths regarding the development of PV, involving hurtful statements like "it is all in your head." Recent research has proven that the pain arises from local, organic, and vestibular sensitivity. Approximately 50% women with PV experience sensitivity only in the posterior half of the vestibule.[2] The others have both anterior and posterior allodynia.

The data provided in Table 1 indicate that idiopathic vulvar pain and vulvodynia have been recognized since the first century

Address for Correspondence: Jacob Bornstein, Department of Obstetrics and Gynaecology, Galilee Medical Center and Azrieli Faculty of Medicine, Bar-Ilan University, Nahariya, Israel **E-mail:** mdjacob@gmail.com **ORCID ID:** orcid.org/0000-0003-1932-5270
Received: 20 July 2020 **Accepted:** 26 July 2020

AD. However, between 1928 and 1976, this syndrome was not reported in the medical literature, possibly due to ignorance owing to failure in curing vulvar pain and vulvodynia. Various treatments have been attempted for PV, but so far, the effective treatment is vestibulectomy, a surgical removal of the vestibule.

Although progress in the diagnosis and treatment of PV has been made,[1,2] the etiology remains unknown. Nevertheless, a breakthrough in understanding the pathogenesis of vulvodynia was achieved with the introduction of a list of evidence-based factors associated with vulvodynia in the 2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia (Table 2).[3] Peripheral neurologic mechanism is a remarkable factor associated with vulvodynia;[1,3] however, the trigger for this mechanism remains unknown. One hypothesis is that laxity of the uterosacral ligaments causes loss of support to the Frankenhauser's plexus, initiating the development of the pain of PV.[4] The present review discusses this peripheral neurologic mechanism as a cause of PV.

Table 1. Idiopathic vulvar pain: Historic terminologies*

Period, author	Term or terminology
First Century AD, Soranus	Satyriasis in females
1880, Thomas	Excessive hypersensibility of the nerves
1889, Kellogg	Sensitive points
1889, Skene	Super-sensitiveness of the vulva
1928, Kelly	Exquisitely sensitive in hymeneal ring
1976, Weisfogel	The burning vulva
1976, ISSVD	The burning vulva syndrome
1978, Dodson and Friedrich	Psychosomatic vulvovaginitis
1978, Tovell and Young	Vulvodynia or pudendagra
1983, ISSVD task force	Vulvodynia or burning vulva syndrome
1983, Friedrich	Vestibular adenitis
1983, Woodruff and Parmley	Infection of the minor vestibular glands
1986, Peckham	Focal vulvitis
1987, Friedrich	Vulvar vestibulitis syndrome
1988, McKay	Classification: Vestibulitis and dysesthetic vulvodynia
1997, Bornstein	Vestibulodynia
1999, ISSVD	Terminology: Generalized and localized vulvar dysesthesia
2001, ISSVD	Terminology: Provoked and spontaneous vulvar dysesthesia, each with subsets of generalized and localized
2003, ISSVD	2003 ISSVD terminology
2015, ISSVD, IPPS, ISSWSH	2015 consensus terminology

ISSVD: International Society for the Study of Vulvovaginal Disease, IPPS: International Pelvic Pain Society, ISSWSH: International Society for the Study of Women's Sexual Health

Peripheral neurologic findings in women with provoked vulvodynia

As shown in Table 3, several studies have reported on hyperinnervation and nerve sprouting in the stroma of the vestibule of women with PV.[5-15] The proliferating nerve fibres were reportedly nociceptors.[16] Further, increased vanilloid receptor VR1 (TRPV1) density caused an increase in allodynia.[17] To obtain accurate and objective quantitative data regarding hyperinnervation, we applied computerized histomorphometry to images of immunohistochemically stained sections from women with PV and controls; when the immunohistochemical S100 stain was used, the density of nerve fibres in the vestibular stroma of women with PV was 10 times greater than that in the vestibular stroma of controls.[8] Moreover, these nerve fibres showed collateral sprouting that resembled nerve-ending trauma, which develops in women with chronic inflammation or major trauma such as amputation.

We have also proposed an objective histopathological criterion for establishing PV diagnosis: the total calculated area of nerve fibres (per the same microscopic field) is 10 times higher in women with PV than in controls.[8] Although tissue analysis is not currently required for PV diagnosis, a morphological diagnosis may be useful for research purposes.

In another study, to further characterize PV hyperinnervation, we stained the tissue excised during vestibulectomy of women with

Table 2. Potential factors associated with Vulvodynia as per the 2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia

• Comorbidities and other pain syndromes (e.g., painful bladder syndrome, fibromyalgia, irritable bowel syndrome, and temporomandibular disorder [level of evidence, 2)
• Genetics [level of evidence, 2]
• Hormonal factors (e.g., pharmacologically induced) [level of evidence, 2]
• Inflammation [level of evidence, 2]
• Musculoskeletal (e.g., pelvic muscle overactivity, myofascial, and biomechanical) [level of evidence, 2]
• Neurologic mechanisms:
o Central (spinal and brain-related) [level of evidence, 2]
o Peripheral neuroproliferation [level of evidence, 2]
• Psychosocial factors (e.g., mood, interpersonal, coping roles, and sexual function) [level of evidence, 2]
• Structural defects (e.g., perineal descent) [level of evidence, 3]
*The factors are listed as per alphabetical order.

severe PV using protein gene product (PGP) 9.5.[10] PGP 9.5 detects the thinnest unmyelinated sensory C fibres (<1 mm thick). We demonstrated that in women with PV, the innervation not only occurred in the stroma (Figure 1a) but also penetrated the basal membrane and continued vertically for >50% of the distance to the epithelial surface (Figure 1b), almost reaching the epithelial surface. Very thin intraepithelial nerve fibres ending within the basal layers of the epithelium were also detected. Parallel sections incubated with only secondary antiserum were not stained. Control tissues showed no intraepithelial innervation. As such, in addition to the increased density of nociceptors, the nociceptors were located much closer to the mucosal surface. This combination can explain the severe allodynia experienced by women with PV.

Women with primary PV (identified at their first attempt at intercourse or physical contact) reportedly have a higher degree of neuroproliferation than those with secondary PV.[11] In such cases, the hyperinnervation may be congenital. In another study

Table 3. Studies documenting nerve fibre proliferation in provoked vulvodynia

Authors	Number of patients	Number of controls	Type of study	NFP* in patients	NFP* in controls	p value
Weström and Willén[5]	47	6	Descriptive	44	0	<0.05
Bohm-Starke et al.[6]	13	8	Prospective	5.65[a]	1.125[a]	<0.001
Tympanidis et al.[7]	12	8	Prospective, case-control	32.9±18.5[b]	13.0±9.2[b]	0.0015
Bornstein et al.[8]	40	7	Retrospective (S100 staining)	4190 µm^2	425 µm^2	0.01
Halperin et al.[9]	24	16	Case-control	19±79.1[c]	0[c]	<0.0001
Bornstein et al.[10]	7	7	Retrospective (PGP 9.5 staining)	Intraepithelial 2.0±0	0.71±0.488	0.001[d]
				Stroma 2.0±0	0.14±0.378	0.001[d]
Goetsch et al.[11]	10 primary	4	Neural hyperplasia	Primary 8	All negative	0.01
	10 secondary			Secondary 3	4	
Leclair et al.[12]	42 primary	-	Retrospective neural hyperplasia (0-3)	Primary ~2.5 mean (0-3)	Secondary ~2.0 mean (0-3)	OR=3.01 p=0.02
	46 secondary					
Brokenshire et al.[13]	23 early responders	27 late responders	Case-control	16.4 (0-40)/mm^2 (early responders)	16.4 (0-52)/mm^2 (late responders)	NS (only patients)
Liao et al.[14]	10	7	Case-control (PGP 9.5 staining)	Tender 167%[e]	Control 100%	0.021
				Tender 169%	Non-tender 100%	0.027
	5	5	Case-control (TRPV4 axon density)	Tender 139%	Control 100%	0.011
				Tender 115%	Non-tender 100%	0.002
Tommola et al.[15]	27	15	Case-control (PGP 9.5 staining)	6.3 (0.0-15.8)/mm	2.0 (0.0-12.0)/mm	0.006
			Case-control (NF2F11 staining)	63.0%	0.0%	-

NFP: Nerve fibre proliferation, PGP: Protein gene product, OR: Odds ratio, NS: Not significant, TRPV4: Transient receptor potential vanilloid-4, NF2411: Neuron specific neurofilament, SD: Standard deviation
[a]Values are expressed as mean number of nerve fibres per section.
[b]Values are expressed as mean ± SD. Area is expressed as µm2 of immunostaining.
[c]Values are expressed as mean ± SD, calculated per 10 high power fields (HPFs). Nerve fibre area was an independent variable significantly associated with provoked vulvodynia.
[d]Semi-quantification, 0-3; result in mean ± SD.
[e]Values are expressed in percentage increase of nerve fibre number

involving 10 women with PV, sensitive areas contained increased numbers of mechanoreceptive nociceptor axons relative to nontender foci and to that in 7 controls.[14] The sensitive areas also contained increased T-cell, macrophage, and B-cell numbers. Local renin-angiotensin system protein levels were increased because more T-cells and B-cells expressed angiotensinogen. In another study, the hyperinnervation was more pronounced in foci with marked B-cell but not T-cell infiltration.[15]

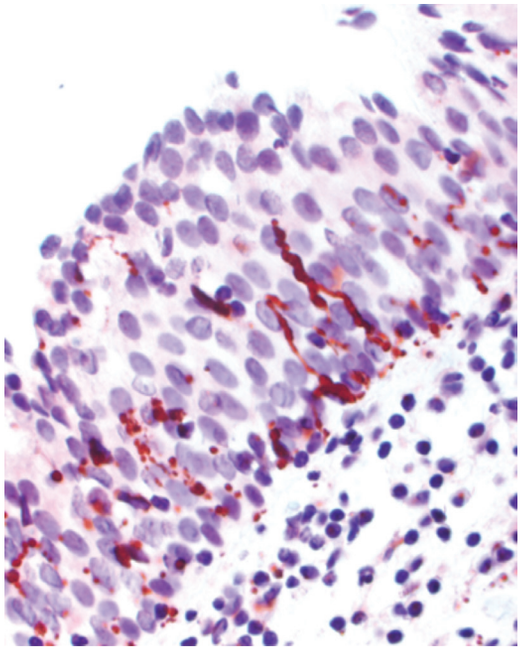

Figure 1a. PGP 9.5 stain in a tissue specimen from a woman with provoked vulvodynia showing nerve fibres intruding into the epithelium to >50% of its depth. Magnification: ×400
PGP: Protein gene product

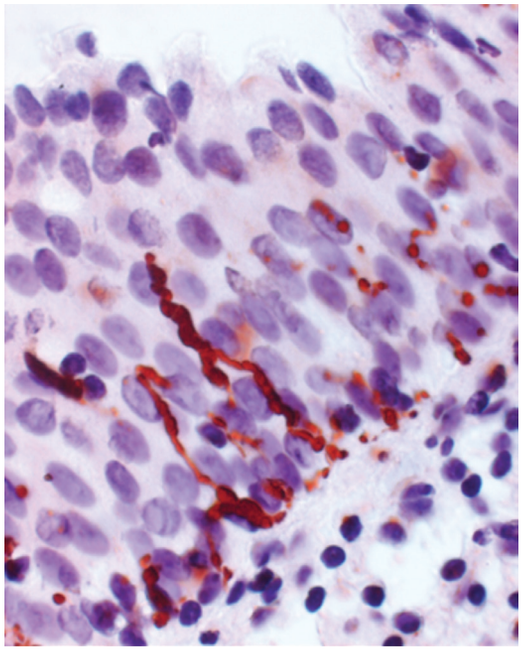

Figure 1b. Same as **Figure 1a**, but with magnification: ×600

Inflammation and provoked vulvodynia

Acute inflammation may lead to chronic sensitization that persists even after the inflammation resolves.[18,20] However, results regarding cytokine, prostaglandin E2 levels, T-cell, B-cell, natural killer cell, and macrophage numbers have been inconsistent in women with PV.[21] Studies on proinflammatory vaginal or plasma cytokine profiles in vulvodynia are ongoing.[22-24]

Some women with vulvodynia have reported recurrent yeast infections;[25] this, together with the reduced systemic number of natural killer cells in women with vulvodynia compared with that in controls,[26] led to the hypothesis that deficiency in natural killer cell numbers is correlated with recurrent *Candida* infections in these women. Vulnerability to *Candida* infection associated with the reduced capability to stop the resulting inflammation has been described; however, a causal relationship between *Candida* infection and vulvodynia development cannot be determined via these observations.

Mast cells and hyperinnervation

Findings concerning hyperinnervation in women with PV prompted a search for agents that could enhance nerve growth. One of the potential agents may be mast cells. Mast cells discharge various mediators from their granules, such as histamine, tryptase, nerve growth factor (*NGF*), and bradykinin.[27,28] Some of these directly cause pain, whereas the others cause pain by stimulating peripheral neurons. An increase in the number of mucosal mast cells has been demonstrated in women with PV,[29-31] and in an animal model of vulvodynia.[32] We assessed women with severe PV undergoing vestibulectomy and compared them with those of a similar age undergoing vestibular biopsy due to other conditions.[33] Mast cell detection was conducted not only using Giemsa stain (Figure 2) but also immunostaining for c-KIT (Figure 3) and mast cell tryptase.[8,10,33] c-KIT is a membrane proto-oncogene encoding a type 3 tyrosine kinase protein receptor. In contrast, tryptase is a specific protein present in granules secreted from mast cells. Positive tryptase staining indicates that the mast cells were activated and degranulated. Using both c-KIT and tryptase staining, we observed a significant number of mast cells in the superficial dermis, mostly activated, in women with PV compared to that in controls. An increase in the number of stromal mast cells has also been demonstrated in animal models of PV.[29-31] In another study, although the number of mast cells was not increased, they were activated in sensitive vestibular areas, as indicated via chymase discharge.[14] Chymase is one of three peptidases capable of converting angiotensin I to angiotensin II, which is a promoter of axon sprouting and regeneration.[34]

While some studies have not demonstrated an increase in mast cell numbers in women with PV, these studies were limited

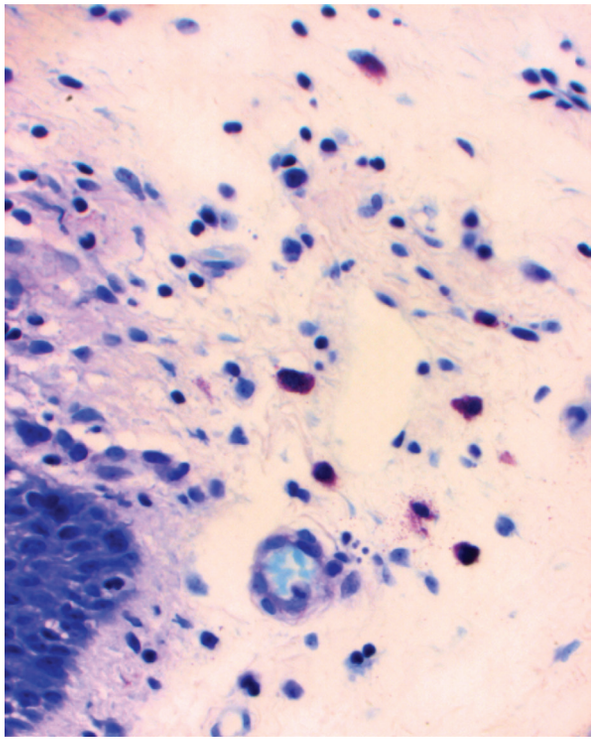

Figure 2. Giemsa staining of a specimen from a woman with provoked vulvodynia showing mast cells in the subepithelium. Magnification: ×600

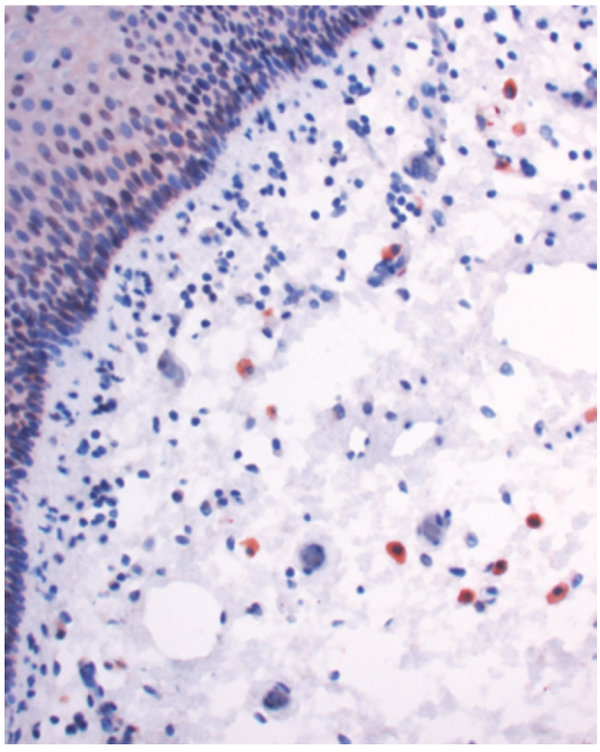

Figure 3a. CD117 (c-KIT) staining in a specimen from a woman with provoked vulvodynia showing mast cells in the subepithelium, among other inflammatory cells. Magnification: ×400
c-KIT: gene encoding the receptor tyrosine kinase protein known as tyrosine-protein kinase, CD117: Cluster of differentiation 117

because they only used Giemsa staining or c-KIT staining but not a marker of mast cell activation, such as tryptase.[35] Another limitation was that these studies sampled only one fixed area of the vestibule, regardless of whether that focus was sensitive. In another study that compared tender and non-tender foci, mast cell numbers were significantly increased in the tender foci.[11]

Heparanase (HPSE) is another enzyme secreted by mast cell granules.[36] We immunostained surgical specimens from women undergoing vestibulectomy and from controls for HPSE and demonstrated the presence of this enzyme in the subepithelial cells of the vestibule in women with PV (Figure 4).[10,33] HPSE is a mammalian endoglycosidase (endo-alpha-D-glucuronidase) that can cleave heparan sulfate, a proteoglycan that stabilizes the connective tissues,[36] thereby releasing heparin-binding growth factors, enzymes, and plasma proteins that further weaken the extracellular matrix. Conceivably, HPSE degrades the connective tissue and epithelial basement membrane, allowing proliferating nerve fibres to penetrate the degraded epithelial basement membrane to the epithelial surface. This intraepithelial hyperinnervation results in local hyperesthesia characteristic of PV.

This proposed mechanism raised the hypothesis that blocking HPSE activity might halt PV development. Such blockade may be achieved by an anti-HPSE agent such as unfractionated or low-molecular-weight heparin; heparin is reportedly a powerful inhibitor of the activity of HPSE on antithrombin-binding

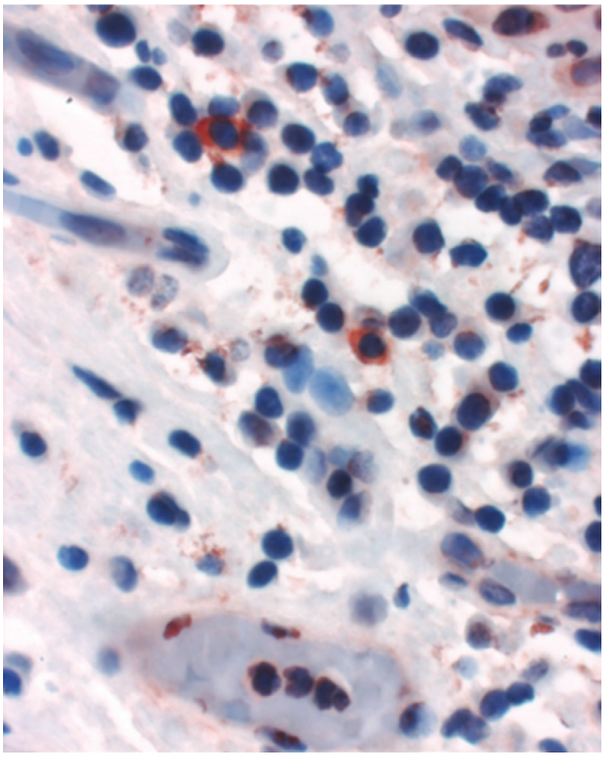

Figure 3b. Same as **Figure 3a**, Magnification: ×600

oligosaccharides.[37] We therefore conducted a randomized controlled trial of an anti-HPSE agent (enoxaparin) for the treatment of PV.[33] This treatment led to a greater reduction of clinical and subjective pain scores in women treated with enoxaparin than in a placebo-controlled group. Pain reduction was correlated with a diminishing number of intraepithelial-free nerve fibres in the enoxaparin group but not in the placebo group.[33] The anti-HPSE therapy may have worked by strengthening the stroma, thereby inhibiting neuronal sprouting and proliferation.

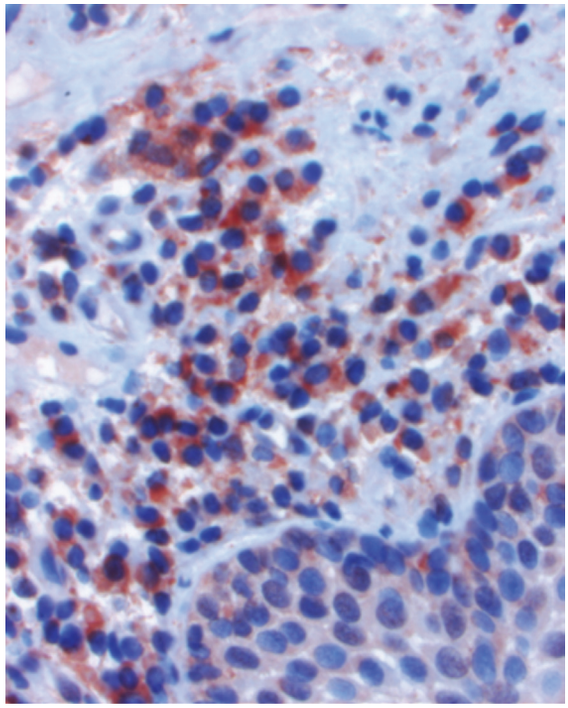

Figure 4a. Heparanase expression in a specimen from a woman with provoked vulvodynia. Positive cytoplasmic staining is seen in the subepithelial layer, close to the epithelial basement membrane. Magnification: ×400

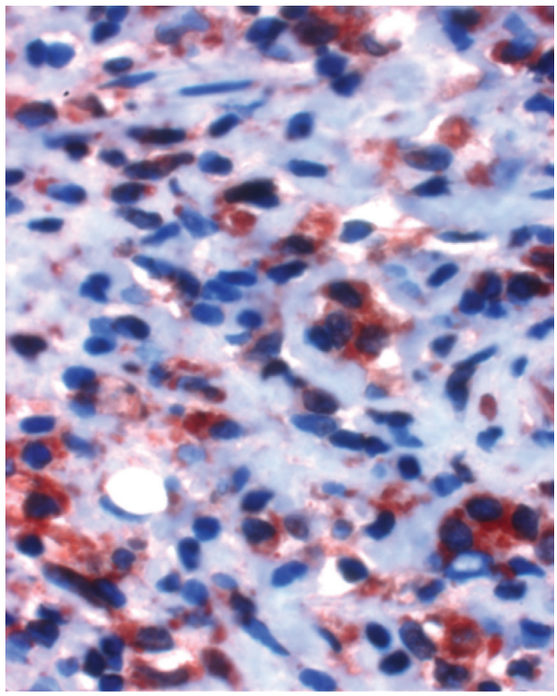

Figure 4b. Same as **Figure 4a**, Magnification: ×600

Genetic predisposition to neuroproliferation and provoked vulvodynia

Consequent to our studies associating mast cell increase and activation, HPSE excretion, and hyperinnervation with vulvodynia, we examined a possible genetic predisposition of women with PV to these phenomena.[38] We examined several single nucleotide polymorphisms (SNPs) in *TRPV1*, *NGF*, and *HPSE* genes in 65 women with moderate or severe primary PV, comparing them to 126 healthy, ethnically matched controls. Genotyping analyses revealed a novel, statistically significant and elevated prevalence of SNPs in TRPV1 and in the promoter region of *NGF* in women with PV than in controls. The amino acid substitution resulting from SNPs in TRPV1 modifies the functional properties of the channel and induces increased TRPV1 protein expression due to an increased copy number.[39] Women with PV exhibit lower thresholds for heat pain as well as increased expression of the receptor.[17,40]

Our finding of a polymorphism in *NGF* is further supported by another study that demonstrated increased blood levels of *NGF* in response to *Candida* antigen stimulation in women with vulvodynia than in controls.[41] In another study, an increase in *NGF* levels was detected in vestibular tissues from women with PV, but only in areas with abundant B-cells.[15] *NGF* plays a role in the development of peripheral nerves by promoting neuronal growth and survival.[42,43] *NGF* produces pain directly by acting on the nerves and indirectly by affecting mast cells.[44] *NGF* also increases TRPV1 expression.[45] Additionally, hyperalgesia was shown to be extensively mediated by *NGF*-positive regulation of the TRPV1-promoter system via Sp1 and Sp4 transcription factors.[34,46]

Animal models of provoked vulvodynia

Animal models of PV have been developed to monitor the progression of PV. Hyperinnervation has been elicited in the vestibule of mice and rodents in which vulvodynia was induced via various topical vestibular stimuli. Hyperinnervation persisted even after the initial local inflammatory reaction subsided. In an established mouse model,[47] a significant increase in the density of nerve fibres, immunostained by PGP 9.5, developed in 40% of the mice repeatedly infected with *Candida albicans* strain SC5314 or by zymosan (a mixture of fungal antigens). There was

a 300-400% increase in the number of nerve fibres in the mice that developed hyperinnervation. Furthermore, an elevation in the density of peptidergic fibres, as revealed by calcitonin gene-related peptide (CGRP) levels was depicted in the allodynic group. The hyperinnervation was observed throughout the lamina propria, with some thin nerves penetrating the lamina propria beneath the epithelium. An increase in sympathetic innervation, as revealed by the vesicular monoamine transporter 2 levels, was shown in allodynic mice. No inflammation was noted in the tissues. The finding of hyperinnervation and allodynia in only 40% of the treated mice was attributed to the variable genetic predisposition of the mice to vulvodynia.

In another mouse vulvodynia model, allodynia was achieved through topical application of the proinflammatory hapten oxazolone.[48] In oxazolone-sensitized female ND4 Swiss mice, a single labial oxazolone challenge provoked vulvar mechanical hyperalgesia for up to 24 h. This was accompanied by neutrophil influx, increased inflammatory cytokine gene expression, and increased density of cutaneous CGRP and PGP 9.5-immunostained nerve fibres. Moreover, a 3-day consecutive oxazolone challenge caused vulvar hyperalgesia that was persistent for up to 5 days, even after the initial local inflammatory reaction subsided.

In another study performed by the same group,[49] oxazolone-challenged mice developed significant tactile hypersensitivity that persisted for >3 weeks, even after exposure to vestibular allergen was discontinued. The hypersensitivity only disappeared 6 weeks after the exposure. In the allergen-challenged mice, >3-fold increase in cutaneous vestibular CGRP nerve intensity was detected compared with that in vehicle-challenged and untreated controls. A 10-fold increase was noted in RNA expression for transcripts encoding *NGF* and the nerve/mast cell synapse marker cell adhesion molecule 1. This indicates that the local environment supported neuronal growth and maintenance. These sites were characterized by increases in mast cell numbers as well as regulatory CD4, CD25, FoxP3, and T cell infiltration. Local depletion of mast cells by intralabial administration of the mast cell degranulation compound 48/80 led to reduction in both nerve density and tactile sensitivity.

In a placebo-controlled study,[50] an increased number of CD68-immunoreactive cells was demonstrated in the distal vagina of C57BL/6 mice after microinjection of complete Freund's adjuvant (CFA) versus saline. Inflammation and innervation density were assessed at 7 and 28 days following the single administration or 14 days following the repeated administration of CFA or saline. Increased mast cell numbers were demonstrated. Hyperinnervation was evident in CFA mice via staining with PGP 9.5, CGRP, substance P, vasoactive intestinal peptide, and neuropeptide Y.

DISCUSSION

The 2015 Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia regards the peripheral neurologic mechanism as one of several factors associated with vulvodynia.[3] The data reviewed in this study support the hypothesis that neuropathy or hyperinnervation is the actual cause of allodynia in women with PV. Several groups, including ours, have successfully shown that neuroproliferation developed only in women with PV and not in healthy women. Subsequently, removal of the hyperinnervated tissue may explain the successful outcome of the surgical excision of the vestibule-vestibulectomy, in women with PV. Non-invasive treatment approaches, aiming at preventing or reducing the effect of hyperinnervation may be developed in the future.

In animal models, hyperinnervation persisted for many days, even after the topical application of an anti-irritant and the initial local inflammatory reaction subsided. In terms of the etiopathogenesis of neuroproliferation, several researchers have demonstrated a correlation between hyperinnervation and the increased presence of mast cells in local tissues and their activation in women with PV. Consequently, we hypothesized that mast cell activation triggers the increase in the numbers of nerve fibres, with granule discharge of various mediators such as *NGF*, histamine, bradykinin, tryptase, prostaglandins, serotonin, and leukotriene. These mediators can sensitize C fibres and induce their proliferation, causing pain. *NGF* may be secreted by both mast cells and neurons and can induce neuronal growth and reduce the subsequent neuronal firing threshold, causing increased pain perception.[29] The SNPs in *NGF* and TRPV1 demonstrated by us may be the reason for the uncontrolled production of *NGF*, leading to excessive neuroproliferation in some women with PV. This is a vicious cycle as *NGF* also attracts mast cells and stimulates its own synthesis via *NGF* receptors on the mast cell membranes and nerves alike. Nerve sprouting and penetration of the newly formed nerve fibres into the epithelium is then made possible by HPSE.

Alternatively, another potential etiological mechanism for the increased mast cell numbers in women with PV is neurogenic inflammation. In this regard, stimulated nociceptors cause neurons to discharge neuropeptides that draw and stimulate local mast cells. Indeed, electron microscopic studies have shown that mast cells are closely related to sensory nerve fibres containing neuropeptides that induce mast cell degranulation. A similar mechanism has been reported in interstitial cystitis/bladder pain syndrome, a condition that may occur simultaneously with PV.

In addition, pelvic organ prolapse has been associated with vulvodynia.[51] Further studies may explore the association between

pelvic organ prolapse, laxity of the uterosacral ligaments and PV, and possibly the peripheral neurologic mechanism of PV.

CONCLUSION

In conclusion, vestibular neuroproliferation has been repeatedly depicted to be a substantial associated factor of PV.

ETHICS

Peer-review: Externally peer-review.

DISCLOSURES

Conflict of Interest: There are no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

DOI: 10.34057/PPj.2020.39.03.002
Pelviperineology 2020;39(3):77-84

Anatomical outcomes of laparoscopic high uterosacral ligament suspension for primary apical prolapse

BURAK SEZGİN[1], FATİH PİRİNÇÇİ[1], EREN AKBABA[1], AYSUN CAMUZCUOĞLU[2], EDA ADEVİYE ŞAHİN[3], AHMET AKIN SİVASLIOĞLU[1], HAKAN CAMUZCUOĞLU[4]

[1]Department of Obstetrics and Gynaecology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey
[2]Department of Obstetrics and Gynaecology, Private Adatıp Sakarya Hospital, Sakarya, Turkey
[3]Department of Obstetrics and Gynaecology, Malatya Training and Research Hospital, Malatya, Turkey
[4]Private Clinic, Department of Gynaecologic Oncology, Sakarya, Turkey

ABSTRACT

Objective: We aimed to evaluate the short-term anatomical results of laparoscopic high uterosacral ligament suspension (LHUSLS) in the surgical treatment of apical prolapse.

Materials and Methods: Medical records of thirty women with stage 2 or higher cuff or uterine apical prolapse who underwent LHUSLS operations were retrospectively analysed. Preoperative, intraoperative, and 6- and 12-month short-term postoperative data were recorded. Anatomical success was defined as no prolapse for any Pelvic Organ Prolapse Quantification (POP-Q) point at or below 1 cm above the hymen. To evaluate prolapse symptoms, we used the Pelvic Organ Prolapse Distress Inventory (POPDI)-6 questionnaire.

Results: Based on stage II of POP-Q as the recurrence criteria, the anatomical success rate was 100%. The POP-Q point C, Aa, Ap, Ba and Bp measurements were significantly higher after surgery than the preoperative values. There was no recurrence or ureteral injury in any case. The scores of POPDI-6 before and after LHUSLS were significantly lower in all patients after surgery ($p<0.001$).

Conclusion: LHUSLS is a simple and effective procedure that has been found to provide successful anatomical outcomes and reduced ureteral injury for apical prolapse. However, the long-term results of this procedure require further investigation.

Keywords: Apical prolapse; high uterosacral ligament suspension; laparoscopy; native tissue repair

INTRODUCTION

Pelvic organ prolapse (POP) is a clinical condition that affects approximately half of women who have given birth.[1] The lifetime probability of a woman undergoing POP surgery was reported to be between 11 and 19%.[2] Apical prolapse affects 11% of women.[3] Currently, conservative and surgical treatment modalities are available for POP. POP repair can be performed vaginally or abdominally for patients who do not benefit from conservative methods or who require surgical treatment. Although mesh or natural tissue could be used during these interventions, the FDA recommendations regarding mesh usage have led many surgeons to negative thoughts regarding these methods.[4] Therefore, alternative treatment modalities using native tissue are gaining popularity. Recent technological advances increase the preferability of minimally invasive approaches for both the surgeon and the patient.

Address for Correspondence: Burak Sezgin, Department of Obstetrics and Gynaecology, Muğla Sıtkı Koçman University Faculty of Medicine, Muğla, Turkey
E-mail: buraksezgin@yahoo.com **ORCID ID:** orcid.org/0000-0003-2938-5816
Received: 31 October 2019 **Accepted:** 12 May 2020

Although the most common type of prolapse is anterior vaginal prolapse, the loss of apical support is typically present in prolapses below the hymen. The belief in providing adequate support to the vaginal apex for a durable and long-lasting surgical repair of patients with advanced stage prolapse is increasing.[5] Anterior and posterior vaginal repairment may fail if adequate apex support is not provided, as the apex provides significant support to the vaginal wall.

Abdominal (laparoscopic/robotic) sacrocolpopexy is the gold standard method for apical prolapse treatment. Although this method has a high success rate, it has serious complications, such as nerve plexus and vascular damage.[6] However, uterosacral ligament suspension (USLS) is a method that can be performed without mesh usage. According to the FIGO© working group study, USLS can improve the vaginal apex to an anatomically better position than sacro spinous ligament fixation. Moreover, it has been reported that USLS has a high success rate and is a safe method (grade A recommendation).[7]

The uterosacral ligament is anatomically divided into three parts, including the proximal, intermediate and distal parts. The proximal part is the strongest part and is composed of connective tissue, fat and lymphatics. The distal part is often weak and damaged in POP patients. USLS has been shown to improve the apical compartment with a success rate of 98.3%.[8] However, in USLS cases performed with a vaginal route, the ureter damage ratio may reach 11%, but this rate may decrease to a lower level with a laparoscopic approach as better anatomic visualization can be achieved with laparoscopy.[8]

USLS was first described by Miller, and various modifications have been developed over time. Recently, a high uterosacral ligament suspension (HUSLS) technique has been developed by suturing the proximal part of the uterosacral ligament.[9-11] This method is thought to provide a strong apical support to the vaginal cuff.

HUSLS is performed with native tissue without the use of mesh. Using this approach, mesh complications, which account for an important part of POP operation complications, can be eliminated. For this reason, we applied the laparoscopic high uterosacral ligament suspension (LHUSLS) method in our cases. In the literature, there are several video articles showing the LHUSLS surgical technique as a new and alternative method in the treatment of POP. However, we did not identify any study showing the effectiveness of this method in the postoperative period.

The aims of the study are to describe a new modification of LHUSLS and assess the efficacy of LHUSLS in the surgical treatment of apical prolapse.

MATERIALS AND METHODS

This retrospective case series study was approved by the Local Ethics Committee for Clinical Research of Muğla Sıtkı Koçman University, Faculty of Medicine, Muğla, Turkey (date: 07.02.19, decision no: 6). Between January 2015 and March 2018, data from patients who underwent LHUSLS for apical POPs (POP-Q ≥2) in our obstetrics and gyneacology clinics were retrospectively analysed.[12] In the given period, only this technique was performed as the standard procedure for primary apical prolapse repairment in women with cuff prolapses or no demand of uterine preservation. The necessary information was obtained from the hospital database and patient files.

During this period, 45 patients underwent LHUSLS operation for apical prolapse by two surgeons with advanced laparoscopy experience. The data of 14 patients with a POP-Q stage value ≤1, an abnormal pap smear and a suspected adnexial mass or malignancy were excluded from the study. The medical records of only one patient could not be found and were lost to follow up. Twenty-one women with uterine prolapse and nine women with vaginal cuff prolapse were included. Patient characteristics, such as age, gravidity, parity, body mass index (BMI), comorbidities (anaemia, diabetes, hypertension, and cardiac disease), menopausal status, hormone replacement therapy, tobacco usage, history of previous prolapse surgery, history of previous incontinence surgery, operation time, intraoperative complications, postoperative complications, and duration of hospital stay, were recorded from the hospital database. The records of the preoperative and 6th and 12th month postoperative POP-Q stages were also obtained from patient files. Anatomical success was defined as no prolapse of any POP-Q point at or below 1 cm above the hymen. The duration of hospitalization was calculated in days from the first postoperative day until the discharge time. Patient demographics were described. The preoperative and 6th and 12th month postoperative POP-Q stages were compared and analysed. Transvaginal ultrasonography scans, abdominal magnetic resonance imaging examinations (if performed) and Papanicolaou smear records were also analysed. The patients were grouped as uterine prolapse (n=21) and cuff prolapse (n=9). To evaluate prolapse symptoms, we used the Pelvic Organ Prolapse Distress Inventory (POPDI)-6 questionnaire.[13] The Turkish validation of POPDI-6 questionnaire was also performed.[14]

Description of LHUSLS technique

A standard laparoscopic hysterectomy is undertaken; nevertheless, bilateral uterosacral ligaments are not cut and preserved during hysterectomy. After the hysterectomy procedure, the vaginal

cuff is closed intracorporeally with No: 0 absorbable polyglactin (MITSUTM, Meril Endo Surgery Private Limited, Muktanand Marg, Chala, Vapi 396191, Gujarat, India) in a single layer continuously. Then, in all cases, bilateral ureters are released by entering into the retroperitoneal space. The ureters are craniocaudally dissected and laterally shifted to the uterosacral ligaments. Using No: 2 polyglactin (MITSUTM, Meril Endo Surgery Private Limited, Muktanand Marg, Chala, Vapi 396191, Gujarat, India) in a circular fashion, we first sutured the proximal part of the uterosacral ligament, followed by the intermediate and distal parts, respectively. We subsequently stitch up two bites suture from the pubocervical fascia through the rectovaginal fascia and continue with the opposite uterosacral ligament. The distal, intermediate and proximal circular sutures are stitched up on the opposite side, respectively. Finally, two sutures in the proximal uterosacral ligaments are ligated together, and the suture is tightened (Figure 1). Moreover, an assistant checks the total vaginal length (TVL) transvaginally. The process is completed after ensuring that the desired suspension is achieved for the patient. In cases of cuff prolapse, an assistant helps to clarify the vaginal vault using the rectal anal dilator transvaginally. In this way, the bladder is initially dissected. The pubocervical fascia is then exposed anteriorly and the rectovaginal fascia posteriorly.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software, version 23 (SPSS, Inc., Chicago, IL). The data were expressed as the mean and range for continuous variables, and binary variables were reported as numbers and percentages. The Friedman's test, an alternative to the single factor variance analysis, was used for the not normally distributed data. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

The baseline clinical and demographic characteristics of the patients are listed in Table 1. In particular, the mean BMI was 28±2.07 kg/m^2, and the mean age of the women was 54.6±4.48 years. Eighty percent of the patients were postmenopausal. In regards to the preoperative POP-Q stages, 10 patients were in POP-Q stage 4, 15 patients were in POP-Q stage 3 and five patients were in POP-Q stage 2. None of the patients had previous uterine prolapse surgery. A history of previous incontinence surgery was found in 16.6% of the patients. No hormone replacement therapy was identified in the patients. Tobacco usage was reported as 23.3%. Medical comorbidities were reported as 50%

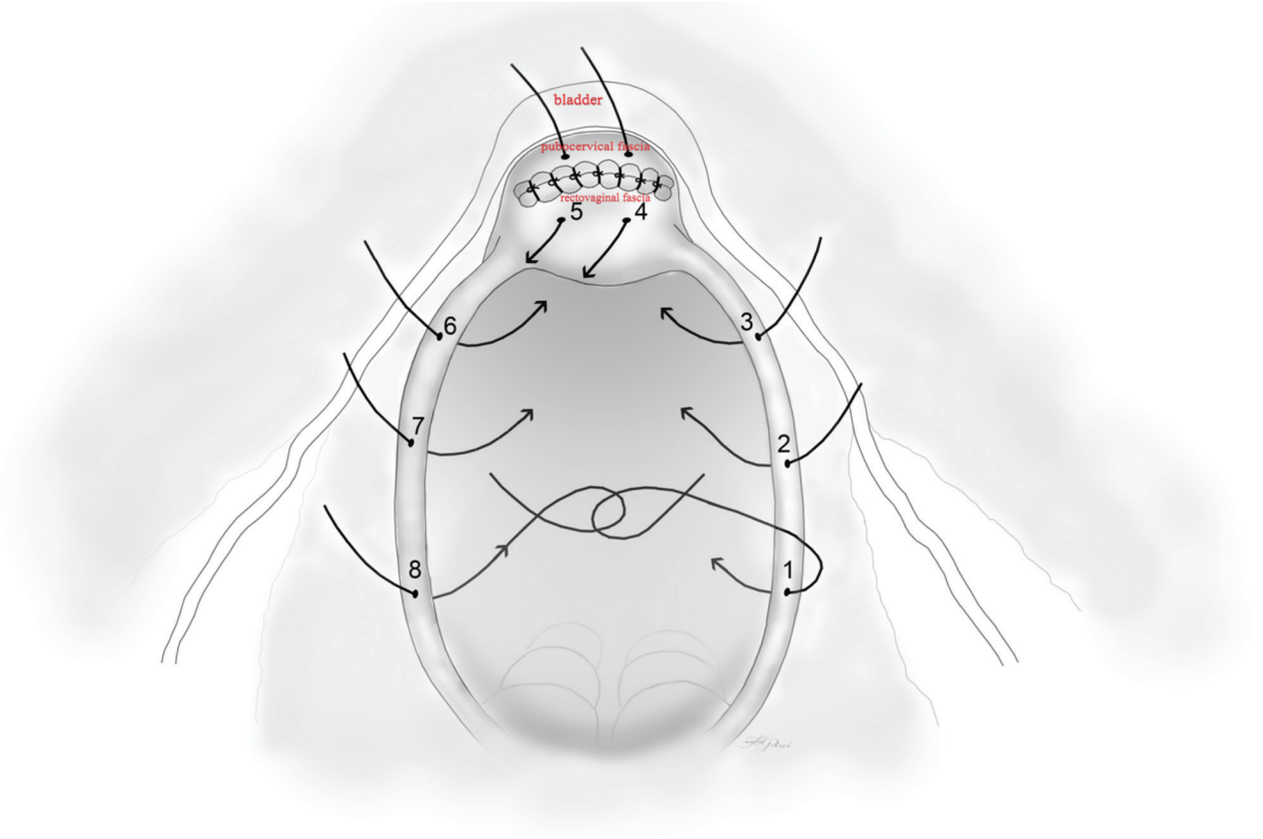

Figure 1. Description of LHUSLS technique
LHUSLS: Laparoscopic high uterosacral ligament suspension

Table 1. Baseline characteristics of patients (n=30)	
	Mean ± SD
Age	54.6±4.48
Gravid	4.13±1.70
Parity	2.93±1.05
BMI	28±2.07
Menopausal status (%)	
Postmenopausal	80
Premenopausal	20
Tobacco usage (%)	23.3
Previous incontinence surgery (%)	16.6
Comorbidities (%)	
No comorbidities	50
Anaemia	20
Cardiac disease	6.7
Hypertension	16.7
Diabetes	6.7
Preop POP-Q stage (n=30)	
Stage 1	0
Stage 2	5/30
Stage 3	15/30
Stage 4	10/30

BMI: Body mass index, POP-Q: Pelvic Organ Prolapse Quantification, SD: Standard deviation, n: Number
Data are presented as mean ± standard deviation or number (%)

in the patients (anaemia 20%, cardiac disease 6.7%, hypertension 16.7%, and diabetes 6.7%).

All patients were followed up at the 6th and 12th months. Based on stage II of POP-Q as the recurrence criteria, the anatomical success rate was 100% (30/30) for both 6 and 12 months. We did not identify recurrence in any patient. The POP-Q point C, Aa, Ap, Ba and Bp measurements were significantly higher at the 6th and 12th months after surgery than those at the preoperative time point in both groups ($p<0.05$) (Table 2A and 2B) (Figure 2A and 2B). However, no significant difference was identified between the 6th and 12th months postoperatively. In both groups, there was no significant difference between the preoperative and postoperative measurements of the TVL ($p>0.05$). The mean improvement for the Aa, Ap, Ba and Bp points was 2.9 cm, 2.09 cm, 3.38 cm and 2.81 cm, respectively, in the uterine prolapse group at 12 months postoperatively. The mean improvement for the Aa, Ap, Ba and Bp points was 2.77 cm, 2.22 cm, 3.45 cm and 2.78 cm, respectively, in the cuff prolapse group at 12 months postoperatively. Preoperative and postoperative 12 months of POPDI-6 questionnaire results were presented at Table 3.

No cases of intraoperative complications, such as urinary tract injury, bowel/intestinal injury, or intraoperative blood transfusion due to massive haemorrhage, were reported. The mean operative duration time of the cuff prolapses group and the uterine prolapses group was 93.88±6.97 minutes and 119.04±6.82 minutes, respectively. No case of postoperative

Table 2A. Preoperative and postoperative POP-Q measurements in uterine prolapse group, (n=21)									
		Aa	**Ba**	**C**	**Ap**	**Bp**	**Gh**	**Pb**	**TVL**
Pre	**Mean (SD)**	0.76 (1.34)	1.05 (2.20)	3.33 (2.31)	0.33 (1.15)	0.62 (2.14)	4.74 (0.70)	2.40 (0.78)	8.14 (1.12)
	Median	1	1	3	0.0	0.0	5	2.5	8
	Range	5	10	8	5	10	2.5	2.5	4
	Mean rank	2.95^{aa}	2.98^{ac}	3^{af}	2.79^{ah}	2.88^{ak}	2.36^{aab}	2.17^{aba}	2.05
POP-Q6	**Mean (SD)**	-2.14 (0.96)	-2.52 (1.08)	-7.48 (0.81)	-1.90 (0.89)	-2.24 (0.77)	4.5 (0.71)	2.33 (0.73)	8.05 (1.08)
	Median	-2	-3	-8	-2	-2	4.5	2.5	8
	Range	3	4	3	3	2	3	2.5	4
	Mean rank	1.52^{ab}	1.40^{ad}	1.38^{ae}	1.50^{ag}	1.52^{al}	1.90^{aab}	1.95^{aba}	1.95
POP-Q12	**Mean (SD)**	-2.14 (1.01)	-2.33 (1.06)	-7.29 (0.94)	-1.76 (0.99)	-2.19 (0.93)	4.43 (0.78)	2.31 (0.72)	8.10 (1.06)
	Median	-2	-3	-7	-2	-2	4.5	2.5	8
	Range	3	4	3.5	3	3	3	2.5	4
	Mean rank	1.52^{ab}	1.62^{ad}	1.62^{ae}	1.71^{ag}	1.60^{al}	1.74^{dab}	1.88^{dba}	2
Pre - POP-Q6 - POP-Q12	**Chi-square**	37.5	38.82	39.65	27	33.19	13.92	6.5	0.5
	p value	$<0.05^{*}$	$<0.05^{*}$	$<0.05^{*}$	$<0.05^{*}$	$<0.05^{*}$	$<0.05^{*}$	$<0.05^{*}$	>0.05

POP-Q: Pelvic Organ Prolapse Quantification, SD: Standard deviation, TVL: Total vaginal length, Gh: Genital hiatus, Pb: Perineal body, n: Number
*Statistically significant difference. Friedman's test ($\chi^2=39.65$; $p<0.05$)
¥value that makes a difference between Pre, POP-Q6 and POP-Q12 values

Table 2B. Preoperative and postoperative POP-Q measurements in cuff prolapse group (n=9)

		Aa	Ba	C	Ap	Bp	Gh	Pb	TVL
Pre	**Mean (SD)**	1.33 (1.12)	1.67 (1.22)	5.67 (1.66)	0.89 (1.27)	1 (1.58)	5.22 (0.83)	2.33 (0.87)	8 (1.41)
	Median	1	2	6	1	1	5	2.5	8
	Range	4	4	5	4	4	2	2.5	4
	Mean rank	2.78[aa]	2.78[ac]	3[af]	2.78[ah]	2.89[ak]	2.67[aab]	2.28	2
POP-Q6	**Mean (SD)**	-1.67 (1.5)	-1.89 (1.54)	-7.67 (1.12)	-1.11 (0.78)	-1.78 (0.67)	4.83 (0.56)	2.22 (0.79)	8 (1.22)
	Median	-2	-2	-7	-1	-2	5	2.5	8
	Range	5	5	3	2	2	1.5	2	4
	Mean rank	1.50[ab]	1.56[ad]	1.44[ae]	1.67[ag]	1.56[al]	1.83[aab]	1.78	2
POP-Q12	**Mean (SD)**	-1.44 (1.13)	-1.78 (1.48)	-7.56 (1.24)	-1.33 (0.87)	-1.78 (0.67)	4.72 (0.67)	2.17 (0.79)	8 (1.22)
	Median	-2	-2	-7	-2	-2	5	2	8
	Range	4	5	3	2	2	2	2	4
	Mean rank	1.72[ab]	1.67[ad]	1.56[ae]	1.56[ag]	1.56[al]	1.50[dab]	1.94	2
Pre - POP-Q6 - POP-Q12	**Chi-square**	9.74	10.57	17.43	9.87	16	11.14	4.67	0.0
	p value	<0.05*	<0.05*	<0.05*	<0.05*	<0.05*	<0.05*	>0.05	>0.05

POP-Q: Pelvic Organ Prolapse Quantification, SD: Standard deviation, TVL: Total vaginal length, Gh: Genital hiatus, Pb: Perineal body, n: Number
*Statistically significant difference. Friedman's test (χ^2=17.43; p<0.05)
¥value that makes a difference between Pre, POP-Q6 and POP-Q12 values

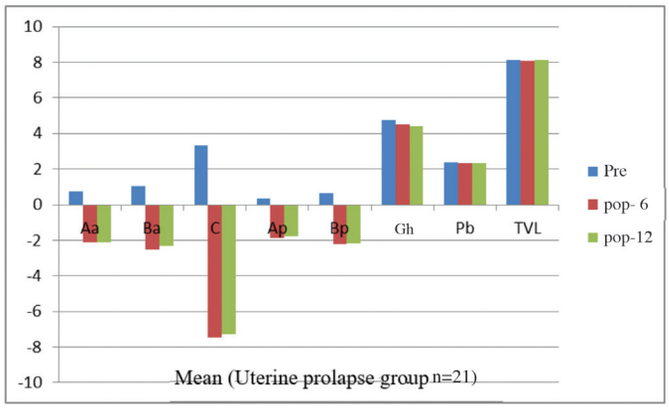

Figure 2A. Anatomical outcomes according to POP-Q points in Uterine prolapse group
POP-Q: Pelvic Organ Prolapse Quantification, Gh: Genital hiatus, Pb: Perineal body, TVL: Total vaginal length, n: Number

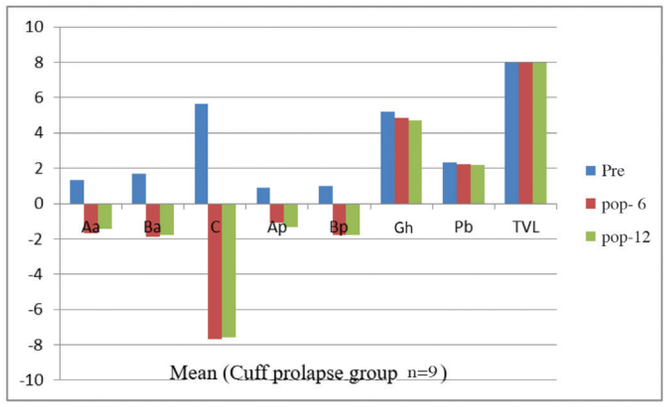

Figure 2B. Anatomical outcomes according to POP-Q points in Cuff prolapse group
POP-Q: Pelvic Organ Prolapse Quantification, Gh: Genital hiatus, Pb: Perineal body, TVL: Total vaginal length, n: Number

complications, such as haemorrhage, need for blood transfusion or fever was reported. The postoperative hospital stay was 2 days.

DISCUSSION

This is the first report to describe a case series study of LHUSLS performed with our technique. In this study, we aimed to demonstrate the efficacy and the short-term results of our LHUSLS technique in the treatment of apical prolapse. In the 12-month follow-up period, we obtained high success rates in all apical, anterior and posterior compartments. Furthermore, we obtained low recurrence and complication rates.

Table 3. Pre- and postoperative POPDI-6 data

Questionnaire	Before (n=30)	After (n=30)	p
POPDI-6	74.55±13.63	21.91±9.90	<0.001

POPDI-6: Pelvic Organ Prolapse Distress Inventory, n: Number, SD: Standard deviation
Values are presented as mean score ± SD

In the study of Sun et al.[15], they performed LHUSLS with cervical amputation in 34 patients and achieved a 100% anatomical success rate as in our study. In the study of Smith et al.[16], they compared vaginal HUSLS and robotic sacrocolpopexy (RSC)

in the long term, and they found that HUSLS was as effective as RSC (93.2% for USLS vs 91.3% for RSC). They also reported a mesh erosion rate of 3.2% in the RSC group. Nishimura et al.[17] evaluated perioperative complications and the anatomical outcomes of laparoscopic uterosacral colpopexy in 152 uterine prolapse patients. They reported a 19% of total recurrence rate. In our study, we also found an anatomical success rate of 100% using native tissue in the 12-month follow up period. We believe that apical suspension procedures using native tissue will gain more popularity following the mesh related recommendations of the FDA.

Dallas et al.[18] suggested that hysterectomy should be performed in patients undergoing prolapse surgery in a large population-based cohort study and found that the risk of prolapse surgery in the future is reduced by 1-3% using this approach. We also performed apical suspension together with hysterectomy in patients who did not demand uterine preservation. We did not have a recurrence surgery during the 12-month follow up period.

Milnerowicz-Nabzdyk and Zimmer[19] described the technique of laparoscopic trans-teres vault suspension and suspended the vaginal stump to the anterior rectus fascia in eight patients. Although they obtained anatomically pleasing results, fibular nerve damage developed in one of the eight patients. They also performed anterior and posterior vaginal repairment in addition to standard procedures in patients with an advanced stage. Although alternative pop treatment options using different anatomic structures are offered, such as in Milnerowicz's study, the complications are not clearly established. In our study, no complication was observed in any of our patients, and we did not perform an additional surgical procedure other than LHUSLS even in patients with stage 4 prolapse. In our study, we achieved satisfactory improvements in both the anterior and posterior compartments after adequate apical suspension.

In a retrospective study by Haj Yahya et al.[20], 48 patients had hysteropexy with LUSLS and anterior colporrhaphy for anterior and apical prolapse. They reported an 85,4% anatomical success rate. In contrast to our study, they fixed the pubocervical fascia to the pericervical ring during anterior colporrhaphy. As indicated in their study, they maintained the continuity of strong supporting structures, such as the pubocervical fascia and uterosacral ligament. We also believe that the continuity of strong supporting structures is critical. However, we employed a different approach to ensure the direct continuity of the uterosacral ligament and pubocervical ligament. We suggest that the reason why the HUSLS applied in our practice is more effective may be the direct continuity of the pubocervical fascia and uterosacral ligament, which was provided by laparoscopic suturing.

It has been reported that intraperitoneal USLS techniques performed by a laparoscopical or transvaginal route have a high rate of ureteric injury, between 0 and 10.9%.[21] Karmakar et al.[22] reported three ureteral injuries in the first 100 cases of extraperitoneal vaginal HUSLS, and they had to open the sutures. In the study of Houlihan et al.[23], they did not report any ureteral damage in 54 cases of laparoscopic USLS as in our study. One of the main advantages of the laparoscopy is the improved visualization of the anatomic structures. In addition, because of the close proximity of the proximal part of the uterosacral ligament and the ureter, we dissected and lateralized the ureters. Using this approach, the possibility of ureter damage was minimized. In the Karmakar et al.[22] study, while the anatomic success rate was 76%, the recurrence rate requiring surgery was reported to be 14%. Houlihan et al.[23] found the recurrent prolapse rate to be lower in the laparoscopic group than in the vaginal group, at 4% and 15%, respectively. In our study, the anatomic success rate was 100% in the 12-month period and there was no recurrence. Thus, we suggest that the intraperitoneal approach can provide better results in terms of both ureteral injury and anatomical success than an extraperitoneal approach in the early period. However, it is clear that long-term results are required.

Milani et al.[24] sutured the intermediate section of the uterosacral ligament in their study of transvaginal HUSLS. They reported a 2.6% ureteral kinking rate and a 13.7% total recurrence rate. In our laparoscopic approach study, the sutures were first placed in the proximal part where the uterosacral ligament is the strongest. Furthermore, after completion of the suspension procedure, the degree of suspension can be viewed and evaluated directly. It is also possible to provide suspension support with extra sutures to the uterosacral ligament if necessary. Although the follow-up period of our study was limited to 12 months, it has been suggested that the laparoscopic approach may be more effective than the transvaginal approach in terms of ureteral injury and recurrence rates in the short term.

Turner et al.[25] compared laparoscopic and transvaginal USLS ligament suspension and found that both methods had similar anatomical results. In their study, the median follow-up time was 21.5 weeks, and the median TVL was significantly longer in the laparoscopic group than it was in the vaginal group (8.3±1.1 cm vs 7.4±1.2 cm). Similarly, in our study, the TVL was 8.10 cm and 8 cm in the uterine and cuff prolapse patients, respectively, at the 12th month follow up. In the same study, they performed preoperative ureteral stenting in all cases with USLS. Nevertheless, the ureteral injury rate was 1.9% in their laparoscopic USLS cases. According to these data, we suggest that preoperative ureteral stent insertion might reduce but not eliminate ureteral injury risk. Although we did not insert a ureteral stent in any

of our cases, we did not experience any ureteral injury. We want to emphasize that to prevent or minimize ureteral injury, bilateral ureteral releasing, lateralizing and suturing after visualization of the bilateral ureters is the most important step of our modification. Furthermore, according to our experience, the presence of a stent in the ureter during laparoscopy may reduce the ureter flexibility, which may thus complicate ureter dissection.

The limitations of our study included the low number of patients, the short follow-up period, and the retrospective nature. To generalize the results of this study, randomized controlled studies with larger patient groups and longer follow-up periods are required. The positive aspects of our study included the standardization of the follow-up periods and patient symptom assessment by a validated questionnaire. Although our study lacks the advantages of prospective studies, we believe that our preliminary data will guide future studies.

CONCLUSIONS

In conclusion, LHUSLS is a simple and effective procedure that has been found to provide successful anatomical outcomes and reduce ureteral injury for apical prolapse. However, in addition to this knowledge of ureteral releasing, lateralizing and uterosacral ligament suturing after visualization of the ureters with the advantage of laparoscopy, the anatomical results may be improved and complications may be minimized with this presented technique.

ACKNOWLEDGMENTS

The authors thank to Dr. Gülin YEĞİN for her assistance on statistical analysis.

ETHICS

Ethics Committee Approval: This retrospective case series study was approved by the Local Ethics Committee for Clinical Research of Muğla Sıtkı Koçman University, Faculty of Medicine, Muğla, Turkey (date: 07.02.19, decision no: 6).

Informed Consent: Informed patient consent was obtained.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Conflict of Interest: There was no conflict of interest.

Financial Disclosure: The authors of the publication did not receive any financial support by any grant/research sponsor.

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DOI: 10.34057/PPj.2020.39.03.003
Pelviperineology 2020;39(3):85-89

Bilateral Sacrospineous Colposupension in the treatment of female genital prolapse: Risk-Benefit Considerations and Six Months Follow-up

FRANZISKA C. HEMPTENMACHER[1], STEFAN OLLIG[2], ALEXANDER WAGNER[1], ANNE DE VRIES[1], DIRK G. KIEBACK[1]

[1]Department of Obstetrics and Gynaecology, Ev.-Luth. Diakonissenanstalt Knuthstrasse 1, 24939 Flensburg, Germany
[2]Department of Obstetrics and Gynaecology Diakonissenkrankenhaus Dresden, Holzhofgasse 29, 01099 Dresden, Germany

ABSTRACT

Objective: Central defects in the stability of the pelvic floor present an anatomical problem that afflict women frequently at an advanced age, but also are observed in young women with typical risk factors i.e. obesity and high parity.

Materials and Methods: Based on the encouraging results of the transperineal bilateral sacrospineous colpofixation technique (TPBCF). the vaginal minimally invasive single incision Bilateral Sacrospineous Colposuspension (BSC) using the extremely macroporous lightweight HexaPro polypropylene tape in combination with the i-Stitch instrumentation was developed in order to minimize the amount of foreign body implanted into the patient, facilitate ingrowth of the mesh and for the first time add elasticity and a self-adjusting character to the profile of apical suspension.

Results: In a study of 132 patients with vaginal prolapse surgical and functional outcomes of BSC have been evaluated with 6 months follow-up. No rectal injury was observed nor was any re-intervention required for any complications. Apical support was reliably achieved. These results were stable when compared with follow-up data at six months postoperatively. No erosion was seen with the exception of a traumatic mesh exposure after vaginal delivery.

Conclusion: The authors conclude, that BSC is an efficient minimally invasive technique for the treatment of female genital prolapse with a very favourable risk/benefit ratio.

Keywords: Bilateral sacrospineous colposuspension; operative therapy; single incision; HexaPro mesh; tape; monofilament; porosity; minimally invasive; vaginal vault prolapse; cervical prolapse; uterine prolapse; surgery; complications; outcome; 6 months results

INTRODUCTION

Central defects in the stability of the pelvic floor present an anatomical problem afflicting women frequently at an advanced age, but also observed in young women with typical risk factor i.e. obesity and high parity. Recently, encouraging results have been reported after transperineal bilateral sacrospineous colpofixation (TPBCF).[1,2]

Historical treatment options include abdominal surgical interventions such as sacrocolpopexy or fascial slings,[3,4] and operations via the vaginal approach such as the unilateral

Address for Correspondence: Dirk G. Kieback, Department of Obstetrics and Gynaecology, Ev.-Luth. Diakonissenanstalt Knuthstrasse 1, 24939 Flensburg, Germany
E-mail: dirk.kieback@diako.de **ORCID ID:** orcid.org/0000-0001-8651-9353
Received: 10 February 2020 **Accepted:** 12 May 2020

Amreich-Richter operation with the vaginal apex sutured to the uterosacral ligament or other lateral structures after hysterectomy.[5] More recently, extensive reconstructions using prosthetic mesh for the induction of neo-ligaments and neo-fasciae have been advocated,[6] sometimes also in the context of primary surgical interventions in the unpretreated patient.[7]

Intravaginal slings (IVS) placed transischiorectally have been proposed by Farnsworth[8] and Petros[9] shown to be promising in a small series of cases. However, rectal injury and erosions were identified as major problems of this technique which led to the abandonment of IVS.[10] A refined approach to TPBCF utilizing a standardized 12-step procedure was developed.[1] Five-year results have recently been reported.[2] The Bilateral Sacrospineous Colposuspension (BSC) was thereafter developed as a standardized reproducible procedure.[11] It further minimizes the amount of foreign body implanted into the patient. The HexaPro polypropylene structure facilitates ingrowth of the mesh and in the BSC application for the first time adds elasticity and a self-adjusting character to the profile of apical suspension.

MATERIALS AND METHODS

The premanufactured BSC-Kit (A.M.I. Inc.) combines a U-shaped structure designed on the basis of the pelvic anatomy, that is comparable to an angulated tape made of HexaPro monofilament macroporous mesh, with two loading units of the I-Stitch-Instrumentation. At a material weight of 21 g/m^2 the entire implant weighs 0.054 g compared to a regular postal stamp at 0.085g. The mesh is isoelastic due to its hexagonal structure: 93% of the mesh surface consists of pores. The tensile strength is >16 N/cm.

In histological sections of a human explant on the occasion of a hysterectomy 3 months after previous uterus-sparing BSC the formation of limited fibrosis around each individual HexaPro fiber without confluence was substantiated (Figure 1).

In a prospective study 132 patients were treated by BSC according to the published standardized single incision technique at Elblandklinikum Riesa in an open single centre design.[11] Patients with significant anatomical defects in the median pelvic compartment resulting in various stages of vaginal, utero-vaginal or cervical prolapse were included. Primary and secondary cases were admitted to the trial. There was no patient selection and no other treatment modality for the treatment of prolapse was used for the duration of the study. There was no simultaneous tension-free vaginal tape or transobturator tape placement at the time of BSC in patients complaining of stress urinary incontinence (SUI).

Vaginal estriol pre-treatment for at least two weeks was mandatory.

Surgery was performed by two designated surgeons under general or regional anaesthesia following the published method.[11] Follow-up examinations including pelvic ultrasound were performed upon discharge from the hospital and at 6 months after surgery. The efficacy of the apical suspension was assessed as were surgical complications and quality of life parameters.

Intraoperative variables included feasibility of BSC placement, length of surgery, blood loss, injury to adjacent organs. Postoperative parameters were pain, complications i.e. hematoma formation and/or infection and duration of hospital stay. Also, symptoms of SUI, urge, dyschezia, dyspareunia were assessed.

Statistical Analysis

All postoperative examinations and determinations were performed by a single gyneacology specialist trained as a pelvic floor surgeon, but not otherwise involved in the trial.

Differences between frequencies were assessed using distribution-free statistics i.e Fisher's exact test for small sample sizes or the Wilcoxon-test for differences of medians.

RESULTS

The mean age of the 132 participants was 68.1 years (standard deviation: 10.3, Table 1). 93% (n=123) were postmenopausal, 7% (n=9) premenopausal, the median body mass index was 27 [(range: 19-39) with parity at 2.2 (range: 1-7)]. The mean American Society of Anaesthesiology patient classification status was 2 (range: 1-3) (Table 2,3).

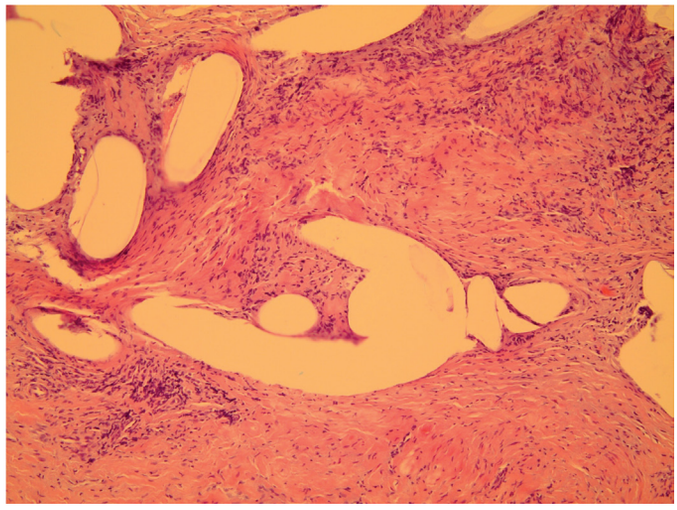

Figure 1. H&E staining of BSC histology after 3 months (vacuoles represent fibers removed by preparatory process)
H&E: Hematoxylin, BSC: Bilateral Sacrospineous Colposuspension

Forty-eight patients (36.4%) had previously undergone hysterectomy (Table 4).

Preoperatively 73 patients (55.3%) complained of SUI, 76 (57.6) of urge symptoms and 30 (22.7%) of nycturia. Eight patients (6%) reported dyspareunia preoperatively (Table 5).

BSC was performed preserving the uterus or in combination with hysterectomy (53.8%). Median operating time was 53 minutes and median blood loss was found to be only 10 mL. Anterior colporrhaphy was performed in 97 patients (73.5%), posterior colporrhaphy in 46 women (34.8%). During the course of the hospitalization of 3.3 days (1-6) pain assessed by a visual analogue scale of 1-10 was a median of 2 (0-8) on the day of surgery, 1.8, 0.8 and 0.4 on the following postoperative days (Table 3). No postoperative infections of the surgical field or hematomas were observed.

There were no failures of apical fixation after six months in the 56 patients (42%) following the invitation for a follow-up visit.

One patient was pregnant and later delivered spontaneously. After delivery, exposure of the BSC was observed behind a unilateral vaginal tear and 2 cm of tape were resected at that time. The result of the BSC remained stable. This was the only patient with an "erosion" of the tape, which as such was caused by the obstetrical trauma rather than an adverse tissue reaction.

SUI was present preoperatively in 59% of the patients presenting for follow-up and remained a problem in 21%. Nycturia had been present in 25% preoperatively and was reduced to 16%. Dyschezia was reduced from 18% to 5%.

The frequency of dyspareunia remained numerically unchanged at 6% with 2% of patients reporting new onset of dyspareunia while the same number reported being cured of this problem by the surgery (Table 6).

Of the 56 patients presenting for follow-up, 26 (46.4) had preoperative urge problems. Seven of those reported no change in symptoms, four observed de novo symptoms and 19 of those preoperatively afflicted declared having been cured from this problem by the surgery representing 73% of those present at follow-up with preoperative complaints, the equivalent of a marked reduction in frequency (Table 7).

Table 1. Patient age distribution

	n	Mean	SD	Range	Youngest	Oldest
Age	132	68.1	10.34	46	43	89

SD: Standard deviation, n: Number

Table 2. Menopausal status

Menopausal status	n	%
pre-menopausal	9	7
post-menopausal	123	93

n: Number

Table 3. Patient characteristics

Patient characteristics		
Height (m)	1.61	143-175
Weight (kg)	70	48-109
BMI	27	19-39
Parity	2.2	1-7
ASA	2	1-3

BMI: Body mass index, ASA: American Society of Anaesthesiology patient classification status

Table 4. Surgical Pre-treatment prior to BSC

Surgery	n
Hysterectomy	48
Colpopexy	4
Anterior repair	24
Posterior repair	20

BSC: Bilateral Sacrospineous Colposuspension, n: Number

Table 5. Preoperative symptoms

	n	%	Frequency
SUI	73	55.3	-
Urge	76	57.6	-
Nycturia	30	22.7	2.6/night (1-8)
Dyspareunia	8	6	-

SUI: Stress urinary incontinence, Urge: Urge urinary incontinence, n: Number

Table 6. Comparison of preoperative and postoperative symptoms

(n=56)	% Pre	% Post	Difference
SUI	59	21	38%
Nycturia	25 (3/n)	16 (2/n)	9%
Dyschezia	18	5	13%
Dyspareunia	6	6 (+2/-2)	-

SUI: Stress urinary incontinence, Pre: Preoperative, Post: Postoperative, n: Number

Table 7. Comparison of preoperative and postoperative URGE symptoms

(n=56)	Pre, n	Post, n	Relative difference
Urge	26	Unchanged: 7	-
		De novo: 4	-
		Cured: 19	73%

Urge: Urge urinary incontinence, Pre: Preoperative, Post: Postoperative, n: Number

DISCUSSION

Fascia lata slings and suspension procedures using the round ligaments have been abandoned as have resorbable meshes due to the fact, that the body does not maintain neo-ligaments without continuing stimulation of fibroblasts on site. Sacrocolpopexy with or without prosthetic mesh interposition should be combined with a Burch procedure for optimal results as shown by the studies of the NIH Pelvic Floor Disease Network.[12-14] In sum, this amounts to a significant surgical intervention with laparoscopic techniques adding their own spectrum of possible complications due to their transabdominal nature.

Amreich-Richter results are known for their surgery-induced dyspareunia, deep pelvic pain and secondary urinary continence problems making them unattractive especially for, but not limited to, the younger patient.[15] While having been in clinical use for a long time, systematic studies of this entity are few. Modifications using unilateral or bilateral non-resorbable sutures that serve as fixing strings suspending the vaginal apex at a distance from the sacrum, unilateral resorbable suturing and other modifications are based merely on physician preference and have never been formally evaluated and remain experimental with anecdotal results. Therefore, there is no option of a randomized clinical trial comparing new methods against an apical fixation "gold standard".

Large prosthetic implants as a primary treatment approach for female genital prolapse are meeting with increased scepticism due to their potential for complications. The FDA has recently issued a statement to the effect, that large meshes are contraindicated as primary treatment in such situations.[16] Recently, there are encouraging results using the extremely lightweight high-porosity HexaPro Mesh, a material, that is also employed in the BSC procedure.[17,18]

HexaPro Mesh is one of the most macroporous low-density monofilament meshes available. The use of polypropylene capitalizes on the enormous experience with the biocompatibility of this fiber. The mass of foreign body left in the patient weighs less than a postal stamp and is no larger than that of a suture i.e. during an Amreich-Richter procedure.[11] It is hard to imagine, that this can be reduced any further without compromising the excellent stability of the result. The isoelasticity of the material is important, because it allows for the *in situ* self-compensation of any anatomical asymmetry in the placement of the two i-Stich sutures in the pelvis. Their position closely mimics the original anatomy of the uterosacral ligaments recreating the physiological pelvic situation. In the situation after hysterectomy bilateral vagino-sacral support is created.

The principal weakness of the present study lies in the possible selection bias induced by the decline in the number of patients following the invitation for re-examination after 6 months.

Strengths of this trial lie in the still comparably large number of patients and the meticulously standardized surgical procedure. The complete absence of patient selection and the assessment of study endpoints by a non-involved specialist to increase objectivity of the reported outcomes data and their applicability in the routine clinical setting.

Our data show minimal blood loss and an almost complete absence of surgical complications. The risk/benefit ratio of BSC can therefore be considered extremely favourable.

In comparison to other similar approaches of the past such as the IVS and the efficient and well-tolerated TPBCF it still further reduces surgical risks (Table 4) while maintaining excellent stability of the result.[2] While long-term results have not been made available for BSC so far, it can be expected from the analogy to the anatomical correction with TPBCF, that also in BSC the stability of the apical suspension at six months will translate into similar data at 5 years.[2]

BSC is a standardized, few-step, reproducible and thereby teachable procedure with a steep learning curve.[11] Designed for a broad clinical application as a single incision minimally invasive vaginal operation under general or spinal anaesthesia it lends itself to the treatment of all age groups from the young premenopausal patient in need of vaginal anatomical correction to women of advanced age. The indication for BSC is vaginal vault, cervical or uterine prolapse including complete procidentia. It is not designed to correct anterior, posterior or lateral pelvic floor defects. While women of child-bearing age should be encouraged to complete family planning before any surgical correction of anatomical pelvic floor problems, it appears, that in the incidental case of a pregnancy after BSC vaginal delivery may be safely considered.

Given the fact, that apical fixation increases the efficacy of anterior colporrhaphy,[19] it is to be expected, that the combination of these two components will become standard in the near future. Also, in this respect, the compatibility of BSC with additional simultaneous vaginal surgical interventions is an additional advantage of this method.

BSC has the potential to successfully treat SUI as a single intervention or in combination with anterior colporrhaphy. Therefore, any additional procedure addressing the suburethral support should be deferred to the completion of BSC integration and at that point considered after reassessment.

A result that warrants special attention is the marked decrease in urge complaints after BSC. In view of multi-component complex surgical interventions such as Cesa/Vasa often in combination with suburethral sling operations during secondary operations reporting results around 70-80% improvement in meeting abstracts, the Australian IVS data and now the BSC data show similar if not better potential for surgically addressing this problem, albeit in a much less invasive fashion with markedly less risk.[8,20] This property of BSC is currently under more detailed investigation in an international multi-centre trial.

CONCLUSION

The data of TPBCF were already suggesting refining the concept of generalized statements regarding meshes currently published by the FDA and others. This position is now further substantiated by the data on BSC. The sum of the available data on the isolated apical fixation of the vagina or uterus or uterine cervix by polypropylene mesh indicates, that this approach to pelvic floor repair combining high efficacy and result stability with low operative and postoperative morbidity warrants a consideration separate from larger meshes, especially made out of the older generation of materials.

ETHICS

Ethics Committee Approval: Routine QM procedure, no specific approval process required.

Informed Consent: It was obtained from the patient.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Conflict of Interest: Dirk G. Kieback receives royalties and Expert Advisory Fees from the Agency for Medical Innovation (A.M.I.).

Financial Disclosure: The authors declared that this study received no financial support.

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ORIGINAL ARTICLE

DOI: 10.34057/PPj.2020.39.03.004
Pelviperineology 2020;39(3):90-95

Impact of labour and delivery on pelvic floor: perineometry and clinical evaluation. Any protecting factor?

MARIA GRAZIA MATARAZZO[1], SALVATORE DI PASQUA[1], GIUSEPPE SARPIETRO[1], GAETANO VALENTI[1], FRANCESCO SGALAMBRO[1], MARIA FIORE[2], ANTONIO CIANCI[1]

[1]Department of General Surgery and Medical Surgical Specialties, Gynaecological Clinic, Università degli Studi di Catania, Catania, Italy
[2]Department of Medical, Surgical Sciences and Advanced Technologies "G. F. Ingrassia", Catania University, Catania, Italy

ABSTRACT

Objective: Instrumental delivery, anal sphincter laceration and long second stage are considered the main obstetric risk factors contributing to cause injuries to the levator ani muscle (LAM). The primary aim of our study was to compare pelvic floor muscles strength (PFMS) out of labour, during labour and after delivery through clinical evaluation by pubococcigeal test and instrumental evaluation by perineometry. The secondary aim was to investigate some variables related to pregnancy and delivery as potential predictors of pelvic floor dysfunctions.

Materials and Methods: This longitudinal study included nulliparous pregnant women who were enrolled between October and December 2018. Women underwent pubococcigeal test and perineometry to assess PFMS before labour (T_0), during labour (T_1) and at puerperium (T_2). Then we analysed which obstetric parameters had influenced our results.

Results: Forty-nine women completed the study. Pubococcigeal test and perineometry at maximal LAM contraction showed a decrease in strength between T_0 and T_2. Basal perineometry showed no statistical difference throughout the time. Urinary symptoms had not impact on our results while episiotomy, perineal lacerations, duration of labour and participation to a childbirth class were influent on LAM at rest or at contraction.

Conclusion: Labour and delivery alter the contraction force of the PFMs, but not the resting muscle tone. Episiotomy, perineal lacerations and duration of labour have negative impact on PFMs; participation to the childbirth, instead, could be a protecting factor for pelvic floor muscle strength.

Keywords: Pelvic floor dysfunction; pelvic floor muscle strength; perineometry; pubococcygeus test; vaginal delivery

INTRODUCTION

Pelvic floor dysfunctions (PFDs) include disorders like pelvic organ prolapse (POP), overactive bladder, stress urinary incontinence (SUI) and faecal incontinence.[1] Pelvic floor muscles (PFMs) are striated muscles that give support for pelvic organs and provide continuous tone to guarantee urinary and faecal continence together with the urinary and faecal sphincter. Weak PFMs are risk factors for PFDs. Women usually complain of these symptoms after menopause, even if in several epidemiological studies these disorders were associated with vaginal delivery.[2] Uterine contractions and maternal expulsive efforts determine an excessive stretching of the levator ani muscle (LAM) with deformation of collagenous structures, compression of the

Address for Correspondence: Salvatore Di Pasqua, Department of General Surgery and Medical Surgical Specialties, Gynaecological Clinic, Università degli Studi di Catania, Catania, Italy **E-mail:** salvatoredipasqua1990@gmail.com **ORCID ID:** orcid.org/0000-0002-7892-5615
Received: 25 February 2020 **Accepted:** 10 July 2020

pelvic floor nerves, ischemia and muscle atrophy. This stress can lead to stretch-related injuries, such as muscle tearing and striated muscle atrophy, owing to pudendal denervation, localized primarily to the region of the pubococcygeus muscle. During vaginal birth it needs to be stretched to over three times its original length. This elongation is more than twice that the striated muscle can withstand without damage in a non-pregnant animal model.[3] The main obstetric risk factors that can contribute to cause injuries to the LAM are operative vaginal delivery, anal sphincter laceration and prolonged second stage of labour.[4] There are many different methods used to assess pelvic floor muscle function and diagnose PFDs: magnetic resonance, manometry, anal endosonography, translabial ultrasound, electromyography, perineometry, digital vaginal palpation, and neurophysiological and urodynamic studies of the pelvic floor.[5] Perineometry and digital vaginal palpation are the most frequently used methods to measure pelvic floor muscle strength (PFMS) in clinical practice because they are easily applicable, well accepted by women in general and they are not expensive.[6] Evaluating PFMS can be essential in determining the type of treatment for women who present certain morbidities in the genitourinary tract. It is possible to measure the pressure developed by LAM both clinically through vaginal digital palpation or using perineometer through pressure biofeedback. The primary aim of our study was to compare PFMS out of labour, during labour and after delivery through clinical evaluation by pubococcigeus test and instrumental evaluation by perineometry. The secondary aim was to investigate some variables related to pregnancy and delivery as potential predictors of PFDs.

MATERIALS AND METHODS

We carried out a longitudinal follow up study at the Obstetric Unit of our University Hospital. A written informed consent was obtained from each participant. The women recruited met the following inclusion criteria: nulliparous, pregnancy at 37-41 weeks of gestation, no previous PFDs or pelvic surgery. The exclusion criteria included pluriparous women, twin pregnancy, comorbidities involving muscles or neurological system. Recruitment, examination and data collection were carried out by urogynaecological team of our unit. For each patient enrolled some anamnestic data we recorded as pre-labour delivery course, episiotomy, perineal lacerations (second-degree or more), SUI and other lower urinary tract symptoms (LUTS) complained during pregnancy and active labour duration. Data collection was carried out at before labour (T_0), during labour (5 cm dilatation) (T_1) and during puerperium (36 to 48 hours postpartum) (T_2). The pobococcygeal test (PC test) was our method to misure PFMS. It was performed inserting two fingers in the vagina and asking to contract giving a score for phasic contraction (0-3), endurance (0-3, depending on the duration of contraction from 0 to 9 second) and fatigue (0-3, depending on the number of contraction repetition from <2 to >9); the total score was 0-9, were 0 was the less PFMS and 9 the maximal PFMS. After this evaluation a perineometer was used to register the potential action of PFMS. The perineometer (Laborie-Urostym®) measured PFMS in centimetres of water through a vaginal probe inserted 3 to 4 cm in the vagina and recording both basal muscle tone and mean value of three voluntary maximum muscle contractions. Between contractions there was a relaxation of 20 seconds to release muscles. Perineal laceration and episiotomy variables could not affect T_0 and T_1 clinical and perineometric evauluation, so we assessed their influence only at T_2 evaluation.

Since our study does not involve the administration of drugs or other invasive procedures, the ethics committee replied that authorization was not required, according to the Helsinki declaration.

Statistical Analysis

Arithmetic mean and standard deviation (SD) were calculated for continuous variables. Percentage and frequencies were presented to describe the qualitative information. The relationship between PC test and perineometry was investigated using the Spearman's rank correlation coefficient. One-way repeated measures analysis of variance (RM-ANOVA) was used to assess the changes in PC test, basal perineometry, and maximal perineometry mean score over the predetermined time points (T_0, T_1, T_2), and the means with SD were computed. Two-way RM-ANOVA was used to assess the effect of pre-labour course, duration of labour and urinary symptoms (SUI and other LUTS) on the changes in PC test, basal perineometry, and maximal perineometry mean score over the predetermined time points (T_0, T_1, T_2). When the F-ratio of the ANOVA reached a critical level (corresponding to $p<0.05$), post hoc analysis with Bonferroni adjustment was used. Episiotomy and perineal tears were evaluated only at T_2. The SPSS 21.0 software was used for the statistical analysis. The statistical significance was set at p-value <0.05.

RESULTS

A total of 49 women were included in our study between October and December 2018; of these 34 completed the study, nine dropped out and six women missed labour evaluation because they did caesarean section (Figure 1).

The patients' characteristics and obstetric variables are reported in Table 1. Table 2 shows mean values and SDs of PC test and

perineometry at rest and at maximal contraction during the three evaluations. The results highlight a statistically significant decrease in PC test and perineometry values at maximal LAM contraction between T_0 and T_1 and between T_1 and T_2. Particularly, the PC test shows a reduction in muscle contraction strength by 18% between T0 and T1 (p=0.002) and 44% between T_1 and T_2 (p=0.0001). Perineometry evaluation at maximal contraction also differed significantly between time points dropping by approximately 28% between T_0 and T_1 and 45% between T_1 and T_2. Conversely, basal perineometry showed no statistical difference throughout the time.

The results, clinically and instrumentally obtained under maximal contraction, were then compared. A weak statistically significant correlation was found out of labour (rho=0.49, p=0.003) and during puerperium (rho=0.37, p=0.040). At T_1 no correlation was found. Finally, we evaluated potential predictors of PFDs. Urinary symptoms in pregnancy (SUI and other LUTS) did not influence PFMS both at PC test and perineometry during all evaluations. Perineal lacerations and duration of labour (>5 hours), considered at T_2 evaluation, interfered negatively with the values obtained at perineometry at rest and after maximal contraction. No participation to pre-labour course was negatively associated to weak muscle tone at rest perineometry.

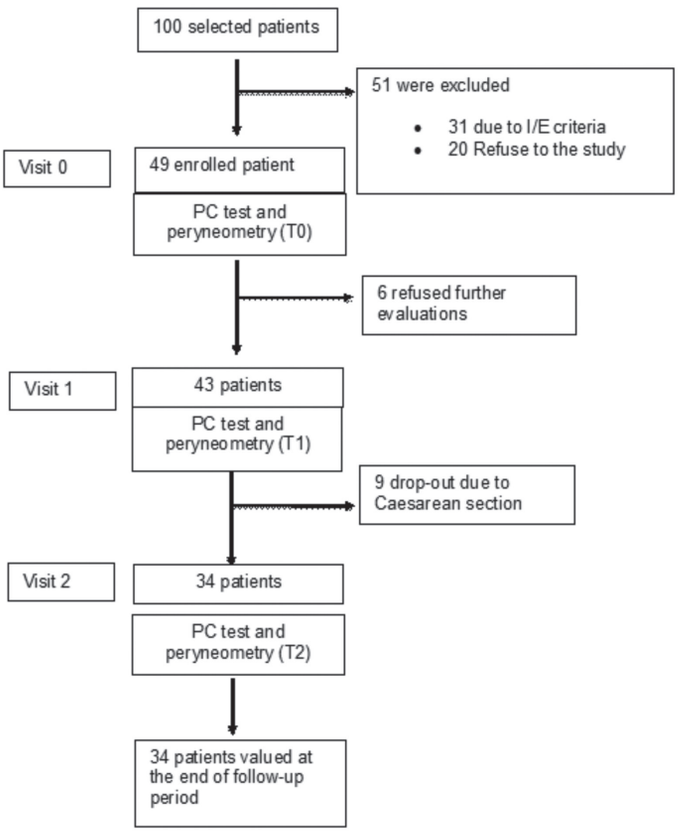

Figure 1. Study flow-chart
I/E: Inclusion and exclusion criteria, PC test: The pobococcygeal test

Episiotomy affected our measurement at maximal perineometry in puerperium (T_2) (Table 3).

DISCUSSION

Our results are both clinical and instrumental, resulting in a modification of the PFMS detected during labour and vaginal

Table 1. Patients' characteristics and obstetric variables (n=49)

Variables	n (%)
Mean age (years) ± SD	28±5.2
Age (years)	
<27	12 (35.3)
28-31	14 (41.2)
>32	8 (23.5)
Pre-labour delivery course	
Yes	10 (29.4)
No	24 (70.6)
Episiotomy	
Yes	12 (37.5)
No	20 (62.5)
Grade of perineal tears	
0	18 (52.9)
1	8 (23.5)
2	8 (23.5)
Time of labour (hours) (IQR)	5 (3-9)
Pre-pregnancy weight (kg) (IQR)	59 (54-71)
Post-pregnancy weight (kg) (IQR)	74 (66-81)
Weight gain (kg) (IQR)	14 (10-16)
SUI	
Yes	14 (41.2)
No	20 (58.8)
LUTS	
Yes	2 (5.9)
No	32 (94.1)

SD: Standard deviation, IQR: Interquartile range, SUI: Stress urinary incontinence, LUTS: Lower urinary tract symptoms, n: Number

Table 2. Values of mean and standard deviation of PC-test, basal and maximal perineometry at 3 time points (T_0, T_1, and T_2)

Dependent variables	T_0	T_1	T_2
PC-test (score 0-9)	5.0±2.1	4.1±1.9	2.3±1.1
Basal perineometry (cmH_2O)	5.1±1.1	4.7±1.4	4.8±2.3
Maximal perineometry (cmH_2O)	26.3±13.4	18.9±9.6	10.3±6.2

PC-test: The pobococcygeal test

Table 3. Two-way RM-ANOVA for baseline-to-endpoint PC-test, perineometry, maximal perineometry level changes

Dependent variable	PC-test			
Independent variables	**df**	**F**	**p valuea**	**Error**
Pre-labour delivery course	1.634	2.258	0.124	53
SUI	1.669	1.905	0.165	53
LUTS	2	1.039	0.360	64
Age	1.668	1.422	0.249	53
Labour duration	1.964	1.426	0.248	54
Perineometry				
Pre-labour delivery course	1.615	4.346	**0.025**	51
SUI	1.640	2.054	0.146	52
LUTS	1.596	0.563	0.535	51
Age	1.550	1.325	0.270	49
Labour duration	1.378	7.089	**0.006**	44
Maximal perineometry				
Pre-labour delivery course	1.452	0.162	0.781	46
SUI	1.405	0.837	0.402	45
LUTS	1.479	1.839	0.178	47
Age	1.413	2.331	0.124	45
Labour duration	1.544	11.067	**0.000**	49

RM-ANOVA: Repeated measures analysis of variance, PC-test: The pobococcygeal test, SUI: stress urinary incontinence, LUTS: lower urinary tract symptoms

delivery. Several authors have, already, published that the obstetric factors responsible for anal sphincter rupture are instrumental delivery and prolonged second stage of labor.[7,8] Moreover Kearney et al.[9], through magnetic resonance in nulliparous women, have shown that these obstetric factors are responsible for injuries to the LAM after delivery, with an increased risk of POP. Unlike us that evaluated the birth trauma by perineometry, Dietz[10] assessed the birth trauma with other methods comparing some instrumental diagnostic techniques such as magnetic resonance and 4D ultrasound, concluding that the latter, together with PC test with the digital vaginal palpation, are sufficient methods for the diagnosis of avulsion or injury of the LAMs. In the literature, another study, had evaluated the correlation between the measurements obtained with perineometry and the clinical ones obtained with the vaginal examination.[5] Riesco et al.[5], in fact, showed the possibility of measuring the tone of the pelvic floor musculature with these two methods, demonstrating a concordance between the results obtained. Our data were recorded subjectively by PC test, and objectively by perineometry: the results of clinical and instrumental evaluation agree before delivery and in puerperium but not during labour, probably because this phase is influenced by emotional factors related to pain. Macêdo et al.[11] evaluated the impact of childbirth in nulliparous women on pelvic musculature comparing the data obtained at perineometry and electromyography and demonstrating a strong correlation (r=0.968) between the perineometric and electromyographic findings in the functional evaluation of the PFMs, following appropriate training. Our results showed that the childbirth class was a protective factor for the resting muscle tone, possibly due to the positive effect of various breathing techniques and perineal massage that improve elasticity and the ability to stretch muscle fibers. Indeed, the muscle fibers of the LAM, according to Lien et al.[12], undergo considerable stretching during delivery; each fiber has a stretch ratio that can be increased with perineal massages as preparation for childbirth.

CONCLUSION

These measures can therefore make a protective action on the pubococcygeal muscle with a long-term positive effect on the stability of the structures that support the pelvic floor. Instead, variations in maternal pelvic shape, foetal head shape, the degree of moulding during delivery, ymphyseal diastasis and the types of episiotomies may undoubtedly affect the maximum muscle stretch ratios.[13] Based on our results, the occurrence of SUI or other urinary symptoms in pregnancy, such as urgency and frequency, does not seem to be associated with a decrease nor in perineal tone at rest neither in PFMS. In fact, during pregnancy many factors can explain the transient SUI, such as the release of relaxin, the weight exercised by the foetal head and the increase in maternal weight.[14] Moreover, in our study, we focused on the duration of first-stage of labour, not of the expulsion stage, as possible main risk factor for uterine-vaginal prolapse. Patients in whom labour is prolonged for more than five hours experienced a lower muscle tone at rest and after childbirth as well as a lower strength of contraction. In the literature it has, already, been highlighted that an extension of the expulsion stage is one of the main risk factors for uterine-vaginal prolapse.[15,16] On the contrary, Uma et al.[17] investigated on risk factors related to POP and they found no significant association to labour prolonged >12 hours [Odds ratio (OR): 1.51, 95% Confidence interval (CI): 1.00-2.27]. Finally vaginal lacerations and episiotomy, as already known in the literature, alter PFMS after delivery in the patients studied. It was demonstrated that episiotomy decreased the likelihood of obstetric anal sphincter rupture (OASR) for the primiparous [OR: 0.83, 95% CI: 0.75-0.92], but not for the multiparous women (OR: 2.01, 95% CI: 1.67-2.44). Episiotomy was associated with decreased risks for OASR in vacuum assisted deliveries (OR: 0.70, 95% CI: 0.57-0.85).[18] In a recent study of Bø

et al.[19], aiming to compare vaginal resting pressure, PFMS and endurance and prevalence of urinary incontinence at 6 weeks postpartum in women with and without episiotomy, the authors conclude that pelvic floor muscle function and prevalence of postpartum urinary incontinence were not affected by a lateral or mediolateral episiotomy. Oliveira et al.[20], in a biomechanical analysis on the impact of episiotomy during childbirth, demonstrated that a mediolateral episiotomy has a protective effect, reducing the stress on the muscles, and the force required to delivery successfully up to 52.2%. The intervention, also, has benefits on muscle injury, reducing the damage to a small zone. Other studies with the same aim have already been published, considering a time interval of about 6 weeks after delivery.[21,22] Instead, we restricted the interval to 48 hours to evaluate a possible faster return to normal strength. The peculiarity of our study compared to the others present in the literature is the assessment of muscle function even during the active phase of labour and the interpretation of some variables as predictor factors.

The limitations of our study consist in the small number of enrolled patients and the lack of prolonged follow-up giving information on the possible recovery of muscular function of the levator ani.

CONCLUSIONS

We can affirm that labour and delivery alter the contraction force of the PFMs, but not the resting muscle tone. Episiotomy, vaginal lacerations and duration of labour have negative impact on PFMs; participation to the childbirth, instead, could be a protecting factor for PFMS.

Ethics

Ethics Committee Approval: Since our study does not involve the administration of drugs or other invasive procedures, the ethics committee replied that authorization was not required, according to the Helsinki declaration.

Informed Consent: A written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT

DOI: 10.34057/PPj.2020.39.03.005
Pelviperineology 2020;39(3):96-98

Medical approach to urinary retention after vaginal hysterectomy

İLKER GÜLBAŞARAN[1], AYTEKİN TOKMAK[2]

[1]Salihli State Hospital, Clinic of Gynaecology and Obstetrics, Manisa, Turkey
[2]Zekai Tahir Burak Women's Health Training and Research Hospital, Clinic of Gynaecology and Obstetrics, Ankara, Turkey

ABSTRACT

A 65 years old women presented with grade 3 descensus, grade 4 cystocele, grade 2 rectocele. The patient had no complaints of urinary incontinence. She underwent vaginal hysterectomy, colporrhaphy anterior, colporrhaphy posterior and sacrospinous fixation operations. On the postoperative first day, after removal of the catheter, the patient developed glob vesicale. The urinary retention was thought to be due to oedema secondary to surgical operation and urinary antiseptic and anti-inflammatory treatment was started. The catheter was removed 5 days later but re-inserted due to urinary retention. Alpha-adrenergic blocker (doxazosin) was added to the medical treatment. After 3 days, the catheter was removed, and spontaneous urination was observed and doxazosin treatment was stopped.

Keywords: Alpha-adrenergic blocker; urinary retention; vaginal hysterectomy

INTRODUCTION

Hysterectomy is one of the most widely used major surgical procedures in gynaecology practice.[1] Patient's anatomy is important as well as the experience of the surgeon in the choice of laparotomic, vaginal or laparoscopic approaches. Vaginal hysterectomy is the most preferred method in the cases of prolapsus. The advantages of vaginal hysterectomy are lower rates of infection, fewer complications, less pain, shorter hospital stay, shorter operating time and better cosmetic outcome. Micturition difficulty and urinary retention are common complications after abdominal or vaginal hysterectomy.

There are various medications for treatment of postoperative urinary retention, including cholinergic agents, anticholinesterase agents, alpha-blockers, sedatives and prostaglandin.[2,3]

Neostigmine is an acetylcholinesterase inhibitor or anticholinesterase agent. It causes accumulation of acetylcholine around the cholinergic nerve terminals.[4] Urinary bladder contraction is critically dependent on acetylcholine-induced stimulation of contractile muscarinic receptors on the smooth muscle (detrusor) of the urinary bladder.[5,6] Intramuscular injection of neostigmine is only effective in 70% of patients, and it is associated with many side effects such as bradycardia, bronchoconstriction, increased secretions, nausea, and vomiting.[7]

Alpha-adrenergic receptors are located in the bladder neck and proximal urethra, and blocking these receptors with alpha-blockers may facilitate urine flow and prevent postoperative urinary retention.[8]

In this report, we aimed to present the medical management of the patient who underwent vaginal hysterectomy, colporrhaphy anterior, colporrhaphy posterior and sacrospinous fixation and developed urinary retention after catheter removal.

Address for Correspondence: İlker Gülbaşaran, Salihli State Hospital, Clinic of Gynaecology and Obstetrics, Manisa, Turkey
E-mail: ilkergulbasaran@gmail.com **ORCID ID:** orcid.org/0000-0001-5504-8755
Received: 02.02.2020 **Accepted:** 07 July 2020

CASE REPORT

A 65-year-old female patient (gravida: 3, parity: 2, abortus: 1) was admitted to the outpatient clinic with the complaint of uterine prolapse. The patient was prepared for operation due to grade 3 descensus, grade 4 cystocele, grade 2 rectocele on vaginal examination. The patient had no complaints of urinary incontinence. The patient's medical history revealed that she had been receiving medical treatment for hypertension and had been postmenopausal for 20 years. Preoperative complete blood count (Hb=12.3 g/dL), complete urinalysis and routine biochemical values were normal. In transvaginal ultrasonography, the uterus was atrophic and the endometrial thickness was 3 mm and there was no adnexal pathology. The patient underwent vaginal hysterectomy, colporrhaphy anterior, colporrhaphy posterior and sacrospinous fixation operations under spinal anaesthesia. After the surgery, a catheter into the bladder, and a vaginal pack were placed. On the postoperative first day, the patient had a haemoglobin value of 10.8 g/dL, and her vaginal pack and catheter were removed. After removal of the catheter, the patient developed globe vesicale (distended bladder), therefore foley catheter was inserted again. The urinary retention was thought due to oedema secondary to surgical operation and urinary antiseptic and anti-inflammatory treatment was started and urine culture was performed. The urine culture was negative and the catheter was removed 5 days later but reinserted due to urinary retention. Alpha-adrenergic blocker (doxazosin 1x8 mg/day) was added to the medical treatment. After 3 days, the catheter was removed, and spontaneous urination was observed and doxazosin treatment was stopped. The residual urine volume was 30 cc. The patient was discharged on the 11th postoperative day. Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION

Vaginal hysterectomy with or without colporrhaphy is one of the most common surgical procedures for the treatment of symptomatic pelvic organ prolapse.[9] In the literature, the incidence of postoperative urinary retention after any vaginal prolapse surgery is reported to be between 6% and 29%.[10-12] Known risk factors for urinary retention after vaginal prolapse surgery include advanced age, high-grade cystocele, severe intraoperative blood loss, levator and Kelly plication, postoperative pelvic hematoma, and removal of the catheter in a short time.[12,13] In a study by Leung at al.[1], it was found that postoperative urinary retention was more common in women older than 63 years. In our case, we think that the presence of advanced age and high-grade cystocele may be risk factors for urinary retention.

However, there is no consensus regarding the time of urinary catheter removal after vaginal propapsus surgery. In the literature, there was no significant difference in the rates of urinary retention between the removal of urinary catheter on postoperative day 1 and day 3 in some studies.[14] However, a randomized controlled trial by Hakvoort et al.[15] showed a significant difference in urinary retention between day 1 and day 5 catheter removal (recateterization rate 9-40%).

The longer the duration of catheterization, the greater the incidence of urinary tract infection and the duration of hospital stay. For this reason, we usually remove the urinary catheter on the 1st postoperative day. In the literature, the incidence of urinary retention after vaginal hysterectomy was 6-27%, while in our series we found 1.49% (1/67).

It is known that there are alpha-adrenergic receptors in urinary tract especially along the bladder neck and urethra.[16] Stimulation of these receptors causes an increase in smooth muscle contraction and bladder neck resistance, whereas alpha-adrenergic blockage causes smooth muscle relaxation and a decrease in bladder output resistance.[17] For many years, alpha-adrenergic blockers have been used for the treatment of benign prostatic hypertrophy to reduce resistance to the bladder neck and to relieve the flow of urine.

Livne et al.[8] suggested that alpha-blockers should be used prophylactically in order to prevent urinary retention after abdominal or vaginal hysterectomy. The incidence of postoperative urinary retention in our hospital is quite low, because of this we do not use prophylactic alpha-adrenergic blockers.

In conclusion, urinary retention is common after vaginal hysterectomy. The course and clinical management of this process carry some difficulties for both the surgeon and the patient. We think that medical therapies such as alpha-adrenergic blockers may be useful in providing spontaneous micturition in patients who have no additional complication and palliative methods is not successful.

ETHICS

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.34057/PPj.2020.39.03.006
Pelviperineology 2020;39(3):99-104

The frontispiece of Vesalius' Fabrica

ANDREA MENEGHINI, NICOLA MENEGHINI

School of Medicine, University of Padova, Padova, Italy

ABSTRACT

The frontispiece of the *De Humani Corporis Fabrica*, painted by a pupil of Titian, shows a neoclassical amphitheater in which the scene is represented of an autopsy performed by Andreas Vesalius, just appointed as Professor of Anatomy at the University of Padua. The body on which Vesalius is carrying out the anatomical investigation is that of a woman executed for committing a crime and who had attempted to escape execution by claiming to be pregnant. The autopsy therefore had the purpose of verifying the veracity of her statements, but also the professionalism of the midwife who, expressing her negative opinion, had determined the execution of the sentence. Many figures are around to assist, differently motivated, each representing a quite singular aspect. Under the sector table, two menials (cerusics) are arguing with each other to maintain a role that, with the advent of Vesalius, will no longer be up to them but to the medical sector.

Keywords: Anatomy; Andreas Vesalius; De Humani Corporis Fabrica; Frontispiece; Padua anatomy theater

INTRODUCTION

The frontispiece of the *De humani corporis fabrica* can be considered as the manifest of a new way of thinking anatomy. In fact, this imposing work by Vesalius will determine a profound break between what was before and what will later become the study of the human body. It is not a revolution in itself but rather the beginning of a revolution, and the latin title *De fabbrica* implies the concept of arguing about an inert system which is analytically split and studied in smaller parts. The evolution of Vesalius by Realdo Colombo will be very different: "De re anatomica", translated into modern terms, would sound as "on anatomical activities", i.e. no longer just the study of inanimate elements, but the study of their functioning, what today we name *physiology*.[1] Among the many merits of Andreas Vesalius we must recognize the speculative method that leads him to verify the age-old postulates of Galen and if necessary to refute them, but certainly the great innovation is in the addition to the text of a rich and detailed iconography. No anatomy text will ever be considered as such again, after the *De humani corporis fabrica* if not accompanied by a clear and exhaustive sequence of explanatory images. This makes it one of the most beautiful chapters in the entire history of medicine, and one of the best books ever published, a sort of *divine anatomy*, if we can pass the parallel with the poem of the great poet Dante. Sir William Osler described the *Fabrica* as "the greatest medical work ever printed."

The Book

De humani corporis fabrica for its fine Latin and depth of topics covered is, from the start, not a manual for students but a text from consultation reserved

Part of this article was the topic of a presentation made at the International Meeting of the European Society of Pathology on the History of Medicine and Pathology, University of Padua 4-6 June 2015.

Address for Correspondence: Andrea Meneghini, School of Medicine, University of Padova, Padova, Italy
E-mail: dott.andreameneghini@gmail.com **ORCID ID:** orcid.org/0000-0003-0197-1266
Received: 24 June 2020 **Accepted:** 26 July 2020

for scholars culturally very prepared and wealthy. Since the beginning, the purchase price was high and accessible to a few (five guilders, the first documented price) and, it must be said, that over time has maintained its value. Out of curiosity, visiting some sites of online booksellers offering ancient texts and finding it, the price for a copy in good condition, including the title page, is around €400,000.00; you can get it for €250,000.00 without the title page. The rise in value of a copy of *Fabrica* 1543, over the last 75 years equals nearly a hundredfold increase of purchasing power during the same period. On 18 March 1998 the so called "imperial" *Fabrica*, partially hand-coloured, was auctioned by Christie's with a base price of £500,000; it was sold for £1,652,500 to a collector whose name remains unknown. Maybe it was a second copy, on vellum, that the Emperor Charles V gave to the French ambassador Jaques Mesnage when he was resident at the imperial court. The first vellum copy, partially hand-coloured, that Vesalius gave to Charles V and kept in the University library of Leuven went, in fact, destroyed in a raging fire, broke out in August 28, 1914. The design of the drawings has been developed in the atelier of Titian. Though the graphic work is attributed to Stephan Van Calcar, many authors now agree on a supervision of Titian and some substantial contribution by Domenico Campagnola. Worth a special mention the precise and elegant wood engraving performed by talented Francesco Marcolino da Forlì.[2] Thanks to their unsurpassed mastery, we have still today an image viewing with a sharpness truly unique.

In the dedication of the work to the Emperor Charles V, Vesalius places considerable emphasis on the fact that Galen had written about anatomy without ever having dissected human bodies. He complains the decline of medicine, from his proper state in the time of the Ancients, due to people ceasing to use the hands in medicine: "*When the hand is used, medicine flourishes; when it is neglected, medicine languishes; when it is restored to use, medicine can flourish again*", he wrote, and accused his contemporaries of repeating "*like crows*" a knowledge based solely on the authority of classical texts and not on direct observation.[3] Very briefly, the *Fabrica* originates from the need to revisit the human anatomy with a "scientific" method, as already tested in 270 BC in Alexandria of Egypt by Andrea of Caristo, Marino of Alessandria, Eròfilo of Calcedonia and Erasìstrato of Ceo, emphasizing with punctuality the discrepancies verified by the statements in the dissecting table as reported in the canonical texts. He could not accept the assertion of his first former professor, the parisian Jacques Dubois (Jacobus Silvius),[1] "*Galen said it all; nothing can be further discovered. The reported differences are only due to the change of the human body from the time of Galen*". Perhaps, for this reason too, Sylvius is not ranked in the top ten of the best teachers of medicine of the past and few know him! The "*confutations"* to the dogmas of Galen (over two hundred) have been duly listed in the index, at the end of the seven books, to the letter G.[4] The *Fabrica* was printed by Johannes Oporinus, in Basel. Vesalius chose this city because it had become the largest publishing center in Europe, surpassing Venice. But mainly because Oporinus, studying Medicine, Latin, Greek and Hebrew, could easily understand the contents of the work: he could appreciate what was written, following a logical thread and putting more passion into printing texts. He is also considered to be a typographer meticulous and innovative, therefore suitable to work on a book that contains many new features and destined to be successful. The ambitious Vesalius may have chosen Basel also because of its better location for the book distribution, down the Rhine to France and Germany, or over the Alps to Italy, and he had also published twice before with the firm of Oporinus. In fact the *Fabrica* is considered a masterpiece of Renaissance typography. The *Fabrica* itself, therefore, includes three revolutions linked together: the anatomical revolution, the pictorial representation of nature, and, last but not least, the new printing techniques. For these reasons the frontispiece (Figure 1) is a real *manifest* of modern anatomy. It is the figurative representation of a giant cultural step, elegantly played. "*That's one small step for man, one giant leap for mankind*" as said Neil Armstrong, in descending the ladder of the lunar module, after the moon landing, in July 20, 1969. Considering the enormity of the event, the comparison is not misplaced or exaggerated.

The Frontispiece: Obstetrics, Art, History

Let's start by looking at the picture as a piece of theater, a real event dramatically captured as if on a photograph. **The anatomy lesson** is open, and accessible to everybody, in a wooden theater built on purpose, in Palladian style on the model of Alessandro Benedetti, in a semicircular frame; the bystanders, over a hundred people, are placed on three-levels platform. Vesalius is the man dissecting and giving instructions, serving as the professor, dissector, and ostensor. In the center of the scene he stands surrounded not only by his students and fellow physicians but also by the Rectors of the city and university, councilors and representatives of the nobility and church. The author himself is standing, while his hands are unmistakably engaged in demonstration. Not only he is demonstrating from the cadaver, but he himself is the prosecutor. He signalizes the break with authority - by descending from the *chair,* and dispensing with the ostensors or demonstrators - and relegates the menials, who formerly did the dissection, to a position beneath the table

Figure 1. Frontispiece of the *De humani corporis fabrica*. Overview of the neoclassical anatomical theatre. The scene is majestic. Over a hundred figures flock to the steps of a neoclassical theatre, to attend the autopsy of the Professor from Brussels. Between symbols and allegories, these characters tell their own story, and on closer inspection the medical students, the only ones entitled to attend a truly macabre show, are a small minority. This crowd for disparate reasons rushes to see the autopsy of a woman, perhaps pregnant, executed for a crime that not even an alleged pregnancy has been able to prevent. And close to the corpse is He, proud and elegant as one would not expect from a medical sector, but the representation is important and he is the leading actor. The spectacle of a new anatomy is staged, where the anatomist can now demonstrate his knowledge by comparing it with the evidence of a still "hot" human body

where they are seen quarreling among themselves. In this way the reader is prepared for the subject matter of the book, expecting a description of the human body that will be based on the author's observations. In the foreword Vesalius specifically mentions the use of the hands which, he says, has been "*completely neglected*" by physicians since the time of the Romans.[3] "*Medici manuum munus ad alios reijcientes, Anatomen perdiderunt", "doctors by abandoning surgery to others lost their knowledge of anatomy"* according to the translation of Loris Premuda[5-7] medicine itself had declined from its former splendor. The tools needed for the surgery are laid on the table: a sponge, a scalpel, a razor, a candle, but also a pen, an inkwell and a sheet as if to emphasize that the text should follow the experience observational and not precede it. Vesalius is unveiling the innermost secrets of God's creation, **the internal organs of a woman**. In the entire history of anatomy, this is the first time we can see the union between practice and theory: there is no more the differentiation of roles. Vesalius is portrayed at the dissection table, engaged in a performance: he is actually doing a dissection with his left hand raised, to emphasize what explains during the demonstration; the right hand dipped in the first venter of a woman, and his gaze looking out of the picture.

Pregnant or not pregnant? The body belongs to a woman who, as the same author tells us[7], is a Paduan prostitute, hanged because guilty of some horrible crime, having tried to avoid the condemnation by falsely declaring herself pregnant. Marcantonio Contarini, magistrate of the criminal court of the Venetian Republic, subjected her to examination by a midwife who expressed serious doubts; perhaps the figure of a woman peeping out, in the shadows, behind the right-hand column. The magistrate authorized the execution and ordered an **autopsy** for verification and confirmation. Looking carefully at the picture one can see the marks of the rope on the neck of the deceased woman (Figure 2). First important message is that is the human body, in its centrality, demonstrative and representative, till now relegated to the comment function, to dictate text. No longer built on writing, the figure relates directly to itself; it is the same text that one browses on the dissecting table.[8] On the entablature above the sumptuous Corinthian columns between the triglyphs appear the *bucranium* (ox's head) and the lion of St. Mark. The colonnade is reminiscent of the old courtyard of the Bò (ox), the ancient site of the University of Padua founded in 1222, at that time in major restructuring, and that one can still admire before entering into the wonderful *Aula Magna* of the Bò. More on the top, on the left on the parapet of the window, from which leans a figure of young man, you can notice a symbol that

Figure 2. Detail of the frontispiece of the *De humani corporis fabrica* which highlights Vesalius in the act of describing the visceral anatomy of the corpse

resembles the Greek capital letter phi. It is the monogram of Johannes Oporinus, publisher of the Treaty.

On this young man leans many critics have wanted to see the representation of the advancing *new*, and he is in full light, as opposed to the *old*, represented by the senile bearded figure who looks out the window right in the twilight. Some critics interpret the whole scene in the light of this separation; on the left the modernity, to the right the past.[9] The nude figure clinging to the column on the left indicates the importance of surface anatomy as shown in the *Epitome* and draws attention to the functional aspects which Vesalius is teaching. Vesalius is topped by an articulated skeleton (true representation of what he prepared and presented at the University of Basel of infamous Swiss criminal Jakob Karrer), who appears to be seated upon a railing with its legs dangling, holding a magisterial cane (perhaps the one used by demonstrator during the autopsies): *"Hic est locus ubi mors gaudet succurrere vitae"* seems to say to the bystanders, anticipating the *motto* engraved on the lintel of the gateway to the anatomical theater of the Bò. However,

many Authors stress the fundamental importance of the osteology in the study of anatomy. By a twist of perspective, the pole extends upward so far that its proximity to the decorative cartouche enclosing the title, makes it look like a trident. The skeleton is surmounted by the heraldic shield of Vesalius. The coat of arms supported by two cherubs displays three weasels coursing greyhounds, the emblem of the anatomist's ancestral home (Wesel in Cleves) and a play on the vernacular version of his name. Below, one can see the cartouche with the title of the work. The author's name is with larger fonts, followed by citizenship his official role, and finally with the minor fonts the real title. The exact opposite of what is happening now. The two interesting mythological animals, placed alongside, recall the Chimeras placed on the facade of Notre Dame in Paris. A second cartouche, placed at the base of the image bears the Privileges, protecting the *Fabrica* from unauthorized copying, were obtained from the Venetian Senate and from Charles V, and one was promised from France. A fore-running attempt of copyright that was not sufficient to protect the work from a multitude of plagiarism. It is also curious to notice the naked figure peeping from the column on the left of the scene. According to the intentions is an allegory that stresses the importance of appearance, a study of the artistic nude serving anatomist to know the anatomy of the surface, which is important both for the artists and for the anatomists. The austere character in classic suits and thick beard on the right of the table is supposed to be, by most of the commentators of this table, Renaldo Colombo, Vesalius' assistant and successor. One of the friends mentioned cordially in the 1543 *Fabrica,* later became a critic and rival. The anatomist Colombo is mentioned as "*My good friend now a professor of sophistic at Padua, a most diligent student of anatomy*".[3] For others scholars, he represents the Golden Age, or Aristotle, or Marcantonio Genoa, philosopher and close Andrea's friend that greatly encouraged the *Fabrica* composition.[10] He is represented in the act of admonishing the keeper of the dog, that is behind, not to disturb and remove the animal that is stamping his toe with the paw. About paws, look at the back of the dog, it's just a game of perspective, if you look carefully you see that is the foot of the keeper, with six fingers. The figure back on the right side of the table is assumed to be Wolfgang Herwart friend and financier."*He first inspired me to begin this work, and has been no less my eager counselor than the rare model of virtue"*, wrote about him Andrea.[3]

Another graph joke on the right side of the figure, a rascal hand, that seems to come from nowhere. In the face that appears above the right shoulder of the anatomist some scholars see Titian.

Some figures in the title page seem to ask the viewer to keep the focus on the center of the stage: the surgical demonstration. On the right we can see a noble figure of an old man with a closed book in his hand indicating to someone the dissection table to signify its acknowledgment of *experientia* on ancient texts. See also the explosive curiosity of the young man, on the left, who in the desire to penetrate into the scene leans on the railing overhanging the person standing in front of him appearing annoyed. See also on the right, the figure of an elegant old man of brooding monk engaged in an exchange of views with a neighbor. In contrast on the right we can see an old, cowled, bearded man with classic suits, sitting on a stool, assisting the demonstration with intense but restrained interest, such as those who see their certainties disappear. For some commentators he might be Galen himself in an attitude not oppositive but of disconsolate acceptance, in front of the truth of the advancing *new.* A little to the left, another animal, a noisy monkey, busy biting the hand of the keeper, also held with a chain. It represents, with the dog, the animal anatomy. An interesting interpretation of this particular was given me by an art expert who reminded me that the tied monkey symbolizes the primal instincts kept in check; therefore, the representation of a concept of the anatomy that must be contained in the fields of comparative anatomy and thus of secondary importance. On the left, on the second order of tier there is a young man who follows the scene with an open book, just to the left of the dark and brooding monk. Harvey Cushing (a great student of Vesalius) claims he is Jan Stephen von Calcar, the author of the illustrations, in the act of taking sketches for subsequent tables. The character with the beard to the left of the skeleton, wearing characteristically Jewish garb, could represent Lazarus de Frigeis[6] great Talmudist that Vesalius credits, "*a distinguished Jewish physician and close friend*" He is looking with sad and compassionating eyes the old man sitting on his left which we have just assumed to represent Galen. Lazarus assisted him with the Hebrew translation in the *Fabrica.* More direct evidence that Jewish medical students and physicians studied the works of Vesalius lies in the existence of a rare manuscript of the *Fabrica* in Yiddish, dating from the late 1500s. Another relationship between Vesalius and the Jews is shown by his tenure as a lecturer at the University of Padua. Our University, indeed, was one of the few institutions of higher learning in the Medieval and Renaissance periods that admitted Jews. As a result, many European Jews attended his classic dissections. On the right of the dissection table, the spectators are giving rapt attention, but one has an added advantage: the eyeglass!

CONCLUSION

We leave the reader with an invitation to look with new eyes at this title page, hoping that he can find pleasure in searching the so many messages that since five hundred years the Vesalius' frontispiece brings to all of us.

ETHICS

Peer-review: Externally peer-reviewed.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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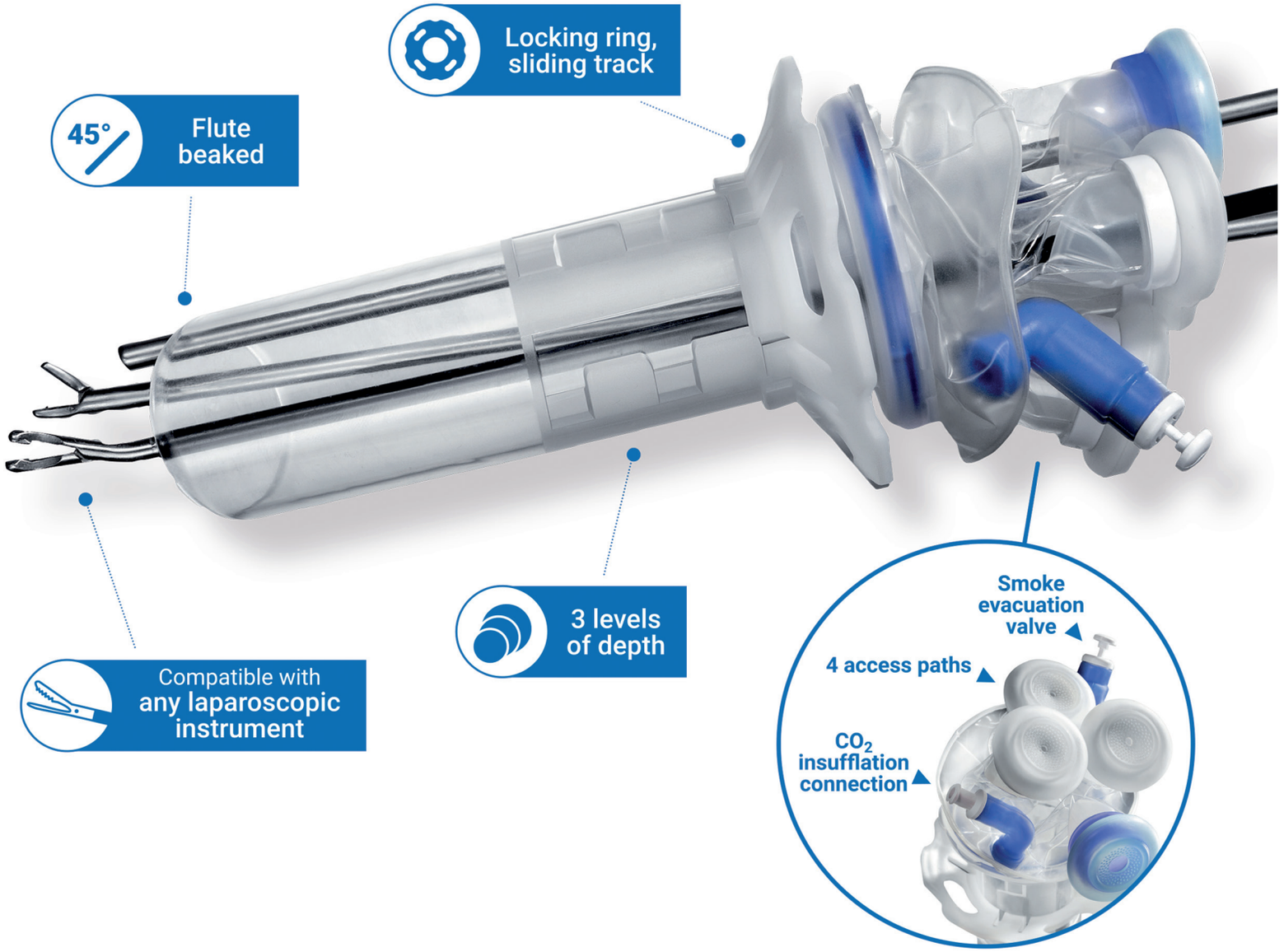

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Return to normal activities in a few days

SECCA PATIENTS **84%** experienced significant improvement

Greater Quality of Life

Less than **1%** complications

MEDERI

Distributore esclusivo:

INNOVA medica SPA