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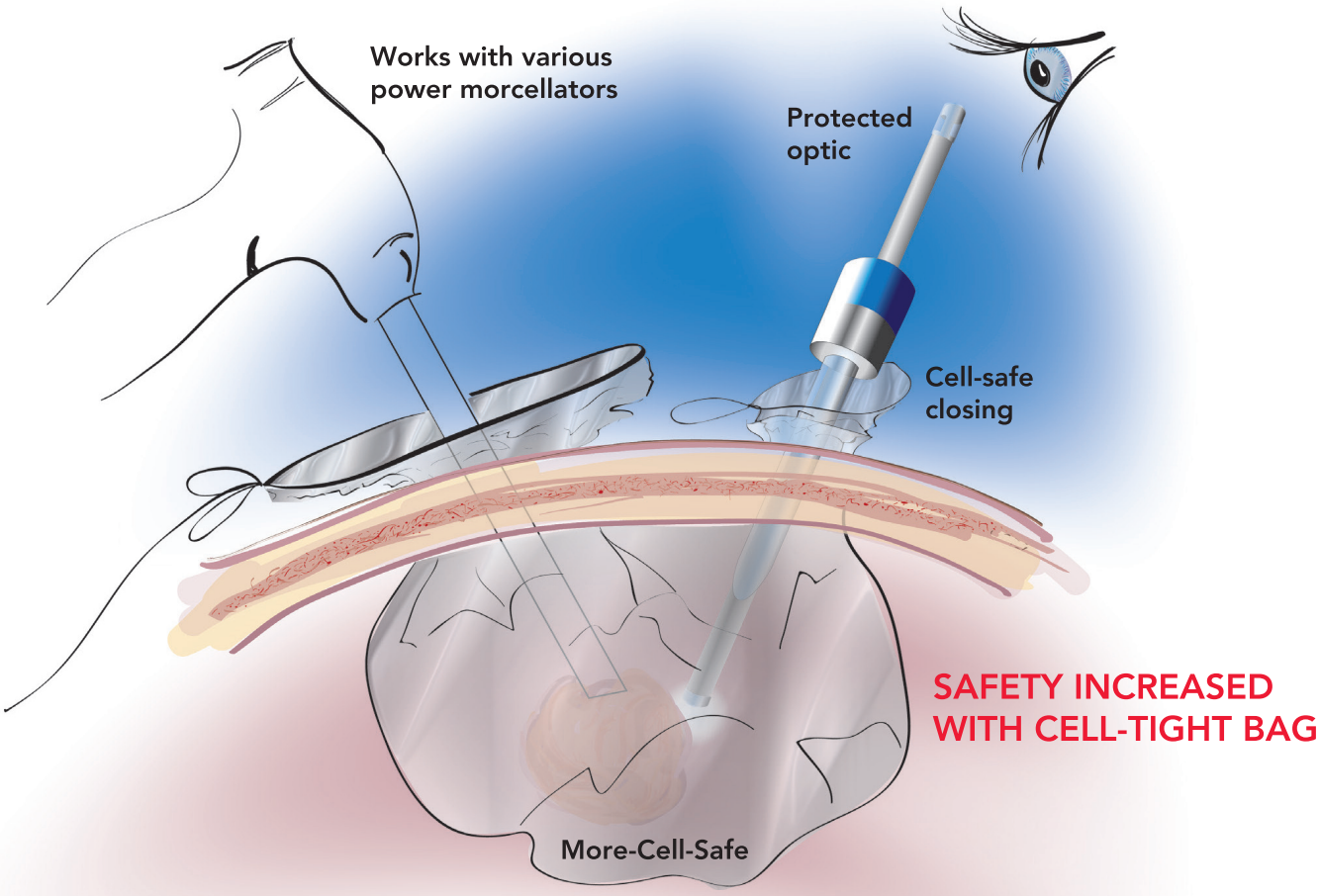


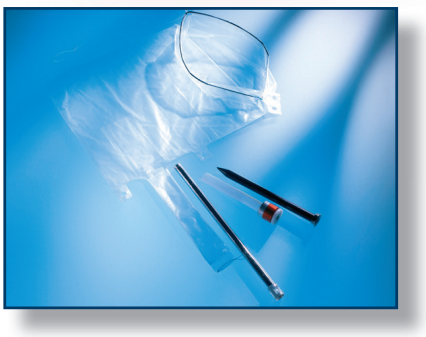

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# *PELVIPERINEOLOGY*

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**Editorial**

# Dedicated to Professor Heinrich Martius, pioneer in the ligamentous origin of chronic pelvic pain in the female

At the turn of the 20th century and up to World War II, Germany was an undoubted leader in all the sciences, including medicine, with German an important language in the literature. Though names like Trendelenburg, Langenbeck, Billroth remain part of daily surgical nomenclature today, many more important discoveries written in the German language, have been entirely forgotten. WWII was catastrophic for German science and especially for the German language as a vehicle of science[1]. Many important historical writings became unavailable to the now dominant Anglophone scientific community[1].

Amongst the lost and forgotten works were the pre-war German language writings of Heinrich Martius[2] on the role of loose uterosacral ligaments in the causation of chronic pelvic pain. It is an accident of fate that these writings were recently brought to the surface by Professor Klaus Goeschen. Goeschen was trained in gynecological surgery by Gerhard Martius, son of Heinrich. He had the knowledge and access to the literature needed to recover these 'lost' writings. In 2015 Goeschen wrote[3]:

*"Since some decades, Heinrich Martius published in the German literature that in about 30% of cases, backaches are provoked by damaged suspending or supporting ligaments of the pelvic organs. The paired "Ligamenta recto-uterina", which are connected via paraproctium to the bony sacrum and therefore in general are termed "plica or ligamenta sacro-uterina" or "uterosacral ligaments" (USL), are placed in the centre of numerous pathophysiological considerations. Unfortunately, Martius's concepts have remained largely unknown in the English literature. In 1993, Petros and Ulmsten independently described CPPS as being caused by lax uterosacral ligaments as part of the "Posterior Fornix Syndrome", along with other pelvic symptoms, nocturia, urgency, abnormal emptying. They reported a significant cure rate of CPPS and other posterior fornix symptoms following repair of the uterosacral ligaments. Petros wrote a classic description of this pain in 1996".*

Heinrich Martius wrote detailed descriptions of the role of uterosacral ligament laxity, Frankenhauser and Sacral ganglia in the causation of chronic pelvic pain (CPP), 60 years before Petros's 1996 publication. Sixty lost years in a world where 20% of all women have CPP! Even today, 2017, expert committees from learned societies such as the International Continence Society state that the cause of CPP is unknown and that it is incurable. How can this be?

The Pelviperineology pain issue will be published in two issues, Part I, September 2017 and Part II, March 2018. Part I is faithful to the tradition of Heinrich Martius. The lead paper by Bert Messelink introduces CPP as an evolving and rapidly changing area that is associated with bladder bowel and sexual dysfunctions. In his vision for the future, Bert emphasizes the importance of definitions and guidelines. These include treating the patient as a unique individual requiring a total integrated approach. The "re-discovery" of USL laxity by Petros as a major cause of CPP to which Goeschen refers, is reprinted in full, by permission of ANZJOG. Yuki Sekiguchi et al. elaborate the Messelink vision. They demonstrate co-occurrence of chronic pain, bladder and bowel symptoms with uterine prolapse and cure thereof with a posterior sling which shortens and reinforces the uterosacral ligaments. Patricia Skilling shows how squatting-based pelvic floor exercises can improve CPP as well as bladder & bowel symptoms; Doron Zarfati describes a test which objectively identifies the neurological ganglia as a cause (or not) of the pain; Goeschen and Gold describe the 'iceberg phenomenon', that despite CPP being the presenting symptom, other pelvic symptoms are invariably present and need to be elicited by direct questioning.

It is the hope of Pelviperineology journal that this Pain Issue will go some way to inform the scientific community (and women!) that many aspects of chronic pelvic pain are potentially curable. It is also hoped that the research directions outlined in this issue, some original, some controversial will continue to be examined.

ADI Y. WEINTRAUB, PETER P. PETROS
*Editors*

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**Original article**

# Perspective - Chronic Pelvic Pain needs an integral approach

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*Abstract:* Chronic Pelvic Pain needs an integral approach, based on the principles of non-organ based terminology and pain mechanisms, provided by a team of experts with the patient at the best place on the discussion table. Realizing that pelvic pain is quite a private subject and that we are the guest and the patient is the hostess who lets us look into her life. That is what makes caring for patients with pelvic pain, based on an integral approach, so special.

*Key words:* Chronic pelvic pain; Health; Multidisciplinary; Team and Integral.

## INTRODUCTION

Chronic Pelvic Pain is a rather young area of interest in the world of pain. It is an area that is also changing quite rapidly. Pain in the pelvic area is primarily pain and needs to be addressed as pain.

At the same time, we need to realize that pelvic pain patients have to deal with changes in voiding, defecation and sexual functioning. This makes every pelvic pain patient even more unique for the caregiver. An open-minded approach of listening in an atmosphere in which a patient feels heard, is the basis for all that is said and taught and discussed about Chronic Pelvic Pain.

This perspective has 4 different sections:

1. Definitions and guidelines
2. Phenotyping and teamwork
3. New ways to explore
4. Integral approach.

## 1. DEFINITIONS AND GUIDELINES

There can be no guidelines without definitions, and no definitions without understanding the item that is defined. The definitions and terminology we use reflect our present knowledge. When our knowledge improves, our terminology and definitions will change subsequently[1]. Definitions and terms are of utmost importance because they are the basis for the language we use. If terms are spurious or incorrectly used, we will never understand each other and that leads to confusion. Definitions and terms need therefore to be validated by experts based within an independent international organization. Several organizations in the world have been and are working on definitions. The International Association for the Study of Pain (IASP) is the most general oriented organization which has a large set of terms in the field of pain[2]. The subset of terms on pelvic pain has been accepted a few years ago. This subset is made by a group of experts from many different disciplines, thereby guaranteeing an integral approach. Many of these experts are also working for the European Association of Urology (EAU) who made one of the first guidelines on CPP and is still leading in the development of terminology and guidance on this subject[3].

The definition of chronic pelvic pain that is accepted by the IASP is the one constructed and used by the EAU guideline[4]. The definition goes as follows: "*Chronic Pelvic Pain is chronic or persistent pain perceived in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioral, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynecological dysfunction*"[5].

A few remarks about this definition from within its developmental process.

• The basic idea in the world of chronic pain that has changed our way of thinking and working is that we recognize that pain is a 'disease in its own rights', and not necessarily an organ-based problem. Moving away from the one-to-one relation of organ pathology and pain has helped us in better understanding the pain and the pain-patients. And that changed not only the way we talk about pain e.g. in scientific ways but also in the way we treat our CPP-patients.

• The use of the word 'perceived' is following this non-organ-based terminology. Patients and caregivers talking and discussing may together come to the conclusion that the pain is perceived in a pelvic organ like the bladder. Perceived is subjective in the way that it is a feeling. It does not mean that something is wrong with the bladder. In taking a pain history this wording might help to start pain education from the beginning. "Where do you perceive your pain?" is a different question than "Where is your pain coming from?" Asking this question might be new but in daily practice one will feel and experience the difference. In easy language, explaining this goes like: 'the site of your pain is not necessarily the origin'.

• The definition is broad: 'structures related to the pelvis'. By using this broad description, the unity of the pelvis is accentuated. Remember that we once started with an organ-based idea and now we know that other structures like muscles, tendons, nerves and soft tissue all together play a role in the process of CPP.

A good illustration of these changes, is the name change of the special interest group of IASP. Formerly it was called 'Pain of Urogenital Origin' and now its name is 'Abdominal and pelvic pain'[6].

In the EAU guideline about CPP the tour starts with this definition. In healthcare practice a patient will come and tell you that she has pain for a longer period and that it doesn't disappear. She perceives the pain in her bladder and it is often very tough to go on with what she is doing. It affects her bladder- and bowel function as well as her working- and family life.

*First step* is to confirm the fact that she has pain. She has pain when she says so and it is there any time she states it is. For pain patients, this unconditional acceptance of their pain message is the basis for any further discussion, diagnostic and treatment. Be aware that you, as caregiver cannot objectify her pain. We still do not have a dolorimeter.

*Second step* is to rule out well-known-diseases. And here we must take notice of the fact that moving away from an organ based pain theory does not mean that we put the organ completely away. We need to know if there is a pathological process in the organ going on that needs treatment. Another way to say it: is there nociception going on based on a well-known disease process. This is an illustration of the important role of pain-mechanisms in dealing with CPP.

The EAU guideline says: "Chronic pelvic pain may be subdivided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology. For the purpose of this classification, the term "specific disease-associated pelvic pain" is proposed for the former, and "chronic pelvic pain syndrome (CPPS)" for the latter." [Figure 1] In the definition of CPPS we also read: "… CPP is often associated with negative cognitive, behavioral, sexual or emotional consequences". This sentence indicates that we might need to look even further than the patient itself. Attention must be paid to cognitions, (pain) behavior, sexual (and relational) consequences and the emotions that we often can feel and hear during the first talk with the patient.

## 2. PHENOTYPING AND TEAMWORK

Moving away from the organ-based pain construct, means that we need other ways to characterize patients with CPP. Phenotyping is the method used in the guideline and in many other advices about classifying CPP patients. A useful figure is the snowflake which illustrates that every patient is special and has its own features which need to be recognized to build the snowflake[7]. Phenotyping means looking at all the aspects of the pain and of the patient. In daily practice, it often helps to do a good history, a good physical examination and tailored diagnostics to rule out well-known diseases. Attention should be paid to already know psychological items in the past or presented during taking history. Attention also for the social surrounding: partner, kids, family, working place. By reading this, one might realize that it is time consuming to do a thorough investigation. True, so be honest and explain this to the patient by saying that it takes time to listen carefully and that a second talk might be necessary. When you are working in a clinical setting you should consider forming a team that constitutes of specialist in the different areas.

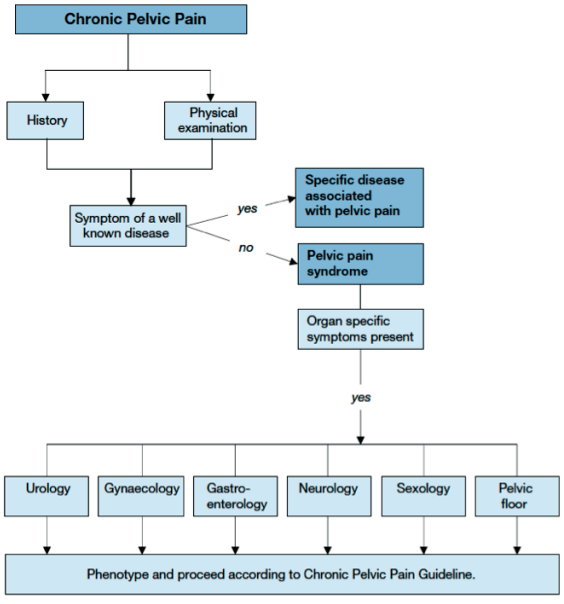


Figure 1. – EAU Guideline Chronic Pelvic Pain, 2016. Figure 1 page 32

Phenotyping helps to get a clear picture of the pain patient and it avoids doing procedures over and over again. Drawing a good picture of the phenotype supports you in doing all the investigations that are recommended by the guideline(s). Patient organizations often ask attention for one of the main problems with pain-care, which is that doctors keep on doing things like endoscopy, MRI, functional tests etcetera. The same is heard about seeing many different doctors, one after another. Patient call this the 'revolving door'. An approach based on phenotyping before starting with treatment, makes it transparent, easier to discuss and more helpful for the patient. It also helps the caregiver to guide him in the assessment, treatment and follow up of these patients.

Treatment of CPPS is seldom a mono-therapy thing. It always needs more than one approach. A combination of two or three of the most offered forms of therapy is a good start. By these three forms we mean: organ- and nerve-based, musculoskeletal and psychological. Providing patient tailored treatment means that the patient is included as a member of the team and that the whole team discusses the situation and constructs the best applicable snow-flake. The conclusion of the team discussion can be a plan to do more diagnostic (organ or pain based) or to start the therapeutic route. Making a plan as a team is helpful for both the caregiver and the patient. It is a joined effort to start dealing with the pain. Patients will feel the support from the whole team and realize that they do not stand alone with their pain. Presence of an important relative during the presentation of the plan may be helpful and gives the patient the opportunity to talk it over with that relative when they are back home after a session with the team that is often felt as impressive.

Pain education is a kind of common thread in the communication with CPP patients. For many patients, the idea that pain is made by the brain and not by the organ can be an eye-opener. Some patients will be enlightened by this, others might feel disappointed because an organ based problem is easier to understand. Listen, observe and discuss the reaction. Pain education is successful when patients understand that this is the mechanism nature uses, instead that they end up with the feeling that it is a way of explaining the doctor's inability or, even worse, saying that 'it is all in your head'. Explaining processes like central sensitization, using drawings and pictures, is often very much appreciated. The Australian Neuro Orthopedic Institute has done a lot in this field by publishing their "Explain pain" books[8]. The content of these books is valuable for both caregiver and patient and the illustrations and metaphors might help the patient understand the saying "no brain, no pain". Using patient based language, taking into account the education level of the patient, is always a principle in talking to patients.

## 3. NEW WAYS TO EXPLORE

As said before, definitions reflect the modern ideas and ways of thinking. As a consequence of developments in the way we think about pain and health, new definitions were proposed and discussed.

### IASP

The first new definition, proposed in 2016, is that of pain in general. The prevailing IASP definition, dating from 1979 goes as follows.

• Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[9].

The leading word in this definition is '*experience'*. Pain is defined as an emotional or sensory experience. This wording is comparable to the word that is used in the EAU guideline: '*perceived'* (as in experience in the first line).

The use of this word reflects the basic idea about what pain is. And it can help both pain patients and those who care for pain patients. Stressing the character of pain being an experience of a feeling perceived in a certain part of the body, helps patients in understanding both the pain itself and the treatment options offered. Only by speaking in a clear and understandable language we can build up a conversation and a care-relation.

The *potential tissue damage* is another term that should be highlighted. Patients will often describe their pain using words that reflect this idea of damage: stabbing, burning, cutting. Caregivers should just listen and notice the words used and realize that this is how the patient thinks about it. Cognition comes into play at this moment and gives the caregiver an opportunity to address this as part of pain education. Because patients speak and think in terms of damage, it is not surprising that they are in a hurry to get good treatment for this damaging and thereby threatening pain. At the same time, it will affect their family members and friends. They also might get worried about this pain that is damaging their relative. And subsequently they might re-inforce the ideas of the patient and their need for ongoing searches for causes. In case the doctor does not address this way of thinking and this reaction, patients will not only be disappointed but they may become scared or even angry. The doctor must explain that chronic pain does not necessarily mean there is danger, and that cognitions interfere with our experience of pain. The idea "I do not get the treatment that repairs the danger" can otherwise introduce a feeling of perceived injustice and that in itself may strongly effect the pain in a negative way.

Last year a new definition was proposed to get a discussion on how we will implicate modern scientific developments into our terminology.

• Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components[10].

Two items have changed: unpleasant has become distressing and cognitive and social have been added. Looking at the addition it becomes clear that cognitions have been recognized as a valuable factor in the field of chronic pain. The authors of the new definition tried to illustrate this in their article by mentioning some models used in pain research and pain treatment. They say that models based on fear and avoidance and on catastrophic thinking "… have identified important pain-associated beliefs and cognitive biases, with emotional and behavioral consequences ..."

The strong message that hopefully comes from this article and the new definition, is that pain is not just about nociception. Cognitions are not only a psychological phenomenon, cognitions are a human feature. We all have our cognitions and they are often based on what we have experienced in life and how we were trained in the jobs we do.

Pain is seen as an illness and therefore placed within the healthcare systems. The nature and structure of our healthcare system is dependent on the definition of health that is used. In this field, new definitions have also been proposed and discussed and partly accepted. The difference between old and new definitions can be a good illustration for the daily practice of healthcare providers, also for those dealing with pain patients.

World Health Organization (WHO) 1948

• a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity[11].

This definition is old but was quite modern when it was first suggested and it has been proven useful in the past decades. Some have tried to rewrite the definition, with extra attention for the environment for instance, including natural, built and social environment. But the need for a change remained. One of the best, although not fully accepted new approaches, is the one made by the people who talk about *'positive health'*.

Institute for Positive Health (IPH) 2011

• Health as the ability to adapt and self-manage, in light of the physical, emotional and social challenges of life.

In her article about this definition Machteld Huber[12] says that the most direct reason for change is the fact that the old definition is static and the newly proposed one is dynamic. In the positive health view, health is seen as an ability. Not something you are, but something you can. Not about how much the environment gives you a state of social well-being but about how well you can adapt to the environment you live in. Not about what limitations the pain has brought you but about how to adapt your life and develop new options with what is still possible. Note that *social challenges* have been introduced into the definition and compare this with the adding of *social components* to the definition of pain.

Apart from adaptation, this definition talks about self-management: "manage one's own well-being". Here we find a good similarity with what is seen as important in treating chronic pain. In the EAU guideline on CPP, management of one's own pain is described in the management section. All patients with pain and maybe especially those who did not react on diverse treatment options, will need to find out how to live with their pain. Incorporating self-management is best done from the start of the therapeutic relation in patients with chronic pain. It should not be seen as a kind of "last resort" therapy. Patients should be aware that caregivers often cannot explain their pain, neither in a physical way nor in a psychological or social way. Self-managing their pain is what is at hand every day of the week and is therefore of basic importance. Knowing this, the definition based on positive health fits well in the ideas about chronic pain. Patients need to adapt to their pain and need to manage their pain and all its consequences by themselves. However, let us not forget the social components that are not only challenges but also opportunities. Patients can go and search for others to join and support their self-management. When they find a caregiver who wants to support them, we call it shared care. But, not only doctors or psychologist can support the self-management, also lay people can (and maybe even better). By talking with other pain patient-companions they can interchange ideas on how to manage. They can form groups on social media or whatever medium that suites them. Many questions will be practical or about experiences and both type of questions can be answered by companions. For healthcare institutes, it is necessary to provide information on chronic pain and on self-management of that pain. Health care institutes should consider to invest in developing these programs for patients and relatives.

This new approach to health and healthcare is characterized by a positive view on health and also by a patient centered approach. The patient in the center, not as someone to be looked at by many different healthcare workers, but as the main participant at the round table where the team is listening to what the patient wants, where the sit-

uation, the plan and the support is constructed and discussed. Would be great if this will be daily practice in pain-centers.

## 4. INTEGRAL APPROACH

The patient with chronic pelvic pain deserves an integral approach. And, although it sounds complicated, that is quite easy. If we succeed in building our care system with the patient in the lead, we might all benefit.

An integral approach is based on the biopsychosocial model.

– Bio: we need to be aware of the fact that biological or somatic aspects play a role. Nociception is not obligatory but it can play a role in CPP. Understanding pain mechanisms is important to educate the patient and to help guiding the management program. A well-defined and balanced diagnostic protocol must be followed to rule out and treat well-known diseases and to get insight in pain mechanisms like peripheral and central sensitization.

– Psycho: psychological diagnostics and management should be part of the program from the very beginning. Whether or not there's a somatic origin found, it will be helpful to elucidate what pain does with a person and how you can learn to implement it into your life. Even if the pain can be cured it might help to reinforce the human system and thereby lower the risks to get a recurrence or another chronic pain problem. History has its influence on how the brain deals with your pain. Chronic or acute pain episodes will leave memories in the brain and the way they were dealt with can influence the chronification of pain. Fear and anxiety, as well as catastrophizing and perceived injustice are well-known aspects influencing the way our brain deals with pain.

– Social: the social environment plays a special and recently better understood role in chronic pain. Pain patients can easily become isolated because of their limitations but also because of their thinking: 'they don't understand my problem, it is invisible'. The way the environment reacts will influence the process of self-management either in a positive or a negative way. Remember the new proposed definition of pain talking about social components. Society can be helpful in so many ways that it is very important that we look at his aspects more and better than we have done in the past. Social media, patient organizations, positive health, they are all focused on this aspect.

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**Original article**

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# Severe chronic pelvic pain in women may be caused by ligamentous laxity in the posterior fornix of the vagina

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*Summary:* The aim was to prospectively study the relationship between pelvic pain of otherwise unknown origin and laxity in the posterior vaginal fornix. Twenty-eight patients with negative laparoscopy findings, lower abdominal pain and laxity in the posterior ligamentous supports of the uterus underwent surgical approximation of their uterosacral ligaments. At 3-month review, *85%* of patients were cured, and at 12 months, 70%. Nonorganic pelvic pain has frequently been attributed to psychological factors. However, the results suggest that this may be a T12-Ll sympathetic pain referred to the lower abdomen, perhaps due to the force of gravity stimulating pain nerves unable to be supported by the lax uterosacral ligaments in which they are contained. It was concluded that laxity in the posterior ligaments of the vagina should first be excluded before referring patients with pelvic floor discomfort or pain for psychiatric care.

*Key words:* Chronic pelvic pain; Uterosacral ligaments; Surgical cure.

## INTRODUCTION

Historically, laxity in the ligamentous supports of the uterus has been described as a cause of pelvic pain[1]. However, opinions have varied, ranging from strongly delivered negation[2] to qualified acceptance[3]. In more recent years, pelvic pain without a commonly recognized organic cause has almost universally been attributed to psychological factors[4]. This concept has gained such widespread acceptance amongst practitioners, that surgical correction of a retroverted uterus has virtually disappeared from the operating lists of gynaecological surgeons. Sacral pain, Iumbosacral backache, low abdominal pain, often unilateral, dyspareunia and postcoital ache[2-6] are principal symptoms of such a condition, worsening during the day, and relieved by lying down, or by inserting a ring pessary[3,6]. In these circumstances, ventrosuspension[1-3,6] or hysterectomy[3,6] may give good results.

Anecdotal reports (unpublished data) from patients cured of severe chronic pelvic pain following correction of uterovaginal prolapse and/or enterocele suggested that pelvic pain of hitherto unknown origin was frequently surgically correctable, and therefore may not have been primarily of psychological origin.The common factor in all instances appeared to be correction of laxity in the posterior ligamentous supports of the vagina.

The aim of this study was to prospectively trace the fate of low abdominal pain and deep dyspareunia after surgically tightening the ligamentous supports of the posterior vaginal fornix.

## PATIENTS, MATERIALS AND METHODS

The study consisted of 28 patients, all of whom were referred with symptoms of pelvic pain. The mean age was 43 years (range *20-76),* mean parity 3.1, (range *0-8).* A routine history was taken, (including a structured questionnaire completed by the patient), and pelvic examination performed. In particular, the following specific symptoms were noted pain in the lower abdomen relieved on lying down, pain on deep penetration with intercourse, 'tiredness and irritability at the end of the day'.

*Exclusion criteria.* Known causes of pelvic pain such as chronic pelvic inflammatory disease, or endometriosis were excluded by prior laparoscopy.

*Inclusion criteria for surgery.* Lax ligamentous supports, specifically, the presence of uterosacral ligaments separated by more than 5 cm, with an enterocele 'bulge' of vaginal tissue in between protruding *2.5* cm or more on straining; alternatively, descent of the uterus by more than 5 cm on pulling gently on the cervix with a tenaculum; reproduction of the patient's lower abdominal pain by palpating the cervix.

### *Operation*

All 28 patients studied had a posterior fornix repair (figure 1) performed as a day procedure, mainly under local analgesia, with the assistance of intravenous midazolam (dosage 5- 12 mg) administered by an anaesthetist. The patient was placed in the lithotomy position. The corners of the posterior fornix on each side of the uterosacral ligaments approximately 4cm below the posterior lip of cervix were gently grasped by Littlewood forceps without applying pressure. Using a long needle with a shield over the point, the operation site was infiitrated with 5-10 mL of 0.5% lignocaine with 1/200,000 adrenalin. Under tension from the forceps, a full thickness 5 cm horizontal vaginal incision was made between the tips of the forceps using a scalpel. The points of long-handled scissors were inserted into the incision, stretching it in an anteroposterior plane. If possible, the uterosacral ligaments were identified, approximated in the midline, followed down posteriorly and further approximated with No 1 Vicryl. The needle point was frequently used to locate the often deeply set ligaments, pulling them to the midline, along with the vaginal epithelium which was approximated side to side i.e. vertically. No vaginal tissue was excised.

Care was taken not to create excessive tension, so as not to cause postoperative pain to the patient. If an enterocele or high rectocele were present, they were appropriately repaired at the same time. A 0.5 x 0.5 cm biopsy of the uterosacral ligament was performed in 12 patients. With this operation the vaginal axis remains unchanged. Excess

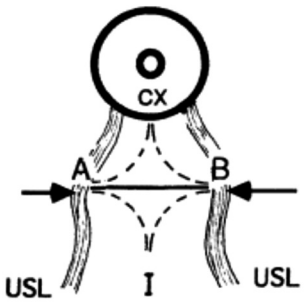


Figure 1. – Surgical correction of laxity in the posterior vaginal fornix. A full thickness transverse incision (solid line) is made in the vagina at the apex of the enterocele bulge. between Aand B. the borders of the uterosacral ligaments (USL), 4-5 cm below the cervix (CX). The vagina is separated from the underlying tissues anteroposteriorly (broken lines) without entering the enterocele sac. and the incision further opened out by insertion of a Sim's speculum between the cervix (CX) and introitus (1). The uterosacral ligaments are automatically tightened by approximating A to B, and by suturing them and the horizontal vaginal incision vertically between the cervix and introitus. No tissue is excised.

TABLE 1. Details Assessed in Questionnaire.

| Questionnaire | YES | NO |
|---|---|---|
| Do you have deep pain on intercourse? | ( ) | ( ) |
| Do you have a pain down at the bottom of your spine? | ( ) | ( ) |
| Do you have a pain down at the bottom of your abdomen? | ( ) | ( ) |
| Do you feel tired and iritable at the end of the day? | ( ) | ( ) |

width (vaginal prolapse, enterocele) is converted to length. The process is one of anatomical restoration, not alteration.

*Postoperative assessment*

No patients were lost from the study. The post- operative assessment was performed. using the questionnaire (Table 1 ), personal interview, and examination, immediately postoperatively, at 3 months, and 12 months.

*Notes on methodology*

Initially, a subjective analogue scale of 1-10 was considered and commenced. However, difficulties were experienced in putting this into effect, principally because preoperatively the character of the pain was such, that it varied considerably from time to time as concerns intensity. On discussing this with the initial group of patients, it was concluded that the criterion for cure should be all-or none. This appeared to work very well, as pain relief from a successful operation was immediate and dramatic.

## RESULTS

*Description of lower abdominal pain*

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, and reproducible on palpating the cervix and displacing it posteriorly with the patient in the supine position. Although the pain was chronic in nature, it varied considerably from time to time as concerns intensity. Six patients (two of whom were nulliparas) entered the study through casualty as emergency pain becoming sufficiently acute at time as to seek emergency care. Almost all patients complained of tiredness and irritability by the end of the day. A ring pessary considerably relieved the symptoms in approximately half of the patients, but on occasions, if the pessary was too small, it fell out, or no effect was noted: if too large, the symptoms frequently worsened.

*Description of deep dyspareunia*

This symptom was not often volunteered. The pain only occurred on deep penetration, or in specific positions. Frequently the patient complained of a constant lower abdominal pain the day after intercourse. Again, palpation of the cervix generally reproduced the pain experienced during intercourse.

*Surgical results*

At laparoscopy, varicosities were frequently seen in the region of the uterosacral ligaments, and also, broad ligament. After posterior fornix repair, cure, where effected, was instant and dramatic. The cure rate for lower abdominal pain at 3 months was 85%,and at 12 months 70%. Almost all patients returned to normal activities within days of the operation, with no specific instructions other than to avoid heavy lifting and intercourse for 6 weeks. Approximately *50%* of patients who were cured of their low abdominal pain also reported cure of their low sacral backache.

*Histology*

Histological examination typically demonstrated the presence of smooth muscle, collagen, elastin, and nerve endings, both myelinated and unmyelinated in all specimens examined.

## DISCUSSION

This pain was described by patients as intolerable, and was almost invariably associated with a lack of gross laparoscopic findings. Many stated that they were almost suicidal after interminable attacks of pain. The results confirm that laxity in the posterior vaginal fornix may be associated with pelvic pain and dyspareunia[1,3,6], and that such pain is potentially curable with a minor surgical procedure, undoubtedly a preferable alternative to hysterectomy. Occurrence of this condition in nulliparas indicates that such laxity may occur congenitally. Recurrence of symptoms appeared to be associated with recurrence of laxity i.e. it is possible that surgical failure may have been partly due to the damaged quality of the tissues being repaired. Subsequent cure of pain in some of these patients following sacropexy (unpublished data) appeared to confirm the hypothesis of this type of pelvic pain being caused by laxity in the posterior ligamentous supports of the vagina. Cure of similar pain in patients with prior hysterectomy has also been achieved using similar surgical methods (unpublished data).

*A hypothesis for pathogenesis of the pain*

The nerve fibres in the uterosacral ligaments are visceral fibres. A visceral innervation incorporating fibres from T12-L1 and S2-4 adequately explains anatomical distribution of the pain. It is hypothesized that stretching of lax ligaments by gravity may stimulate the nerve endings within these tissues, and cause pain. Lying down would relieve

such pressure, and the associated pain, as noted in this study. A ring pessary may work by providing mechanical support for the ligaments, and therefore, the nerve endings contained within. Findings of pelvic congestion are explained as follows: the uterus is normally supported by the cardinal and uterosacral ligaments, possibly assisted by contraction of the pelvic floor muscles. It is hypothesized that where the supporting ligaments are lax, the force of gravity acting on the uterus could cause congestion by 'kinking' of the pelvic veins within these tissues, preventing outflow, thereby causing congestion.

*Psychological aspects*

The improvement in patients' sense of well-being and psychological state was immediate and obvious. Given the high surgical cure rate in this study, 'functional' or psychological causation[2,4] is most likely a secondary, not a primary manifestation, *at least in the 70% of patients cured by this procedure*. Chronic pain may cause tiredness and irritability[6], decreasing libido and creating marital stress and depression, all of which, in another context, could be interpreted as psychological associations, or even causes.

It is recommended that laxity in the posterior ligaments of the vagina should first be excluded before referring patients with severe chronic pelvic pain or dyspareunia for psychiatric care.

ACKNOWLEDGEMENTS

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**Original article**

# Is Chronic Pelvic Pain in the female surgically curable by uterosacral/cardinal ligament repair?

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*Abstract: Background*. Learned institutions do not consider symptoms of chronic pelvic pain (CPP) to be surgically curable. The Integral Theory hypothesizes that CPP where no obvious cause is evident, is mainly caused by loose suspensory ligaments; hence it is potentially curable surgically by repairing such ligaments. This type of CPP generally co-occurs with one or more symptoms of bladder and bowel dysfunctions which may occur with even minimal apical prolapse. *Objective*. To test this hypothesis by surgical repair of loose cardinal and uterosacral ligaments in patients who have 2nd degree or greater uterine or apical prolapse. *Material and methods*. This was a multicenter prospective case control audit comprising 614 women, mean age 70 years. *Inclusion criteria*: symptomatic apical prolapse (POPQ stages 2-4), plus OAB symptom(s). *Exclusion criteria:* Comorbid medical problems. *Surgery*: minimally invasive cardinal/uterosacral ligament repair was performed using the TFS (Tissue Fixation System) minisling. *Primary outcome* was uterine prolapse cure. *Secondary outcomes* were bladder, bowel, pain, symptom improvement. *Results***.** Prolapse cure was noted in 90% of 614 patients. Symptom incidence and % cure at 12 months (in brackets) were as follows: chronic pelvic pain: n= 197 (79%); urge incontinence: n= 320 (86%); frequency: n= 313 (84%); nocturia: n=257 (69%); fecal incontinence: n= 93 (65%). Statistics: $x^2$-tests of McNemar to test for significance in symptom incidence-frequency from preoperative to postoperative phase. *Conclusions*. Chronic pelvic pain, bladder & bowel incontinence occur in predictable symptom groupings which are associated with apical prolapse. Application of the Integral Theory System has the potential to improve clinical practice, QoL for women and open new research directions.

*Key words:* Chronic pelvic pain; Urge; Nocturia; Fecal incontinence; TFS; Cardinal ligaments' Uterosacral ligaments.

## INTRODUCTION

The International Continence Society defines Chronic Pelvic Pain Syndrome (CPPS) as: *"Genitourinary pain syndromes are all chronic in their nature. Pain is a major complaint but concomitant complaints are of lower urinary tract, bowel, sexual or gynecological in nature where there was no infection or other obvious pathology"*[1]. Chronic pain is thought to be associated with changes in the central nervous system (CNS) which may maintain the perception of pain in the absence of acute injury. Such changes may magnify perception in that non painful stimuli are perceived as painful (allodynia); painful stimuli are perceived as more painful than expected (hyperalgesia)[2].

Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans[3]. The health costs of chronic pain to the community are significant: hundreds of millions of dollars p.a.. In addition, the reported time lost from paid work was 15% with 45% reduced work productivity[4].

The pathogenesis of chronic pelvic pain is still not well understood. It is hypothesized that there is both peripheral and central hypersensitization[2]. Peripheral hypersensitization describes augmented sensory pain input from the peripheral nervous system. Central hypersensitization describes a predisposition to dysfunctional central regulation of the sensory input[5]. In parallel, there are accompanying symptoms, for example, urinary symptoms or frequently, psycho-social symptoms.

The main treatments at present available include counseling, psychotherapy, physical therapy, medications, psychosomatic therapy laparoscopic uterine nerve ablation, presacral neurectomy, hysterectomy (with or without removal of the ovaries[6] and more recently, neuromodulation, which reported 40% improvement in pain symptoms and 26% improvement in urinary symptoms at 15 months mean follow-up[7].

As described in the 1993 publication of the Integral Theory[8], chronic pelvic pain is linked to a specific symptom complex known as the "posterior fornix syndrome", caused by lax apical support. The "posterior fornix syndrome" variously encompasses chronic pelvic pain and bladder symptoms of urgency, abnormal emptying, nocturia[8]. Such patients rarely present with single symptoms. They occur in predictable groupings. Significant cure of these symptoms was achieved by plication of the uterosacral ligaments, fig1. A classical detailed description of the pain was described in 1996[9]. Initially, an 85% cure rate was reported at 3 month following approximation of the uterosacral ligaments (USL). The etiology of USL laxity is generally attributed to age or birth related collagen damage, or hormone induced depolymerization during pregnancy[10].

Our primary aim was to investigate whether lax apical support (uterosacral and cardinal ligaments) was a causative factor in chronic pelvic pain by prospectively evaluating their fate. We also hypothesized that peripheral hypersensitisation of the chronic pelvic pain circuit might be potentially reversible by treating the underlying causes, if no central hypersensitisation circuits have been activated.

A secondary aim was to compare the efficacy of the TFS operation as cure of other posterior fornix syndrome symptoms such as urinary urgency, frequency, nocturia, faecal incontinence and anatomical restoration of apical/uterine prolapse.

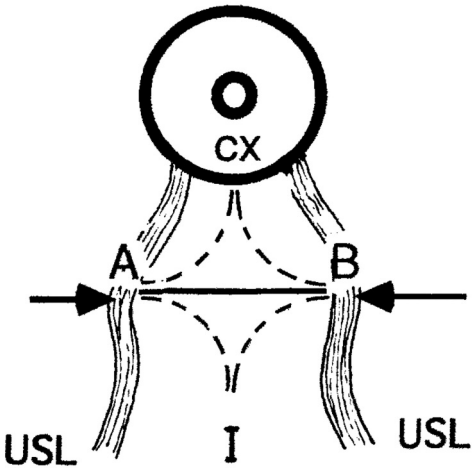


Figure 1. – Approximation of uterosacral ligaments (USL) (9). A 5cm long transverse incision is made in the posterior fornix 3-4 cm below the cervix (A-B), The loose USLs are approximated (arrows) with strong sutures. Reprinted by permission ANZJOG.

## PATIENTS AND METHODS

Six tertiary referral pelvic flor centres participated in the study between January 2009 to January 2012. All patients completed the validated self-administered ITSQ pelvic symptom questionnaire[11]. The symptom replies were transferred to a pictorial algorithm, figure 2, which guided diagnosis and surgery of ligament damage, figure 3. Vaginal examination confirmed specific ligament damage and degree of prolapse.

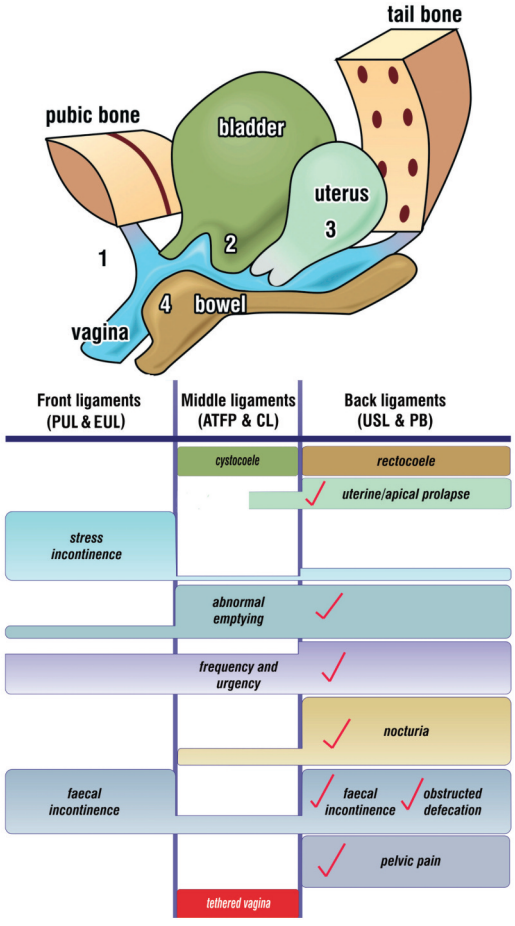


Figure 2. – Simplified diagnostic algorithm relates symptoms and prolapses to damaged ligaments in the front, middle, and back parts of the vagina. PUL-pubourethral ligament; EUL-extraurethral ligament; ATFP = arcus tendineus fasciae pelvis; CL = cardinal ligament; USL = uterosacral ligament; PB = perineal body Patients rarely present with single symptoms of single ligament loss. The height of the bar indicates presumed prevalence of a symptom caused by the respective anatomical region.

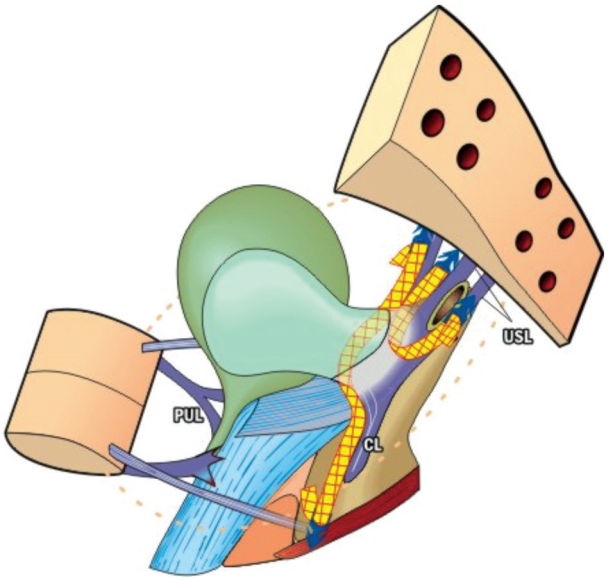


Figure 3. – The cardinal (CL) and uterosacral (USL) ligaments were reconstructed with the TFS mini sling procedure.

*Inclusion criteria:* consecutive patients with symptomatic apical prolapse of 2nd or greater degree, (POPQ stages 2-4), and at least two pelvic symptoms:
- *Fecal incontinence* (non sphincteric): Loss of either gas, liquid or solid feces more than once per week[11].
- *Pelvic pain* symptoms consistent with ICS descriptions[1].
- *Frequency* Emptying the bladder >8 times/day[1].
- *Nocturia*: two or more episodes of waking to micturate at night[1].
- *Urge incontinence*: at least one episode per day of wetting prior to arrival at the toilet[1].

### *Exclusion criteria*

Known causes of fecal incontinence such as external anal sphincter damage; endometriosis; neurological diseases such as multiple sclerosis, proven organ infection, carcinoma or other conditions known to cause pain, bladder or bowel symptoms.

### *Intervention*

All 614 patients underwent a cardinal/ uterosacral sling operation (TFS), figure 2.

### *Follow-up and end point measurements*

At 12 months follow up, a full assessment was made using the self-administered ITSQ questionnaire[11], as well as vaginal examination.

### *Criteria for a positive response*

*Fecal incontinence*: Zero episodes of soiling.

*Chronic pelvic pain*: A self-assessed 80% improvement over the baseline symptom at the 12 month visit. "On the whole, how much improvement do you experience now compared to your pre-operative symptoms"? We chose this criterion because of concerns that VAS could mislead because of day to day symptom variation.

*Frequency* Eight or less times per day. *Nocturia*: Reduction from 2 or more episodes per night to one or nil.

*Urge incontinence*: Zero episodes of wetting prior to arrival at the toilet.

*Abnormal emptying*: Self-assessed 80% improvement. The patient was asked to determine, "On the whole, how much improvement do you experience now compared to your pre-operative symptoms"?

*Criteria for anatomical failure* Organ prolapse at POPQ stage 2 or beyond.

*Surgery*

*Cardinal (CL) and uterosacral (USL) TFS sling*[12]. A transverse incision 5cm wide was made 1cm above the cervix or hysterectomy scar to access the CLs and 3-4 cm below the cervix to access the USLs. Bladder and enterocele were dissected clear. The cardinal and uterosacral ligaments were identified. A channel was created through the ligaments, the TFS applicator was inserted into the channel and the anchor released. The procedure was repeated on the contralateral side; the tape was tightened until a resistance was felt . TFS slings for urinary stress incontinence , cystocele , rectocele and perineal body repairs were performed as required , taking care to avoid any excision of vagina.

*Statistical analysis*

We applied $x^2$-tests of McNemar to test for significance changes in the symptom incidence-frequency from baseline (preoperative) to postoperative phase. For each symptom the null hypothesis $H_0$: $P_{(baseline)} = P_{(12\ months\ after\ surgery)}$ versus $H_1$: $P_{(baseline)} \neq P_{(12\ months\ after\ surgery)}$ was tested, with P indicating prevalence or incidence rate. An $\alpha = 0.05$ was accepted as nominal level of significance. Because of multiple testing the p-values of the tests were compared to a Bonferroni corrected a (say $\alpha^*$) for keeping the type I error less or equal 0.05.

*ETHICS*: This was a prospective case study audit. Prior to undertaking this study, each unit obtained EC approval for use of the TFS instrument in prolapse and incontinence surgery as standard hospital practice. Written consent was obtained from all patients . The principles of the Helsinki Declaration (2008) were followed.

## RESULTS

614 patients with apical prolapse and concurrent symptoms were assessed with 12 month follow up presented. Mean age: 69.62 ± 13.17 years. Prolapse: 2nd degree POPQ (n = 210) and 3rd /4th degree POPQ (n=394). Associated symptoms: 93 (15%) had faecal incontinence; 197 (33%) pelvic pain; 257 (42%) nocturia; 320 (53%) urinary urge incontinence; 313 (52%) frequency, Table 1. Applying McNemar tests we obtained for each considered symptom p-values being all less than a*, where a* a Bonferroni corrected level of significance (table).

TABLE 1. Symptoms and apical prolapse at baseline and after 12 months in patients operated by the Tissue Fixation System (TFS). '*' indicate statistical significance at a Bonferroni corrected level of significance $\alpha^*$ ($\alpha^* = 0.05/6 \approx 0.01$)

| | Number of patients with symptom or condition/total patients (%) | | significance of the $x^2$ values of the McNemar tests when testing: H0 vs. H1 |
|---|---|---|---|
| | pre-TFS | post-TFS | * |
| Pelvic pain | 197/614 (32%) | 42/614 (7%) | * |
| Nocturia | 257/614 (42%) | 77/614 (12%) | * |
| Urge/ Urge incontinence | 320/614 (52%) | 51/614 (8%) | * |
| Frequency | 313/614 (51%) | 55/614 (9%) | * |
| Fecal incontinence | 93/532 (17%) | 34/532 (6%) | * |
| Apical prolapse | 614/614 (100%) | 63/614 (10%) | * |

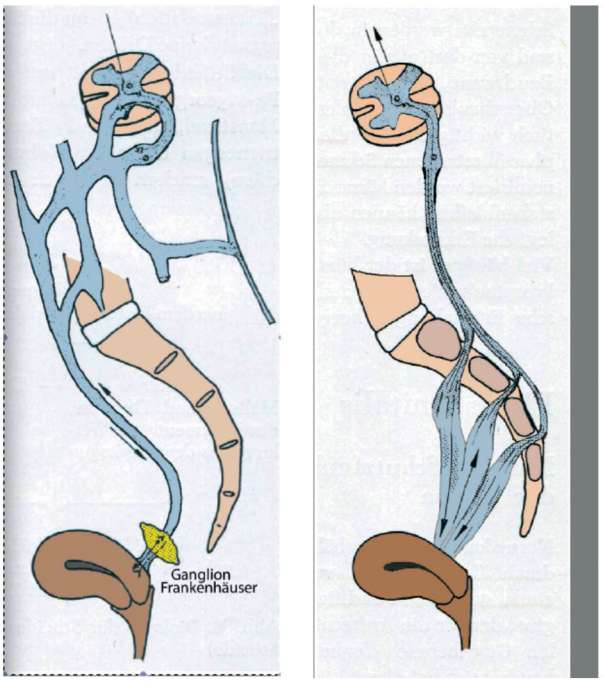


Figure 4. – The visceral pelvic pain pathway. The 1st pathway is transmitted from Frankenhauser's plexus (left) which is situated approximately 2cm lateral to the cervix. It lies at the distal end of the hypogastric plexus. The 2nd pathway involves the sacral plexus pains.

*Operative and peri-operative details*

The mean operation time varied between 12.5 and 23 minutes per TFS tape insertion. Mean blood loss per surgery was 21gm. The post-operative pain was minimal. This allowed early discharge from hospital. The mean discharge time from hospital was less than 24 hours (0.4-3 days). The mean return to reasonably normal activities was 2.2 days (1-28). Post-operative urinary retention beyond 24 hours occurred in 5 patients: two for 48 hours, one for 4 days and one for 2 weeks.

*Complications*. There was one rectal mucosal buttonhole injury sustained at initial dissection. It was treated successfully with primary repair. There was one rectal serosal penetration with the prosthesis. It was recognized and removed immediately and successfully without sequelae. Both patients were scarred from previous multiple perineal and posterior compartment surgeries. There were three hematomas which required re-admission to hospital, but these all settled without further surgery. No transfusion was required. Tape erosion at 12 months varied between centres, from minimum 0% to maximum 3%. There was a 40% association of tape erosion with failed surgery. All erosions were trimmed in the outpatient clinic. None required surgical intervention.

*At 12 months following TFS surgery*. Anatomical recurrence of vaginal prolapse: 63/614 (10%) after 12 months. All symptoms improved (% Cure at 12 months in brackets): chronic pelvic pain: n = 197 (79%); urge incontinence: n = 320 (86%); frequency: n = 313 (84%); nocturia: n = 257 (69%); (77%); fecal incontinence: n = 93 (65%). Statistics: $x^2$-tests of McNemar to test for significance in symptom.

## DISCUSSION

This study is a natural evolution of the 1993 publication of the "Posterior Fornix Syndrome"[8]. In that study, symptoms of urinary urge incontinence, nocturia, pain were cured or improved by surgical repair of the uterosacral ligaments.

The native tissue repair method, figure 1, was initially effective for chronic pelvic pain. The cure rate had deteriorated by 12 months and rapidly thereafter[13]. The failed patients required ligament reinforcement with thin strips of alloplastic material applied exactly along the line of the USLs[14]. Though apical support with sling techniques had previously successfully cured chronic pelvic pain and other posterior fornix symptoms[14-20], these studies were from single units, with mainly small numbers. The strength of this study derived from much larger numbers from multiple centres, giving greater statistical validity to its conclusions: loose posterior suspensory ligaments are most likely an important cause of chronic pelvic pain and other posterior fornix symptoms such as urgency, nocturia, frequency.

Heinrich Martius described two pathways for CPP, visceral and mechanical[23,24], figure 4. The pain originating from the visceral pathway was transmitted from Frankenhauser's plexus which is situated approximately 2cm lateral to the cervix. It lies at the distal end of the hypogastric plexus. The second pathway originates from stimulation of the sacral plexus. These pains radiate mainly to the lumbosacral region, the anterior and lateral abdominal wall, the inguinal region and the thighs.

These pains radiate mainly to the lumbosacral region, characterized by low dragging abdominal pain or deep sacral backache. The pelvic pain addressed by this study, is consistent with both of these descriptions. According to the Theory, loose USLs fail to support the Frankenhauser and Sacral plexuses and these can fire off whenever tension is applied, either by gravity, intraabdominal contents, or during intercourse ('contact dyspareunia').

### *Peripheral and central hypersensitization*[2,5]

Our results do not support these hypotheses. Cure, when it occurred, was almost invariably immediate, usually by the following day.

### *Cure of co-occurring bladder and bowel symptoms*

Our results confirm that CPP co-occurs with bladder and bowel symptoms and these are usually, but not always, cured at the same time as cure of CPP.

### *Pre-operative confirmation of USL as a cause of CPP*

We discuss two office tests which help predict results of surgery.

*The Bornstein test* (see article this issue) is a definitive test for determining whether CPP may be caused by lax USLs. The question of loose USL as an etiological factor was tested in 10 patients with chronic extreme vulvodynia in 2005[23]. Two ml of 2% lidnocaine was injected transvaginally at the junction of USL to cervix. On retesting after 5 minutes, 8 patients reported complete disappearance of introital sensitivity and this was confirmed by two separate examiners. In the other two patients, direct testing confirmed that the allodynia (exaggerated sensitivity) had disappeared on one side, but remained on the other. Re-testing the patients at 30 minutes confirmed that the blocking effect on the pain had disappeared[23].

A similar test was made in 3 patients with CPP and symptoms of bladder pain syndrome. The abdominal, urethral, introital and cervical tenderness which were demonstrated objectively pre-test in all 3 patients disappeared entirely, or were substantially improved, within 5 minutes of the injection[24].

*The speculum test* In 2013, a simple office 'simulated operation' test normally used to determine apical cause of urgency[25], gentle insertion of the bottom part of a bivalve speculum into the posterior fornix of vagina was applied to a patient with feelings of urgency, lower abdominal pain and extreme tenderness in the suburethral area of the vagina[26]. The urge and pain symptoms were immediately alleviated[26]. This test has since been repeated subsequently on patients with CPP including severe low sacral backache with (anecdotally) similar results.

## CONCLUSIONS

The study shows that chronic pelvic pain co-occurs with symptoms of bladder and bowel dysfunction. This is an important diagnostic point. Symptoms of isolated pelvic pain, with no symptoms of bladder and bowel dysfunction very rarely are associated with USL laxity. Along with CPP, very significant cure /improvement was noted in bladder symptoms such as nocturia, frequency, urgency and non-sphincteric fecal incontinence by reinforcing the apical ligamentous supports of the vagina with the TFS minisling.

*Financial support* none

*Conflicts* none

*Contributions* All the authors contributed to data, collection, ordering, interpretation, and writing. AY performed the statistical analysis.

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## Commentary

Chronic pelvic pain can have multiple causes and is a complex and challenging clinical dilemma for evaluation and management. It can be a symptom of another disease, or a condition by its own right. In many cases it's not possible to identify a single cause for chronic pelvic pain. In those cases the goal of treatment is to reduce pain and other symptoms and improve the patients' quality of life.

The International Continence Society defines Chronic Pelvic Pain Syndrome (CPPS) as: *"Genitourinary pain syndromes that are all chronic in their nature. Pain is a major complaint but concomitant complaints are of lower urinary tract, bowel, sexual or gynecological in nature where there was no infection or other obvious pathology"*.

The theory hypothesized by the authors is that CPP where no obvious cause is evident, might be caused by loose \ stretched main suspensory pelvic ligaments with the concurrence of Pelvic Organ Prolapse (POP) of at least POPQ stage 2 and is hence potentially curable surgically by repairing such ligaments. This type of CPP generally co-occurs with one or more symptoms of bladder and bowel dysfunctions which may occur with even minimal apical prolapse.

The researchers method for alleviating CPP in this clinical circumstance was to perform a surgical correction of the loose cardinal and uterosacral ligaments in those women who suffer from CPP symptoms concomitant with at least stage 2 POP apical defect and have at least two other pelvic symptoms of the lower urinary and lower gastrointestinal tract as mentioned in their inclusion criteria.

The surgical technique used was applying a minimally invasive TFS (Tissue Fixation System) minisling with the primary outcome being uterine prolapse repair and secondary outcomes of improving pain, bladder and bowel symptoms.

In this series 33% (197 of 614) of the women having at least stage 2 POP had symptoms of chronic pelvic pain in addition to their prolapse, bowel and urinary symptoms and the authors describe a possible mechanism for pain relive in those women when they achieved an anatomical and support reconstruction with good improvement rates and acceptable complication rates.

This group of women represents a unique type of women from the spectrum of CPP associated with pelvic organ prolapse and functional lower urinary and bowel symptoms. In this particular group of patients one can expect improvement of the pain symptoms.

From the results here it can be concluded that pelvic surgeons performing POP repairs should pay more attention to pain symptoms which are occasionally underestimated on clinical evaluation prior to surgery in view of significant prolapse degree and its associated spectrum of symptoms.

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**Review**

# Pelvic floor exercises according to the Integral Theory - strengthening the 3 directional muscle forces improves chronic pelvic pain, bladder & bowel dysfunctions

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*Abstract*. *Background*: By 1995 it was evident from the surgical data that a substantial percentage of chronic pelvic pain, bladder & bowel dysfunctions in the female could be cured by surgical repair of the pelvic suspensory ligaments. *Aims:* Using a squatting-based regime, we aimed to strengthen the 3 directional muscle forces and the ligaments against which they contract, to improve urethral closure (incontinence) opening (bladder emptying), support of the bladder base stretch receptors (urge incontinence) and, Frankenhauser and Sacral nerve plexuses (chronic pelvic pain). *Results:* The standard regime comprised four visits in 3 months. HRT was administered to all patients, electrotherapy 20 min per day for 4 weeks with a 50Hz probe placed into the posterior fornix of the vagina, squeezing 3x12 per day, reverse pushdowns 3x12 per day and squatting or equivalent up to 20 min per day as part of daily routine (such as household tasks). Of 147 patients (mean age 52.5 years), 53% completed the programme. Median QOL improvement reported was 66%, mean cough stress test urine loss reduced from 2.2 g (range 0-20.3 g) to 0.2 g (range 0-1.4 g), p =<0.005, and 24-h pad loss from a mean of 3.7 g (range 0-21.8 g) to a mean of 0.76 g (range 0-9.3 m), p=<0.005. Frequency, nocturia and pelvic pain were significantly improved (p=<0.005). Residual urine reduced from mean 202 ml to mean 71 ml (p=<0.005). This method extends indications for nonsurgical therapy beyond stress incontinence, and the results appear to encourage this approach. Approximately 3% of patients reported worsening of their stress incontinence and these were referred for surgery. *Conclusions:* The 50% dropout rate was a concern. Subsequently we performed a small pilot study (unpublished) using a simpler regime: electrotherapy, situps before getting out of bed, developing a "squatting culture" as part of a daily routine, sitting on a round fitball instead of a chair. The initial results suggested better compliance and equivalent improvement. This method, though promising, awaits rigorous scientific assessment.

*Key words*: Integral Theory; Pelvic floor rehabilitation; PFR; Urge; Nocturia; USI; Constipation.

## INTRODUCTION

Current pelvic floor rehabilitation (PFR) methods in the female address mainly stress incontinence. Though it is implicit that pelvic floor rehabilitation exercises cure stress incontinence by strengthening the pelvic floor muscles, how this occurs is rarely mentioned in the literature. Though many variations involving various abdominal muscles have been added from time to time, ''squeezing'' upwards, or upward pulling of the pelvic diaphragm, as described by Kegel[1] is the core element of all modern methods. Squeezing upwards, figure 1, is unidirectional and is not the natural closure mechanism, so it must be learnt. The natural closure mechanism, figure 2, is activated by 3 opposite directional forces as described in the 1990 Integral Theory[2].

As regards urge, frequency and nocturia, the current view is that such symptoms should be treated with ''bladder training'', a methodology which trains the inhibitory circuits of the brain. The patient is taught to 'hold on'. Pain treatment depends on site. It consistes of biofeedback, identifying and treating 'trigger points' in the pelvis and often 'psychological' treatment.

### Origins of the pelvic floor exercises based on the Integral Theory

Because the normal pelvic floor functions as a balanced synergistic system composed of muscle, ligaments, connective tissue, we reasoned that if we could strengthen the 3 directional forces, figure 2 using a squatting-based regime, it would also strengthen the suspensory ligaments, in particulae pubourethral (PUL) and uterosacral (USL), figure 2. In deciding to proceed with squatting as an exercise, we were encouraged by Zacharin's findings of thickened collagenous muscle insertions of levator ani in patients who squatted as part of their daily routine[3].

### As regards urinary stress incontinence and bladder evacuation

The extra muscle strength would pull on PUL and USL to strengthen them. Stronger muscles improve the strength of urethral closure (incontinence) and also stretch open the posterior wall of the urerthra more strongly, improving bladder emptying.

### As regards urinary urge incontinence

The extra muscle strength would stretch the vaginal membrane to better support the bladder base stretch receptors, thereby preventing the micturition reflex from being inappropriately activated, and so improve urge incontinence, figure 3.

In the normal patient, figure 3, central inhibition (white arrow) and reflex stretching of the vagina by opposite muscle forces (arrows) to support the stretch receptors 'N'. Connective tissue laxity in the suspensory ligaments or vaginal membrane (figure 3) may not transmit the forces applied and so the vagina cannot be adequately stretched; the stretch receptors (N) may 'fire off' at a lower hydrostatic pressure (smaller bladder volume) and the cortex interprets this as urgency At night, there is nocturia. The sensitivity of the stretch receptors is clearly an important variable.

The original aim was to address a wide range of pelvic floor dysfunctions by strengthening all possible components of the system, in particular ligaments and muscles, as much as possible. We aimed for minimal time loss, weaving every element of treatment seamlessly into a daily routine. On this basis, we included the Kegel regime, even though the muscle responsible for squeezing upwards, puborectalis muscle, does not contract against the suspensory ligaments, but directly against the pubic bone, figure 1.

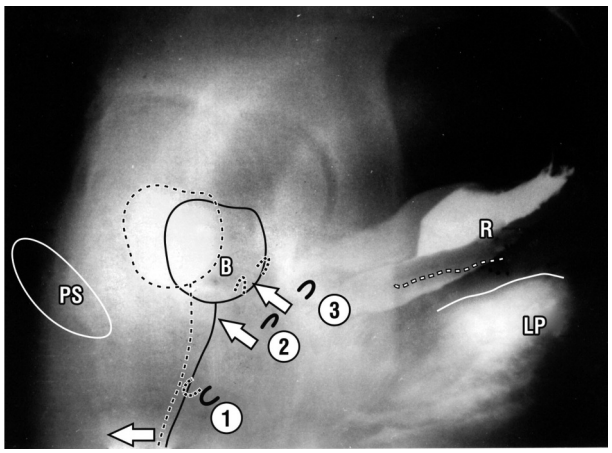


Figure 1. – Squeezing. 'Kegel Exercise'. Standing lateral xray, the squeezing film (broken lines) is superimposed on the resting film (unbroken lines). Vascular clips have been applied to the anterior vaginal wall: '1' to midurethra; '2' to bladder neck; '3' to bladder base. The unbroken lines represent the resting position and the broken lines the squeezing position. The muscle movements during 'squeezing' elevate vagina, bladder 'B', rectum 'R' and levator plate 'LP' upwards and forwards. Note the difference with the movements in figure 2. Because 'squeezing' is not the natural mechanism, it must be learnt (Kegel 1948).

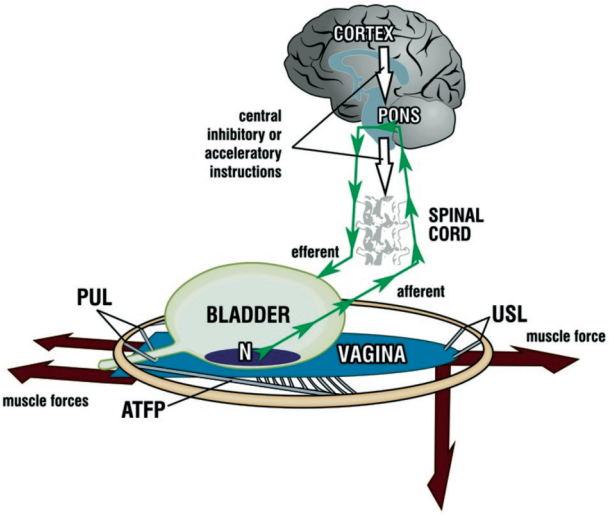


Figure 3. – Trampoline analogy- Function. How the muscle forces control peripheral neurological function. Like a trampoline, laxity in even one suspensory ligament, PUL, ATFP or USL, may prevent the muscle forces (arrows) from tensioning the vaginal membrane. The stretch receptors 'N' cannot be supported, and fire off prematurely. The cortex perceives the afferent impulses as urge symptoms.

## RATIONALE FOR THE TREATMENT PROTOCOL

As one can never be certain of the contribution of a particular component in pathogenesis, we aimed to strengthen each of these components where possible, the rationale being that even a few percentage points from each component can achieve a significant total improvement. Kegel-type exercises and endovaginal electrotherapy are proven staples of PFR, and they were in this study. We hypothesized that electrotherapy stimulates the neuromuscular junction, and that ''squeezing'' stimulates the puborectalis and the forward closure forces (Figure 1). Prolonged squatting "squatting culture" as part of a normal daily routine and downward reverse pushdowns were introduced to strengthen the natural slow and fast-twitch components of all three directional muscle closure forces (Figure 2). These are the natural movements of closure as proven during radiological studies, figure 1. Squatting not only strengthens the muscle, it also strengthens its collagenous (ligamentous) insertion points . How these exercises may improve urge, frequency and nocturia is explained by the trampoline analogy (Figure 3). Good posture was emphasized, as it promotes optimal muscle leverage. All postmenopausal patients were encouraged to take estrogen, systemic or local, to thicken vaginal mucosa and decrease collagen loss . Time efficiency was addressed by limiting attendance at the clinic to a total of four visits in 3 months, by making the pelvic floor methods part of the fabric of a patient's daily routine, and enlisting the patient's participation in planning the treatment.

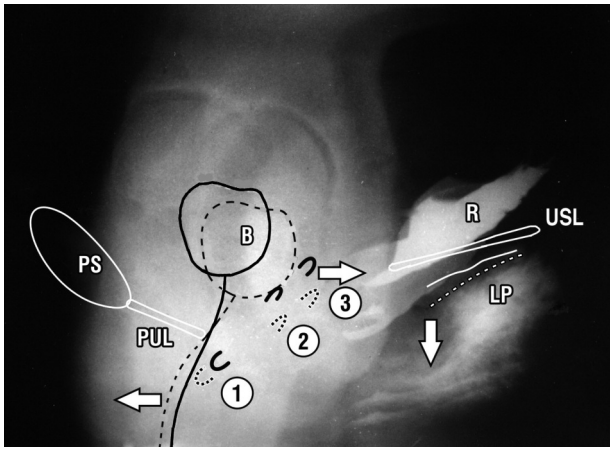


Figure 2. – Same patient and labeling as figure 1. The 3 directional movements which close the urethra during effort. Standing lateral xray, the squeezing film (broken lines) is superimposed on the resting film (unbroken lines). Vascular clips have been applied to the anterior vaginal wall: '1' to midurethra; '2' to bladder neck; '3' to bladder base. The unbroken lines represent the resting position and the broken lines the straining or coughing position. Reflex muscle movements stretch the distal urethra '1' forwards and downwards around the pubourethral ligament 'PUL' to close it. The bladder neck '2' and bladder base '3', are stretched backwards against PUL by LP and downwards by the downward angulation of levator plate 'LP', (downward arrow). This action closes proximal urethra and bladder neck. The downward forces (arrow) pull against the uterosacral ligaments (USL).

## TREATMENT PROTOCOL

Much of the next sections have been reprinted, by permission, from the publishers.

Age, activity, hormonal status and posture were assessed. Some types of HRT oral or vaginal estrogens were prescribed. General exercise and good posture were encouraged. To assist compliance, the patient was required to complete a daily diary.

### Electrotherapy

Electrotherapy was introduced at the 1st visit, along with squatting and squeezing exercises. A simple low-cost battery-operated electrical stimulator, the Pelvitoner 2000 (Medhealth Pty Ltd, Perth,WA), was used for 4 weeks. This delivered a square 50-Hz pulse every 2 s. Positioning of the probe was guided by a pictorial algorithm which diagnosed whether symptoms originated from ligament looseness in the front or back of the vagina. For purely posterior defects (e.g. pelvic pain, high residual urine, nocturia), the probe was inserted into the posterior fornix for 20 min per day. Bladder suppressant drugs were never used.

Pelvic floor exercises

Squatting and Kegel-type pelvic floor squeezes were introduced at the 1st visit, the latter performed with legs apart according to the methods of Bo[5]. Co-ordination with the electrical stimulator light (biofeedback) was encouraged if possible. At the 2nd visit, a reverse downward thrust was introduced (3 sets of 12 per day) to alternate with squeezing (3 sets of 12 per day). The patient pushed vigorously downwards while pressing upwards with one finger placed on one side of the urethra, approximately 2 cm from the introitus. These exercises aimed to strengthen the tridirectional fast twitch muscle fibres (Figure 2, arrows). The ''reverse pushdown'' exercises were not well tolerated in 2/3 patients, and these patients were told to substitute Kegel exercises.

Squatting was encouraged as a universal slow-twitch exercise, 20 min per day in divided segments, preferably while performing some household task. In patients who could not or would not squat, sitting on a large rubber ''fitball'' during work or household duties was encouraged. Time management was improved by encouraging patients to perform one group of twelve exercises on waking, retiring, and on visiting the toilet. Also, to substitute squatting for bending at all times. If a patient had arthritis, she was encouraged to sit on the end of a chair or a fitball with legs apart.

The 3rd and 4th visits checked patient compliance (diary), discussed how the patient had incorporated the programme into her daily routine, and reinforced the aims and principles of the programme.

Maintenance PFR

By the end of 3 months, it was assumed that the patients had incorporated the exercises into their normal routine. Maintenance electrotherapy was to be performed for 5 days per month. The patient was advised to continue this routine on an ongoing basis. If the patient came to surgery, then it was advised that the PFR be recommenced 12 weeks after surgery.

RESULTS

The 1st study Results of the First study[6]. Sixty patients completed the study. Improvement was defined as >50% improvement in their symptoms (see Table 1).

The 2nd study One hundred and forty-seven patients, mean age 52.5 years (range 25-76) and mean parity 2.25 (range 0-5), commenced the full regime. Ten patients were nulliparous. Surgery included, the dropout rate was 1st visit 17%; 2nd visit 19%; 3rd visit 11%; Total 47%.

**Table 1**

**Fate of Individual Symptoms (n=60)**

| condition | >50% improvement |
|---|---|
| stress (n=42) | 78% |
| urge (n=39) | 61% |
| frequency (n=53) | 62% |
| nocturia (n=24) | 75% |
| pelvic pain (n=20) | 65% |
| leakage (n=50) | 68% |
| bowel problems (n=28) | 78% |

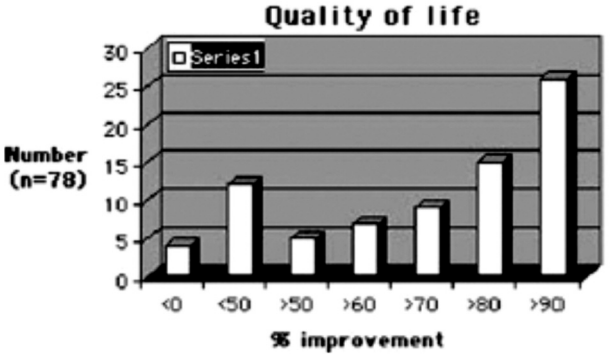


Figure 4. – Quality of life improvement. The vertical axis represents actual numbers, and the horizontal axis represents % improvement of that particular group. Thus 25 patients improved their QOL by 90%, 11 patients by 50% and so on. On a total symptom basis, the median QOL improvement reported was 66%. In such patients, improvement was evident by the 2nd visit (4 weeks).

**Table 2**

**Fate of Individual Symptoms (n=78)**

| condition | >50% improvement |
|---|---|
| stress incontinence (n=69) | 57 (82%) |
| urge incontinence (n=44) | 33 (68%) |
| frequency only (n=12) | 10 (83%) |
| nocturia (n=32) | 29 (90%) |
| pelvic pain (n=17) | 13 (76%) |

The principal reasons for non-compliance were lack of time, or insufficient motivation. Quality of life (QOL) improvement rate is summarized in Figure 4 and symptom improvement in Table 2. QOL was a separate question which the patient was asked to answer: Has your quality of life improved/not improved and by what percentage? The symptoms improvement was based on the same self-administered questionnaire filled in by the patient prior to her 1st visit. Improvement rates for individual symptoms are summarized in Table 2. Urine loss for cough stress testing reduced from a mean of 2.2 g (range 0-20.3 g) to 0.2 g (range 0-1.4 g), p =<0.005 (Student's t test), and 24-h pad loss from a mean of 3.7 g (range 0-21.8 g) to a mean of 0.76 g (range 0-9.3 g), p =<0.005.

The patients reported that control of urine loss, when achieved, happened even when not ''en garde''. The cutoff point for determining frequency improvement was eight times per day and nocturia two times per night. Total number of frequency events for the twelve patients with only frequency reduced from 140 to 80 per day (P=<0.005). Total number of nocturia events for the 32 patients reduced from 98 events per night to 25 per night (P =<.005). In 23 patients with residual urines greater than 50 ml (pre-treatment mean 202 ml, range 50-550 ml), post-treatment residual was reduced to 71 ml (range 15-450 ml) (p=<0.005). Thirteen patients (9% of total) elected to have surgery prior to completion of their course for non-improvement or worsening of stress incontinence. Three patients reported significant worsening of their stress symptoms, and no improvement was noted in nine others. Three patients report-

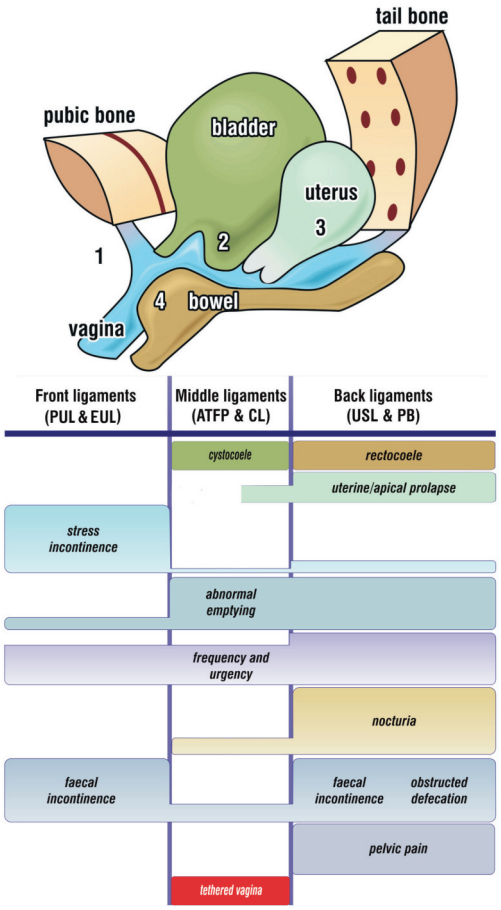


Figure 5. – Simplified Pictorial Diagnostic Algorithm. Relates structural damage (prolapse) to symptoms: 1: stress incontinence; 2: cystocele; 3: uterine prolapse; 4: rectocele. The size of the bar gives an approximate indication of the prevalence (probability) of the symptom. Ligaments which can be surgically repaired and therefore potentially strengthened by squatting are: External urethral ligament (EUL), pubourethral ligament (PUL); CX ring/cardinal ligament (CL); arcus tendineus fascia pelvis (ATFP); uterosacral ligament (USL); perineal body (PB).

ed worsening of their urge symptoms, and no improvement was noted in six others. It was not always possible to predict an outcome. The highest cough stress test loss, 20.3 g reduced to 0 g on re-testing. The highest 24-h test loss, 21.8 g reduced to 2.3 g. Yet other patients with far less objective loss required surgery. All patients complied with HRT treatment during the 3-month period

## DISCUSSION

As a general rule, the younger the patient, the better the results. Very rarely were good results seen in older postmenopausal women, certainly in those who were beyond the late 60s.

Though the emphasis of this review was originally chronic pelvic pain, the data from Tables 1&2 confirms that pelvic symptoms occur in groups, figure 5, and that chronic pelvic pain (CPP) in the female co-occurs with other posterior zone symptoms, nocturia, urgency, abnormal bladder emptying, fecal incontinence and obstructive defecation. The rationale for squatting PFR cure of CPP is that as the USLs strengthen, they better support the sympathetic T11-12 and parasympathetic S2-4 nerve plexuses which are contained within them. The distribution of the pain varies with these nerves. T11-12, lower abdomen, groin. S2-4 vulva (vulvodynia), bladder, pelvic muscles, low sacral backache, deep impact dyspareunia, interstitial cystitis. All of these sites were variously improved as per Tables 1&2.

The methods used in this study appear to extend the scope of PFR beyond stress incontinence to urge, frequency, nocturia, abnormal emptying and pelvic pain. This was attributed to the squatting exercise and reverse pushdowns, both of which are needed to strengthen the uterosacral ligaments (USL), the key posterior support of the vaginal membrane. According to Petros and Ulmsten[4], damaged USL may cause posterior zone defects, expressed as FNU pelvic pain and abnormal emptying (Figure 1). On the negative side, if the damage extends beyond a critical point, as we suspect it did with some older patients, there may be no improvement or in some cases, worsening of symptoms because the now strengthened muscles may further weaken the ligaments.

Those patients improved of their stress incontinence symptoms reported that they did not leak even when caught "off guard", in contrast to improvement with Kegel exercises. Kegel patients almost invariably leak when caught "off guard".

Almost 70% of patients who completed the treatment seemed unwilling to perform the reverse pushdown exercises. Squatting, Kegel and electrotherapy were well received.

### Dropout

We attribute the high dropout rate principally to our attitude to treatment, placing responsibility entirely on the patient. Our rationale was that if such a programme was to have any lasting benefit, it needed a disciplined long-term commitment by the patient and a close to zero time impact on her lifestyle. Continuation rate was 52%, inferior to the results from Bo's intensive approach[5], but a median figure compared with other reports which vary between 10 and 80%[7]. The high dropout rate led to a 3rd pilot study.

Future directions the 3rd (unpublished) study -towards a more time efficient method for pelvic floor rehabilitation.

Despite conscientious application and follow-up, the dropout rate for the PFR methods used in the 1st and 2nd studies was 50%. On analysis, it appeared that a principal reason many of the patients discontinued was lack of time. It was reasoned that sitting on a rubber "fitball" would strengthen the same pelvic muscles and ligaments as the squatting exercise. Therefore patients were advised to use a rubber "fitball" instead of a chair at work or at home. It was also reasoned that the Kegel exercises could be dispensed with, as they did not address the natural closure muscles (figure 1). Instead, patients were encouraged to do core sit-up exercises immediately before getting out of bed. The rationale for this is that the anterior abdominal muscles and pelvic floor muscles have a common embryological origin. Therefore strengthening the abdominal muscles simultaneously strengthens the pelvic floor muscles. Electrotherapy using a small portable unit which could be used discreetly was also advised, according to the protocols detailed below. The anecdotal results in more than 30 patients appeared to be equivalent to the more involved techniques used in the studies 1&2. Clearly this method needs to be fully tested with an RCT.

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## Commentary

This study leads us to reflect on the characteristics of the connective tissue, which is not often considered by physiotherapists. According to Integral Theory, almost all pelvic floor disorders, such as stress incontinence, urgency but also pelvic pain, fecal incontinence, and defecatory difficulties are related to a change in connective tissue. The ligament laxity can therefore affect the strength of the muscles so making it responsible for prolapse of the organs and dysfunctions of the pelvic floor.

According to this theory, a rehabilitation protocol was thought including not only Kegel's exercises but also HRT, electrotherapy, squatting and squeezing exercises. In particular, patients were encouraged to introduce squatting as part of daily routine.

The rehabilitation process takes place in 4 meetings, leaving patients managing rehabilitation by themself at home. Perhaps for that reason a significant percentage (almost 50%) of the study group leave the protocol. As in all types of rehabilitation, the constant relationship between patient and therapist is not only important to perform a good exercise but also to maintain and increase the compliance, keeping focus on rehabilitation goals. The results of the study are however encouraging and show significant improvements in stress and urgency and, above all, a reduction in pelvic pain. The protocol's limitation is related to the high number of patients leaving the rehabilitation path. The continuity of the relationship with the therapist is so important that can be crucial in carrying out rehabilitation.

Also important is to increase all strategies aimed to preserve the structure of connective tissue and collagen, its main constituent. New frontiers can also be explored for stimulation of collagen reshaping in the direction of a dense collagen through the activation of collagenase and HSP by the heat given in various modalities e.c. Radiofrequency and Laser.

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**Original article**

# Surgical cure of chronic pelvic pain, associated bladder & bowel symptoms by posterior sling in 198 patients validates the Pescatori Iceberg principle of pelvic symptom co-occurrence

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*Abstract: Purpose:* The treatment of pelvic organ prolapse, chronic pelvic pain, bladder and bowel dysfunction is largely single-symptom specific and frequently treated by a singular discipline; urology, gynaecology or coloproctology. The presence of occult symptoms in colorectal pelvic floor patients has previously been demonstrated by the Pescatori 'iceberg' concept: other symptoms are latent and often ignored. *Methods:* One hundred and ninety-eight patients, mean age 69 years (48-72), presenting with chronic pelvic pain (CPP) were evaluated using the validated Integral Theory System Questionnaire (ITSQ), which diagnosed pubourethral, uterosacral and cardinal ligament laxity as the principal causes of the apical prolapse, CPP, bladder and bowel symptoms. These were reinforced with transobturator and infracoccygeal sacropexy tapes. *Results:* CPP and apical prolapse were present in 198 patients; apical prolapse Grade 1 (n=15), Grade 2 (n=39), Grade 3 (n=107) and Grade 4 (n=37). Anatomic cure rate for apical prolapse was 99% ($p<0.001$). Symptom prevalence (% cure at 12 months in brackets): pelvic pain 198 (74%, $p<0.001$); urinary frequency: 127 (80%, $p<0.001$); bladder emptying difficulties: 68 (54%, $p<0.001$); urinary stress incontinence: 66 (95%, $p<0.001$); nocturia: 63 (79%, $p<0.001$); obstructive defecation: 59 (80%, $p<0.001$); urge incontinence: 55 (80%, $p<0.001$); residual urine >50ml: 44 (55%, $p<0.001$). Two (1%) of 198 patients with grade 3 prolapse developed a high grade 2 cystocele, which was subsequently repaired. No tape erosions were observed at 12 months. *Conclusions:* Identification and cure of 'latent' symptoms affirmed the validity of Pescatori's 'Iceberg' concept and the theory, on which the surgery is based.

*Key words:* Chronic pelvic pain; PIVS; Infracoccygeal sacropexy; Pescatori iceberg.

## INTRODUCTION

The association of chronic pelvic pain (CPP) with other urogenital disorders is well known and has been especially noted by Expert committees from the International Continence Society (ICS)[1] and the European Urology Association[2]. However, no specific relationship between specific symptoms was described by these committees in their deliberations. Recommendations for treatment of organ prolapse, chronic pelvic pain, bladder and bowel dysfunction is largely single-symptom specific. The result is that treatment is carried out by three different disciplines; urology, gynecology or coloproctology. Other conditions frequently remain latent or ignored.

The problem of the fractured uni-disciplinary approach to this problem was addressed by Pescatori et al.[3]. One hundred consecutive patients, who presented with Obstructive Defecation Syndrome (ODS), were investigated thoroughly for other conditions, and these were noted in a novel "iceberg' diagram (Figure 1).

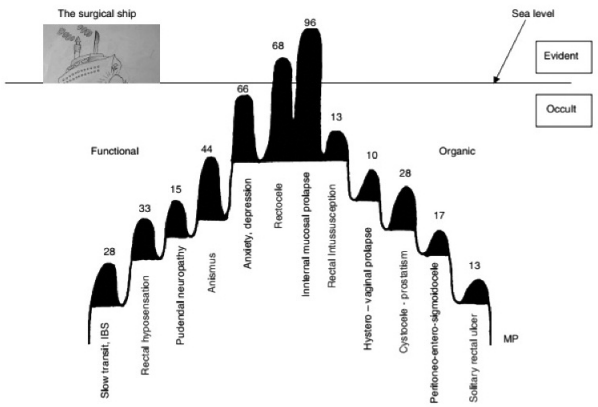


Figure 1. – *Original Pescatori Iceberg*. The presenting symptoms ODS is above the waterline. This was the patient's presenting symptom and focus. After and with Permission from M. Pescatori[3].

These symptoms, though present, were not uppermost in patients' consciousness and had to be searched for.

A specific association between apical prolapse and CPP, bladder symptoms of urgency, nocturia and abnormal emptying was described in 1993 as "Posterior Fornix Syndrome", as part of the Integral Theory[4]. The Posterior Fornix Syndrome was expanded by Abendstein et al. in 2008 to include anorectal disorders[5]. The authors reported a significant cure rate of obstructive defecation (ODS), faecal incontinence, CPP and other posterior fornix symptoms following repair of the uterosacral ligaments[5].

We report a prospective study of 198 patients from the European Centre of Excellence For Reconstructive Pelvic Surgery, a tertiary referral clinic from Hannover, Germany. In all 198 patients, the presenting symptom was chronic pelvic pain, 'CPP' as described in 1996[6].

The aim of the study was

1. To investigate the incidence of other pelvic floor symptoms and derive an odds ratio for each symptom relevant to CPP, and
2. To assess the improvement of CPP and the other symptoms following a posterior sling to correct the apical prolapse.

This study was approved by the Ethics Committees of the Kvinno Center Hannover. Written informed consent was obtained from all patients. The principles of the Helsinki Declaration (2008) were followed.

## MATERIALS AND METHODS

One hundred and ninety-eight patients, mean age 69 years (48-72), presenting with chronic pelvic pain (CPP) were prospectively assessed for 'latent' symptoms using the Integral Theory System Questionnaire (ITSQ). At the first consultation, all patients completed a self-administered validated ITSQ[7], whose answers were transferred to a Pictorial Diagnostic Algorithm , which served as a guide to surgery.

TABLE 1. Association of pelvic symptoms with Chronic Pelvic Pain (n=198).

| | No Hysterectomy n=132 (100%) | Hysterectomy n=66 (100%) | Total n=198 |
|---|---|---|---|
| Frequency/ Urge | 81 (61%) | 46 (70%) | 127 (64%) |
| Nocturia | 42 (32%) | 21 (32%) | 63 (32%) |
| Bladder Emptying | 40 (30%) | 28 (42%) | 68 (34%) |
| Urge incontinence | 25 (19%) | 30 (45%) | 55 (28%) |
| Stress incontinence | 40 (30%) | 26 (39%) | 66 (33%) |
| Obstructed defaecation | 35 (27%) | 26 (39%) | 61 (31%) |
| Faecal incontinence | 31 (23%) | 25 (38%) | 56 (28%) |

All patients were examined (pre- and postoperatively) and operated upon by the senior author (KG). Pre-operative cystometry was performed in all patients. Additionally the amount of residual urine was calculated by ultrasound[8]. All patients underwent a vaginal examination to assess the degree of prolapse and to detect specific anatomical defects according to the ITS.

*Inclusion criteria* (Table1.) CPP as previously described [4] and some degree of uterine/apical prolapse where no other cause was evident.

*Exclusion criteria*. Younger patients with other known causes of CPP such as chronic pelvic inflammatory disease, endometriosis etc.

The pain was invariably severe, frequently one-sided, but often bilateral, situated low in the right or left iliac fossa, usually relieved on lying down. Frequently it could be relieved by insertion of a ring pessary and/or reproduced on palpating the cervix and displacing it posteriorly with the patient in the supine position. Although the pain was chronic in nature, it varied considerably over time with regard to intensity. There was often 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. Patients often complained of low sacral backache[4].

Included in this study were only patients presenting with CPP and at least two Posterior Fornix Syndrome symptoms as detailed in Table1; the percentage ratio of a symptom to CPP is indicated in brackets separately for patients with and without prior hysterectomy (HX); the combined numbers and percentage frequencies are recorded in Figure 2.

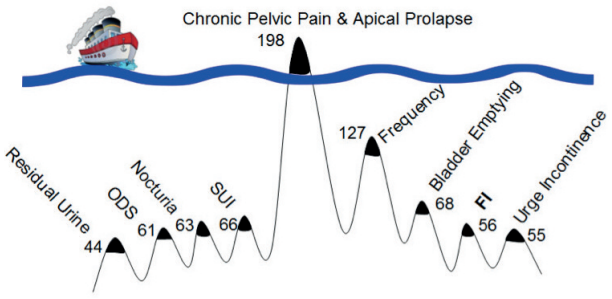


Figure 2. – *Pescatori Iceberg applied to Chronic Pelvic Pain (CPP).*
The symptom prevalence is graphically indicated in the iceberg diagram, latent symptoms below the waterline. All symptoms derived from the Integral Theory Symptom Questionnaire (ITSQ). Numbers indicate combined total of the hysterectomy and non-hysterectomy cohorts.

The percentage ratio of a symptom to CPP is indicated in brackets. The combined numbers are recorded in Figure 2 and the odds ratio per symptom for the whole cohort (198) is indicated in next to the symptom.

*Surgery*

Patients with stress incontinence were treated with a sub-urethral sling inserted by the transobturator technique.

*Level 1 Vaginal Repair - Restoration of the uterosacral ligaments with a polypropylene tape*

The aim of level 1 repair is to insert a polypropylene tape in the exact position of the uterosacral ligaments. To get access to the uterosacral ligaments a transverse 4 -5 cm long incision was made in the posterior vaginal wall 1,5 cm below cervix or the hysterectomy scar. A Sims speculum opened out the incision. If necessary, the enterocele was opened and ligated with a high purse-string suture. Blunt dissection was performed to the sacrospinous ligaments and insertion of a 2-0 prolene suture through the ligament was achieved using a special purpose designed instrument on both sides.

Bilateral 8 mm perineal skin incisions were made 2 cm lateral and below the external anal sphincter at 4 and 8 o'-clock. The IVS-Tunneler was placed into the ischiorectal fossa for a distance of 4-5 cm. Under rectal examination control, the instrument was gently turned inwards. The blunt tip was brought through the levator plate, until it reached the transverse incision. A 8 mm Polypropylene tape was threaded into the eye of the stylus and brought into the transverse incision. The procedure was repeated on the other side. Both sacrospinous prolene sutures were brought through the tape to a distance of 4cm. The tape was sutured with no 1 Vicryl to the cervical ring or vaginal vault and also to the remnants of the uterosacral ligaments.

*Level 2 Vaginal Bridge Repair*

The aim of this procedure was to approximate the laterally displaced rectovaginal fascia towards the midline and to stretch the posterior vaginal wall including rectum. Two parallel full-thickness incisions were made in the posterior vaginal wall, extending from the transverse incision to 1 cm proximal to the introitus. On both sides adherent skin was freed from the rectum laterally to get access to the rectovaginal fascia.

The superficial epithelium was thoroughly destroyed by diathermy and the top of the bridge anchored onto the tape. Two transverse vaginal holding sutures (no 1 PDS) were placed as laterally as possible, one at the level of the uterosacral ligaments and the other at the level of the rectovaginal fascia and left untied. These sutures run subepithelially as a horizontal mattress suture through the rectovaginal fascia, back to the bridge and contralaterally. The purpose of this suture is to approximate the laterally displaced

TABLE 2.

| | Incidence before Surgery % in brackets | Incidence after Surgery | Chi² test p-value |
|---|---|---|---|
| Pelvic Pain | 198 (100) | 52 (26) | P < 0.001 |
| Urinary Freqency | 127 (64) | 26 (13) | P < 0.001 |
| Bladder emptying difficulties | 68 (34) | 32 (16) | P < 0.01 |
| SUI | 66 (33) | 4 (2) | P < 0.001 |
| ODS | 59 (30) | 12 (6) | P < 0.001 |
| Urge incontinence | 55 (28) | 11 (6) | P < 0.001 |
| Residual urine >50ml | 44 (22) | 20 (10) | P < 0.001 |

retovaginal fascia towards the midline, and to hold the tissues in place during healing.

*Level 3 Vaginal Repair*

The aim of this procedure was to restore the integrity of the perineal body as an anchoring point for the backwards and downwards forces. The perineal body was restored with two horizontal mattress sutures inserted subepithelially into both rectovaginal fascias. The distal part of the bridge was included.

The transverse incision was sutured with mattress suture, followed by a continuous layer (no 1 Vicryl). The bridge was buried below the lateral flaps with mattress and continuous sutures in the same way. The coccygeal ends of the tape were cut. Only the skin incision was sutured.

*Data acquisition*

A prospective audit based on 198 patients with posterior fornix syndrome between January 2009 and December 2012.

*Statistics*. A 2-tailed Student's t-test was applied (http://www.socscistatistics.com/tests/studentttest)

*Follow-up and end point measurements*

At 12 months follow up a full assessment was made using the self-administered ITS questionnaire[7], as well as vaginal examination.

*Criteria for a positive response*

– Pain: A global self-assessed 80% improvement over the baseline symptom at the 12 month visit.
– Nocturia: Reduction from 2 or more episodes per night to one or none.
– Urge incontinence: Zero episodes of wetting prior to arrival at the toilet.
– Fecal incontinence: Zero episodes of soiling prior to arrival at the toilet.
– Obstructed defecation syndrome 'ODS': difficulty in bowel evacuation.

## RESULTS

Pelvic pain and apical prolapse were present in 198 patients. The Baden- Walker classification for prolapse was used pre and post-operatively; apical Grade 1: n=15 (7,5%); Grade 2: n=39 (19,5%); Grade 3: n=107 (54%); Grade 4: n=37(19%).

The symptom prevalence is graphically indicated in an iceberg diagram, Figure 2, latent symptoms below the waterline.

*Surgery*

The mean operating time was 65 minutes (range 41-85 min). There was no serious bleeding. No patient required blood transfusion. Mean hospital stay was 5 days (range 2 – 9 days).

All patients were treated with 600mg Ibuprofen postoperatively every 6 hours, and the following days on demand. Serious complications such as rectal perforation, embolic problems, pyrexia did not occur. One urinary tract infections was observed, within the first week after surgery. This patient was successfully treated with broad-spectrum antibiotics. There were no hematomas, only minor bruising was noted in 5 patients around the incision. In 6 patients a permanent catheter was necessary for 2-5 days, because they were not able to empty their bladder properly. After at least 5 days the micturition was normal in all cases.

A post op follow up including vaginal examination and ultrasound was performed 7 days, 3 month and 12 months after the operation by the senior author (KG).

Of the 198 patients, 196 (99%) patients had normal vaginal anatomy 3 month after the operation and at 12 month review. Two (1%) patients with grade 3 prolapse developed a high grade 2 cystocele. Repair of the cystocele was successful at the 6 month review. No tape erosion was observed.

*Symptoms*

Symptom prevalence and % cure in brackets for both cohorts combined was: pelvic pain 198 (74%, $p<0.001$); urinary frequency: 127 (80%, $p<0.001$); bladder emptying difficulties: 68 (54%, $p<0.001$); urinary stress incontinence: 66 (95%, $p<0.001$); nocturia: 63 (79%, $p<0.001$); obstructive defecation: 59 (80%, $p<0.001$); urge incontinence: 55 (80%, $p<0.001$); residual urine >50ml: 44 (55%, $p<0.001$).

## DISCUSSION

Though it is universally acknowledged, that CPP occurs in association with bladder and bowel symptoms[1,2], individual dysfunction continues to be treated individually: CPP by referral to a pain specialist; bladder conditions by a urologist; vaginal prolapse by a gynecologist; anorectal problems by a coloproctologist. A recent technique for repair of rectal prolapse[9] makes no reference to alternative minimally invasive vaginal methods or other associated symptoms, nor does a comprehensive meta-analysis[10].

A review on descending perineal syndrome[11] does not address co-existing pain and bladder symptoms nor successful simple recent vaginal methods for repair. A laparoscopic ventral rectopexy makes no mention of the far easier and safer vaginal route, which can reinforce the uterosacral ligaments directly[12].

The Pescatori Iceberg is an important concept, as it visually summarizes the problems with the fragmented assessment by 3 different disciplines and individual symptom by symptom management recommended by Expert Groups. Though we have applied the iceberg concept from the perspective of CPP, figure 2, the conclusion is the same as that of Pescatori et al.: bladder, bowel, pain and other symptoms co-exist with prolapse, albeit as 'latent' submerged symptoms. With the exception of the sensation of urgency/frequency, we found the frequency of an association of bladder and bowel incontinence or evacuation difficulty varying between 30% and 40%, Table1. Yet another characteristic of the iceberg concept is fluidity. For example, we have seen many patients with stress urinary incontinence successfully treated elsewhere with a midurethral sling, only to attend our clinic months or years later complaining of other conditions such as prolapse, urgency, nocturia, chronic pelvic pain, ODS, fecal incontinence. Some symptoms were present previously, some not. The former had emerged from below the iceberg surface to become presenting symptoms.

The inevitable conclusion from figure 1, previous data (9-12) and our data, figure 2, is, that assessment needs to be multicompartmental, as does the treatment. We use the IT-SQ[7] as it not only addresses all the main symptoms from the three pelviperineal surgical disciplines, it accurately guides the diagnosis and therefore surgery of specific ligament damage.

Our results demonstrating improvement/cure of CPP, bladder and bowel symptoms by re-inforcing just two suspensory ligaments support the application of a different paradigm, namely, the Integral Theory System. The Theory essentially states, that pelvic organ prolapse, CPP, bladder and bowel dysfunction are mainly caused by laxity in 5 suspensory ligaments as a result of altered collagen/elastin[14]. It

follows from this, tightening and reinforcing the damaged ligament(s) will restore structure (prolapse) and reverse the cascade of events leading to CPP, bladder and bowel dysfunction.

The data from this paper is but another addition to similar data from many surgeons, who have tested the Integral Theory System paradigm by shortening and reinforcing the cardinal/uterosacral ligament complex (15-25). This method, with a less invasive approach and overnight stay outlines the apparent differences between the holistic Integral System approach to management compared to the often fragmented approach of the individual disciplines towards diagnosis and treatment.

## CONCLUSIONS

Our pre-operative data supports the Iceberg concept of Pescatori, that patients usually present with one main symptom, while other symptoms, though present may be latent. We found a 30-40% co-existence of bladder and bowel dysfunctions in patients presenting with chronic pelvic pain. All symptoms improved significantly following repair of two main suspensory ligaments, namely pubourethral and uterosacral. This can be explained by application of the Integral Theory System, which relates ligamentous weakness to pelvic organ prolapse and symptoms.

It can therefore be argued, that the majority of patients presenting to either a urologist, uro/gynaecologist or coloproctologist will have occult symptoms normally associated with a different specialty and these should be accurately determined. Perhaps the time has come to accept the contribution made by the Integral Theory to our understanding of pelvic dysfunction and pain and approach these patients from a global perspective. Where surgery is indicated, it should be the primary objective to perform procedures aimed at addressing all the symptoms and perhaps unify the three specialties into a new discipline of "pelviperineology."

*Conflicts*. None by any authors.

*Preparation of paper*

Patient assessment, surgery, data collection: Goeschen
Conceptualization, writing, statistics: all authors

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## Comment

Thank you for asking me to comment on how the iceberg concept evolved. I am very pleased to see that this concept is being successfully applied in a different but related field. The origins of the Iceberg Concept are as follows. We revised all our rectal mucosal prolapse patients with obstructed defecation, those who had undergone an operation. This was published by our group in 2006.

On further analysis, we found that those with anismus had a good outcome in about 30% of cases, whereas those without anismus had good outcomes in about 80% of cases. Those with psychological problems and those without had the same figures.

We hypothesized that the so-called hidden functional or organic lesions might have a pivotal role in determining the outcome of surgery for obstructed defecation.

We made a prospective study, 100 patients, where we searched out a large array of symptoms which we then analysed. We found that all of the 100 patients had at least two occult disorders. We assessed the percentages of those occult disorders, psychological disorders, anismus, rectal hyposensation, enterocele etc. and published the results in the Journal of Colorectal Diseases 2007[1] which has been referenced by the authors Goeschen and Gold.

I agree with the authors that patients tend to present with a singular symptom but many other symptoms are almost invariably present, hidden, like an iceberg, below the surface of the water. These other symptoms must be elicited by specific questioning, as we did in our 2007 work.

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**Original article**

# The Bornstein Test- a local anaesthetic technique for testing uterosacral nerve plexus origins of chronic pelvic pain

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*Abstract:* The Bornstein Test to check for origin of chronic pelvic pain was first applied in 2005 to challenge the hypothesis that the causation of vulvodynia may not be from the vulva itself, but from laxity in the uterosacral ligaments. It has been subsequently successfully applied to patients with Interstitial Cystitis. *The Bornstein local anesthetic (LA) test technique:* The lower half of a bivalve speculum is inserted into the vagina. The cervix or hysterectomy scar are visualized, gently grasped with an Allis forceps then gently stretched towards the introitus. The USLs are located by digital palpation. A 21 gauge needle attached to a 10ml syringe loaded with 1% xylocaine is inserted through the vaginal mucosa to a depth of 1.5 cm at 4 and 8 o'clock in a position just lateral to the uterosacral ligaments (USLs). 5 ml of 1% xylocaine are injected on each side. After the elapse of 5 minutes, the patient is checked to see if sensitivity is relieved. *Conclusions:* The Bornstein Test is a valuable clinical and research tool for assessing whether chronic pelvic pain has its origins in the nerve plexuses of the uterosacral ligaments.

*Key words:* Bornstein Test; Vulvodynia; Interstitial cystitis.

## INTRODUCTION

In 2004, 3 patients aged 45, 45 and 47 years of age presented with localized provoked vulvodynia (LPV, Vestibulitis, Vestibulodynia, confirmed by Q-tip testing), chronic pelvic pain and other 'posterior fornix syndrome symptoms, nocturia, urgency, frequency, abnormal emptying, Table 1[1]. The pain in all 3 patients was consistent with the 1996 description[2].

"*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 ,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*[2]".

Besides pain, the 3 patients had other manifestations of the Posterior Fornix syndrome, nocturia, urge incontinence, emptying difficulties, frequency, Table 1. These symptoms occur in predictable groupings and all can be cured or improved by reinforcing the uterosacral ligaments.

The three vulvodynia patients each had a posterior sling placement and were discharged the day of or day after surgery. The vulvodynia was cured in all 3 patients in the 3 months follow up examination[1].

*The hypothesis*. Based on these data[1], we hypothesized that vulvodynia was part of the chronic pelvic pain complex described in 1996[2], in turn due to laxity in the uterosacral ligaments causing the Frankenhauser and Sacral plexuses to fire off and cause referred pain to the perineum.

### *The Bornstein Test- testing the hypothesis of USL origin of vulvodynia*

The hypothesis was tested in Nahariya, Israel by Professor Bornstein's team[3]. It was reasoned, that if this hypothesis was valid, injection of local anesthetic into the USLs would abate the pain.

Two cc of 2% Xylocaine was injected into each one of the uterosacral ligaments, at the posterior fornix of the vagina of 10 consecutive patients diagnosed with localized provoked vulvodynia.

These women had been referred to the Nahariya vulvar clinic for extreme dyspareunia, lasting one to eight years, preventing them from experiencing intercourse. Their age ranged between 18 and 51, parity, 0 to 4. They had not been treated specifically for that condition so far.

Local conditions such as vulvovaginal candidiasis, vaginitis or dermatosis had been ruled out in all of them by colposcopy and wet mount microscopic examinations. All were diagnosed with Vulvar Vestibulitis according to the Friedrich's criteria, involving gentle touching the vestibule by a Q-tip in foci around the introitus and external urethral meatus.

The 10 patients were retested five minutes after the LA injection. Eight patients reported complete disappearance of introital sensitivity, by two separate examiners. In the other two patients, direct testing confirmed that the allodynia (exaggerated sensitivity) had disappeared on one side, but remained on the other side. Retesting the patients after 30 and 60 minutes showed that the blocking effects disappeared after 30 minutes.

The short-term disappearance of introital pain especially on one side was an important step in further substantiating the hypothesis that Vulvar Vestibulitis may be a referred pain originating from the inability of weakened uterosacral ligaments to support the nerves running along these ligaments. Based on the findings of that study, the new 2015 consensus terminology of vulvar pain and vulvodynia included "Structural defect" as a potential factor associated with vulvodynia[4].

### *Analysis*

The somatic nerve supply to the vulva is via the pudendal nerve exiting from Alcock's canal. We believe that the mechanism for cure as reported for vulvodynia is that the now retensioned USLs can better support the nerve ganglia and prevent them firing off whatever the stimulus, pressure on the nerves during intercourse, stretched by the gravity etc.

The hypothesis has been criticized on the basis that vulvodynia is a visceral nerve pain, sympathetic or parasympathetic and that the LA injection merely blocked afferent transmission of these nerves. However, this criticism fails in one key respect: these vulvodynia patients were cured by USL repair, an observation confirmed subsequently by many other authors (personal communication Dr Gold Australia, Dr Gunnemann and Dr Liedl Germany) and in a previous study[1].

TABLE 1. Outcome of Posterior Intravaginal Slingplasty

| Patient No | Test occasion | Symptom change with treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Entry Dyspareunia | Nocturia times/night | frequency times/day | Urge incontinence times/day | Pelvic pain | Emptying difficulties |
| **1** | Preoperative | Yes | 5 | 10 | 5 | Yes | Yes |
| | Post.op | No | 3 | 8 | 0 | Cured | Improved |
| **2** | Preoperative | Yes | 8 | >20 | 3-5 | Yes | Yes |
| | Post.op | No | 3 | 5 | 0 | Cured | Cured |
| **3** | Preoperative | Yes | 5 | 12 | 1-2 | Yes | Yes |
| | Post-op | No | 0 | 6 | 0 | Cured | Cured |

*Rationale for application of the Bornstein Test to Intersititial Cystitis (IC) patients*

The pathways from the bladder stretch receptors to the sensory nerves include TRPs (transient receptor potential channels), Calcium ion permeable cation channels. TRP channels function as multifunctional sensors at a cellular level. They can be activated by heat, cold, mechanical stress, and by altered pH and osmolality[5]. (Everaerts et al 2008).

The sensory nerves supplying the bladder are either thin myelinated A-delta fibres, or unmyelinated C-fibres. A-delta fibres constitute the afferent limb of the micturition reflex. These remain silent until a volume threshold is reached.

They may become more sensitive in the presence of inflammatory states.

Unmyelinated C-fibres are not normally mechanosensitive, but according to Wyndaele et al. 2008[6], may become so during inflammation, unmasking a new afferent pathway to express urge and pain symptoms experienced at low bladder volume. It is known that bladder afferents travel via S2-4 (parasympathetic) or via the hypogastric plexus T11-12 (sympathetic).

In a group of 408 patients, Butrick et al reported findings on 4 equal groups[7]: Interstitial Cystitis (IC), Chronic Pelvic Pain, Vulvodynia/dyspareunia and "Other". They found a high rate of complaints of voiding dysfunction, dyspareunia, pain, urgency, frequency[7]. These are classical manifestations of the Posterior Fornix Syndrome[8].

*Analysis*

It was hypothesized from these data that IC may be an extension of the posterior fornix syndrome with its origins not in the bladder, but in the unsupported nerve plexuses of the USLs.

*Application of Bornstein Test to patients with Interstitial Cystitis*

In 2009, the Bornstein Test was applied to 3 IC patients in Italy[8]. The aim was to directly test the hypothesis that painful bladder syndrome/interstitial cystitis may be a referred pain from the uterosacral ligaments.

All 3 patients had a history of glomerulation formation observed by cystoscopy during bladder distension. The aim of the intervention, to see if their bladder pain originated from lax uterosacral ligaments, was explained to the patients prior to the injection. It was also carefully explained that the local anaesthetic injection would cause very minimal pain, as the innervation of that part of the vagina was by visceral nerves, which were almost insensitive to needle penetration.

It was found that the abdominal, urethral, introital and cervical tenderness and pain which were demonstrated objectively in all 3 patients immediately before the intervention, disappeared entirely, or were substantially improved, within 5 minutes of the injection.

**Mrs GP, aged 42 years**, para 2, had an 8 year history of chronic bladder and abdominal pain, and dyspareunia. She had typical symptoms of the posterior fornix syndrome, nocturia x2 per night, urgency (but no incontinence) and abnormal bladder emptying. When assessed she was complaining of low abdominal and bladder pain.

On examination she had tenderness in the centre and right hand side of her lower abdomen, extreme sensitivity at the introitus during assessment with a Q-tip, and tenderness on palpating the urethra and also, the cervix. Within 5 minutes of the injection, her central pain had moved from a VAS (visual analogue scale) of 8 to 0, and her right-sided pain from a VAS of 9 to 4. Her vestibular hypersensitivity, suburethral tenderness, and cervical excitation pain had all disappeared. There was only 1st degree prolapse on speculum examination, with separation of the uterosacral ligaments.

**Mrs AA aged 51 years**, para 2, had a 10 year history of chronic bladder pain, left-sided abdominal pain, and dyspareunia. She had typical symptoms of the posterior fornix syndrome, nocturia x3-8 per night, urgency (but no incontinence) and abnormal bladder emptying. On examination she had tenderness on the left side of her lower abdomen, extreme sensitivity on palpating the urethra and the cervix and introital sensitivity. Within 5 minutes of the injection, her left sided pain had moved from a VAS) of 9 to 0. Her suburethral tenderness, and cervical excitation pain had all disappeared. On speculum examination, there was separation of the uterosacral ligaments, but no obvious uterine prolapse.

**Mrs ML aged 40 years**, para 2, had undergone a hysterectomy 5 years earlier, and presented with left-sided pain, bladder tenderness, vulvodynia, which had worsened over the past 2 years. She also had nocturia x2 per night, hourly frequency, urgency (but no incontinence). On testing, she had hypersensitivity only on the left side of her introitus, and tenderness over the lower left side of her abdomen and vaginal fornix. Following the local anaesthetic injection, her left-sided pain decreased by an estimated 40% on a VAS scale. The suburethral tenderness, introital sensitivity, vaginal fornix tenderness found pre-intervention all decreased to zero on a VAS scale.

*Analysis*

Though only 3 IC patients were tested, the association of painful bladder syndrome/interstitial cystitis, localized provoked vulvodynia, lower abdominal pain, nocturia, urgency and abnormal emptying symptoms suggests a possible link with previous studies, where such symptoms improved following surgical tensioning of the uterosacral ligaments. The hypothesis concerning IC patients awaits this crucial test, cure or improvement by repair of the uterosacral ligaments.

## CONCLUSIONS

The Bornstein Test is a valuable clinical and research tool for assessing whether chronic pelvic pain has its origins in the nerve plexuses of the uterosacral ligaments. Application of the test will be required across all pelvic pain manifestations if the general theory of USL nerve ganglion origin for chronic pelvic pain is to be validated. Following that, whether the test can serve as an effective predictor of surgical success by USL reinforcement.

*Conflicts*. none

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**Original article**

# Micronized palmitoylethanolamide reduces bladder chronic pelvic pain due to different etiologies and improves bladder functions

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*Abstract:* Chronic pelvic pain (CPP) is a common condition among women of reproductive age. It frequently co-occurs with other pelvic and extra-pelvic pain conditions, including immunologic disorders. The co-occurrence of immunologic hyperstimulation and diffuse mast cell activation might have a negative impact on the progression of CPP diseases and also influence outcome of therapeutic treatment. The aim of this study is to assess the effect of micronized palmitoylethanolamide (m-PEA), an N-acylethanolamine known to modulate mast cell activity, on bladder pain and bladder functions in patients with CPP with and without concomitant allergy. Bladder pain was evaluated using the visual analog scale, while functional bladder capacity, daily frequency and nocturia were obtained from bladder diary and uroflometry. The presence of allergy did not change pain intensity mean scores. Average pain intensity score significantly decreased with m-PEA adjuvant therapy. The functional bladder capacity was lower while daily frequency and nocturia were higher in CPP patients with allergy. Functional bladder capacity increased while daily frequency and nocturia decreased after m-PEA adjuvant therapy in both CPP patients with and without allergy. The quality of life (12-item Short Form Health Survey) was not modified by allergy co-occurrence. m-PEA treatment improved the quality of life and physical and mental components in CPP patients with and without allergy. These results support the hypothesis of an important role of mast cell activation in symptomatology and organ functionality in CPP patients and confirm the ability of m-PEA to reduce CPP and limit pelvic disease progression by controlling mast cell activation.

*Keywords:* Chronic pelvic pain; Micronized palmitoylethanolamide; Mast cells; Allergy; Bladder dysfunctions.

## INTRODUCTION

Chronic pelvic pain (CPP) involves up to 38% of all women ages from 15 and 73 years. In United Kingdom and United States up to 24% of all women of reproductive age are affected by CPP. Its incidence is higher than other common disorders such as headache, asthma and low back pain (incidence of 2.1%, 3.7% and 4.1%, respectively)[1-3]. CPP seems to have multifactorial etiology involving the urogynaecologic, gastroenteric, musculoskeletal, and nervous systems. Indeed, CPP in women is often related with different chronic pelvic painful conditions, such as interstitial, post-radiotherapy and recurrent cystitis, irritable bowel syndrome, gynaecologycal disorder and extra-pelvic painful conditions: fibromyalgia, headache, temporomandibular disorder, and chronic fatigue syndrome[4]. Moreover, there is strong evidence for the involvement of peripheral somatosensory alterations in pelvic structures that are sources of pelvic pain, including the sprouting of new fibers and peripheral sensitization[4]. Central sensitization pain mechanisms as well as other spinal and encephalic changes in areas devoted to pain transmission and elaboration have also be described, confirming the intricacies involved and suggesting these alterations might be connected with cognitive and emotional processes in pain processing in CPP disorders[5,6]. This central hypersensitivity explains the chronic pain in the absence of detectable peripheral pathology and the discrepancy between the magnitude of tissue damage and pain and disability in CPP syndrome[7].

It is also relevant that conditions associated with mast cell activation (allergies, asthma, atopy, food intolerances and autoimmune diseases) co-occur with high frequency in CPP[8]. On the other hand, all conditions associated with CPP are characterized by an altered density of mast cells in pelvic tissues as well as a their shift from quiescent to activated phenotype[9]. This evidence suggests that inappropriate mast cell activation may represent an underlying unifying mechanism in all these conditions, and proposed as the basis of modern epidemic noninfectious inflammatory disorders[8].

Since inappropriate mast cell activation may result in both local and/or central neuroimmune dysfunctions leading to peripheral and/or central sensitization, its pharmacological control could limit progression of inflammatory processes, reduce chronic pain and improve organ functions. In this regard, N-acylethanolamines are endogenous lipid mediators able to promote the resolution of inflammation and restore tissue homeostasis. Among N-acylethanolamines, palmitoylethanolamide (PEA), an endogenous fatty acid amide congener of the endocannabinoid anandamide, has been reported to reduce pain behaviors, and to inhibit somatosensory activation and correlated events in different models of pelvic inflammation[9,10]. Importantly, in a standardized rat model of viscerovisceral hyperalgesia obtained with induction of endometriosis plus ureteral calculosis (which closely mimics the clinical condition in comorbid women), prolonged oral treatment with ultramicronized PEA (um-PEA) significantly reduced the behavioral indices of uterine and ureteral pain, along with a reduction in cyst diameter. These effects were associated with a significantly lower mast cell number and the mast cell algogenic markers chymase and nerve growth factor in cysts and dorsal root ganglia, suggesting that um-PEA reduces viscerovisceral hyperalgesia by modulating mast cell activation. In a murine model, PEA protected against 2,4-dinitrofluorobenzene-induced keratinocyte inflammation, proposing its therapeutic use against contact allergic dermatitis[11].

Products based on micronized- (m-) and um-PEA have also been reported to reduce CPP in patients with different pelvic conditions such as endometriosis[12-14] primary dysmenorrhea[15] and vulvodynia[16,17]. This evidence prompted us to assess the efficacy m-PEA in patients with CPP due to different conditions with or without allergy.

## MATERIAL AND METHODS

In our referral center (Urology Division, G. Fornaroli Hospital Magenta- Milan, Italy), from January 2011 to December 2012, 75 female patients affected by CPP due to interstitial cystitis/bladder pain syndrome (BPS/IC) and CPP due to other conditions, with or without allergic history, were enrolled in this study. All patients displayed long-lasting irritative bladder symptoms, including bladder pain, urgency, daytime frequency of six or more episodes, nocturia and pain in the perineum, lower abdomen, lower back or vagina for at least six months. Inclusion criteria were: age >18 years, ability to read, understand and fill a bladder diary, presence of pelvic chronic pain, and pain intensity score ≥4 evaluated using the visual analog scale (VAS). Exclusion criteria were: bacterial cystitis demonstrated by urinoculture, previous pelvic radiotherapy or chemotherapy, history or presence of cancer, neurologic bladder or neuro-psychiatric disorder, bladder or ureteral stones, post-voiding residual >150 cc.

According to inclusion and exclusion criteria, all patients received, beyond standard therapy according to good clinical practice and international guidelines, m-PEA treatment (Normast, Epitech Group SpA) at dose of 300 mg, 2 tablets daily for 1 month, followed by 1 table/day for 2 months.

Pain intensity score was assessed by VAS: a 10 cm long line, with the leftmost side representing 0 (no pain) and the rightmost side representing 10 (unbearable pain). The participants marked their current level of pain on the scale after normal daily activities. All patients had uroflow (UFM) with post voiding residual (PVR). All patients were evaluated 3 times. The pretreatment visit (baseline V0): for all patients comprised an anamnestic evaluation, clinical examination and metabolic features recorded in a data base. All patients received VAS evaluation, Short Form Health Survey (SF12) questionnaire to evaluate quality of life, UFM+PVR and voiding diary. After initiation of m-PEA treatment, patients underwent follow-ups at 30 (V1) and 90 (V2) days.

Visit at 30 (V1) and 90 (V2) days: All patients received VAS evaluation, SF12 questionnaire to evaluate quality of life, UFM+PVR and voiding diary. SF12 measures eight domains of health: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations and mental health. This yielded a total score regarding mental health and physical health. Higher scores indicate a better quality of life.

All patients were properly informed about the study. The study was carried out in accordance with Declaration of Helsinki and Good Clinical Practice Guidelines.

### *Statistical analysis*

This study used the SAS system (SAS 9.2 System for Windows, SAS Institute, Cary, NC, USA) to conduct all statistical analyses. The results obtained by evaluating VAS pain intensity score, mental health and physical health total scores of SF12 questionnaire, bladder capacity, urinary frequency and nocturia were analyzed using the GLMM (Generalized Linear Mixed Model) in order to evaluate mean changes across m-PEA treatment time. m-PEA treatment time, presence of allergy, presence of concomitant disease were used as covariates. Data are expressed as mean ± standard error (SE), if not otherwise stated. Results are considered significant for p values less than 0.05.

## RESULTS

All patients were compliant with treatment. The patient's age ranged from 18 to 75 years. The duration of CPP ranged from 2 to 20 years. Fifty-five of the 75 patients (73%) had one or more forms of allergy, including those of the respiratory tract and food-related. Among CPP allergic patients, 25 (45%) were affected by IC/PBS and 30 (54%) presented other forms of CPP derived from urethral syndrome, suprapubic pain, coccydynia, perineal pain, recto-ulcerative colitis, irritable bowel syndrome and vulvodynia. In addition to CPP and allergies, 24 patients (32%) displayed other painful pelvic or extra-pelvic conditions. Twenty CPP patients (27%) had no form of allergy; of these last group, 5 (25%) had other painful pelvic or extra-pelvic conditions.

Average pain intensity score decreased from 8.4 ± 0.3 at baseline to 2.9 ± 0.2 at 90 days, and from 8.7 ± 0.2 to 2.1 ± 0.2 with m-PEA adjuvant therapy in CPP patients without and with concomitant allergy, respectively. This reduction in mean score was highly significant (p=0.0001). The presence of allergy did not change pain intensity score at all times analyzed (p<0.6966). However, the time trend was influenced by allergy presence, i.e. a constant and progressive score reduction was observed in CPP + allergy patients while a slower reduction in CPP patients was observed after the first month of treatment (p<0.0010) (Figure 1).

Functional bladder capacity was evaluated by measuring the mean voided volume recorded on a bladder diary and UFM. Functional bladder capacity at baseline was 155.00 ± 17 ml in CPP patients without concomitant allergy and

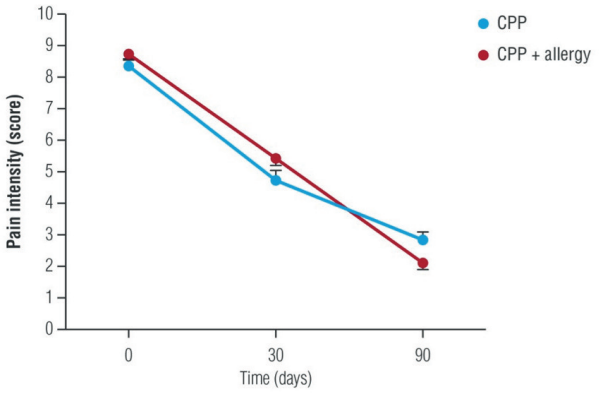


Figure 1. – Effect of m-PEA addition on pain intensity scores in CPP patients undergoing therapy, with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups pain intensity score decreases with m-PEA treatment over time: p<0.0001.

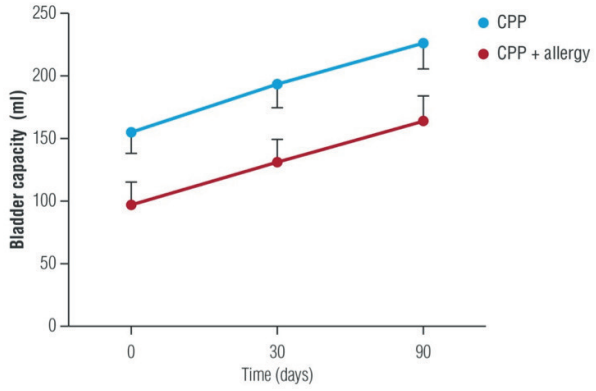


Figure 2. – Effect of m-PEA addition on bladder capacity in CPP patients undergoing therapy and with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups the bladder capacity increased with m-PEA treatment over time (p<0.0001) with the same time trend (p<0.7921).

TABLE 1. Effect of m-PEA addition on physical health (PCS12) and mental health (MCS12) in patients with CPP with or without concomitant allergy. Data are expressed as means +/- SE; n = 20 for CPP and 55 for CPP + allergy.

| Time (days) | | 0 | 90 | p |
|---|---|---|---|---|
| PCS12 | CPP | 41.1 ± 1.7 | 44.3 ± 1.5 | < 0.0001 |
| | CPP + allergy | 42.1 ± 1.0 | 46.6 ± 0.5 | |
| MCS12 | CPP | 39.1 ± 2.1 | 45.9 ± 1.9 | < 0.0001 |
| | CPP + allergy | 37.1 ± 1.0 | 43.8± 0.89 | |

98.00 ± 6 in CPP patients with allergy (Figure 2). In both groups, functional bladder capacity increased at 30 and 90 days after m-PEA adjuvant therapy, rising from 155.00 ± 17 ml to 193.50 ± 19 and 226.00 ± 20, respectively, in CPP patients without allergy (p<0.0001), and from 98.00 ± 6 to 130.36 ± 9 and 163.45 ± 10 in CPP patients with allergy (p<0.0001). In CPP + allergy functional bladder capacity was lower at all times analyzed (p<0.0006) while the time trend after m-PEA therapy was not influenced (p<0.7921) (Figure 2).

The urinary daily frequency and nocturia in CPP patients with and without allergy at baseline and after m-PEA therapy are reported in Figure 3. Daily frequency was 8.4 ± 0.3 at baseline in CPP patients and was reduced to 7.0 ± 0.3 following 90 days of m-PEA therapy (p<0.0001). A similar reduction in daily frequency was observed in CPP + allergy patients: mean value at baseline of 11.3 ± 0.5 decreased to 8.7 at 90 days after m-PEA therapy (p<0.0001). Daily frequency was higher at all times analyzed in CPP + allergy patients (p<0.0011). The presence of allergy modified the time trend after m-PEA therapy (p<0.0142). Nocturia was 2.9 ± 0.4 at baseline in CPP patients and decreased to 1.8 ± 0.3 after 90 days of m-PEA therapy (p<0.0001). A similar reduction in nocturia was observed in CPP + allergy patients: baseline mean value of 4.5 ± 0.2 decreased to 3.1 ± 0.2 at 90 days after m-PEA therapy (p<0.0001). Nocturia was higher at all times analyzed in CPP + allergy patients (p<0.0002). The presence of allergy did not modify the time trend after m-PEA therapy (p<0.2265) (Figure 3).

The impact of CPP on quality of life was not modified by allergy co-occurrence, as demonstrated by p<0.2613 for physical health (PCS12) and p<0.2236 for mental health (MCS12). An improvement of quality of life was observed in both CPP patients with and without allergy (p<0.0001 for both groups) (Table 1).

## DISCUSSION

CPP is frequently associated with diseases characterized by mast cell activation such as allergies, asthma, atopy, food intolerances and autoimmune diseases[5]. The concomitant occurrence of allergy or syndromes characterized by mast cell activation may have a negative impact on the progression of diseases associated with CPP and may also influence the outcome of therapeutic treatment. The present clearly shows that the bladder functional parameters, e. g. daily frequency and nocturia as well as bladder capacity, are compromised by the presence of allergy. In fact, at all times analyzed bladder capacity was lower and daily frequency and nocturia higher in CPP with concomitant allergy compared to patients with CPP alone. This result might in part be due to the presence of a high number of patients affected by IC/PBS in the CPP + allergy (25/55) group. However, the differences remained also when IC/PBS patients were excluded from the analysis, suggesting that the occurrence of allergy might directly affect bladder functions. In support of this hypothesis, bladder symptoms of frequency, urgency and pelvic pain in a patient with asthma and allergic rhinitis was subsided after anti-IgE therapy and specific immunotherapy with omalizumab[18,19]. These findings further support the involvement of mast cell activation in CPP conditions, particularly those associated with bladder dysfunctions. There is general agreement that mast cells play an important role in pain syndromes and, in particular, in BPS/IC, as they participate early in disease development in nociceptive pain, e.g., by sensitization of nerve fibers. Yet, little is known about mast cell activation and organ function where mast cell activation is dysfunctional. Our findings suggest that mast cell activation might significantly worsened organ function while continuing to perpetuate both acute and chronic pain.

In the present analysis, pain intensity did not seem to be worse in CPP patients with allergy. However, at baseline in both groups pain intensity was near the maximal value, suggestive of severe pain. Also the quality of life, both in physical and mental health terms, was not affected by the co-occurrence of allergy.

Notably, addition of m-PEA evoked a significant reduction of pain intensity and improved bladder functional parameters as well as quality of life in CPP patients with and without concomitant allergy. The m-PEA-induced reduction in pain intensity and improvement of daily frequency was similar in patients with and without allergy, although different response trends could lead one to hypothesize that subjects with allergy achieve more benefit.

The m-PEA-induced pain intensity reduction confirms the ability of the micronized PEA formulation to exert pain-reducing effects in chronic conditions affecting pelvic organs. This action of m-PEA has been reported in patients with chronic pain associated to endometriosis[12-14], perineal pain[20], vulvodynia[17], and irritable bowel syndrome. However, here we provide the first evidence specifically for chronic bladder pain. This finding is particularly relevant for patients affected by IC/PBS, since this group represents one-third of all patients analyzed in the current observational study. Importantly, in addition to providing pain relief m-PEA treatment led to an improvement in bladder functions. Worsening of bladder capacity along with daily frequency and nocturia in CPP patients greatly contribute to the progressive decline in quality of life. The ability ofm-PEA to reduce pain and bladder dysfunctions throughout

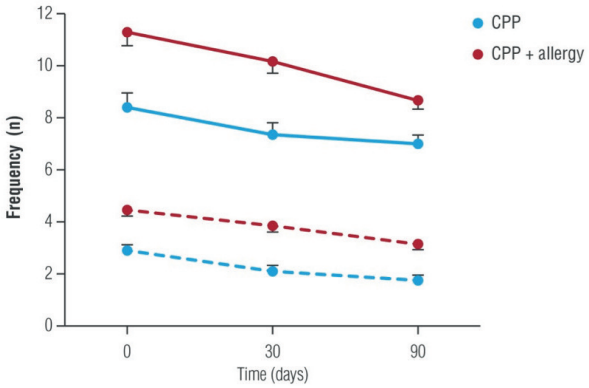


Figure 3. – Effect of m-PEA addition on daily frequency (solid line) and nocturia (dashed line) in CPP patients undergoing therapy and with or without concomitant allergy. Data are expressed as means ± SE; n = 20 for CPP and 55 for CPP + allergy. Note that in both groups the daily frequency and nocturia decreased with m-PEA treatment over time (p<0.0001, both groups). The time trend after m-PEA therapy was modified by allergy co-occurrence in the case of daily frequency (p<0.0142) but not for nocturia (p<0.2265).

the treatment period supports a disease-modifying action of the NAE, as observed in other conditions associated to chronic pain[21]. In chronic models of pain, PEA not only prevents pain threshold alterations, but also preserves nerve morphology spares from nerve degeneration[22,23]. In these studies, the neuroprotective effect of PEA was associated with a limited recruitment and activation of immune cells in the nerve as well as a reduced activation of spinal cord glia. Conceivably, in CPP associated with bladder dysfunctions, m-PEA might promote recovery of damaged tissues by facilitating resolution of inflammatory processes and allowing for improved organ functions. This view is supported by evidence showing that um-PEA attenuated pain behavior, voids and gross bladder damage in an experimental model of cystitis[24].

m-PEA was efficacious in CPP patients with and without concomitant allergy. However, the m-PEA-induced reduction of pain intensity and improvement of daily frequency was slight but significantly higher in CPP patients with allergy. This finding might be related to ability of m-PEA to directly act both on mast cell activation-mediated pelvic organ dysfunctions and mast cell activation mediated-allergic processes. The current study is one of the very few in this area, at the same time, caveats include the non-homogeneity of patients at baseline and absence of a control group.

In conclusion, the results obtained underscore the potential benefit of m-PEA in patients with CPP, especially in subjects with allergy - thus supporting the proposed importance of mast cell activation in modern epidemic non-infectious inflammatory disorders. Clearly, the present data need to be confirmed in a placebo-controlled, double-blind clinical study. Even so, these results suggest that the control of mast cell activation with m-PEA might represent a novel opportunity to reduce CPP and limit the progression of pelvic diseases.

## DISCLOSURES

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## Comment

The theme of this chronic pelvic pain (CPP) issue is largely anatomical, the role of loose uterosacral ligaments unable to support the Frankenhauser nerve plexus and treatment thereof by some thype of ligament repair operation. Sekiguchi et al. (this issue) achieved a 79% cure/improvement rate with TFS cardinal/uterosacral repair. This is historically a fairly optimal result for this type of surgery. All of which raises the question, 'what about the other 21% of patients? Was there some other cause? How many of these patients had the 'other etiologies' referenced by Somamriva et al.? Sommariva et al give statistically valid evidence of significant improvement in CPP. Average pain intensity score decreased from 8.4 ± 0.3 at baseline to 2.9 ± 0.2 at 90 days, and from 8.7 ± 0.2 to 2.1 ± 0.2 with m-PEA adjuvant therapy in CPP patients without and with concomitant allergy, respectively.

These results need to be seen in the context of symptom variation. There is a wide variation in how patients experience pain symptoms, from fairly minor to very severe requiring emergency hospital admission[1,2].

So it is not so much that the palmitoylethanolamide treatment more than halves the pain intensity. It can reduce it to a tolerable level, perhaps reducing or even preventing the hospital admissions required with severe episodes of pain.

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