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A multidisciplinary pelvic floor journal

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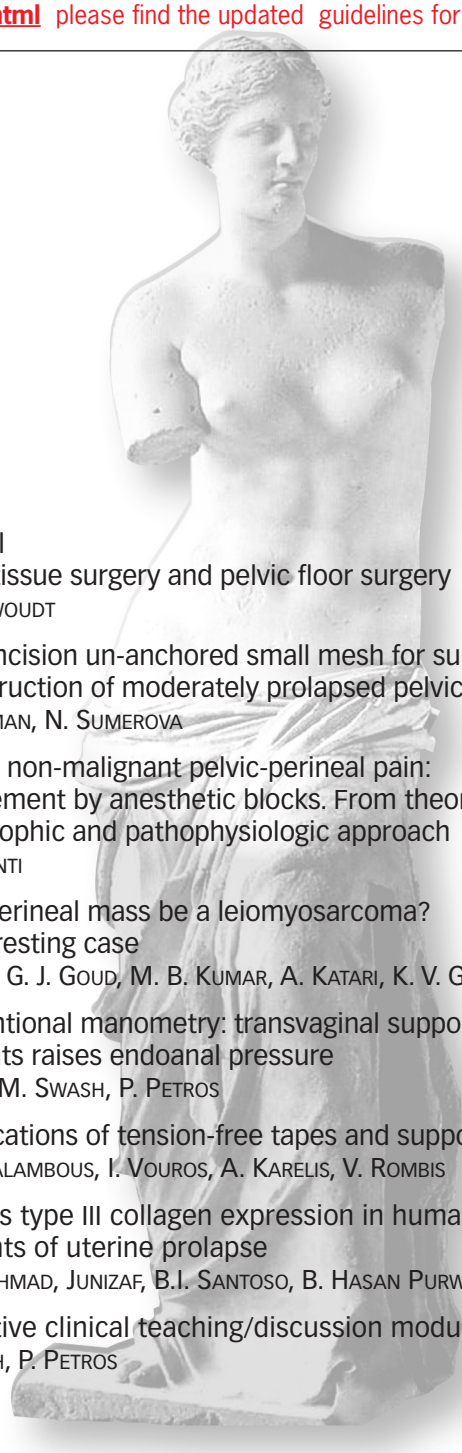

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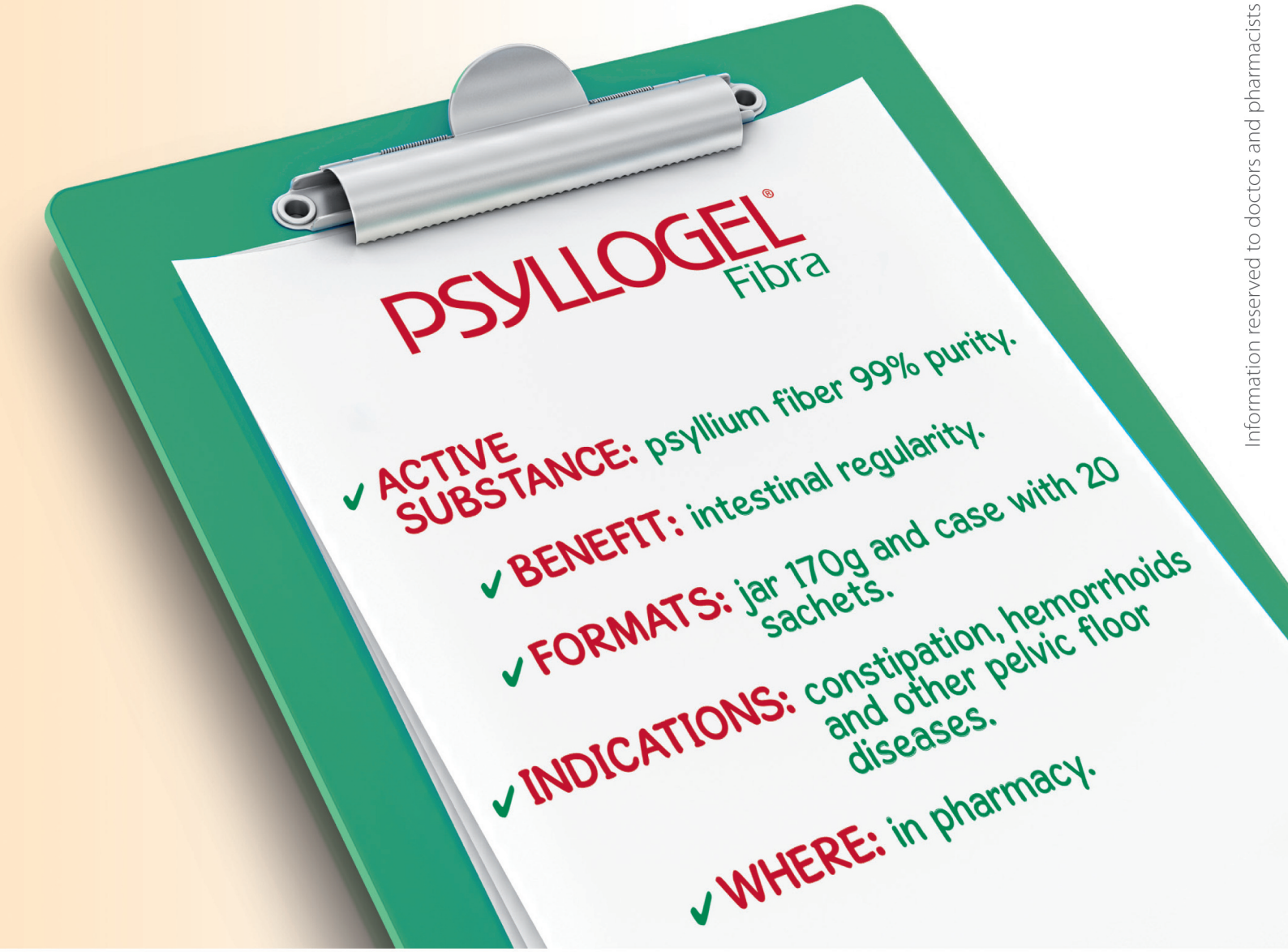

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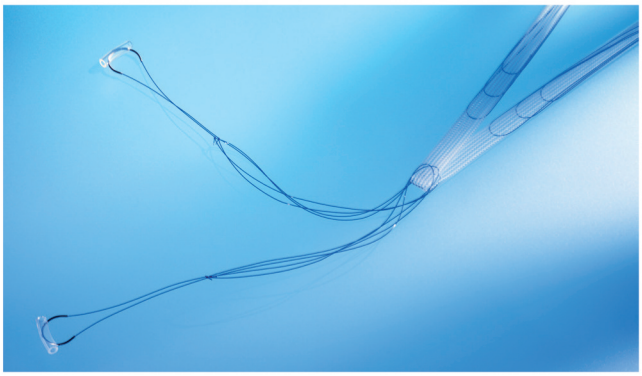

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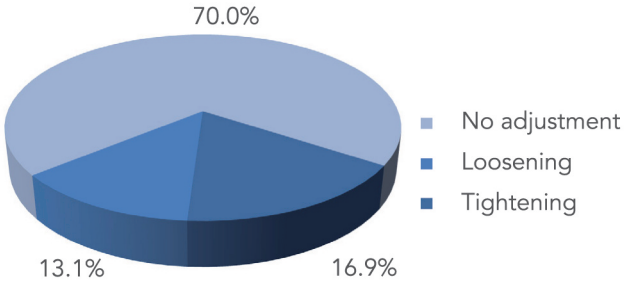

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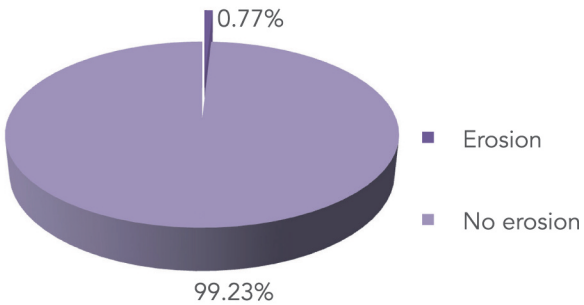

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Editorial

Native tissue surgery and pelvic floor surgery

ANDRI NIEUWOUDT

During the Kelly[1] and White[2] era the only building blocks available to the surgeon were the tissues in front of him. Transfer of tissues from distant sites in the body - or from external sites - only became available late in the 20th century. These were called upon when the primary tissue was judged to be inadequate. In due course the implant materials were primarily utilized as mesh kits with primary native tissue surgery being ignored as part of the "reconstructive" process. The resulting complications led to a kneejerk response where all synthetics were to be banned from vaginal surgery, and a leap back to the previous comfort zones occurred. The conventional colporraphy is again re-introduced as the standard for prolapse surgery. And with this a new catch-phrase is introduced: "native tissue surgery".

But native tissue surgery goes beyond only the utilization of native tissue as the building blocks for reconstructing the vaginal wall supports to get rid of the bulging vaginal wall. It should also include the tissue reaction during wound healing due to the surgical insult. This process will go through its phases of haemostasis, inflammation, proliferation and remodelling. The aim of surgical reconstruction is to re-establish normal anatomy, morphological and functional, with minimal scar tissue formation. This will require tissue dissection in anatomical planes, approximating torn edges of damaged tissue layers, no tension on the native tissue and the use of materials that do not enhance the inflammatory phase: this will support the extracellular matrix in the remodelling phase of wound healing by reducing the impact of the inflammatory phase. These are the requirements of regenerative medicine. Conventional colporraphy gives the opposite effect: tissue is put under tension, normal anatomy is ignored and disregarded and definitely not recreated, and perfectly normal tissue is usually removed. Scar tissue formation is seen as an adjuvant for "good' surgical outcome.

By combining good surgical technique by limiting tissue damage with the regenerative principles of tissue engineering, regenerative surgery is done. This is applied in plastic surgery since 1997. The same principles are found in inguinal hernia repairs.

The same can be done in vaginal wall prolapse surgery. We are now entering what can be called the post mesh kit era. In this era one can return to the surgical techniques of the past, or improve them. In prolapse surgery we are curtailed by either lack of tissue, or poor quality of tissue. Variable tensions are being put on suture lines from the abdominal cavity leading to poor wound healing. To counter these, temporary splinting or support needs to be provided to keep the native tissue in place until proper strong collagen is being produced to strengthen the previous defective areas.[6]

In regenerative surgery new tissue is remodelled under the guidance of a biodegradable synthetic scaffold or biodegradable xenografts. This scaffold will aid in growth of resident-tissue stem cells. These scaffolds can have a dual purpose: they can act as a splint to keep tissues approximated for a sufficient time for wound healing to go through its phases, and can support the extra cellular matrix to control the inflammatory and enhance the remodelling phases of wound healing. This can only happen if the native tissue is respected. Regenerative medicine will only work if combined with good, safe surgical practices.

The first surgeon who attempts to repair the damage that leads to the collapse of the vaginal wall is the most important one. The surgical footprint left behind is not only paramount in the success of the primary surgery, but also may impede secondary surgical reconstructive attempts if the first procedure fails to give an optimal surgical outcome. The secondary procedure must not be an undo-redo process, but rather an add-on process. The minimal damage caused by following regenerative surgical principles will enhance this. The surgeon can control scar tissue formation, improve tissue quality and function using tissue regenerating surgical techniques.

The message is clear. Regenerative surgery puts the focus on the surgeon to do surgery on the do-no-harm principles. Don't ask how big is the vaginal bulge, rather ask why did it happen. The surgeons' ability to dissect, diagnose and repair the defect that led to the prolapse will control the surgical outcome. To rely on the ability of implant materials to give surgical outcome is too unpredictable, and can be damaging to the patient. These must be utilized as an adjuvant to primary tissue healing to improve outcome. This can only happen if the primary tissue handling follows regenerative principles. That is regenerative vaginal surgery.

In a sense one could say that with regenerative vaginal surgery the vaginal surgeon is invited back into the vagina. Vaginal surgery is an art practised by many, but mastered by few.

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Correspondence to:
Andri Nieuwoudt
Obstetrician Gynaecologist
Smaragdboog 11, 4533AZ Terneuzen, Nederland
nieuwoudt@gmail.com

Original article

Single incision un-anchored small mesh for surgical reconstruction of moderately prolapsed pelvic floor

MENAHEM NEUMAN[1], NATALIA SUMEROVA[2]

[1] *Faculty of Medicine in the Galilee, Bar-Ilan University, and Assuta medical center, Tel-Aviv, Urogynecology Unit, Dept. of Obstetrics and Gynecology, Western Galilee Hospital, Nahariya*
[2] *European Medical Center, Moscow*

Abstract: Aims: To evaluate whether the use of single incision un-anchored small mesh implants is feasible, safe and effective for women with moderate pelvic organ prolapse. *Methods*: Patients diagnosed with moderate pelvic organ prolapse were enrolled to undergo a single incision un-anchored mesh operation. Follow-up was 12 to 31 months. The outcome measures for this study were the operative safety and post-operative pain, adverse effects and anatomical as well as functional cure. The operations were performed under general anesthesia according with the reported surgical techniques at university and private hospitals. One hundred and fifty-seven patients diagnosed with moderate pelvic floor prolapse participated in this study. Data regarding cure rate, complications and patient's satisfaction were collected prospectively; patients were interviewed and examined at the end of the first month and interviewed again at the study conclusion. *Results*: Peri-operative and post-operative data were collected from patient's charts. Anatomical findings were measured with the POP-Q system, pain levels were estimated with visual analogue scales and outcome by UDI-6 and IIQ-7 questionnaires. No significant intra- or post-operative complications were reported. At the first and twelve months postoperative follow-up both the recorded observations and patient interviews and physical check-up, as well as tele-interview at the study conclusion, indicated satisfactory cure rates and minimal adverse effects. *Conclusions*: The data presented support the proposition that single incision un-anchored small pelvic floor meshes might be used successfully in patients with moderate pelvic floor prolapse.

Key words: Single incision un-anchored small mesh; Moderate pelvic organ prolapse; Surgical reconstruction; Cure rates; Adverse effects.

INTRODUCTION

Pelvic organ prolapse (POP) occurs in some women when the supporting pelvic floor becomes weakened or stretched, usually caused by childbirth and pre-existing fascial weakness, leading to descent of the pelvic organs to the vagina and beyond. This leads to impairment of pelvic organ function and negatively affects the patient's quality of life. Pelvic floor relaxation and POP is regarded by many as a "pelvic floor herniation" process. Patients with mild, symptomatic POP may benefit from conservative management, such as physiotherapy or the use of vaginal pessaries. However, moderate and advanced POP necessitates surgical reconstruction. Mesh augmentation for pelvic floor reinforcement has been shown to improve reconstruction.[1-2] However, mesh implantation is associated with specific complications such as mesh exposure, pelvic and vaginal pain and dyspareunia, as reported in a recent FDA notification.[3] The AUGS (American Urogynecologic Society), SUFU (Society of Female Urology and Urodynamics) and ACOG (American Congress of Obstetricians and Gynecologists) have all responded to this recent FDA announcement[4-6] on the nature and frequency of POP-mesh complications in comparison with the non-mesh POP reconstruction operations.

Those societies emphasize the importance of looking for new ways to reduce the mesh complication rates. One of the significant mesh complications is post-operative pelvic pain, which is probably related to the mesh surface area and its anchoring arms.This study looked at the feasibility, safety and outcome of a single incision un-anchored small mesh insertion for pelvic floor reconstruction in physically active patients suffering from moderate pelvic floor herniation.

Patients suffering from advanced pelvic floor herniation are unlikely to benefit from reduced size un-anchored meshes, and we are not proposing that approach for this group of patients.

PATIENTS AND METHODS

This study was designed to be open cohort. Patients suffering from moderate prolapse of the pelvic floor, with Ba, Bp or C points from +1 to +3 according to the ICS POP-Q system,[7] were enrolled. Informed consent was obtained after detailed information was presented to the patients. The study procedure was approved by the institutional board committee (Helsinki committee) and carried out according to the previously reported surgical method for anterior mesh implantation.[8-9] The single incision un-anchored small mesh used was Prosima® anterior and/or posterior (Gynecare, Somerville, NJ, USA); the implants were not secured to pelvic ligaments.

All patients were given 1 gr Monocef® (Cefonicid, Beecham Healthcare, Middlesex, UK) intravenously one hour prior to surgery. They all underwent an iodine antiseptic vaginal wash before surgery. General or regional anesthesia was employed, depending on the patient's request. Urinary bladder catheterization or diagnostic cystoscopy were not carried out routinely. Patients also presenting with contralateral vaginal wall relaxation underwent either colporrhaphy or pelvic floor mesh augmentation reconstructive surgery (by Prosima® or Prolift+M®, Gynecare, Somerville, USA), depending on the severity of the herniation process. Mild degree of prolapse was treated with native tissue colporrhaphy, moderate degree with single incision small mesh, and advanced prolapse was treated with needle guided large mesh. Anti-incontinence surgery, using TVT-Obturator®, TVT-SECUR® or TVT-Abbrevo® (Gynecare, Somerville, USA), was added when indicated. Patients were followed up at one month after surgery and again at the study conclusion. All operations were carried out by a single surgeon at both private and university (public) hospitals.

The outcome measures were the anatomical and functional cure rates and the levels of post-operative pain and dyspareunia, which were recorded on special forms and a 0-10 Visual Analog Pain Scale (VAPS). Data were collected by a researcher not involved with the patients' care, based on patients' charts, interviews and pelvic examinations. Subjective data regarding urinary and fecal urgency, frequency, stress and urge incontinence, impairment of sexual function, voiding function, pelvic pain and bulging were obtained at the study conclusion

TABLE 1. – Patient characteristics.

	Patient's group (N=155)	
Age (mean and standard deviation)	59.31 ± 10.7 SD years (range 32-86)	
Parity (mean and standard deviation)	2.72 ± 1.2 SD (range 0-6)	
Ba point (mean and standard deviation)	2.24 ± 1.11 Cm. SD (range 0-2)	
Bp point (mean and standard deviation)	2.24±1.8 SD Cm. (range -3-4)	
C point (mean and standard deviation)	1.5 ± 2.75 SD Cm. (range 2-3)	
Hiatal lump	155 Pts (100%)	
	Mild	Moderate
Frequency	46 Pts (29%)	5 Pts (3%)
Urgency	38 Pts (24%)	9 Pts (6%)
Nocturia	20 Pts (13%)	4 Pts (3%)
Recurrent UTI	1Pt (1%)	0 Pts (0%)
Bladder outlet obstruction	1Pt (1%)	0 Pts (%)
Sexual discomfort	7 Pts (4%)	1 Pt (1%)
Dyspareunia	1 Pt (1%)	0 Pts (0%)
Constipation	0 Pts (0.0%)	0 Pts (0%)
Fecal incontinence	0 Pts (0.0%)	0 Pts (0%)
Stress urinary incontinence	115 Pts (73%)	
UDI 6 (mean and standard deviation)	3.17 ± 1.66 SD (range 0-9)	
Background chronic illness	38 Pts (24%)	
Duration of follow-up (mean and standard deviation)	16.41 months ± 3SD (range 4-23)	

TABLE 2. – Previous operations.

Previous operations (N=155)	**No. Pts.**	**%**
Hysterectomy (Abdominal/vaginal hysterectomy)	28 (22/6)	18% (14%/4%)
Pelvic floor reconstruction (Mesh/No mesh)	16 (10/6)	10% (6%/4%)
Anti-incontinence surgery (Burch/TVT)	11(3/8)	7% (2%/5%)
Total	**55**	**35%**

TABLE 3. – Operation performed.

Operation type (N=155)	**No. of Operations**	**%**
Un-anchored mesh (Anterior/Posterior)	196 (96/100)	126% (62% / 64%)
Anchored mesh (Anterior/Posterior)	33 (6/27)	21% (4% / 17%)
Colporrhaphies (Anterior/Posterior)	55 (39 / 16)	35% (25% / 10%)
Elongated cervix amputation	11	7%
Vaginal Hysterectomy	1	1%
Anti-incontinence surgery (TVTS/TVTA/TVTO)	116 (66 / 11 / 39)	74% (42% / 7% / 25%)

interview by the same uninvolved researcher using the UDI-6 and the IIQ-7 questionnaires. Subjective outcome successes were defined as patient's self-determined satisfaction of the over-all operative results higher than

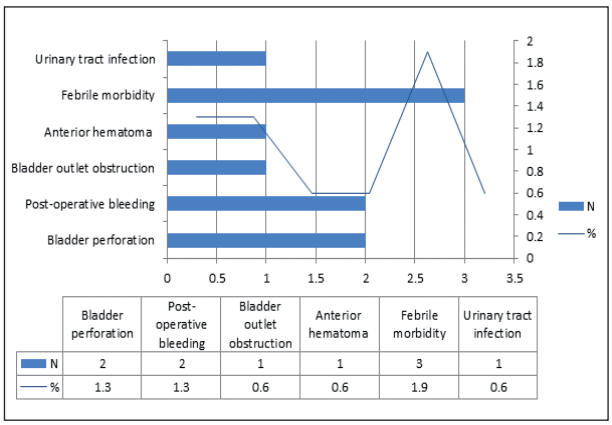

Figure 1. - Operative complications rate.

80. The follow-up period ranged from 12 to 31 months (mean 16.41 months). Objective outcome successes was defined as absence of prolapse of more than 2cm beyond the different POP-Q points, assessed by pelvic examination in accordance with the POP-Q standard ICS-IUGA terminology at the end of the first post-operative year.[7]

Statistical analysis was performed by the Wilcoxon signed-ranks test and Kruskal-Wallis Test (Nonparametric test for the significance of the difference among the distributions of k independent samples, A, B, etc., of sizes na, nb, etc., respectively) that were used to measure "before" and "after" quantitative parameters between groups. Significance was set at $P < .05$.

RESULTS

One hundred and seventy-two patients suffering from moderate pelvic floor prolapse, with either uterine prolapse or post-hysterectomy vaginal vault prolapse (Ba, Bp or C points +1 to +3) were referred for surgery with single incision un-anchored mesh implants. Six patients were excluded from the study because of refusal, 11 patients were not available for follow-up, and thus 155 were enrolled into the study. The operations were performed since January 2010 through December 2011.

The patients' pre-operative personal characteristics are tabulated in tables 1 & 2. Of the 155 study patients 82.1% also had contralateral pelvic floor reconstruction (47.3% with mesh implants) and 73.3% had a concomitant anti-incontinence TVT procedure. Operative details and operative and post-operative complications are shown in

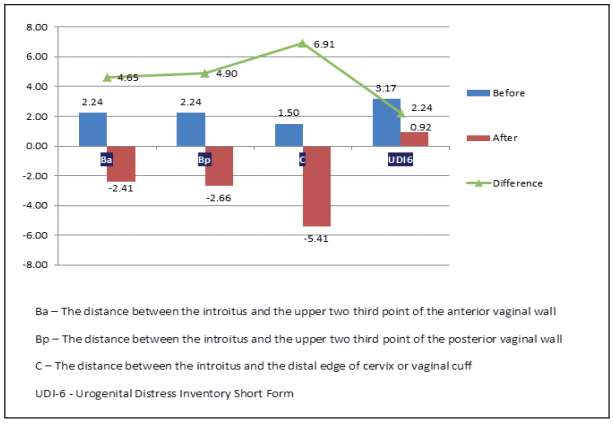

Figure 2. - Pre-operative and post-operative POP-Q system and UDI-6 measurements.

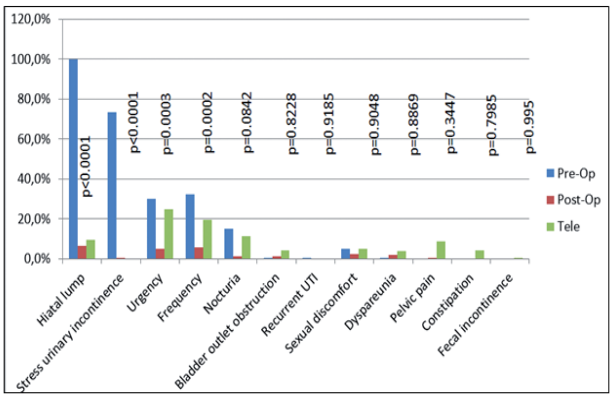

Figure 3. - Pre-operative and post-operative functional status.

table 3 and figure 1. No major complications were reported, two cases of bladder penetration that were repaired vaginally at the time of the primary procedure with no morbid sequelae; no other viscera were injured. Blood transfusion was not indicated, pain rates and severity were mild to moderate. The outcome, shown in figures 1, 2 and 3, was satisfactory both subjectively and objectively. There was anatomical improvement in terms of the various POP-Q points as well as improvement in urinary, sexual and ampular functions, based upon the patients' detailed satisfaction reports.

The POP-Q points measurements showed marked improvements: for the Ba point the average change was 4.65 cm, for the Bp point the change was 4.90 cm, and for the C point it was 6.91 cm. These measurements were all statistically significant. Bladder overactivity symptoms, viz. urgency, frequency and nocturia, were all found to be significantly reduced, as was the sexual discomfort rate. Fecal incontinence, pelvic pain and constipation rates were reduced as well, but these did not achieve statistical significance.

DISCUSSION

It is well recognized that mesh implants provide reinforcement in surgical reconstruction of the prolapsed pelvic floor. However, mesh-related adverse effects pose a troublesome problem, and means should be sought to reduce these adverse effects. Reducing the mesh surface area and removing the anchoring arms might decrease the incidence of complications, while still maintaining the desired beneficial effects.

The cohort of 155 patients presented here, reflects the common population presenting to pelvic floor clinics (Tables 1 and 2), and the outcome data suggest that reduced size single incision un-anchored mesh augmentation is safe and effective for moderate pelvic floor prolapse repair. This technique, requiring less dissection for implantation, is also less hazardous (Figure 1), than are the commonly performed operations.[1,2] The overall outcome results are promising and show statistically significant improvement. This holds true for both the anatomical outcome – demonstrating successful and stable architectural reconstruction of the pelvic floor as measured according to the POP-Q ICS method, and also in terms of the functional results (Figures 1-3). Functional outcome in terms of bladder overactivity symptoms were found to deteriorate over the period of follow-up course for reasons that are not clear. The pain levels reported here, including dyspareunia, vaginal and pelvic pain are markedly lower than those reported previously following pelvic floor reconstruction, both with and without mesh implants (Figure 3). These findings are in accordance with previously reported data regarding new single incision anchored meshes[8-9] and probably better than the data regarding the large anchored meshes.[1-2] This approach is likely to be effective in women with a moderately affected pelvic floor, but probably will not be sufficient for advanced prolapse.

This study strength is limited by being single armed and by having a rather short term follow-up. Further studies should be designed and carried out to shed more light on the issue of optimal anchoring points for reduced size single incision un-anchored versus full size needle guided mesh augmentation. As the particular mesh implant studied here is not available any more, the first author is using since 2012 another small implant, the SeraTom (Serag Wiessner, Naila, Germany).

DISCLOSURE:

Prof. M. Neuman was consultant for J&J before the Prosima production was stopped, and now is consultant to Serag Wiessner; Dr. Sumerova has no conflicts of interests.

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Correspondence to:

Menahem Neuman
7 Teena st. - Carmey Yosef 9979700 - Israel
E-mail: mneuman@netvision.net.il

New trends

Chronic non-malignant pelvic-perineal pain: Management by anesthetic blocks. From theory to practice I: Philosophic and pathophysiologic approach

EZIO VINCENTI
Dolo Hospital, Venice, Italy

Abstract: The principles of treatment of chronic painful diseases have to be understood in the context of the sophisticated warning mechanisms that exist between the brain and peripheral tissue. Current pharmacological approach to pain control is essentially based on acute, nociceptive pain, whereas chronic non malignant pain is different, involving a restructuring of both peripheral and central neural networks, leading to wider cerebral integration and interpretation. New plans of treatment must be developed according to recent pathophysiological data on neuropathic pain, neuroinflammation, and neuroplasticity. Interpretation of physical phenomena occurring in human body derived from the mechanical philosophy of Descartes and linked with materialism and reductionism is today an anachronistic point of view. Data derived from fMRI (functional magnetic resonance imaging) suggest that mind and brain are indistinguishable from each other: behavioural influences, experience, motivation, exercise and drugs may modify neuronal circuits and determine a different response to similar inputs. On the other hand, repeated harmful afferent inputs may induce a chronic pathologic condition difficult to resolve by standard medical therapy: systemic opiates may only represent a way to relieve symptoms, but they are unable to offer a definitive resolution of the chronic painful state. Increased intraepithelial innervation by mast cells hyperactivation and microglia activation in nervous system lead to modifications of central circuits; these structural and functional variations may explain allodynia and hyperalgesia, and burning sensations as well. In vivo studies demonstrate morphological changes in the brain, as a consequence of pain perception, and that these may be reversible in nature if a correct treatment, based on these observations, is provided.

Key words: Neuroinflammation; Chronic pelvic pain; Neuroplasticity.

INTRODUCTION

One of the key principles in the treatment of non-malignant chronic pain may be linked to a philosophic view based on a pyramidal mental construction. When considering the wider dimension of pain, one element of significance is time, in particular time elapsed since the onset of pain.

Nociceptive pain reflects an experience in actual time, and its usefulness can be seen as an alarm or warning to a potentially dangerous situation. The classical physiological understanding has been constructed along the lines of an immediate cause-effect relationship: where nociceptive afferent inputs from peripheral structures are centrally processed and indentified as painful stimulation, under normal circumstances. This is known as acute nociceptive pain which can be managed successfully with many available drugs. When the harmful nociceptive sensation ends, the consequence is a cessation of pain. On the contrary, chronic pain may not only be associated with a simple experience of temporal duration, or continuous nociceptive stimulation, but may linked to a restructuring of both peripheral and central networks, involving cerebral representation. Chronic pain may be expressed as a form of neuropathic pain, in particular when burning sensations are present. Current pharmacological therapy is often unsatisfactory and only a token analgesic effect is obtained at a high price in terms of side effects and quality of life. Standard and consolidated scientific pathophysiological opinions are largely ineffective in explicating clinical suffering due to chronic neuropathic pain or producing a satisfactory solution of the difficult problem. On this account a new perspective is required, especially if we want to meet the patients expectations. As is often the case, a more convincing theory can be proposed by reviewing past assumptions in the context of new insights.

Historical synopsis

At the beginning of civilization, medicine was completely linked to the science of nature and to philosophy, as Empedocles or Pythagoras showed in their vision of life. Likewise, Hippocratic medicine was closely related to nature and its philosophic interpretation.

However, in successive centuries medicine evolved independently of the common *natural* origins to become a practical science devoted to the diagnosis and treatment of diseases. Principles of modern medicine came to be based mainly on the mechanical philosophy of Descartes who believed that man kind (as other living things) is nothing more than complicated machines or artifacts, composed of parts lacking any intrinsic relationship to each other. The universe itself was seen as completely reducible to mechanical principles and this view was closely linked with materialism and reductionism: all phenomenon could eventually be explained in terms of "*mechanical laws*", including the correct interpretation of physiology and, consequently, pathophysiology.

Rapid development of technology and biologic discovery of microscopic living structure together with extraordinary advancement of chemistry and biochemistry led medical scientists to the belief that pure knowledge of biological data was sufficient for interpretation of most phenomena involved in diseases. At the same time, mind was considered to be quite different from the brain, and believed to be a fixed and unchangeable network, with the former being similar to software, and the latter to hardware, speaking in terms of a common day analogy.

Yet, to the contrary, demonstration of neuroplasticity in recent data derived from fMRI (functional magnetic resonance imaging)[1,2] suggest that the mind and the brain are indistinguishable from each other: behavioural influences, experience, motivation, exercise, meditation, drugs, to mention a few factors, may modify neuronal circuits and determine a different response to similar inputs. On the other hand, repeated and potentially harmful inputs may induce a chronic pathologic condition which is often intractable by current medical therapy. As a matter of fact, systemic analgesic drugs, including opiates, may relieve symptoms of chronic pain but are unable to structurally modify the peripheral and central network generating and maintaining persistent pain.

1. Peripheral concerns

Several experimental studies on biochemical and histological characteristics of peripheral tissues, such as vaginal mucosa, removed for examination from patients affected by intractable vaginal/perineal pain, have demonstrated the presence of higher density of nerve fiber endings, many of which are very close to skin surface, when compared with specimens obtained from normal cases (Figure 1).

This reduced distance of nerve fiber endings and skin and the significant increase of total number of nerve fibers, may be clinically related to allodynia and hyperalgesia in chronic neuropathic pain syndromes, such as vulvodynia[3]. It is not difficult to speculate that such an increased peripheral nervous system network might be seen as a protective mechanism warning of potentially harmful and dangerous inputs from skin, even if no injury is really occurring.

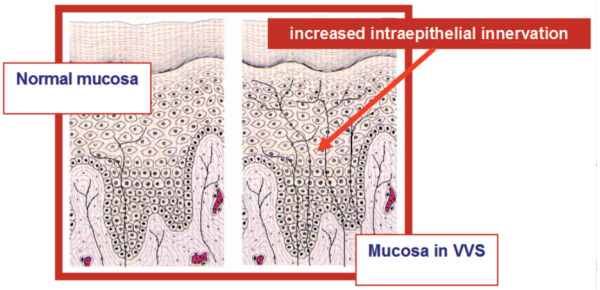

Figure 1. - Schematic representation of histological microscopic view of vulvar mucosa affected by chronic vulvodynia (VVS)(on the right) in comparison with a normal mucosa (on the left). Increased intraepitelial innervation is clearly exemplified.[3]

Recent data[4-7] shows that aggressive factors, such as continuous mechanical peripheral irritants or infections, can induce hyperactivation of mast cells and microglia (Figure 2): where both types of cells are predominantly involved as active immune system, the responses to hostile biological incursions and the weapons of defense consist of mediators that include histamine, tryptase, serotonin, proteoglycans, prostanoids, and newly formed lipid mediators (eicosanoids) as thromboxane, prostaglandins D2, leukotriene C4, platelet-activating factor; and in addition, cytokines such as eosinophil chemotactic factor and TNFalpha, as well as nerve growth factor (NGF).

When irritants such as chemical substances, repetitive mechanical trauma or infective factors become chronic, mast cells becomes up-regulated. Their production of NGF promotes nerve pain fibers proliferation, which correlates with hyperalgesia, and superficial sensitivity causing "allodynia", in which the perception shifts from tactile to burning pain.[8,9] This explains why pain becomes persistent in spite of every current non-invasive treatment. When nerves begin to function in an abnormal fashion, and signal pain is present without any apparent peripheral damage, the term "neuropathic pain" may be applicable. This pain also describes the process by which the neurons involved in pain transmission are converted from a state of normal sensitivity to one in which they are hypersensitive.

Mast cells are heterogeneous and exhibit site-specific adaptations induced by micro-environmental triggers that lead to selective expression of potential mast cell characteristics. This flexibility of phenotype has important functional implications and allows these cells to adapt to organ or tissue specific roles, which range from providing innate defense against bacteria and protection from venom of bees and snakes to participating in multiple aspects of adaptive

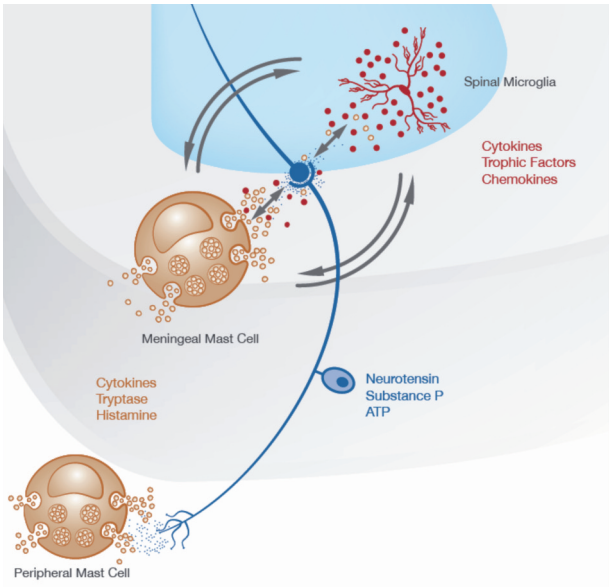

Figure 2. - Interactions between mast cells and microglia in persistent pain. Mast cells may interact with microglia indirectly via primary somatosensory neurons, or directly by interaction of mediators-receptors expressed by both cellular types. Mast cells and microglia directly interact with pain neurons and significantly influence functioning of somatosensory system promoting develop of chronic pain.

immune response such as antigen presentation and lymphocyte recruitment to draining lymph nodes, as well as down-regulation of immune response.

Mast cells and sensory neurons are important sites for the sustained action of NGF in producing increased sensitivity during inflammatory state.[10]

A key characteristic of mast cells is their ability to span across the division between nervous and immune system. Indeed, much of our understanding of the bi-directional relationship between the nervous and immune system has come from the study of mast cell-nerve interaction. In fact, morphologic as well as functional associations between mast cell and nerves are found in most tissues and these interactions are involved in the regulation of physiologic homeostatic processes as well in disease mechanisms.[11]

Mast cells are immunocytes with secretive functions that act locally to maintain tissue integrity, local haemodynamics and tissue homeostatic mechanism; their pathogenic roles have been extended to include not only allergic diseases and helminthiasis, but also autoimmune diseases, such as rheumatoid arthritis, allograft tolerance, angiogenesis in tissue repair and carcinogenesis.

Mast cells can be activated by a range of neurotransmitters and, reciprocally, a variety of molecules synthesized and released by mast cells can influence neuronal activity, while mast cell-derived cytokines, including TNF and NGF, lower the threshold for activation of local neurons and promote nerve fiber growth.

There is anatomical evidence for mast cell association with peripheral myelinated and unmyelinated nerves. In addition, while mast cells are distributed widely in connective tissue and at mucosal surfaces they are concentrated at interfaces with the external environment, near blood vessels, lymphatic vessels, and nerve fibers. Positioned at these strategic locations, mast cells act as sentinels of immune system, protecting against invading microbes and signaling environmental changes.

Close proximity of mast cells and neurons containing Substance P (SP), Calcitonin Gene-Related Peptide (CGRP) or both has been described in a variety of anatomical sites

such as gastrointestinal tract, trachea, peripheral lung, urinary bladder and several other tissues. These interactions underlie the classic inflammatory axon reflex where antigen or noxious stimuli causes the activation of sensory c-fibers that in turn, through collateral axons, provide an efferent route for the lateral spread of inflammatory signals. Mast cells may be implicated in inflammatory processes in which degranulation is generally not observed: in fact, ultrastructural alterations of their electron-dense granular core, frequently seen, are indicative of secretion but without degranulation, a process termed piece-meal degranulation, in which even molecules stored within the same granule can be separately secreted. For example, serotonin can be released independently from histamine as well as differential synthesis and release of prostaglandins and leukotrienes have also been reported.

Also, mast cell granules carry a variety of bioactive chemicals which may be transferred to adjacent cells of the immune system and neurons in a process of transgranulation via mast cell pseudopodia.[12]

Mast cells posses a remarkable degree of plasticity and apparently even fully differentiated CTMC (Connective-Tissue type Mast Cells) will transform their phenotype to that of MMC (Mucosal Mast Cells) if transplanted into a mucosal environment. Alternatively, mast cell may be classified based on the protease content of secretive granules that differ between tissues. Tryptase is present in all cell sybtypes and can activate cells through cleavage of protease-activated receptors (PAR). Protease regulate neurons and glia in the central nervous system by cleaving PAR.

Furthermore, tryptase has been shown to cleave PAR2 on primary spinal afferent neurons, which causes the release of SP and CGRP and sensitization of co-expressed TRP (Transient Receptor Potential) channels that together cause plasma extravasation, amplification of inflammation and consequent hyperalgesia. Mast cell proteases have also been demonstrated to degrade nerve products by enzymatic cleavage and thus may act to limit the effects of neurogenic signals.

NGF receptors found on mast cells act as autoreceptors regulating NGF synthesis and release. NGF has also been shown to induce degranulation and histamine release from mast cells. The NGF produced by mast cells can act on neurons by inducing the expression of neuropeptideds and lowering the threshold of firing. Indeed, mast cell proliferation in response to NGF is partially mediated by mast cell degranulation.

Interestingly, NGF can exhibit anti-inflammatory as well as proinflammatory effects depending on the situation and the concentration of the growth factor.

As far as sensory neuropeptides are concerned, peripheral sensory nerves involved in pain, touch and temperature perception regulate inflammation locally through the release of a number of neuropeptides including SP, CGRP and vasoactive intestinal peptide (VIP). The stimulation of peripheral nerves results in local inflammation (vasodilation, vascular leakiness, edema and pain). In particular, SP, an 11 aminoacid peptide that acts principally at the neurokin-1 (NK-1) G-protein coupled receptor, and is generally regarded as pro-inflammatory, stimulates secretion of TNF, IL-1, Il-2 and IL-6 from macrophages and T lymphocytes. SP is perhaps the best-known and most studied neurotransmitter in relation to mast cell activation. In addition to degranulation, SP also promotes production of lipid mediators such as prostaglandins D2 and leukotriene C4 and proinflammatory cytokines including TNF and Il-6. Low concentration of SP incapable of inducing mediator release can increase cellular responsiveness to subsequent stimulus and so "prime" the cell to degranulate with reapplication of a subthreshold dose. It is important to note that not all mast cells are activated by SP and expression of functional NK-1 receptors appears to be dependent on microenvironmental factors. Neuron-derived SP induces degranulation in associated mast cells and association of mast cells to neurons for several days can change phenotypic and functional characteristics of the mast cell. This functional relationship between mast cells and SP containing sensory nerves is thought to play role in the stress induced exacerbation of a number of inflammatory conditions.

CGRP is a 37 aminoacid neuropeptide that mediates its effects through G-protein coupled receptors and is expressed predominantly in sensor nerve fibers. CGRP can directly activate mast cells and this suggests that this neuropeptide has a role in the functional relationship between mast cells and neuronal network. On the other hand, NGF induces sympathetic postganglionic neural sprouting to encase primary sensory neurons within the dorsal root ganglion (DRG), as well as trkA (tropomyosin receptor kinase A) expressing nociceptor sprouting causing hyperinnervation of the epidermis. Therefore, there is convincing evidence of an NGF-mediated nerve-fiber sprouting.[13] Now, NGF, which is produced from a variety of tissues, in the skin can be released by basal keratinocytes and in hollow viscera by epithelial cells as well as by mast cells, macrophages, and Schwan cells. NGF levels are increased in inflamed tissues and the release of IL-1beta, PDGF (Platelet derived growth factor), TNFalpha, IL-4 and TGF-beta, in turn stimulates a further production of NGF. NGF and its high- and low-affinity receptors, tropomyosin-related kinase receptor (trk)A and trkB, respectively, are up-regulated in the skin of allergic patients. NGF may thereby modulate itch perception in inflamed skin as well as neurogenic inflammation by supporting nerve-sprouting. An experimental study has identified a clear and understandable mechanism by which the blockade of NGF or TrkA could produce a preventive analgesic effect in a chronic pain state.[14] In fact, peripherally produced NGF is involved in the development and maintenance of nociceptive sensory neuron sensitivity and an up-regulation of NGF is responsible for alterations in pain-related behaviour. Therefore, blockade of NGF production and/or its action may be a new strategy to avoid nerve hypersensitivity due to inflammation, and possibly a novel non-canonical anti-inflammatory analgesic treatment.[15]

There are many independent lines of evidence that indicate bidirectional cross-talk between mast cells and sensory nerves, suggesting that in certain instances they can be functionally and anatomically assembled within certain tissues with mast cells being co-localized with nerve fibers expressing SP and CGRP and/or other peptidergic mediators, releasing histamine, serotonin, and tryptase, thus leading to sensory nerves activation and contributing to neurogenic inflammatory reactions. Above all, mast cells by releasing NGF and TNFalpha, are thought to regulate sensory nerves development, degeneration, and regeneration. Therefore, both mast cells and sensory nerves have been suggested to co-orchestrate a variety of physiological and pathological processes, such as wounds healing and stress responses and to contribute to the pathogenesis of inflammatory and autoimmune diseases.

The anatomical and pathophysiological role of mast and neuronal cells in inflamed tissues are important to remember as potential mechanisms involved in neuroinflammation associated with chronic pain syndromes.

2. Central concerns

When a patient is suffering from a form of chronic pain such as the Chronic Pelvic Pain Syndrome (CPPS),[16] not on-

ly are peripheral tissues involved, but also the central nervous system is strongly implicated.

If the pivotal role of mast cells in response to harmful peripheral stimulation is well established, as per the discussion above, the significance of microglia has also been highlighted as a parallel reaction within the central nervous system (CNS) in response to potential threats to the body.

The preservation of the species is one of the most important innate mechanism which the brain continuously tries to maintain pursuing it as a vital goal.

Several clinical studies and investigations have shown the benefits that hypnosis may produce in surgical patients demonstrating positive effects on emotional distress, pain, medication consumption and improved physiological parameters in recovery.[17] Hypnosis decreases the probability of new analgesic requests by distraction mechanisms which cause mainly reduction in frontal lobes activity. Anticipation of pain may in itself induce changes in brain nociceptive networks and hypnotic suggestions may modulate pain-related cortical activity by focusing or diverting away attention.[18] On the other hand, anticipation of a virtual pain can induce a real painful feeling of about 40% of the pain felt under direct nociceptive application.

Of course, every real or potential situation in which the fight or flight response is activated, the sympathetic system is alerted in order to quickly and adequately respond by finding a satisfactory solution to the actual problem. Acute pain is one the fundamental factor activating a rapid sympathetic response, both conscious and unconscious (i.e. automatically produced). In these conditions, pain acts as an alarm bell, and is useful in minimizing tissue damage. But, if the harmful situation is continuously re-occurring or renewed, the unremitting alarm status leads to a permanent physical disorder and chronic pain itself becomes a chronic self-maintaining disease.

Initially, pain is simply a reaction peripheral mechanism, but in time central mechanisms are progressively engaged. The pathophysiology of peripheral neuropathic pain is therefore based both on abnormal peripheral inputs and abnormal central processing.[19] Peripheral mechanisms include (a) nociceptors sensitization, (b) spontaneous activation of primary afferent fibres ectopically firing from the site of lesion and, (c) "neurogenic inflammation", as discussed earlier. The latter is characterized by algogenic substances released which may move backwards along the sensory nerves by the up-regulation and release of mast cells through neurogenic activation and de-granulation. A close interaction between mast cells and pain nerve fibers, with reciprocal potentiation, seems to be a key feature of peripheral neuropathic pain. As far as the central mechanisms are concerned, *wind up* phenomenon occurs due to the progressive increase of cellular firing following repeated identical stimuli.[20] Furthermore, spinal and supraspinal propagation of abnormal local changes caused by peripheral nerve lesions leads to aberrant central elaboration. In the biochemical field, excitatory aminoacids and NMDA (n-methyl-d-aspartate) receptors play a crucial role in the genesis of chronic neuropathic pain.

The dorsal horn of the spinal cord appears to play an important role at the beginning and in the maintenance of neuropathic pain. Tsuda et al[21] have demonstrated that activation of p38 mitogen-activated protein kinase (p38MAPK) in hyperactive microglia of the dorsal horn contributes to pain hypersensitivity in response to innocuous stimuli (tactile allodynia) following peripheral nerve injury. In fact, intrathecal administration of a specific p38MAPK inhibitor (SB203580) suppresses the development of nerve injury-induced tactile allodynia. Other investigations[22] show that galectin-1 (one of the endogenous galactoside-binding lectins, involved in a variety of functions, such as neurite outgrowth, synaptic connectivity, cell proliferation and apoptosis) increases in the dorsal horn at 1 to 2 weeks after axotomy and that intrathecal administration of anti-recombinant human galectin-1 antibody partially but significantly attenuates the upregulation of substance P receptor (SPR) in the spinal dorsal horn and the mechanical hypersensitivity induced by the peripheral nerve injury. These data suggest that endogenous galectin-1 may support neuropathic pain after the peripheral nerve injury at least partly by increasing SPR in the dorsal horn.

Tissue injury of almost any kind, but especially peripheral or central neural tissue injury, can lead to long-lasting spinal and supraspinal re-organization that includes the forebrain.[23] These forebrain changes may be adaptive and facilitate functional recovery, or they may be maladaptive, preventing or prolonging the painful condition.[24] In an experimental model of heat allodynia, functional brain imaging showed that: (a) the forebrain activity during heat allodynia is different from that during normal heat pain, and (b) during heat allodynia, specific cortical areas, in the dorsolateral prefrontal cortex, can attenuate specific components of the pain experience, by reducing the functional connectivity of subcortical pathways. The forebrain of patients with chronic neuropathic pain may undergo pathologically induced changes that can impair the clinical response to all forms of treatment. Therefore, chronic pain can be understood not only as an altered functional state, but also as a consequence of altered neuronal plasticity.

In addition, Baliki et al[25] used in vivo structural MRI to compare global, local, and architectural changes in gray matter properties in patients suffering from chronic back pain (CBP), complex regional pain syndrome (CRPS) and knee osteoarthritis (OA), relative to healthy controls. They found that different chronic pain types exhibit unique anatomical 'brain signatures'. Only the CBP group showed altered whole-brain gray matter volume, while regional gray matter density was distinct for each group. Voxel-wise comparison of gray matter density showed that the impact on the extent of chronicity of pain was localized to a common set of regions across all conditions. When gray matter density was examined for large regions approximating Brodmann areas, it exhibited unique large-scale distribution networks for each group. Also, they showed that brain reorganization with chronic pain was 6 times slower and twice as large in CBP by comparison to CRPS. The results show an exuberance of anatomical brain reorganization peculiar to each condition and as such reflects the unique maladaptive physiology of different types of chronic pain conditions.

Brain reorganization associated with chronic pain has also been investigated by comparing morphology between chronic pain and healthy controls. Altered brain morphology was shown in many pain conditions, including fibromyalgia,[26-27] complex regional pain syndrome (CRPS),[28] osteoarthritis,[29] irritable bowel syndrome,[30] headaches,[31] chronic vulvar pain,[32] and in women suffering from menstrual pains.[33]

However, many of the gray matter changes observed in chronic pain patients subside with cessation of pain.[34,35] In addition, it has been shown that the observed morphological differences in chronic pain conditions often correlate to the duration of pain related suffering as well as its intensity,[36] thus suggesting that the brain morphological changes may be reversible in nature and are a consequence of pain perception.

Chronic pain impacts morphology of whole brain structures, and treatment, in order to be effective, must recognize the importance of cerebral reorganization, but, above all, must induce the return to the *status quo ante*, i.e. to the preexisting peripheral and central anatomical and functional neural state.

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Correspondence to:

Ezio Vincenti, MD,
Chief of Anesthesia, Intensive Care and Anthalgic Therapy,
Dolo Hospital, Venice, Italy
E-mail: evincenti@libero.it

INVITED COMMENTS: Chronic Pelvic Pain

It's always a thought-provoking exercise to read a paper on the topic of non-malignant chronic pain. Pain is, and always has been, a complex phenomenon to study and to manage. It has been one of the most misunderstood conditions in modern medicine. However, with time and increasingly sophisticated scientific methods of study, our understanding of chronic pain continues to evolve and new findings compel us to review existing protocols of pain management.

Many clinicians intuitively or by training associate pain with tissue trauma and search for pathology that may shed insight into its existence, but, unlike acute pain, most chronic pain syndromes exist in the absence of pathology that can explain their actuality and severity. In chronic pain there is no relationship or proportionality between pathology and pain. This gives rise to a fundamental question in the study of chronic pain, "where is the pain coming from?" Some clinicians have been inclined to suggest that the pain is psychological in nature or "in the head." Though patients feel slighted by such an aspersion, with recent scientific evidence, there could be another reasons why this proposition may yet be true. The rationale for such a hypothesis, while ironical is quite rational. Working definitions of pain identify it as a sensory and emotional experience, however, a growing number of investigators are of the view that it is a disease process shaped more by genetically inherited traits that predispose individuals to increased pain sensitivity than by peripheral factors. Greater emphasis is being placed on the neuroplasticity of the central nervous system, than on body regions where pain is reported. Rather then focusing on region specific syndromes greater emphasis is placed on centrally driven variables that give rise to hyperalgesic states. As the focus shifts from "peripheral" to "central" mechanisms of pain current protocols of pain management are being called into question.

There are many other anomalies in the study of pain. Unlike various physiological functions of the body, regulated by well-defined sites within each system, there is no localized center that accounts for the regulation of pain. From overviews of major pain syndromes chronic pain is difficult to localize and its origins are often unrelated to the regions where it is experienced. Furthermore, chronic pain being a very individual and subjective experience is difficult to quantify and appears to be fashioned by a range of unique and peculiar variables that necessitate individualized approach to management. As an anaesthetist, Dr Ezio Vincenti examines recent findings based on functional magnetic resonance imaging studies, and highlights the interaction between peripheral and central factors, in particular the interaction between the immune and nervous systems and how these impact on the temporal experience of pain. His conclusions rightly emphasizes the need to shift from the historically mechanical perspective to one, which recognizes the intrinsic relationship between mind and body and enables the use of more effective pharmaceutical pain management protocols. As a clinician I would agree with such a proposition, but would emphasize that therapies focusing on the peripheral mechanisms of pain, such as dysfunctional pelvic muscle states, can also be an effective means of impacting and modulating the centrally-driven mechanisms of pain.

Whenever I listen to patient account of their symptoms and the various pain management strategies trialed I'm often reminded of a cogent statement made by a former chronic pain specialist, Daniel Brookoff, who in the context of chronic urogenital pain foresaw the need for a shift in our concepts when he said,

> "One factor that has made urogenital pain disorders particularly difficult to manage is that many of the traditional treatments – ranging from caustic bladder instillations to short-lived denervation procedures to the excision of the presumptively "diseased" end-organs in the form of unnecessary hysterectomies, prostatectomies, and cystectomies - often do more to ingrain and accelerate these painful conditions than to relieve them. Recent insights from the study of these syndromes suggest that we should be directing our treatments toward modulating the neurologic generators of nociception and dysfunction rather than removing or destroying the visceral organs that were once presumed to be responsible for chronic pelvic pain or the nerves that innervate them."

He then goes on to say,

> "I tell my patients with chronic urogenital pain that I have two equally important obligations to them. On the one hand, I must make sure that they get all the treatments they need, but on the other hand, I must often expend just as much effort to make sure that they are not subjected to treatments they do not need."

In concluding he makes an important statement that so poignantly reflects the point made by Dr Vincenti of a need to change our thinking on chronic pain,

> "One of the most difficult tasks that we as physicians need to accomplish in reconsidering our treatment of painful urogenital disorders involves the "unlearning" of long-held beliefs rather than the acquisition of new knowledge. Many of the assumptions we have carried with us for years… have contributed to the iatrogenic propagation of pelvic pain syndromes."[1]

If we are to assist our patients and meet their expectation, there is much that needs to be unlearnt before new findings and new insights into the mechanisms of chronic pain can be meaningful applied. It is then, and only then, that our approach to pain management will be truly evidence based and individualized.

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Marek Jantos
e-mail: marekjantos@gmail.com

This is a wonderful erudite summary of the history, philosophy, physiology, microanatomy and biochemistry of pelvic pain. It was interesting to read about altered brain morphology shown in many pelvic pain conditions and how many of the gray matter changes observed in chronic pain patients subside with cessation of pain, suggesting that the brain's morphological changes may be reversible in nature and are a consequence of pain perception.

My perspective is confined to female pelvic pain which we have found can be cured in up to 80% of cases with a posterior sling.

This direction (outlined more fully below) has been ignored by Cochrane review,[1] which confines current approaches to treatment to counseling, psychotherapy, laparoscopic uterine nerve ablation, presacral neurectomy, hysterectomy with or without removal of the ovaries. A neuromodulation reports 40% improvement in pelvic pain symptoms and 26%improvement in their urinary symptoms (UDI-6) at 15 months mean follow-up.[2]

The European Association of Urology (EAU) Guideline Group for CPPS[3] presented a broad classification and a large and complex algorithm for pelvic pain, diagnosis of which was essentially organ based.

In 1993, Ulmsten and I reported CPP as a referred pain caused by laxity in the uterosacral ligaments, as part of the posterior fornix syndrome (urgency, nocturia, abnormal bladder emptying).[4] As such, it was potentially curable , along with other posterior fornix syndrome symptoms, by reinforcing the uterosacral ligaments.

The pelvic pain component of this syndrome was addressed more systematically a 1996 study which included diagnostic laparoscopy: *"In its acute state of manifestation, the pain was invariably severe, frequently one-sided, situated low in the right or left iliac fossa, usually relieved on lying down, frequently relieved by insertion of a ring pessary, reproducible on palpating the cervix and displacing it posteriorly, patient in supine position. Although the pain was chronic in nature, it varied considerably from time to time as concerns intensity. There was a history of deep dyspareunia which only occurred on deep penetration, or in specific positions. Frequently the patient complained of a constant lower abdominal pain the day after intercourse. Half the patients complained of low sacral backache which was also cured by the surgery. Six patients, 2 of whom were nulliparous, entered the study through Emergency".*[5]

85% of patients were cured at 3 months (falling to 70% at 12 months) by plication of the uterosacral ligaments (USL). Further deterioration in cure rate over time necessitated insertion of a posterior sling in the position of the USLs, whose effectiveness was later confirmed by other investigators.

Farnsworth[6] reports the following cure rates at 12 months: apical prolapse 87%; urgency 80%; nocturia 81%; chronic pelvic pain 79%, in a cohort of 90 patients who had undergone prior hysterectomy. Goeschen[7] reported 71% cure of pelvic pain in 59 patients.

A practical test for USL causation. Gently insert the posterior blade of a bivalve vaginal speculum into the posterior fornix of the vagina. Frequently this relieves the pain.[8] Alternatively, a large menstrual pessary inserted into the back part of the vagina can also alleviate CPP.

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Peter Petros
e-mail: pp@kvinno.com

Case report

Can a perineal mass be a leiomyosarcoma? An interesting case

KAVERI SHAW, G. JAGDISHWAR GOUD, M. BALAVIKAS KUMAR, ARUN KATARI, KIRANMAI V. GOTTAPU

Krishna Institute of Medical Sciences - Surgical Oncology & Robotic Surgery, Secunderabad, Andhra Pradesh, India

Abstract: A sarcoma is not so easily recognized due to its wide spectrum of presentation. We describe a rare case of leiomyosarcoma of the perineum which presented as a recurring mass in a young woman, and the plan of management that has been provided. The leiomyosarcoma is one of the rarest varieties of sarcoma. Generally it is observed in the fifth or sixth decade of life. The common site of occurrence is the uterus, and the plan of management is very different compared to other sites. The present case is that of a recurrent perineal mass which was not suspected to be malignant prior to the initial surgery. The patient received chemotherapy once the lesion was diagnosed as rhabdomyosarcoma based on pathology report, immunohistochemistry reports were inconclusive. Recurrance while on chemotherapy lead to change in treatment plan Abdomino-perineal resection was not acceptable to the patient. A treatment plan was decided upon to tailor to the patients needs, a sandwich therapy was decided and pre-operative radiotherapy followed by surgery and adjuvant chemotherapy were given. Patient did not have symptoms of recurrence with a regular three month follow up for one year.

Key words: Adjuvant chemotherapy; Immunohistochemistry; Perineal leiomyosarcoma; Recurrent perineal mass.

INTRODUCTION

Leiomyosarcoma is a relatively rare tumor, which presents in the fifth or sixth decade of life.[1,2] This malignant smooth muscle tumor arises from the wall of the gastrointestinal tract, uterus, soft tissues, and retroperitoneal tissue. It comprises less than 0.1% of all ano-rectal malignancies. The definitive treatment plan depends on the site of tumor, age of patient and recurrence rate. Sixty percent recurrence rate after primary surgery is noted in the literature.[3]

CASE REPORT

A 23 yr old woman presented with a perineal mass (5.7x4.1x5.7cm) which recurred one month after the primary excision at the same site. The initial excision surgery was performed in another hospital where it was diagnosed as a rhabdomyosarcoma on histopathology basis and received chemotherapy with vincristin, adriamycin and cyclophosphamide. In view of progression of tumor despite of two cycles of chemotherapy the case was refered to our center. The revised histology was inconclusive therefore immunohistochemistry was performed which was positive for smooth muscle actin with cytoplasmic activity, negative for desmin, myogenin and s-100. A CT scan of the abdomen and pelvis demonstrated a lesion of 11.4x12.5x15.3cm. On biopsies taken in the recurred lesion immunohistochemistry was positive for desmin, strongly postitve for calponin and had no reaction for CD99 and HMB 45 (Figure 1), therefore it was unlikely to be a rhabdomyosarcoma. The histological features were suggestive of an undifferentiated sarcoma with round to ovoid cells and cigar shaped nuclei, and a final diagnosis was given as "perineal leiomyosarcoma".

In view of the large size of the lesion, an abdomino-perineal resection was planned, but the young patient did not give her consent and after a literature review, a more suitable option was offered.

A 50Gy irradiation in 25 fractions to the whole pelvis and perineum produced a regression of the tumor to 9x9x8cm. On clinical examination a firm swelling in the right side of the perineum with the previous scar were noted. At rectal examination a bulge in the antero-lateral walls of the anal canal could be felt but there was no growth within the anal canal. Informed consent was obtained for a wide excision of the tumor, abdomino-perineal resection being a second option. At surgery (Figure. 2), under general anesthesia, the proximity to postero-lateral vaginal wall and anterior rectal wall were noted. Incision was given keeping 1cm margin from the visible mass, the tumour was excised en bloc. After a wide excision, approximation of skin was achieved successfully. The post-operative period was uneventful, the patient was discharged on the fourth post-operative day. Histopathology reported a diagnosis of leiomyosarcoma with tumor free margins. Six more cycles of ifosfamide, adriamycin and mesna were given successfully . Till last follow up visit patient did not have any complaints of incontinence of flatus or stool, nor any visible or symptomatic recurrence after 12 months of surgery.

DISCUSSION

In the literature perineal leiomyosarcoma is an extremely rare tumour. Among all soft tissue sarcomas 5-10% are leiomyosarcomas.[4] Soft tissue leiomyosarcoma is thought to arise from the smooth muscle cells lining the small blood vessels, usually from the gastrointestinal tract and the uterus, but perineum as primary site is extremely rare and more aggressive than other superficial leiomyosarcoma.[4] Most of the time it presents as a painless, nontender mass and a benign histopathology is expected. It affects women more than men (2:1),[1,2] usually in the 5th and 6th decades of life.[4] The gender distribution has also been attributed to proliferation of smooth muscle in response to estrogens.[2] In a woman with complaint of a slow growing mass on the perineum the initial clinical differential diagnoses are Bartholin abcess, perineal abcesses or leiomyoma.

Histologically leiomyosarcoma has been divided into two subgroups: the superficial dermal form of leiomyosarcoma is thought to arise from the arrector pili muscles, and the deep subcutaneous smooth muscles of vascular wall.

Though histologically they may be same but treatment plan and prognosis differs in various leiomyosarcomas. For treatment purposes they are divided into four groups:[5,6]

Leiomyosarcoma of retroperitoneal somatic soft tissue.

Leiomyosarcoma of cutaneous origin.

Leiomyosarcoma of vascular origin

Leiomyosarcoma in immunocompromised host.

The tumor is composed of highly cellular fascicles of spindle-shaped cells. The cells have nuclei that are elongated and blunt ended giving typical "cigar" appearance. The degree of differentiation may vary within a single tumor itself. Classical immunophenotyping of leiomyosarcoma includes positive vimentin, desmin and smooth muscle actin (SMA) staining.[5] Desmin staining is sensitive and specific but cannot differentiate between rhabdomyosarcoma and leiomyosarcoma. Another histological differential diagno-

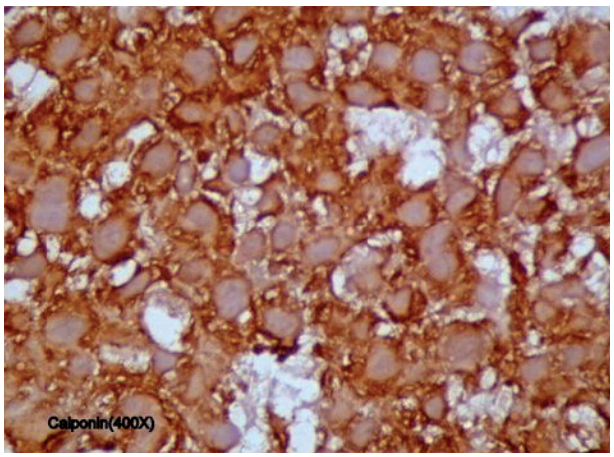

Figure 1. - Immunohistochemistry imaging, colponin postive.

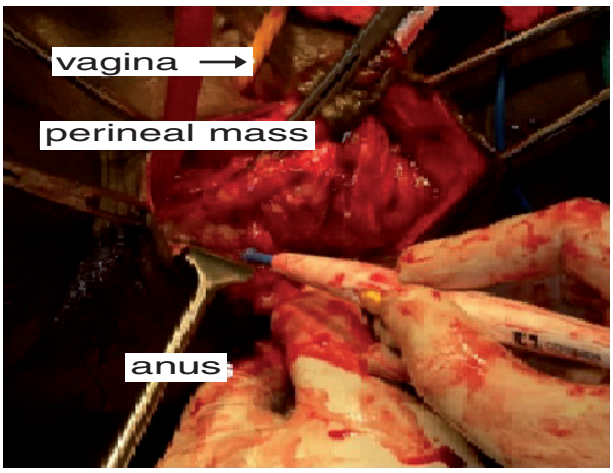

Figure 2. - Intraoperative picture of wide excision of perineal leiomyosarcoma: arrow showing intact vagina, dissected mass and intact anus

sis can be with spindle cell rhabdomyosarcoma which gives positive immunohistochemistry results for SMA and myogenin but no reaction to h-caldesmon which is seen reactive only in smooth muscle cell. Since the present case was SMA positive and myogenin negative it did not require h-caldesmon to differentiate its smooth muscle origin and spindle cell differentiation.To designate a tumor as rhabdomyosarcoma, myogenin should be positive.[5] Therefore rhabdomyosarcoma can be ruled out in this case.

This tumor has a variable prognosis that depends on its location, and treatment differs accordingly. Surgery is the definitive treatment of choice for perineal leiomyosarcoma to avoid metastases. The best approach would be abdomino-perineal resection due to the aggressive nature and the high recurrence rate.[7] Grobmyer et al reported nine cases who received adjuvant external beam radiation following wide excision. The lesions were high grade, up to 5 cm, and recurrence was seen in 60% of the cases. They also reported a median survival of 54 months which seems promising in this disease.[3]

The 50Gy radiation treatment in our patient shrinked the tumor and made it locally resectable avoiding the abdomino-perineal resection.

The chemotherapy agents used in sarcoma include doxorubicin and Ifosfamide, gemcitabine and taxotere (docetexel), dacarbazine and ecteinascidin.[2] Currently ifosfamide is found to be active in sarcomas that have failed to respond to doxorubicin-based regimen, as well as in recurrent or metastatic cases. The results of randomized control trials show that response rate to doxorubicin with or without ifosfamide are significantly higher than the ifosfamide-containing arm.[8] We have opted for ifosfamide and doxorubicin, that have shown promising results.

The median time from treatment to first recurrence noted was 21 months in a previous study.[3] The mean interval of metastases is 31 month (0-12 yr) detected over 5 years after diagnosis of the primary tumor and 8 years in a case report.[9] The earliest death after initial surgery due to recurrence/metastases has been reported by 16 months post surgery. The present case has not been been found with any recurrence till her last follow up 12 months after surgery. Leiomyosarcoma cases need a follow up every three months for the first two years and every six months for the next three years.

CONCLUSION

The perineal leiomyosarcoma in a young woman is rare. Immunohistochemistry is diagnostic when histopatholgy is doubtful. Rhabdomyosarcoma is common in young age and leiomyosarcoma should be considered in the differential diagnosis of asymptomatic perineal mass.Neoadjuvant radiotherapy in a large tumor may make resectable an unresectable disease.

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Correspondence to:
Dr.Kaveri Shaw MS (ob/gyn), Fellow Gyn-Oncology
Deapartment of Surgical Oncology
Krishna Institute of Medical Sciences
Minister road, Secunderabad,ap. Andhra Pradesh India 500003
email: kaverishaw@gmail.com

Original article

Interventional manometry: transvaginal support of pelvic floor ligaments raises endoanal pressure

SHUQING DING[2], MICHAEL SWASH[1], PETER PETROS[3]

[1]*Barts and the London School of Medicine, Queen Mary University of London, Neurology*
[2]*Nanjing University - National center of Colorectal disease of Chinese Medicine*
[3]*St Vincent's Hospital Clinical School, University of NSW, Sydney, Academic Department of Surgery*

Abstract: *Background:* The interaction between pelvic floor ligaments and muscles and anorectal pressure is not well characterized. Pelvic floor muscle vectors act against pelvic floor suspensory ligaments, including pubourethral (PUL) uterosacral (USL) and, inferiorly, perineal body (PB). Laxity of the pelvic floor leads to reduced endoanal pressures at rest and during a voluntary anal squeeze. *Aim:* We tested pelvic floor function using a new technique; interventional anal manometry. *Methods:* In a heterogeneous group of 14 women, with pelvic floor dysfunction of various causes, anorectal pressure measurements were obtained at rest and during maximal voluntary anal squeeze, before and during the following per-vaginal interventions, a] digital support at midurethra to support the pubourethral ligament (PUL); b] after a 3x6 cm tampon was inserted into the posterior fornix to support the uterosacral ligaments (USL); c] with combined PUL and USL support; d] with PUL, USL and perineal body (PB) support. *Results:* Resting and squeeze anorectal pressures increased during the support manoeuvres described, especially during experiment [d]. *Conclusions:* Creation of firm insertion points at PUL, USL, PB enabled muscle vectors to act more efficiently, leading to increased endoanal pressure. These interventions do not increase pressure generation by internal (IAS) and external sphincters (EAS) themselves, but result from changes in anorectal cross-sectional area. "Interventional manometry" offers a method for better understanding functional abnormality in the pelvic floor in women with clinical problems due to pelvic floor weakness.

Key words: Anal manometry; Pubourethral ligament; Uterosacral ligament; Perineal body; Pelvic floor laxity.

INTRODUCTION

Anorectal manometry correlates poorly with diagnosis of pelvic floor dysfunction and prediction for cure after an intervention. Nonetheless resting anal pressure measurements in individuals are reproducible.[1] Although anorectal resting pressure is reduced in subjects with faecal incontinence, there is insufficient sensitivity and specificity to consider anorectal pressure measurement as a specific diagnostic test.[2,3]

We have previously reported that upward pressure applied at midurethra by digital support of the pubourethral ligament caused a mean increase in endoanal pressure of 47cm water in the control group, and a mean 30 cm water pressure increase in a group of women with faecal incontinence ($p = 0.034$), suggesting less tight anal closure by directional muscle forces in the group with faecal incontinence.[4] This increase in endoanal pressure was considered to be due to improved efficiency of the muscle closure mechanism caused by supporting the ligament at the muscle insertion point.[5]

Therefore, as a test of principle, we have studied the effect of pelvic muscle contraction against pelvic floor suspensory ligaments and the perineal body (Figure 1) by measuring endoanal pressure before and during transvaginal digital support to these ligamentous structures in a heterogeneous group of women with pelvic floor disorders.

PATIENTS AND METHODS

Fourteen patients were studied. Eight presented with anorectal pain, five presented with constipation and one had double urinary and faecal incontinence. Mean age was 49.9 years (range 36-64). The principles of the Helsinki Declaration of 2008 were followed.

The interventions

Digital support of the pubourethral ligament (PUL)

The examiner's index finger was inserted into the vagina immediately behind the pubic bone at the level of midurethra and gently pressed upwards.

Tampon support of the uterosacral ligaments (USL).

A 3x6 cm tampon was inserted into the posterior fornix to support the uterosacral ligaments (USL).

Digital support of the perineal body (PB).

Two fingers were inserted into the vagina and separated laterally to support the right and left perineal bodies, taking care not to compress the anus.

Endoanal pressure measurements

Pressure measurements were performed using a ManoScan 360 High-Resolution catheter-based Anorectal Manometry System (Given Image Company, Israel).

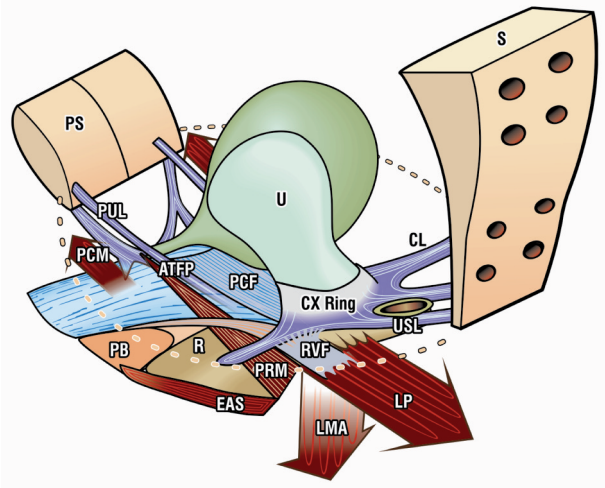

Figure 1. - Muscle vectors (arrows) showing planes of contraction forces against suspensory ligaments and perineal body. Patient in sitting position. According to this model, the action of anal canal "squeezing" is activated by forward contraction of m.puborectalis (PRM) which inserts directly into the posterior surface of the pubic symphysis (PS). M.pubococcygeus (PCM) contracts against the pubourethral ligament (PUL) anteriorly. M. levator plate (LP) contracts against the pubourethral ligament (PUL) anteriorly and against the perineal body (PB) inferiorly via its rectovaginal fascial attachment (RVF). The longitudinal muscle of the anus (LMA) contracts against the cardinal/uterosacral (CL/USL) complex. EAS=external anal sphincter.

Anorectal pressure measurements were made at rest and on maximal voluntary anal squeezing when supporting PUL only, USL only, both PUL and USL, and a final reading when simultaneously supporting all points, i.e., PUL, USL and perineal body (PB).

Statistical analysis:

We used Student's two-tailed t test to test for significance in the paired groups of data. Calculations were performed with Graphpad software.

RESULTS

The mean resting unsupported endoanal pressure before intervention was 70 mmHg (range 49.5-90.3mmHg). The mean unsupported maximum anal squeeze pressure was 125.3mmHg (range 86.6-184.4mmHg). With digital support as described above there was an increase in resting and maximal voluntary squeeze pressures, especially marked with combined support of PUL, USL and PB. Resting pressure increased by 28% and squeeze pressure by 22%. There was relatively little benefit when PUL or USL were supported alone. The full results are given in Table 1. Since the small number of patients studied were heterogeneous in terms of their clinical diagnosis no attempt was made to differentiate the results according to different syndromes.

TABLE 1. – Mean endoanal pressure measurements at rest and during voluntary anal squeeze with the pubourethral (PUL), uterosacral (USL) pelvic floor ligaments and perineal body (PB) unsupported and digitally supported per vaginam. Differences between the mean values at rest (columns 1 and 2) and between mean values during voluntary anal squeeze contraction (columns 3 and 4) were tested using Student's two-tailed t test.

	Resting pressure (range, mm Hg + SD)	**p vs baseline**	**Squeeze pressure (range, mm Hg + SD)**	**p vs baseline**
Baseline	70.1+14.5		125.3+30.5	
	(49.5-90.3)		(86.6-184.4)	
PUL support	81.2+18.5	0.01	130.8+29.9	NS
	(47.2-104.2)		(83.6-175)	
USL support	77.8+16.8	NS	140.5+31.9	0.01
PUL+USL	88.0+21.6	0.008	148.7+27.4	0.008
	(47.8-115.3)		(115.9-210)	
PUL+USL+	90.5+31.1	0.001	153+37.8	0.01
PB support	(56.5-166)		(101.5-242.2)	

DISCUSSION

The pubococcygeal (PCM), levator plate (LP) and conjoint longitudinal muscle of the anus (LMA) components of the pelvic floor musculature insert into pelvic floor connective tissue in relation to the anal canal and, in women, the vagina.[6, 7] These muscles contain a predominance of slow twitch fibres, and are thus adapted to tonic contractile force.[8] Contraction of these muscles stretches and narrows the anorectum causing an increase in intra-anal pressure. In patients with pelvic floor dysfunction, for example, prolapse and faecal or urinary incontinence, pelvic floor muscles are weak and there is associated with laxity and lack of elasticity of pelvic floor ligaments, so that muscle contraction is less effective. Anal squeezing is an important protective mechanism in the maintenance of faecal continence. Our understanding of the dynamics of pelvic floor function (Figure 1) implies that supporting the pubourethral ligament would cause little if any increase in anorectal pressure. We confirmed this in this study (Table 1).

The uterosacral ligament (USL) is attached to the lateral side of the rectum by fascia. Mechanical support of the uterosacral ligament alone creates a firm anchoring point superiorly, leading to an enhanced forward vector during contraction of the puborectalis muscle (PR) which we consider is the main muscle activated during a voluntary anal squeeze. This leads to increased anorectal pressure on squeezing, associated with narrowing of the intra-rectal luminal area. It can be seen from Fig 1 that digital support of the rectovaginal fascia (RVF) and perineal body (PB) should improve levator plate (LP) contraction. This contractile force stiffens the anterior wall of the rectum, permitting a stronger force vector to act during anorectal closure by the puborectalis muscle.

However, viewed from a basic physics perspective, it is not the intra-anal pressure itself which influences continence or defecation, but the frictional resistance to the flow of faeces within the anorectum. In a mathematical model, Bush (9) showed that this resistance followed an exponential relationship with the radius of the anorectum, being inversely proportional to the 3rd power of the radius. However, anorectal diameter is not uniform and this relationship is therefore complex. In addition, local factors such as lubrication of the anorectal wall by mucus, and stool consistency, will both play a role in anorectal frictional resistance to the passage of faeces. Anorectal pressure (Pressure=Force/Area) is itself derived inversely from the 2nd power of the anorectal radius since area can be simplified as $\pi r2$. These concepts indicate that resistance to faecal flow, and anorectal pressure, are related phenomena, so that the increased pressure which we measured on anchoring pelvic floor ligaments would also increase the intra-anal resistance. Thus, changes in anorectal pressure induced by appropriate correction of pelvic floor ligamentous laxity will improve symptomatic pelvic floor dysfunction.

The question arises, "Does interventional manometry have any practical value?" and "Can it serve as a predictive test?" There is evidence that reinforcing the PUL and/or USL suspensory ligaments may improve pelvic floor support and therefore anal closure (10,11) or obstructive defecation (11-13). We consider it likely that pressure measurements made before and after digital support of specific pelvic floor ligaments may become a useful predictive test in planning surgical repair procedures based on ligament reconstruction (10-13). However, this suggestion requires that appropriate measurements should be made before and after surgical techniques designed to restore normal continence by repair of suspensory ligaments and the perineal body in specific pelvic floor syndromes. Such studies remain to be carried out.

CONCLUSION

We have presented a new concept in clinical investigation of the pelvic floor, which we have termed "Interventional manometry". This technique requires digital reinforcement of the ligamentous insertion points of the pelvic muscles while measuring intra-anal pressure. We interpret the results of these interventions as improving muscle vectors during pelvic floor muscular contraction, causing an increased intra-anal resistance by narrowing the anal canal. This technique enables the precise anatomic-physiological deficit due to pelvic floor ligamentous laxity to be characterized and surgical correction to be planned accordingly.

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Correspondence to:

Shuqing Ding
Dept of Colorectal, 3rd Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China
E-mail Shuqing Ding <njgczx@gmail.com>

Original article

Complications of tension-free tapes and support grafts

STAVROS CHARALAMBOUS, IOANNIS VOUROS, ARISTIDIS KARELIS, VASILEIOS ROMBIS

Urological Department - Ippokratio General Hospital - Thessaloniki, Greece

Abstract: Tension free vaginal tape (TVT) has become the treatment of choice for females with stress incontinence (SUI), since the first description from Ulmsten and Petros, in 1995. Success rate for TVT, as long as for the later described supporting the mid-urethra transobturator tapes, have been found high. Complications frequency is low for all types of tapes, but complications do still appear. The necessity for decreased complications led to the development of new supporting tapes such as TVT-secur and Needleless. Success rates concerning continence and quality of life have been evaluated and published, but complications rates and their treatment options still remain controversial. Purpose: To present the complications following application of mid- urethra supporting tapes and pelvic floor grafts, in order to treat SUI and pelvic floor prolapse respectively.

Key words: TVT; Stress urinary incontinence; Complications.

INTRODUCTION

According to the International Continence Society (ICS), SUI is defined as the involuntary urine leakage during physical effort, sneezing, coughing and exercise. MUI (Mixed urinary incontinence) is defined as the involuntary urine leakage due to urgency (a sudden, strong desire for urination which cannot be inhibited) and concomitant stress incontinence.

The prevalence of incontinence ranges from 2 % to 55 % depending on the definition, the type, the data, the sex and the various population groups. The prevalence in young women varies from 10 % to 40 % but in older women and elderly centers[1] it might be found more than 50%.

Incontinence has an important impact in the quality of life (QoL) which often is not properly evaluated by physicians and other health - related professions. Surgical complications following SUI correction might affect QoL more than preoperatively.

TABLE 1. – Complications after MUS application according to the international literature..

OPERATIVE COMPLICATIONS	**Frequency(%)**
Major	
Vascular injury	< 0,01
Nerve injury	< 0,0005
Bowel injury	< 0,007
Minor	
Bladder perforation	0,5 - 14
PERIOPERATIVE COMPLICATIONS	
Retropubic hematoma	2 - 4,3
Blood loss > 200 ml	2,7
Urinary infection	10
Spondylitis	0,3 - 0,8
POSTOPERATIVE COMPLICATIONS	
Temporally voiding dysfunction - Retention	1,4 - 15
Permanent voiding dysfunction – Retention	2,4 - 8
Erosion of the vagina	0,7 - 33
Erosion of the urethra	2.7 - 33
Erosion of the bladder	0.5 - 0.6
De novo urgency	7,2 - 33
Urethral obstruction	3,6 - 6,4

Many techniques, materials and surgical procedures have been described for the correction of the female urinary stress incontinence (SUI), since the first presentation of the mid – urethral slings (MUS).[2]

Although the security, the effectiveness and the complications concerning TVT and transobturator procedures (TOT)[3] have been adequate estimated, this is not a fact when it comes to the treatment of these complications.[4]

The most recently presented tapes (TVT- secur, needleless) have been introduced to the surgical treatment of SUI in order to reduce the frequency and the severity of those complications.[5-6] Surgical treatment of pelvic organ prolapse and SUI is considered to be successful when QoL is improved. It is also considered to be successful in cases where despite the failure of the correction and even the occurrence of certain complications, there isn't any severe impact on patients QoL.[7]

COMPLICATIONS

The use of MUS became a popular way of SUI treatment because of the high success rate. The frequency and the variability of those complications is depended on various factors such as a) surgeon's experience, b) correct diagnosis and report, c) deliberately decreased complication's rates by surgeons who have higher rates, d) reduction of complication's frequency and severity rates, in some clinical trials, due to underestimation. Also, other important factors are the time of diagnosis and the clinical symptoms and evidences.

In table 2 are presented the complication's symptoms.

Urologists and gynecologists must be aware that most of complications appear early after surgery.[8] They also must be able to identify the clinical symptoms in order to resolve the problem as soon as possible. The effectiveness of the new surgical techniques improves with the experience that is gained with time. In our technological era the learning curve is quite prolonged, but it seems that the difficulty of learning is not related with the complications. These complications have to do more with the surgical procedure than with the experience of the surgeon.

Complication rates increase due to co-existing diseases such as diabetes, vascular diseases, obesity, or prior pelvic irradiation applied for gynecological cancer.

TABLE 2. – Complication's symptoms.

COMPLICATIONS	Symptoms
Obstruction	Post void residual urine - incomplete empting
	Voiding dysfunction
	Relapse urinary infections
	Urgency
	Reduced urinary flow
Bladder erosion	Hematuria
	Suprapubic or urethral pain
	Urinary infection
Vaginal erosion	Vaginal Pain
	Dysparuneia
	Voiding dysfunction
	Urinary infection
	Vaginal discomfort
De novo urgency	Frequency
	Urgency
	Nocturia
	Urgency incontinence
Urethral erosion	Pain
	Urethral bleeding
	Urethral discomfort
	Urethretis
	Urgency

TABLE 3. – Etiology of complications.

COMPLICATIONS	Etiology
Vaginal erosion	Incomplete closure of the vaginal wall
	Extensive surgical dissection of the vaginal wall
	Early sexual intercourse
	Previous vaginal operations
	Trauma inflammation
	Wrong surgical incision
	Torsion of the sling
	Ischemia
Urethral erosion	Increased tape tension
	Ischemia
	Extensive dissection
	Previous operations
	Inflammations
	Inappropriate surgical field
	Torsion of the sling
Perforation of vagina	Surgical technique

COMPLICATIONS TREATMENT

Superficial hematomas were treated conservatively.[9] They were caused due to false positioning of the patient on the surgical bed (Figure 1).

The first case of **retropubic hematoma** was observed immediately after TVT application. Surgical exploration and blood transfusion was needed. No major vassal injury was found. The second case of retropubic hematoma was treated conservatively. Only blood transfusion was needed. The case of retropubic hematoma, due to mesh application (cystocele Gr II), was treated at first conservatively. Next day's examination indicated severe bilateral hydronephrosis. Percutaneus nephrostomies were placed. The urine flow in the left ureter was restored after a period of two months, whether the right ureteral orifice had to be transurethricaly resected in order to maintain the urine flow (Figure 2).

If the bladder perforation is promptly diagnosed during the tape application, then the tape must be repositioned. Special care and experience is required during cystoscopy in order to detect bladder perforation or even more a submucosal displacement of the tape, which later on can lead to bladder erosion.

Two cases with **bladder perforation** complained for LUTS six months after the tape application. According to the international literature an open surgical removal of the calcified tape is suggested. In our cases transurethral resection and partial removal of the tape was successfully performed. All symptoms were immediately withdrawn. One patient remains continent and another underwent T.O.T. replacement after two months (Figures 3, 4, 5).

Vaginal erosion was diagnosed in four patients. It was caused by early sexual intercourse, wound infection, and inappropriate vaginal incision closure. In one patient the in-

TABLE 4. – Complications of supporting grafts, according to international literature.

COMPLICATIONS
Vaginal erosion
Urethral erosion
Urinary infection
Relapse of the prolapse
Hematoma
Bladder perforation
Bowel trauma
Dyspareunia
Constipation difficulties
Urgency
Voiding dysfunction
SUI
Pain during walking

TABLE 5. – Complications of vaginal tapes and support grafts which were diagnosed and treated by the Urological Clinic of Ippokratio General hospital of Thessaloniki until November 2007. (Including cases which were sent to Ippokratio from other Medical Centers).

COMPLICATIONS	TVT =265	TVT-O TOT = 112	P	TVT-S NEEDLESS =19	MESH =19h
Retropubic Hematoma	2	-	NS	-	1
Bladder perforation	26	-	0,02	-	-
Vaginal erosion	4	1	NS	-	-
Bladder erosion	2	-	NS	-	-
Retention	3	-	0,45	-	
Voiding dysfunction	27	4	0,02	-	-
Pain	38	14	0,02	-	2
Urinary infection	53	4		1	1
De novo urgency	37	4	NS	2	2
Dyspareunia	-	-			2

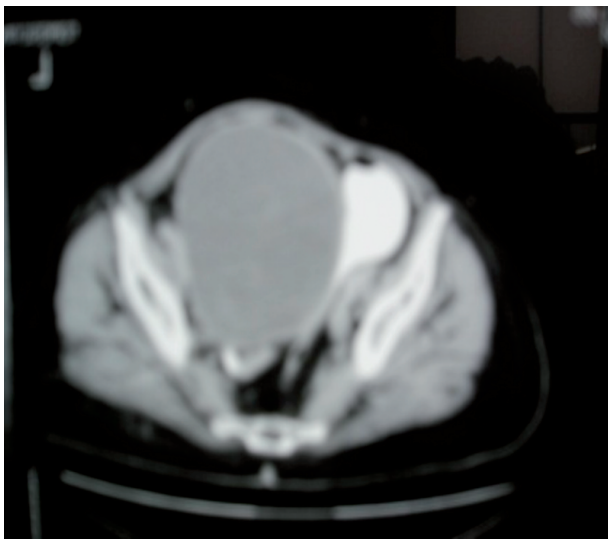

Figure 1. - Retropubic hematoma.

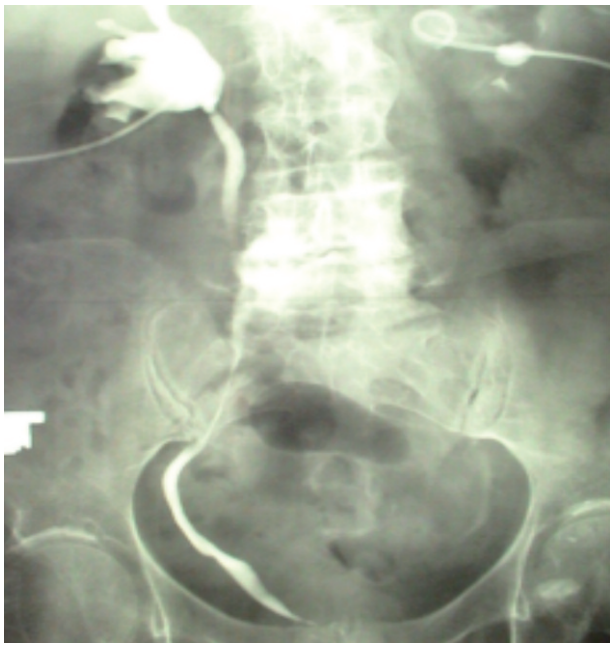

Figure 2. - Percutaneus nephrostomies.

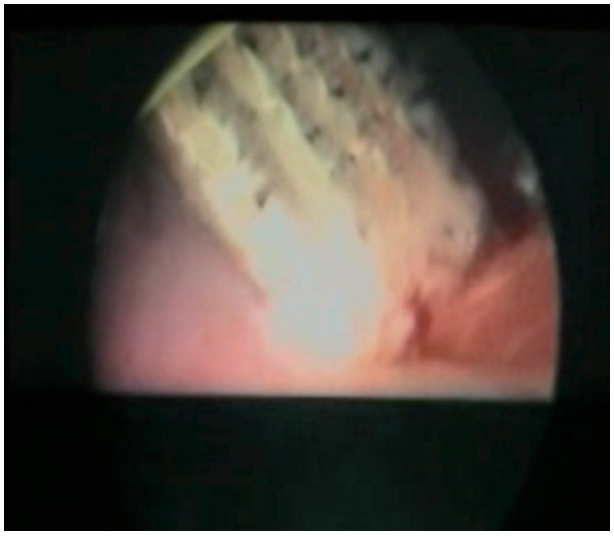

Figure 3. - Intravesical tape migration.

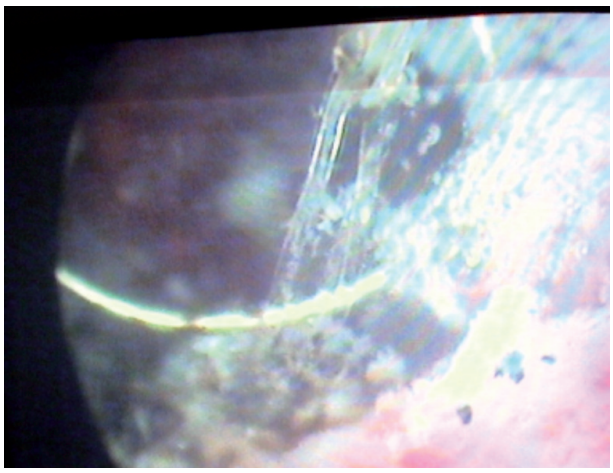

Figure 4. - Transurethral tape removal.

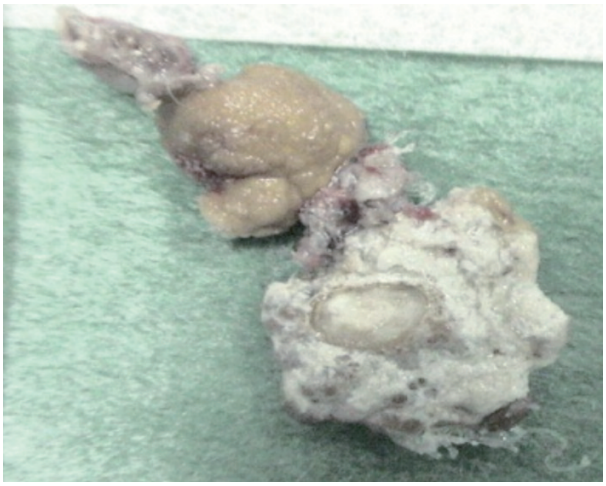

Figure 5. - Removed calcified tape.

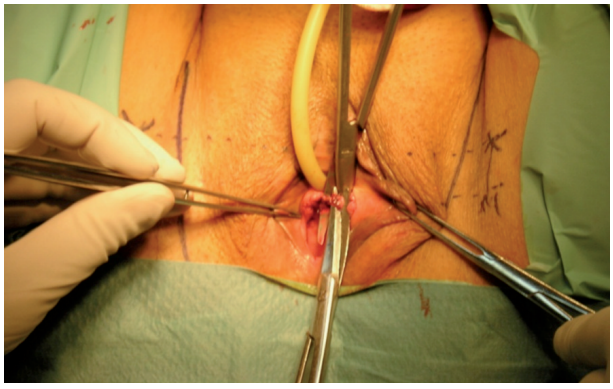

Figure 6. - Tape dissection.

fection was treated by antibiotics and hormonal therapy (oestrogens), which contribute in the healing of the vaginal wall. Three other cases underwent partial dissection of the tape and reconstruction of the vaginal incision margins. (Figure 6)

One patient with voiding dysfunction (dysuria) was treated conservatively.[10] In three other cases with urinary retention the tape had to be removed surgically because of the initial therapy failure to respond in urethral dilatations and intermitted catheterizations. Pain was treated with antiflamatories and analgetics, urinary infections with antibiotics, and de novo urgency with antimuscarinics. Dysparuneia was treated with locally application of oestrogens in the vagina.

CONCLUSION

Treatment of female urinary stress incontinence and pelvic organ prolapse with tension free tapes and mesh respectively are safe and effective procedures. Perioperative and postoperative complications, when promptly recognized can be easily treated. A prolonged follow up is required in order to treat or avoid late complications.

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Correspondence to:

st.charalambous@gmail.com

Original article

Changes type III collagen expression in human uterosacral ligaments of uterine prolapse

EPPY DARMADI ACHMAD[2], JUNIZAF[1], BUDI IMAN SANTOSO[1], BENNY HASAN PURWARA[2], TYAS PRIYATINI[1]

[1] Faculty of Medicine Indonesia University, Division of Urogynecology and Reconstruction, Department of Obstetric and Gynecology Dr. Cipto Mangunkusumo Hospital, Jakarta
[2] Faculty of Medicine Universitas Padjadjaran, Division of Urogynecology and Reconstruction, Department of Obstetric and Gynecology Dr. Hasan Sadikin Hospital, Bandung

Abstract: There are some controversies regarding the content of type III collagen fibers in uterosacral ligaments in pelvic organ prolapse (POP). The role of these fibers are still unclear. This study aims to compare the content of type III collagen fibers in uterosacral ligaments (USL) in patients with or without POP.
This is a cross-sectional analytic study conducted in 23 women with POP from Jakarta Indonesia. The control group were 23 women without POP. The study took place in Dr. Hasan Sadikin Hospital during May-October 2011.
The type III collagen fiber content in USL of women with POP was 50% higher than those in women without POP (p=0.036). In conclusion, the type III collagen fibers content in USL of women with POP is more dense compared with those without POP.

Key words: Type III collagen fibers; Pelvic organ prolapse; Uterosacral ligaments.

INTRODUCTION

Gabriel et al[1] found that there were strong immunohistochemistry reactions of type III collagen fibers in uterosacral ligament (USL) in women with pelvic organ prolapse (POP) compared with type I and type II collagen fibers. Jackson[2] also found that there was reduction of collagen amount with predominantly immature collagen content in women with POP and cystocele, compared with those without POP.

In women with POP, there were several changes in cell transcription program in USL, leading to changes in matrix production, mechanical properties, cell shape, inflammatory reaction, and healing process. Furthermore, the immature collagen content also relatively higher.[3,4]

The study regarding type III collagen fibers in USL of women with POP has been widely conducted worldwide, but mainly in Caucasians. The data from Asian women is still scarce. This is the first study comparing type III collagen fiber content in USL in Indonesian women.

MATERIAL AND METHODS

This is a cross-sectional analytic study, conducted in Dr. Hasan Sadikin Hospital Bandung during May-October 2011. Subjects were women with grade 2, 3 and 4 POP, while the control group was women without POP or with POP grade 1. Women with pelvic organ malignancy, intraabdominal tumors, and previous history of pelvic surgery were excluded from this study. Tissue samples were taken from the uterus after total abdominal or vaginal hysterectomy. To obtain tissue samples, the distal portion of USL (approximately 1 cm from its attachment from cervix) was cut (approximately 0.5 cm^3). Samples were then immersed in formaldehyde solution before being sent to the Department of Pathology for immunohistochemistry examination. The immunohistochemistry assay was done using type III collagen fiber staining (Abcam ab7778 rabbit polyclonal to collagen III). To interpret the immunohistochemistry assay, these guides were used: for determining type III collagen fibers distribution: +1 if distributed less than 20%, +2 if distributed 20-50%, +3 if distributed 50-80%, and +4 if distributed more than 80%. For immunostaining intensity: 0 if no staining, +1 if weakly stained, +2 if moderately stained, and +3 if strongly stained. After determining distribution and intensity, the HistoScore were calculated using the formula: distribution x (intensity+1), and the value range were 1-16.

Data were analyzed using SPSS program version 16.0.

RESULTS

The study was conducted during a six-month period, from May-October 2011. During that period, all subjects fulfilled inclusion criteria were enrolled to this study. There were 23 women with POP, and 23 women without POP or with POP grade 1 served as control group. The characteristics of subjects may be seen in table 1. There were significant differences in age and menopausal status between POP group and control group ($p<0.05$), while parity and BMI were not significantly different ($p>0.05$). No subject had received hormone replacement therapy. Most of POP subjects had grade 3 POP (62.5%), followed by grade 2 (26.1%), and grade 4 (8.7%). There were no grade 1 POP subjects in this study.

TABLE 1. – Subject characteristics (n=46)

Notes: +) Unpaired t test
++) Chi square
+++) Mann Whitney U

Characteristics	Pop (n=23)	Control (n=23)	p
1. Age Mean (SD):	50.2 (9.2)	62.4 (7.8)	0.001^{+}
2. Menopausal status			
Premenopause:	2 (4.3%)	12 (26.1%)	0.001^{++}
Postmenopause:	21 (45.7%)	11 (23.9%)	
3. Parity Median:	4	4	0.645^{++}
Range:	2-12	0-8	
4. BMI (kg/m^2) Median:	21.21	22.97	0.095^{+++}
Range:	16.65-31.18	20-27.77	

The comparison of distribution and intensity of type III collagen fibers between POP and control group may be seen in figure 2a, 2b. The median of type III collagen fibers distribution was significantly higher in POP group ($p<0.05$). The intensity of type III collagen fibers was higher in POP group as well but not significantly different with the control group ($p>0.05$).

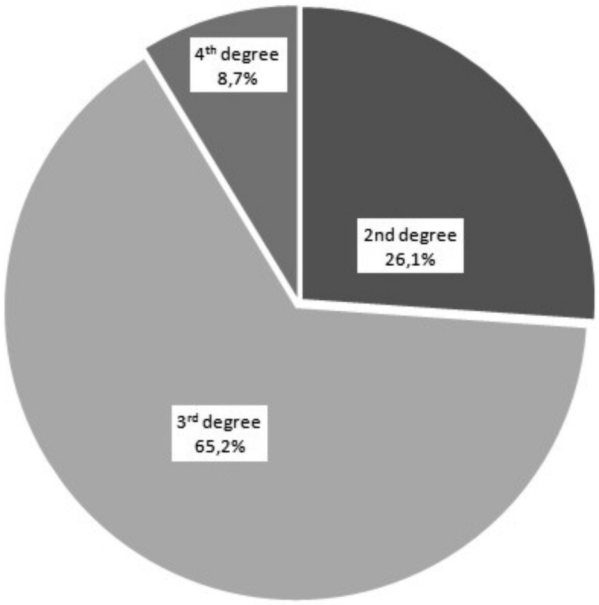

Figure 1. - Prolapse Organ Pelvic distribution.

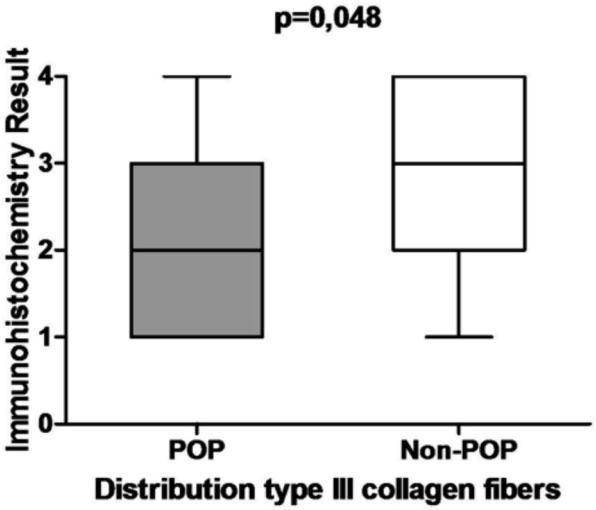

Figure 2a. - Comparison of distribution of type III collagen fibers in women with and without POP. Immunohistochemistry result: +1 (< 20%), +2 (20-50%), +3 (50-80%), and +4 (>80%).
Statistical analysis using Mann-Whitney U nonparametric test.

The comparison of Histo Score between two groups may be seen in figure 3. There was a significant difference of Histo Score between POP and control group (median 12, range 3-16 vs median 8, range 1-16, p<0.05). There was no significant correlation between degree of POP and type III collagen fiber content (p>0.05). Furthermore, there were no significant correlations between age and menopausal status to type III collagen fiber content, as seen in table 3 and figure 4.

DISCUSSION

Although the exact pathophysiology of POP is still unknown, there are some risk factor contributing in the occurence of POP, i.e pregnancy, vaginal delivery, age, elevation of intraabdominal pressure, menopause, hypoestrogenic status, trauma, genetic factor, race, muskuloskeletal disorders, chronic debilitating illness, smoking, and previous history of surgery. From previous studies, mechanical and

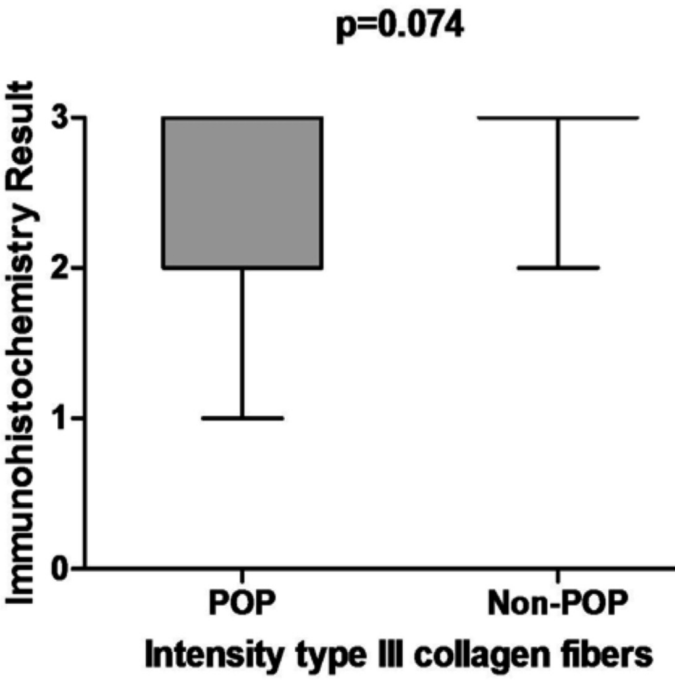

Figure 2b. - Comparison of intensity of type III collagen fibers in women with and without POP. Immunohistochemistry result: 0 (no staining), +1 (weakly stained), +2 (moderately stained), and +3 (strongly stained)
Statistical analysis using Mann-Whitney U nonparametric test.

metabolical changes in connective tissue may serve as predisposing factors for POP.[5-7] Furthermore, the reduction of collagen fiber amount as well as decreasing quality of those fibers also may contribute in POP.[8]

According to WHI study, there are higher risks in older women to develop POP (1.2 times higher in women aged 60-69 years, and 1.4 times higher in women aged 70-79 years compared with those whose aged 50-59 years). In a cross-sectional study of 21,449 menopausal women in Italy, the risk of POP in older women are higher compared to

Table 2. – Effect of degree of POP on the content of type III collagen fibers.

Notes: Kruskal Wallis test

Degree of POP	Mean Rank Histo Score of tipe III collagen	N	P
Degree 2	14.33	6	
Degree 3	10.93	15	0.535
Degree 4	13.00	2	

Table 3. – The influence of age on the content of type III collagen fibers.

Notes: Kruskal Wallis test

Age Classification (years)	Mean Rank Histo Score of tipe III collagen	N	P
30-39	15.25	2	0.547
40-49	27	10	
50-59	20	15	
60-69	25.58	13	
70-79	25.42	6	

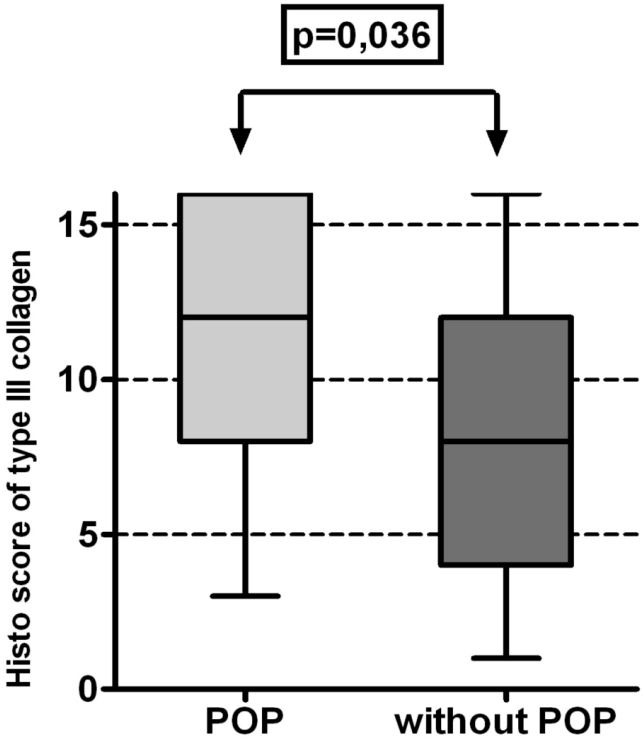

Figure 3. - Comparison of content of typeIIIcollagen fibers in women with and without POP.
Statistical analysis using Mann-Whitney U nonparametric test.

those in less than 51 years age group (1.3 times higher in 52-55 years age group, and 1.7 times higher in >56 years age group).[8] In this study, the mean of age was 50.2+9.2 years.

Women who experienced vaginal delivery have a higher risk of developing POP compared to nulliparas (8.4 and 10.9 times higher for twice and four or more deliveries respectively; 95% CI 4.7-33.8).8 According to Bradley et al.[9] women who experienced 1-2 times vaginal deliveries have 1.28 (0.49-3.32) cm vaginal descent; while in women who have 3-4 and more than 5 vaginal deliveries the vaginal descent was 2.35 (0.98-5.67) cm and 4.82(1.92-12.09) cm respectively. In this study, mean parity was 4 (range 2-12). In our group, high parity is a major factor for POP incidence. In contrast with this condition, in western countries POP may be found in the low parity group. Furthermore, we also found women with POP in low parity group as well.

Increasing BMI also play a role on the incidence of POP. Women who are overweight (BMI 25-30 kg/m^2; OR 2.51, 95% CI 1.18-5.35) and obese (BMI> 30 kg/m^2; OR 2.56, 95% CI 1.23-5.35) are at high risk of developing POP.[8] Some studies suggest an association between POP and increased BMI, but other studies did not find a correlation between the POP and the increase in BMI, so the correlation of the two variables is still a controversy.[7] BMI in this study is still considered within normal limits, so the subject's BMI in this study did not include a risk factor for POP. The higher the BMI, the higher the risk of POP, but with the thought that obese women have higher estrogen level will reduce the risk of incidence of POP. The study specifically to determine the correlation between POP and BMI as confounding factors has not exist, therefore, the opinion is still a matter of controversy among researchers.

Most women with POP in this study were postmenopausal and had received no hormone replacement therapy. These are risk factors for POP.

Comparison of type III collagen in POP and without POP

Increased content of type III collagen fibers that play a role in tissue elasticity and elongation tissue will lead to decrease ratio in the content type I: III of collagen fibers, which will produce tissue laxity.[10]

The median histological score of type III collagen fibers in the uterosacral ligaments POP women in this study was 50% higher compared to women without POP ($p < 0.05$), the situation has been implicated in the occurrence of POP. The high content of type III collagen fibers to women with POP in this study was not sufficient evidence of an increasing in the content of type III collagen fibers because this study is cross-sectional.

The results in this study are in accordance to study conducted by Gabriel et al 1 who showed that the content of type III collagen fibers was significantly higher in uterosacral ligaments in patients with POP. They suggested that the content of smooth muscle in uterosacral ligaments about 20% and collagen type I in the uterosacral ligaments almost the same between postmenopausal women with and without POP, but the content of type III collagen was significantly increased for uterosacral ligaments in patients with POP. Suzme et al[11] found that the hydroxyproline levels decreased in uterosacral ligaments women with POP although in histopathology seen an increase in collagen density. Collagen synthesis in women with POP is increased in fibroblasts compared to control. It shows that the mRNA of collagen types I and III increased. The newly formed immature collagen is more susceptible to endogenous proteases and therefore is unlikely contribute to mature cross-linked collagen that confers strength and durability connective tissues.[4]

Connell et al[12] found that the expression of both collagen type I and collagen type III was significantly reduced 7.3- and 17-fold in the uterosacral ligaments of women with POP compared with controls, due to decrease in procolla-

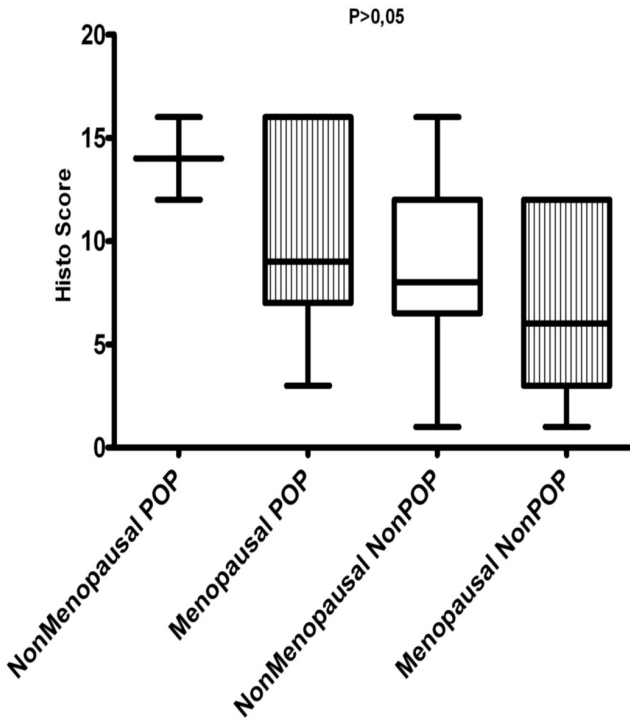

Figure 4. - Effect of menopausal status on the content of type III collagen fibers.
Statistical analysis using the Kruskal-Wallis nonparametric test (Dunn's multiple comparison test).

gen. These results were consistent with the finding of Suzme et al11, who showed that an increase in the diameter of collagen fibers in the uterosacral ligaments fewer in women with POP.

Confounding factors of age and menopausal state in this study were significant differences between the groups, but these factors did not influence to the content of type III collagen fibers in POP statisticaly. According to Kerkhof et al[3] and Jones et al[13] in patients with POP decrease resistance and weakening of the pelvic floor connective tissue, the circumstances associated with increasing age and the occurrence menopause. Increasing age and menopausal state would lead to hypoestrogenism. Chen[14] suggested that estrogen receptor alpha genotype associated with the incidence of POP. Hansen[15] states that estrogen replacement therapy increases the estradiol levels which influence tendon and ligament morphology and biomechanical properties in postmenopausal women. This is related to the smaller fibrils with a higher density. Relative stiffness was lower in estrogen replacement therapy users because lower proportion of immature collagen cross-links will reduce the potential strength of tendon and ligamentum.

Hormone replacement therapy will suppress the increase in content of type III collagen fibers, thus giving hormone replacement therapy can prevent POP.[10] The relationship between hormone replacement therapy and POP cannot be evaluated because all subjects in this study were not use of hormone replacement therapy.

Excessive stretching or tearing ATFP during vaginal delivery will contribute to the incidence of POP.[4] Reisenauer et al[16] found that the distribution of smooth muscle in uterosacral ligaments in patients POP was abnormal. Distribution of parity and BMI data both groups there was no significant difference so that does not affect the content of type III collagen fibers. Assumption of the greater degree of POP the higher the content of type III collagen fibers, according to this assumption resulting in statistical analysis to know the correlation, but the results of the statistical analysis of POP degree turns do not affect the content of type III collagen fibers.

CONCLUSION

The content of collagen type III patients with uterine prolapse is more dense than without uterine prolapse . We were not able to determine whether this was a primary contributor to the POP or a secondary manifestation of the POP itself.

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Correspondence to:

Eppy Darmadi Achmad MD
Faculty of Medicine Indonesia University
Division of Urogynecology and Reconstruction,
Department of Obstetric and Gynecology
E-mail: eppyda@yahoo.com

INVITED COMMENT: Statistical Notes

The authors compare the content of collagen fibers from an histological examination between two groups of women with genital prolapse. The scales used to measure the results are ordinal and they had properly chosen to analyze the data with non parametric tests based on ranks. The use of rank based test should also be considered when data are from continuous variables.

The t-test is known to be the most efficient test to compare the means from two independent samples. This statement is not completely correct since to maintain its optimum properties it is required that the two samples are normally distributed.

The assumption of normality is an assumption therefore supposed true before the experiment. If it is tested before performing the t-test we introduce a multiplicity error, but especially with small sample sizes, most of the time a normality test will not refuse the hypothesis of normal distribution, without proving it.

Looking at the formula of the t statistic it is easy to see that the problem is related mainly to the standard deviation (s), when it is very large and/or it very differs between the two samples. In this case the denominator will be very large and the statistic very close to zero (not significant) although when m is large. As a result the confidence interval, calculated on the normal distribution, tends to be very wide.

A possible solution is to test the distribution of ranks between the two samples. Instead of considering the observed values all the observations are sorted and each value is substituted by its rank position.

Compared to observed values, the information about the distance between two values is lost but outliers can't make the variance grown abnormally. The more the we gain the possibility of comparing results from non metric scales like a Likert scale. In fact the distance between "agree" and "strongly agree" in not necessarily one neither it is the same distance of any other two adjacent position for example "neutral" and "disagree".

A rank based test will evaluate if in the two samples the splitted ranks are concentrated at the top/bottom or homogenously distributed.

The following example comes from an experiment on inhibition in lab animals of response to an allergic challenge.

There are only five observations per group: in the first one (A) the response is inhibited, in the other (B) it's not. Due to the allergic nature of response, observations in group B can be very different.

ID	Group	**obs.**	Rank
3	A	162.6	9
4	A	140.7	10
6	A	190.7	8
7	A	191.2	7
8	A	243.5	6
1	B	250.9	5
2	B	630.7	3
5	B	749.6	2
9	B	2347.3	1
10	B	591.9	4

In group A mean is 158.7±38.58 in group B is 914.1±822.36: it is clear that the inhibitor is working but due to the outlier (id=9) in group B the standard deviation is abnormal and the t-test is not significant ($p<0.08$).

If we censor the observation id=9 the group B mean is 555.8±214.04 and the t-test is significant ($p<0.006$). Not taking into account one value the difference between means dramatically decrease from 728.4 to 370.1 more than 50% but now it is significant. Adopting this approach the point is: the estimate of inhibition is 728.4 or 370.1?

The rank solution is preferable. In this case we have the best possible situation: the first five ranks are in group B ($p<0.03$).

Note that using this approach in general any value greater than the second rank value (in our example 749.6) will give the same result. The last problem is the best estimate of the effect. Using rank based analysis the median should be preferred, in our case 190.7 in group A and 630.7 in group B, the effect on medians is 440.

Talk to your doctor before you take any medicine.
Check a statistician before making an analysis.

Carlo Schievano
e-mail: ciesse@stat.unipd.it

Education

Interactive clinical teaching/discussion module

Application of the Integral System to the management of complex pelvic floor cases

WILLIAM LYNCH, PETER PETROS (pp@kvinno.com)

University of NSW, Kensington, Sydney

Background The Integral System is an entirely anatomical method which attributes causation of prolapse, bladder and bowel symptoms to laxity in four suspensory ligaments of the vagina and the perineal body. Its components are

1. A patient administered validated questionnaire to detect abnormal symptoms (Appendix).
   Positive symptoms are annotated onto the algorithm.
2. A diagnostic pictorial algorithm (Figure 1) guides diagnosis of damaged ligaments and surgery.
3. Simulated operations (Figure 2), specific ligaments are digitally supported to check the diagnosis suggested by figure 1.
4. Site specific ligament repair inserts polypropylene tapes which shorten and strengthen one of 4 lax suspensory ligaments or perineal body (Figures 3).
   The algorithm, examination and simulated operation charts are available free online from www.integraltheory.org.

Comments. The report being placed online (www.pelviperineology.org), comments and questions to the authors are invited.

Patient. Ms JC aged 74. presented with a 5 year history of urine loss with coughing, laughing, exercise, urgency, urge incontinence up to twice per day, nocturia 6-7 times/night and bladder emptying difficulty.

There was no pelvic pain and no history of previous surgery. She was assessed using the questionnaire, algorithm (Figure 1) and simulated operation chart (Figure 2).

Diagnosis. The symptoms from the questionnaire (see Appendix) were entered into the diagnostic algorithm (Figure 1), which showed potential ligamentous defects in the anterior, middle and posterior ligaments of the vagina.

On examination

Anterior zone Lax hammock; urine loss on coughing controlled by unilateral upward pressure at midurethra,

Middle zone 2nd degree high cystocoele with cardinal ligament defect.

Posterior zone 1st degree uterine prolapse.

Simulated operations (Figure 2) were performed in the clinic to confirm the algorithm's indicated diagnosis.

These tests are always performed with a full bladder, checking the diagnosis by digitally supporting specific ligament insertion sites to check for change in symptoms.

There was relief of USI (urinary stress incontinence) by supporting the pubourethral ligaments (positive midurethral cough test). Relief of urgency was achieved by supporting the pubourethral ligaments, uterosacral ligaments (apex) with the lower blade of a bivalve speculum and digital support of the bladder base (cardinal ligaments).

Operation 24th May 2013

Immediately prior to surgery, the 9 potential anatomical defects (Figure 1) were checked while the patient was on the operating table, as frequently anatomical defects are detected which were not present in the outpatient examination.

The damaged ligaments were repaired on 24th May 2013 using the TFS system: a minimally invasive, single incision tensioned sling system to repair pubourethral, cardinal and uterosacral ligaments (Figures 3, 4). The patient was operated on in the afternoon and discharged the next day on paracetamol only. She was advised to "listen to her body", rest where required and avoid any lifting for at least 6 weeks. She could, however, undertake light household duties, drive her car and go shopping after a week.

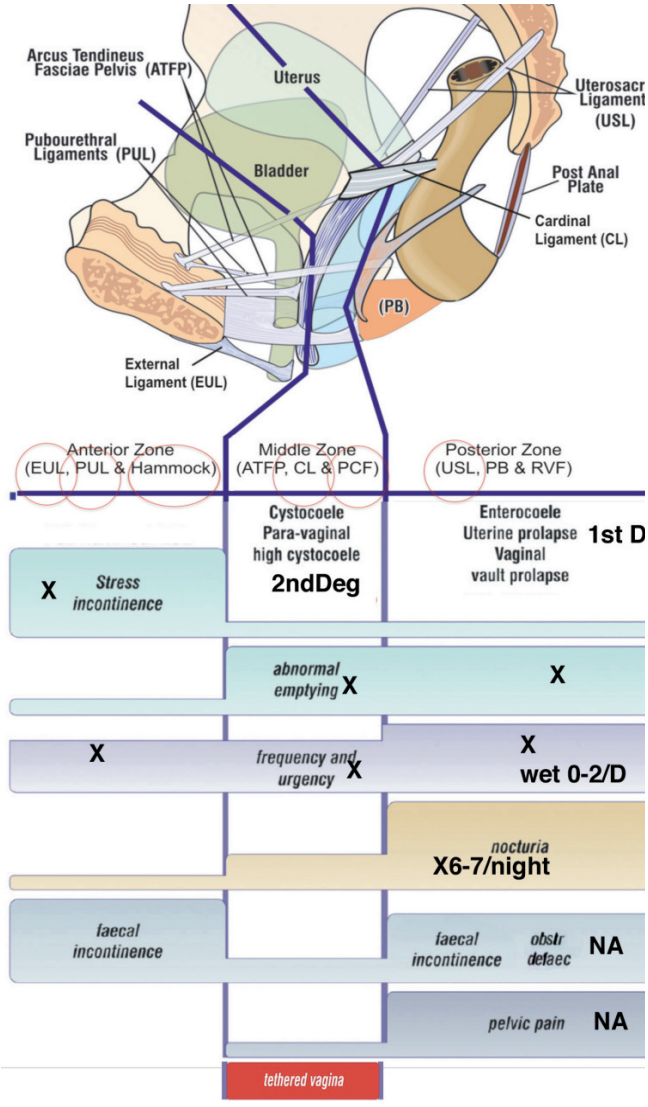
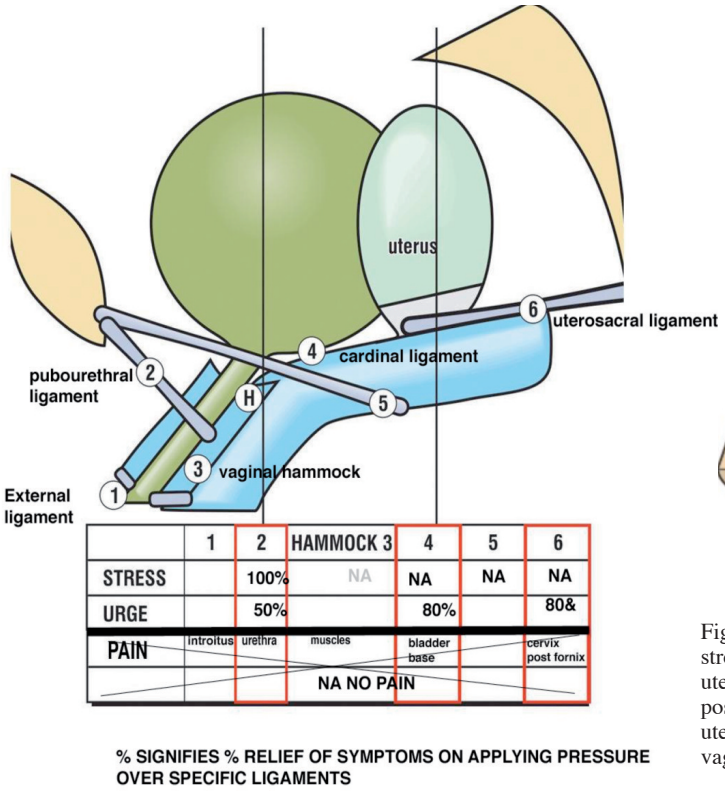


Figure 1. - Diagnostic pictorial algorithm relates symptoms to specific ligament damage in 3 zones of the vagina.
The positive answers to questions from the questionnaire were ticked in the algorithm as are the specific anatomical defects diagnosed on vaginal examination (red circles).



	1	2	HAMMOCK 3	4	5	6
STRESS		100%	NA	NA	NA	NA
URGE		50%		80%		80&
PAIN	introitus	urethra	muscles	bladder base		cervix post fornix
			NA NO PAIN			

% SIGNIFIES % RELIEF OF SYMPTOMS ON APPLYING PRESSURE OVER SPECIFIC LIGAMENTS

Figure 2. - The simulated operation chart. Supporting specific ligaments may relieve urine loss with coughing (pubourethral ligament) or urgency. These are annotated as % relief of the urgency symptom on supporting the pubourethral, (retropubic) cardinal (support of bladder base) or uterosacral ligaments (apex) digitally or with the lower part of a bivalve speculum. In this instance, relief of urgency by supporting the insertion sites of pubourethral ligament "1", cardinal ligament "2", uterosacral ligaments "6" indicated that they may have a role in the causation of urgency and so need to be reconstructed. Specific painful "trigger points" are detailed in the pain section of the chart, but were not relevant for Mrs JC.

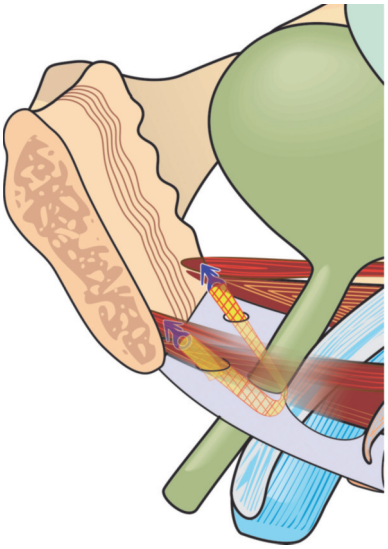


Figure 3. - Midurethral TFS sling reinforces the pubourethral ligament. The anchors are retropubic and insert behind the perineal membrane into the soft tissues in the lower 1/3 of the posterior part of the symphysis at the insertion point of the pubourethral ligaments.

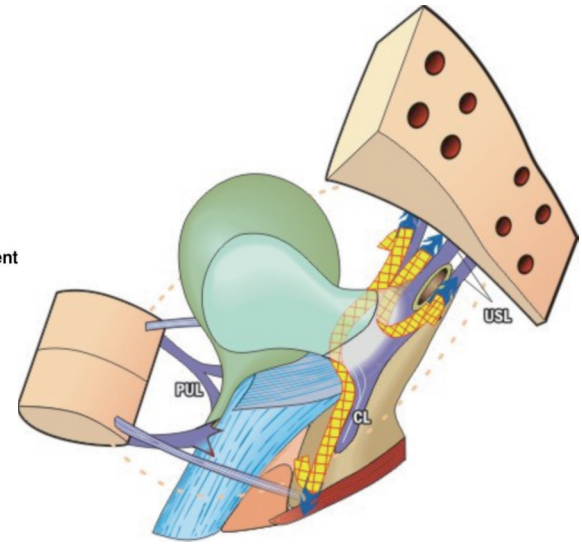


Figure 4. - Cardinal and Uterosacral TFS. The TFS shortens and strengthens the cardinal and uterosacral ligaments. It suspends the uterus apex and rectum and reglues the rectovaginal fascia to the posterior cervical ring. The cardinal ligament TFS resuspends the uterus and vagina to the pelvic side wall and reglues the anterior vaginal wall to the anterior cervical ring.

Post-operative notes 25.5.13

The patient was discharged the day after surgery.

"Bit of a sore tail. More to one side. Getting better."

"No USI." "Nocturia x 3-4 " "Emptying better than before." "Not so much urge. Can hang on. "

Post-operative notes 30.5.13

"No bleeding. Pale pink." "No USI." "Nocturia now x1-2." "Emptying fully now. Don't have to go back." 'Getting better No analgesia."

Post-operative notes 20.10 13

"No USI." "Nocturia x1, occasionally x2". "Emptying fully." "No urgency or UI".

General comment by patient. There was immediate cure as regards urine loss with effort and major improvement in urgency, emptying and nocturia within a few days. There was very little post-operative pain and gradual further improvement of bladder symptoms over the next few weeks.

Comments from the surgeon. This patient had major symptoms associated with minimal prolapse. Symptoms were cured using the same operations as used for major 3rd & 4th degree organ prolapse by applying the Integral System which is summarized in Figure 2. The algorithm links specific symptoms and prolapse to specific damaged ligaments in 3 zones of the vagina, anterior (external meatus to bladder neck), middle (bladder neck to cervix) and posterior (cervix to perineal body).

The TFS works by tightening loose suspensory ligaments. These are essentially the insertion points of the three directional forces which activate urethral/anorectal closure and opening.

"Repair the structure and you will restore the function" - Integral System.

APPENDIX

Patient Questionnaire

Self administered patient questionnaire

Part I Personal Details

Date: _____

Name:
Address:
Weight : _____ kg
Number of vaginal deliveries (4)
Number of caesarean sections (0)

Date of birth : 27.5.39
Telephone:

Part II Symptoms

Describe in your own words your main urinary symptoms and duration:

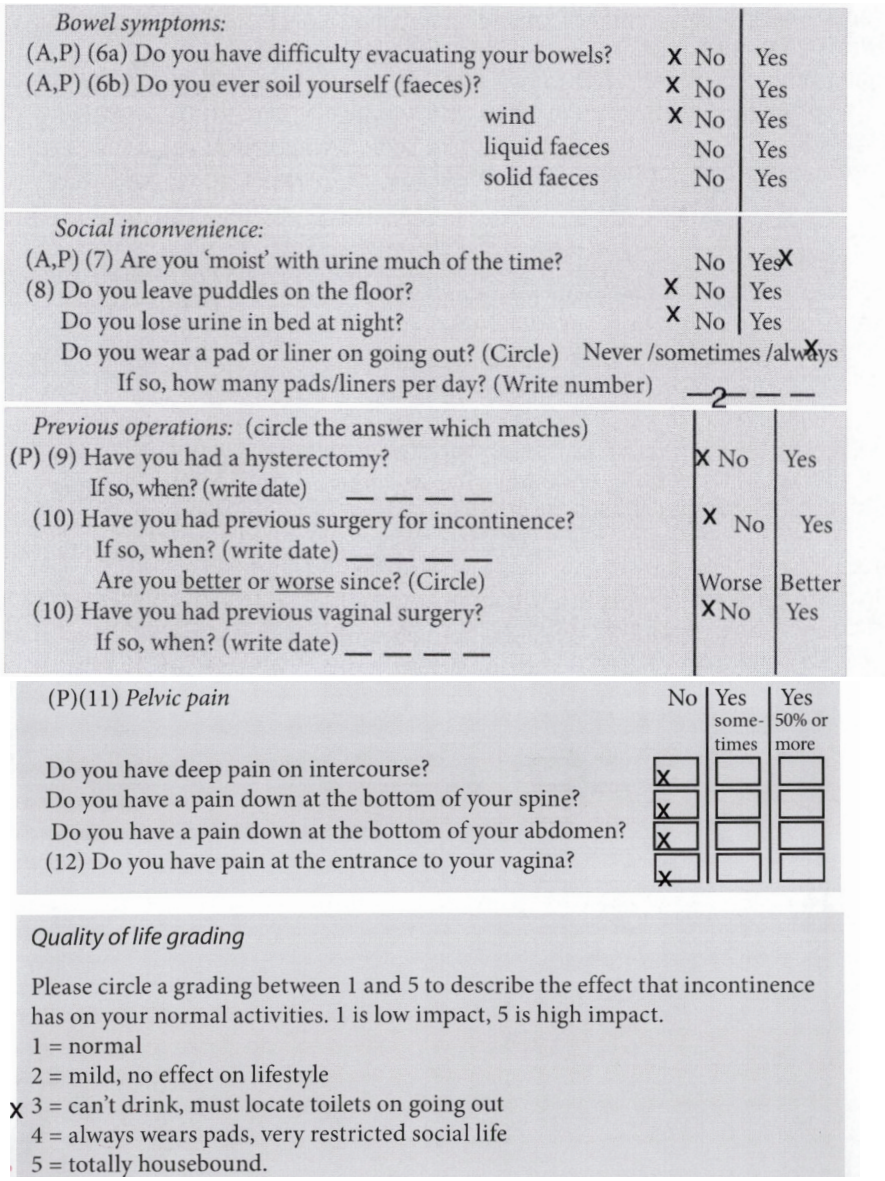
Urine loss coughing, jumping, running. Sometimes wets prior to arrival toilet.
Gets up 3-6/night. Always wears thick pads.

All sections: tick appropriate square . ☐ *Write extra details if you wish.*

A. Stress Incontinence (SI) Symptoms	No	Yes sometimes	Yes 50% or more
Do you lose urine during:			
(A) Sneezing			X *
(A) Coughing			X *
(A) Exercise			X *
(1) Walking	X		
(A) (2) Stooping, squatting or getting up from a chair		X	
(P,M) *Symptoms of deficient emptying*			
(3) Do you feel that your bladder isn't emptying properly?			X
(3) Do you ever have difficulty starting off your stream?		X	
(3) Is it a slow stream?		X	
(3) Does it stop and start involuntarily?		X	

* Note to physician: the filter '50% or more' (column 3) has a proven correlation for SI being caused by anterior zone defect. For all other symptoms a 'sometimes' notation is sufficient to attribute a symptom to a particular zone. 'A', 'M' and 'P' indicate the zone of causation and where the symptoms should be transcribed on the Diagnostic Summary Sheet (fig 3-03). Numbers in parentheses refer to notes at the end of the questionnaire.

	No	Yes sometimes	Yes 50% or more
Urge symptoms:			
Do you ever have an uncontrollable desire to pass urine?		X	
If so, do you wet before arriving at toilet?		X	
If so, how many times a day do you wet? (Write number)			
Good day	0		
Bad day	2		
How much? A few drops	No	Yes	
A teaspoon full	No	Yes	
A tablespoon or more	No	Yes X	
(4) Do you have pain while passing urine?	No	Yes	
(P) How many times during the night do you get up to pass urine?	X 6-7		
How many times do you pass urine during the day? (Write number)	15		
(A, M)(5) In the morning do you wet immediately on getting out of bed?	X		
(A) (5a) Did you wet the bed as a child but not after puberty?	X No	Yes	
(P) (5b) Did your problems begin soon after puberty?	X No	Yes	
(P) (5c) Are your symptoms worse before a period ?	NA No	Yes	



Bowel symptoms:

(A,P) (6a) Do you have difficulty evacuating your bowels?	X No	Yes
(A,P) (6b) Do you ever soil yourself (faeces)?	X No	Yes
wind	X No	Yes
liquid faeces	No	Yes
solid faeces	No	Yes

Social inconvenience:

(A,P) (7) Are you 'moist' with urine much of the time?	No	Yes X
(8) Do you leave puddles on the floor?	X No	Yes
Do you lose urine in bed at night?	X No	Yes
Do you wear a pad or liner on going out? (Circle)	Never /sometimes /always X	
If so, how many pads/liners per day? (Write number)	—2— — —	

Previous operations: (circle the answer which matches)

(P) (9) Have you had a hysterectomy?	X No	Yes
If so, when? (write date)	— — — —	
(10) Have you had previous surgery for incontinence?	X No	Yes
If so, when? (write date)	— — — —	
Are you better or worse since? (Circle)	Worse	Better
(10) Have you had previous vaginal surgery?	X No	Yes
If so, when? (write date)	— — — —	

(P)(11) *Pelvic pain*	No	Yes sometimes	Yes 50% or more
Do you have deep pain on intercourse?	X		
Do you have a pain down at the bottom of your spine?	X		
Do you have a pain down at the bottom of your abdomen?	X		
(12) Do you have pain at the entrance to your vagina?	X		

Quality of life grading

Please circle a grading between 1 and 5 to describe the effect that incontinence has on your normal activities. 1 is low impact, 5 is high impact.

1 = normal
2 = mild, no effect on lifestyle
X 3 = can't drink, must locate toilets on going out
4 = always wears pads, very restricted social life
5 = totally housebound.

Explanatory Code for Physicians - Significance of '50% filter' (column 3)

Symptoms vary because controli is a non-linear interaction of 'mechanical' and 'neurological' phenomena. Therefore when transcribing the response data to the Diagnostic Summary Sheet (figure 3-03), a 'sometimes' response is taken as a positive indication. The exception is stress incontinence (column 3). A tick in column 3 is required for a positive response because of proven correlation of the 50% filter with pad test results. The significance of the 50% filter for the other symptoms has yet to be tested statistically.

Explanatory Notes for the Numbers Preceding the Questionnaire Responses

1) This is usually caused by low urethral pressure (ISD) but may be from lax posterior zone.
2) If there is minimal SI with coughing, it is termed 'paradoxical leakage'. In age group >70 yrs generally due to PUL (pubourethral ligament) defect. Exclude tethered vagina syndrome in patients with previous vaginal surgery if a tight scar at bladder neck.
3) USL (uterosacral ligament) cystocoele, but also after excessive bladder neck elevation, or tight suburethral sling.
4) Exclude UTI, chlamydia, etc.
5) Generally PUL defect even with previous operation, but exclude tethered vagina if tight scar at bladder neck.

5a) This condition runs in families. It indicates congenital PUL weakness.

5b) & 5c) The cervix softens to allow menstruation to pass, weakening the anchoring point of USL.

6a) Posterior zone defect (perineal body/ rectocoele/USL) and sometimes PUL.
6b) Defective PUL/USL and/or anal mucosal prolapse (descending perineal syndrome).
7) Low urethral pressure - usually with lax suburethral vagina (80%), but can be caused by lax posterior zone (20%).
8) This may be defective PUL, but may be also due to USL defect.
9) Suspect posterior zone defect especially in age group > 60 years.
10) Think of tethered vagina syndrome in patients with positive answers for '5' and '2' who have scarring or tightness at bladder neck.
11) Posterior zone defect.
12) Vulvar vestibulitis which may also be caused by posterior zone defect.

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