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Non-Hunner's Interstitial Cystitis Is Different from Hunner's Interstitial Cystitis and May Be Curable by Uterosacral Ligament Repair

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Keywords
Interstitial cystitis · Posterior fornix syndrome · Chronic pelvic pain · Uterosacral ligaments · Urinary urgency

Abstract
Background: The posterior fornix syndrome (PFS) was first described in 1993 as a predictably occurring group of symptoms: chronic pelvic pain (CPP), urge, frequency, nocturia, emptying difficulties/urinary retention, caused by uterosacral ligament (USL) laxity, and cured by repair thereof. ***Summary:*** Our hypothesis was that non-Hunner's interstitial cystitis (IC) and PFS are substantially equivalent conditions. The primary objective was to determine if there was a causal relationship between IC and pelvic organ prolapse (POP). The secondary objective was to assess whether other pelvic symptoms were present in patients with POP-related IC and if so, which ones? How often did they occur? A retrospective study was performed in 198 women who presented with CPP, uterine/apical prolapse (varying degrees), and PFS symptoms, all of whom had been treated by posterior USL sling repair. We compared their PFS symptoms with known definitions of IC, CPP, and bladder symptoms. To check our hypothesis for truth or falsity, we used a validated questionnaire, "simulated operations" (mechanically supporting USLs with a vaginal speculum test to test for reduction of urge and pain), transperineal ultrasound and urodynamics. ***Key Messages:*** 198 patients had CPP and 313 had urinary symptoms which conformed to the definition for non-Hunner's IC. The cure rate after USL sling repair was CPP 74%, urge incontinence 80%, frequency 79.6%, abnormal emptying 53%, nocturia 79%, obstructive defecation 80%. Our findings seem to support our hypothesis that non-Hunner's IC and PFS may be similar conditions; also, non-Hunner IC/BPS may be a separate or lesser disease entity from "Hunner lesion disease". More rigorous scientific investigation, preferably by RCT, will be required.

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Introduction

According to the International Continence Society (ICS), genito-urinary pain syndromes are all chronic in their nature, with pain as the major complaint but with concomitant complaints of lower urinary tract, bowel,

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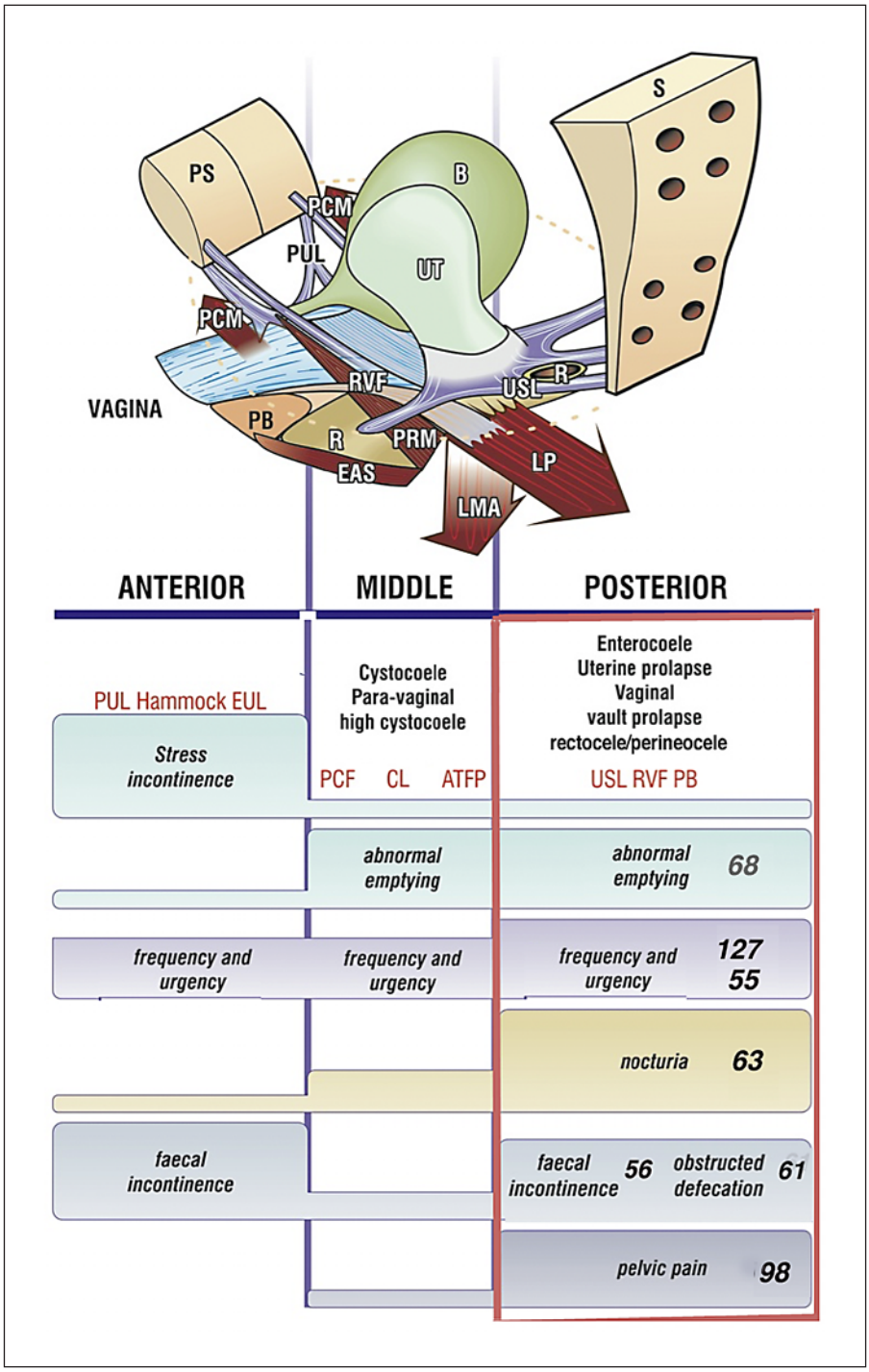

Fig. 1. Diagnostic algorithm. A "shorthand" diagnostic method where symptoms indicate which ligaments are causing which prolapse and which symptoms. The connective tissue structures fall naturally into 3 zones of causation. Ticking symptom occurrence diagnoses ligament defect and serves as a guide to surgery. For example, nocturia and pelvic pain are almost exclusively caused by "USL"; laxity; stress incontinence, by pubourethral laxity "PUL." We have entered quantum of symptoms in numbers instead of ticking the boxes. The conditions in all 3 columns are caused by ligament laxity. Only some conditions in the right column can be attributed to IC, as defined [2]. *Anterior zone* runs from external meatus to bladder neck, and comprises EUL (external urethral ligament); PUL (pubourethral ligament); and suburethral vaginal hammock. *Middle zone* runs from bladder neck to anterior cervical ring and comprises PCF (pubocervical fascia); CL (cardinal ligament); and ATFP (arcus tendineus fascia pelvis). *Posterior zone* runs from USL (uterosacral ligament); RVF (rectovaginal fascia); to PB (perineal body). The height of the bar indicates probability of causation.

sexual, or gynecological in nature [1]. The American Urological Society (AUA) defines interstitial cystitis (IC) as "*An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes*" [2]. The AUA stated it was not known whether IC/bladder pain syndrome (BPS) was a primary bladder disorder or whether the bladder symptoms of IC/BPS were secondary phenomena resulting from another cause and that IC/BPS might be "just a part of the continuum of painful versus nonpainful overactive bladder syndrome"

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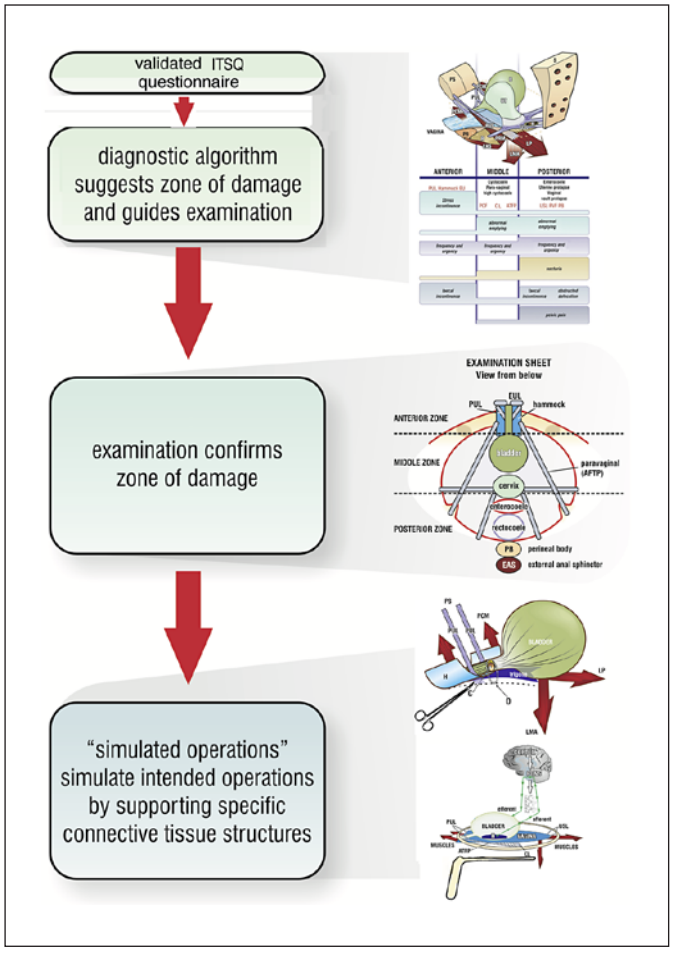

Fig. 2. Integral theory system diagnostic pathway-specific symptoms in the ITSQ questionnaire [8] indicate which ligaments/fascias may be damaged. The symptoms are transferred to the diagnostic algorithm; the diagnosis from the algorithm is checked by vaginal examination [6] to confirm specific ligament laxity; the causative ligaments are then checked by "simulated operations," i.e., mechanical support of pubourethral and uterosacral ligaments to observe change in symptoms.

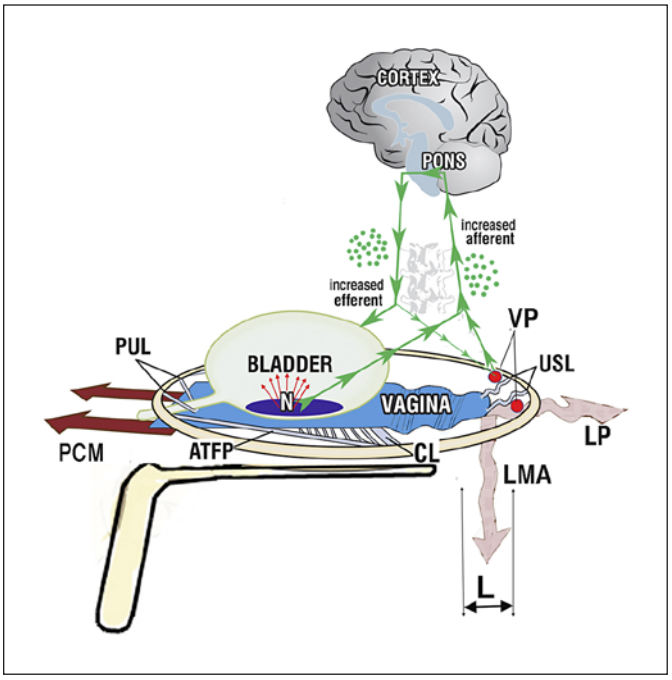

Fig. 3. "Simulated operation" to support uterosacral ligaments "USL." 3D view of PUL and USL attachments to the pelvic brim (circle). A gently inserted speculum mechanically supports USLs. "L" indicates USL laxity. Lax USLs (laxity indicated by wavy lines) cannot support the "VPs" and these fire of impulses to the cortex which are interpreted as pain. Wavy lines in the muscles LP and LMA which contract against USLs indicate weakened muscle forces, as a muscle requires a firm insertion USL point to exert optimal force. The wavy form of the vagina indicates looseness; it cannot be stretched sufficiently to support the urothelial stretch receptors "N" which now fire off excess afferents to activate the micturition reflex prematurely. The cortex interprets these impulses as "urge." The speculum mechanically supports USLs, "N" and stretches vagina to reverse the above processes; the patient reports lessening of pain and urge. LP, levator plate; LMA, conjoint longitudinal muscle of the anus.

[2]. Hunner's lesion, previously a hallmark of IC, is no longer considered essential for diagnosis. In 2018, the then president of the International Painful Bladder Foundation highlighted major gaps in the very concept of IC, its nomenclature, terminology, definitions, diagnostic criteria, and how all this was damaging for research, data sharing, and ultimately patient treatment [3].

The catalyst for this retrospective study was a recent case report of histologically validated cure of IC Hunner's ulcer [4] which was managed by a different paradigm, the posterior fornix syndrome (PFS). The finding of Hunner's ulcer and cure thereof was totally unexpected. The PFS was first described in 1993 [5]. It comprised predictably grouped symptoms of chronic pelvic pain (CPP) "of unknown origin," frequency, nocturia, urgency, abnormal emptying/retention, caused by uterosacral ligament (USL) laxity, Figure 1, cured or improved by repair thereof. The surgeon, Scheffler [4], emphasized he did not set out to cure IC. It was a serendipitous finding. His 73-year-old patient with uterine prolapse, cystocele, and typical PFS symptoms was managed according to the PFS protocols [6] (Fig. 1–3). The prolapses were cured by Tissue Fixation System (TFS) minisling repair of the cardinal ligament and USL) without vaginal excision [4].

We studied data from 198 women whose presenting symptom was chronic pelvic pain of "unknown origin" who were also treated by PFS protocols and also treated

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with a posterior USL sling [6], Figures 1–3. Our aim was to test whether non-Hunner IC as defined [2] was similar to PFS with the primary objective being to test whether there is a causal relationship between IC and POP; the secondary objective being to find other causally related symptoms; if so, which ones and how often were they present in patients with POP-related IC.

This work and its methodology were greatly influenced by conclusions from a recent review of "IC/BPS" by Ueda et al. [7], "*Despite the tremendous medical advances made by developing many testing modalities and biomarkers, there can be no successful treatment in the absence of an accurate diagnosis. Thus, there can be no bright future for IC/BPS without these 3 steps: (1) understanding the symptoms, (2) detecting abnormal findings in or outside the bladder, and (3) verifying that the abnormality is the cause of the symptoms.*"

Methods

This is a retrospective study of 198 patients, mean age 69 years (48–72), who presented with CPP between January 2009 and December 2012 to the Kvinno Center Hannover Germany. It was managed by the standard protocols for diagnosis and treatment of PFS, Figure 2: a self-administered validated ITSQ pelvic symptom questionnaire [8]; ITSQ answers were summarized to a Pictorial Diagnostic Algorithm, Figure 1, which also served as a guide to surgery.

Pre- and postoperative assessments and operations were conducted by the senior author (K.G.). Preoperative cystometry was performed in all patients, with residual urine determined by ultrasound. Vaginal examination assessed stage of prolapse, reproduction of pain by palpating the cervix [9] and specific ligament defects according to standard protocol [6, 10], Figure 2. "Simulated operations," which mechanically support the ligaments, confirmed symptom causation therefrom: SUI by unilateral hemostat support of pubourethral ligament (PUL) immediately behind the pubic symphysis video https://youtu.be/0UZuJtajCQU) and USL causation of urge and pain by the speculum test, Figure 3.

Inclusion criteria for surgery (Table 1) were CPP as previously described [8] plus some stage of uterine/apical prolapse identified [6], and tested, Figure 3. We found that the most severe pain was often associated with minimal prolapse. In order to confirm prolapse in women who had a positive speculum test, Figures 3, and no apparent prolapse, the anterior vaginal was lifted upward with a speculum and the patient was asked to strain down. Appearance of an enterocele confirmed USL laxity. *Exclusion criteria* were patients with known causes of CPP.

Ethics

The posterior sling surgical operation for prolapse and the PFS surgery had been approved a priori by the Ethics Committees of the Kvinno Center Hannover as a standard operating procedure. Written informed consent was obtained from all patients, and the principles of the Helsinki Declaration (2008) were followed.

Table 1. Prevalence (absolute and relative frequencies of the occurrence) of other pelvic symptoms by female patients revealing preoperatively CPP (n = 198)

Patients with CPP			
other pelvic symptoms	no hysterectomy n = 132 (100%)	hysterectomy n = 66 (100%)	Total n = 198
Frequency/urge, *n* (%)	81 (61)	46 (70)	127 (64)
Nocturia, *n* (%)	42 (32)	21 (32)	63 (32)
Bladder emptying, *n* (%)	40 (30)	28 (42)	68 (34)
Urge incontinence, *n* (%)	25 (19)	30 (45)	55 (28)
Stress incontinence, *n* (%)	40 (30)	26 (39)	66 (33)
ODS, *n* (%)	35 (27)	26 (39)	61 (31)
Fecal incontinence, *n* (%)	31 (23)	25 (38)	56 (28)

ODS, obstructed defecation.

Table 2. Patient characteristics at baseline

POP stage (Baden-Walker)	Stage 1	N = 15 (7.5%)
	Stage 2	N = 39 (19.5%)
	Stage 3	N = 107 (54%)
	Stage 4	N = 37 (19%)
Mean age, years	62	Range 43–93
Mean weight, kg	68	Range 52–113

Surgery

In all 198 patients, a posterior intravaginal sling-plasty according to Peter Petros [5] was performed with repair of all 3 levels following the surgical principles described by Petros [6]. Additionally, the tape was fixed to the sacrospinous ligament on both sides with a prolene suture using a special minimally invasive instrument. Levels 2 ("bridge" repair) and 3 (approximation of perineal bodies) were repaired as required. Patients with stress urinary incontinence (n = 66) had a suburethral transobturator sling. In cases of concomitant anterior wall prolapse (n = 96), the posterior IVS was combined with insertion of an anterior transobturator 4-arm mesh. The posterior ATOM arms were attached to the sacrospinous ligaments bilaterally as well.

Statistics

The sample size was chosen according to the period of 3 years: January 2009 to December 2012. Bias does not exist, and there are no missing data.

At 12-month follow-up, a full assessment was made using the self-administered ITS questionnaire, as well as vaginal examination. For pain and each of the coexistent disorders, differences in the prevalence rates before (baseline) and 12 months after surgery were tested about significance with the normal-distributed Z-statistic used approximately (instead of Fisher's test statistic) to test each time equality in the parameters of two binomial distributions.

Additionally, the odds ratios, their 95% confidence intervals (CIs), and the cure rates for the postoperative (12 months after surgery) compared to baseline symptom prevalence rates were cal-

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Table 3. Absolute and relative frequencies of the preoperative (2nd column) and postoperative (3rd column) incidences of other pelvic symptoms for patients revealing CPP (main symptom; *n* = 198) and cure rates 12 months after surgery

	Incidences before surgery, *n* (%)	Incidences 12 months after surgery, *n* (%)	Comparisons (pre- versus post-incidences) (*Z* values)	Odds ratios with 95% CIs (in brackets)	Cure rates 12 mo after surgery, %
Pelvic pain (*main symptom*)	**198** (**100**)	52 (26)	8.690***	n.d.	74.00
Urinary frequency	127 (64)	26 (13)	6.000***	0.085 [0.051; 0.140]	79.69
Nocturia	63 (32)	13 (7)	3.690**	0.151 [0.135; 0.493]	78.13
Bladder emptying difficulties	68 (34)	32 (16)	3.198**	0.369 [0.228; 0.595]	52.94
SUI	66 (33)	4 (2)	4.266***	0.041 [0.015; 0.116]	93.94
ODS	59 (30)	12 (6)	3.596**	0.152 [0.079; 0.294]	80.00
Urge incontinence	55 (28)	11 (6)	3.412**	0.153 [0.077; 0.303]	78.57
Residual urine > 50 mL	44 (22)	20 (10)	2.490*	0.393 [0.222; 0.696]	54.55

Moreover, the values of the approximatively normal-distributed *Z*-statistic used to test for each of the considered symptoms the null hypothesis of equal occurrence rates between baseline and 12-month follow-up period (exactly, Ho: $p_{baseline} = p_{12mo\ after}$) are depicted in the 4th column. The upper symbols "*," "**," and "***" indicate statistically less prevalence rate of a symptom in the follow-up period compared to baseline at the 0.01, 0.001, and 0.0001 level of significance, respectively

culated. *Note: The odds ratio also gives, in our case, the relationship of a risk for a symptom occurrence after surgery compared to baseline occurrence risk.*

Table 1 shows absolute and relative frequencies of the preoperative (2nd column) and postoperative (3rd column) incidences of other pelvic symptoms for patients revealing CPP (main symptom; *n* = 198). Moreover, the values of the approximatively normal-distributed *Z*-statistic used to test for each of the considered symptoms the null hypothesis of equal occurrence rates between baseline and 12-month follow-up period (exactly, Ho: $p_{baseline} = p_{12mo\ after}$) are depicted in the 4th column. The upper symbols "*," "**," and "***" indicate statistically less prevalence rate of a symptom in the follow-up period compared to baseline at the 0.01, 0.001, and 0.0001 level of significance, respectively.

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 (Tables 1, 2) who also had a total of 313 bladder symptoms, excluding SUI (*n* = 66). The Baden-Walker classification for POP was used pre- and postoperatively, apical stage 1: *n* = 15 (7.5%); stage 2: *n* = 39 (19.5%); stage 3: *n* = 107 (54%); stage 4: *n* = 37 (19%) (Table 2).

Symptom prevalences are indicated in Table 1 and Figure 2, algorithm. No patient had Hunner's ulcers. The % co-occurrence of bladder and bowel symptoms relevant to 198 CPP symptoms is summarized in Table 3. In the left column, no hysterectomy, a woman presenting with CPP has a 19–32% probability of bladder symptoms and 23–27% for bowel symptoms.

Mean operating time was 65 min (range 41–85 min). There was no serious bleeding, and no blood transfusion was required. Mean hospital stay was 5 days (range 2–9 days).

All patients were treated with 600 mg ibuprofen postoperatively every 6 h, and the following days if required. Serious complications such as rectal perforation, embolic problems, pyrexia did not occur. One urinary tract infection was observed within the first week after surgery. This patient was successfully treated with broad-spectrum antibiotics. There were no hematomas. Minor bruising was noted in 5 patients around the incision. In 6 patients, an indwelling catheter was required for 2–5 days, as 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 months, and 12 months after the operation by the senior author (KG). Symptom results are summarized in Table 3.

In the 5th and 6th columns, the odds ratios with 95%-CIs and the cure rates for each considered symptom when comparing the baseline with the 12-month follow-up period are seen. Interestingly, cure rates over 78% have turned out for four of the six considered other PFS symp-

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toms. Expectedly, the odds ratios for these symptoms were also very small (less than 0.153) indicating for any of them very low occurrence risk after surgery compared to the corresponding baseline occurrence risk. No significant differences in outcome were seen between women with or no hysterectomy (data not shown).

Anatomical assessment was at 3, 6, 12 months after the operation. Two (1%) patients with stage 3 POP developed a high stage 2 cystocele. Repair of the cystocele was successful at the 6-month review. No tape exposures were observed in any of the patients with the 12-month period.

Discussion

Based on AUA definitions [2], the data in Table 1 are consistent with the findings of Butrick [11] and go some way toward supporting our hypothesis that IC (as now defined) and PFS may be similar conditions. In the left column, no hysterectomy, the 198 women presenting with CPP had a 19–32% probability of co-occurring bladder symptoms.

Are Weak USLs the Pathogenic Endpoint of a PFS Symptom Continuum?

The posterior zone PFS symptoms (Fig. 1) are a concise summary of the PFS continuum: bladder/bowel/pain symptoms extend upward to encompass types of prolapse caused by USL laxity, enterocele, uterine/apical prolapse. Surgical data from Tables 3 and 4 and previously [12–20] show high cure rates for all PFS symptoms, posterior zone (Fig. 1).

How loose/damaged USLs can cause both CPP and urge, which is the actual AUA definition for IC [2], is summarized in Figure 3. Figure 3 also indicates how the hypothesized pathogenesis of both CPP and urge, USL laxity, can be directly tested. Figure 3 can also explain why IC and PFS patients often have a high incidence of bladder emptying symptoms [11] and why they can be cured by posterior slings [12–21]: lax USLs weaken the posterior vectors levator plate (LP)/ conjoint longitudinal muscle of the anus (LMA), which actively pull open the posterior urethral wall to facilitate detrusor emptying, so the detrusor has to expel the urine through a partly opened urethra. This is experienced by the patient as "obstructed micturition," which it is.

The ICS descriptions describe "concomitant complaints of lower urinary tract, bowel, sexual, or gynecological in nature" with CPP. We have been able to provide odds ratios for individual bladder and bowel symptoms co-occurring in 198 women who had CPP and, also, surgical cure thereof by a posterior IVS sling, Table 1. There was no Hunner's ulcer in any of the 198 patients.

Table 4. Similarities and discrepancies between IC symptoms and the PFS

IC (Butrick, *n* = 408)		
other observed symptoms	observed cases (abs. frq.)	cure rates after bladder installations (rel. frq.), %
Bladder pain/IC	157	0.00 NA
CPP	98	0.00 NA
Vulvodynia/dyspareunia	40	0.00 NA
Voiding dysfunction	70	0.00 NA
Dyspareunia	54	0.00 NA
SUI	24	0.00 NA
POP	21	0.00 NA
Hunner's ulcer	14	0.00 NA
PFS (Goeschen, *n* = 198)		
other observed symptoms	observed cases (abs. frq.)	cure rates after uterosacral sling (rel. frq.), %
Urge incontinence	55	80.00
CPP	198	74.00
Voiding dysfunction	68	54.00
Nocturia	63	79.00
SUI	66	95.00
POP	198	90.00
Hunner's ulcer	0	0.00

NA, not available

Our data are supported by other studies who had USL surgery using PFS protocols, Figures 1 and 2. Liedl et al. [12] in a multicenter trial of 611 women reported similar 12-month results using a TFS minisling sling, % cure in brackets: urge incontinence – *n* = 310 (85%); frequency – *n* = 317 (83%); nocturia – *n* = 254 (68%); CPP – *n* = 194 (77%); fecal incontinence – *n* = 93 (65%). Inoue's 5-year data in a 70-year-old group of 68 women have high long-term cure, with only minimal percentage deterioration [13].

Butrick et al. [11] described 408 patients which fitted the wider definition of IC. Only 18 of the 408 women had Hunner's ulcer. Butrick et al.'s [11] data is astounding in its similarity with manifestations of the PFS in this study, Table 4. Butrick warned that up to 10% of patients with more traditional urogynecologic disorders such as urinary incontinence and prolapse may also have BPS/IC and, in a personal communication with one of the authors (P.P.), stated "*If the patient had high tone dysfunction and*

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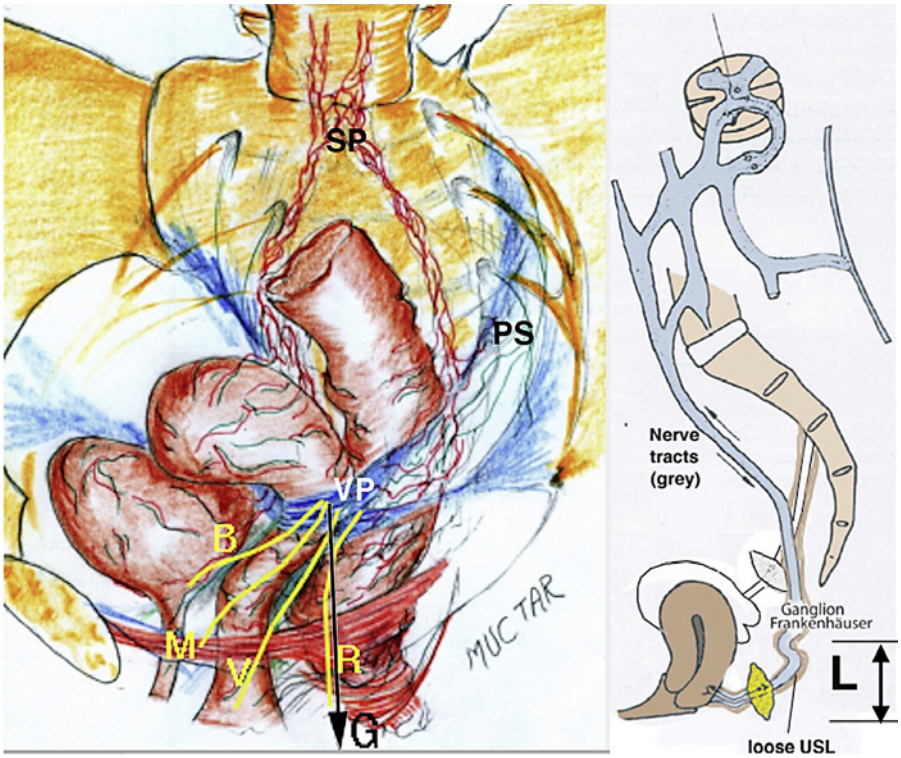

Fig. 4. Mechanism for CPP by stimulation of the VP. Left figure 3D view of organs and VP which serves as a type of "relay" for end organ afferents from bladder "B," lower abdominal and pelvic muscles "M," vagina/vulva "V," rectum "R." G = force of gravity which stimulates VP if they are not sufficiently supported by USLs. By permission S Muctar. Right figure 3D view showing pathways of impulses to and from the cortex (small arrows) via the hypogastric (Frankenhauser) plexus (T11-L2). And the effect of USL laxity "L."

pain as a result of her prolapse, then correcting the prolapse would resolve the pelvic floor dysfunction. This would result in a resolution of their BPS."

In his 2009 paper [11], Butrick described "irritable bowel syndrome" vulvodynia, bladder emptying problems, OAB, all consistent with our data, Table 1. Butrick's descriptions of "pelvic floor hypertonic pain" were viewed as equivalent to "paraurethral tenderness" described by Wu and Luo [21] which was relieved by the speculum test. The same pathogenesis, lax USLs, has been attributed as a cause of the urinary retention in Fowler's syndrome, relieved by TFS USL sling repair [14] where the high midurethral pressure (MUP) noted by Butrick et al. [11] was also observed, with return to normal MUP after cardinal/USL repair [14]. The high MUP was explained as a loss of balance between the opposite muscle forces, PCM anterior, and LP/LMA posterior, Figure 3, causing PCM to dominate [14]. A more normal urethral pressure was found following posterior USL sling surgery [14]. This was attributed to restoration of the balance of forces [14].

A Hypothesis for CPP/IC Pain Causation-Unsupported Visceral Plexus

Collective results of cure of CPP and OAB symptoms [12–21] and Table 3 support the pathogenesis of CPP from afferent visceral plexus (VP) axons, which, being unsupported because of weak USLs, fire off afferent impulses when stimulated by gravity or muscle movement [9], Figures 3 and 4. These impulses are interpreted by the brain as pain. Supporting this hypothesis of visceral nerve etiology, are the anatomical studies of Butler-Manuel who described the close anatomical support of the T11-L2 and parasympathetic S2-4 VPs by USLs [22]. These nerves carry afferent signals from the organ to the cortex and transmit efferent instructions. As we see this system working in normal situations, if there is an injury or infection at the end organ, afferent signals are sent to the brain via the VPs which then respond by sending signals to "sleeper cells" via the visceral efferent pathways (Fig. 4, thin arrows on the right); the "sleeper cells" secrete specific inflammatory cells such as mast cells and leukocytes [23] to "heal" the perceived injury or infection.

Our concept for IC and other pain causation in the absence of infection or injury is diagrammatically indicated in Figure 4 (left): unsupported VPs which contain afferent axons from various end organ sites, e.g., bladder "B," vagina/vulva "V," rectum "R," muscles "M" are stimulated by gravity or muscle movement to send signals to the brain via T11-L2 and S2-4 afferent visceral nerves. The brain (wrongly) interprets these signals as coming

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from the end organs and responds appropriately: it sends efferent signals to "sleeper cells" at the end organ which in the case of urothelium may create an inflammatory response sufficient to cause Hunner's ulcer. We hypothesize that the fragility of the urothelium makes it vulnerable to the more florid inflammatory response seen in ulcerating Hunner's ulcer and end-stage scarring, something not seen in the tissue inflammatory response seen with vulvodynia, which, like IC, exhibits inflammatory cells such as mast cells and leucocytes and neuroproliferation [23] but no redness [24].

Our data of 198 women with CPP and bladder symptoms but no Hunner's ulcer appear to support the statements of Ueda [25] and Fall et al. [26]: "*HIC with significant inflammation in the bladder is clinically and pathologically distinct from non-Hunner IC/BPS and may be categorized as a separate disease entity called 'Hunner lesion disease (HLD),' distinct from other BPS conditions.*" Looked at as an IC continuum, our non-Hunner data could equally be considered an early stage of the more severe manifestations of the inflammatory Ueda/Fall descriptions, with the deeply scarred bladders reported by Badlani and Moldwin [27], as an inflammatory endpoint.

Acknowledgment of Prior Discovery

Though we have elaborated it considerably, the concept of weak USLs unable to support the VPs as a cause of CPP is not new. It was first proposed by Heinrich Martius [28] from Gottingen, Germany, in 1938.

A New Direction for IC Studies?

It is our hope that this study will open new directions for IC studies. We have demonstrated that women with symptoms of BPS/IC as now defined [1, 2] are substantially equivalent to those with the PFS, which is surgically curable by USL sling surgery, Table 1. We respond below to the three Ueda statements [7] which inspired much of our methodology:

1. *understanding the symptoms.* We have provided anatomical pathogenesis for CPP frequency, urge, nocturia, emptying difficulties;
2. *detecting abnormal findings in or outside the bladder.* Our explanations are based on a very substantial body of knowledge [29, 30], which anatomically explains how the muscle/ligament control system, Figure 3, explains pathogenesis and cure.
3. *verifying that the abnormality is the cause of the symptoms."* We refer to the relief of preoperative symptoms, IC symptoms, in this study detailed in Table 1 and supported elsewhere [12–21].

Male IC Hypothesis

Similar clinical symptoms in males with a diagnosis of "chronic prostatitis" beg the question "Is there an analogous unsupported visceral nerve plexus cause in the male caused by a weak USL analogue?" Farag et al. [31] hypothesized this possibility in a recent discovery of a histologically validated male USL analogue in a laparoscopic study.

Conclusions

Our findings seem to support our hypothesis that non-Hunner's IC as defined by learned bodies and PFS may be similar conditions. Our findings also support recent proposals that non-Hunner IC/BPS may be a separate or lesser disease entity from "Hunner lesion disease". More rigorous scientific investigation, preferably by RCT, will be required to further test these hypotheses.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Klaus Goeschen: conceptualization, provision of data, writing, review, and checking. Darren M. Gold: conceptualization, writing, review, and checking. Bernhard Liedl: conceptualization, writing, review, and checking. Alexander Yassouridis: statistics and writing. Peter Petros: conceptualization, review and checking, and figures.

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