The Emerging Presence of Interstitial Cystitis in Gynecologic Patients with Chronic Pelvic Pain

Edward J. Stanford, Jeffrey R. Dell, and C. Lowell Parsons

Emerging data are changing the pelvic pain paradigm for gynecologic patients. Historically, interstitial cystitis (IC) was rarely considered as a cause of chronic pelvic pain (CPP), but recent data suggest that IC is a common cause of CPP in gynecologic patients and perhaps is even the most common cause. It is important to consider the bladder as a generator of symptoms early in the evaluation of the gynecologic patient with CPP. New tools have been developed to aid the gynecologist in ruling out IC in patients with CPP, including a new IC symptom questionnaire and the Potassium Sensitivity Test (PST). By determining whether the pain is of bladder origin, the physician can more successfully treat the patient with CPP. UROLOGY 69 (Suppl 4A): 53–59, 2007. © 2007 Elsevier Inc.

Although the true incidence of chronic pelvic pain (CPP) is unknown, CPP is estimated to affect >9 million women in the United States, with associated healthcare costs approaching $3 billion annually.[1] Women with CPP are often told that there is nothing that can be done for them or, worse, that there is not a clearly definable cause for their symptoms. It is not surprising that 12% of outpatient gynecologic referrals,[2] 10% to 12% of hysterectomies,[3] and approximately 40% of gynecologic laparoscopies are for CPP.[4] In clinical practice, it is common to encounter a patient with CPP who has seen several physicians from various medical and surgical specialties.

Until recently, the urinary bladder was not recognized as an important generator of pelvic pain, and interstitial cystitis (IC) was not often considered in the differential diagnosis of CPP. In patients with CPP it has been standard gynecologic practice to consider laparoscopy to confirm physical findings or to corroborate the patient's symptoms. Unfortunately, laparoscopy may not identify pathology in up to 35% of patients,[5] and it is often unclear whether the identifiable pathology—such as endometriosis, adhesions, ovarian cysts, pelvic congestion, or less common diagnoses—is the cause of the patient's CPP. Further, response to treatment, whether medical, surgical, or combined, is commonly followed by pain recurrence. Consequently, in many cases, these associated findings may obscure the true culprit, the urinary bladder, as the generator of symptoms. To add to the confusion in identifying the cause of CPP, a patient may ignore the symptoms of urgency and frequency, or may not perceive them to be part of the problem. As a result, she may never report these symptoms to her gynecologist. Furthermore, even if the patient does report them, the gynecologist may believe they arise from a gynecologic source.

Recent studies have demonstrated that CPP may be more commonly owing to pain of bladder origin, or IC, than to traditional gynecologic causes. In addition, patient evaluation for CPP is shifting from the hospital to the office setting. It is now possible to use simple office-based tools to detect the presence of IC in a patient with CPP. Once IC is identified, the highly successful IC treatment modalities now available can be used to address the underlying bladder pathology that is causing the patient's symptoms. As it has been estimated that up to 85% of patients with CPP may have IC,[6] these developments represent a dramatic improvement in gynecologists' ability to detect and treat a disorder that affects a large number of patients in their practice.

In this article, we discuss the definition and the differential diagnosis of CPP in light of recent evidence suggesting that many patients with CPP may have pain of bladder origin, or IC. We present an updated algorithm for the evaluation and treatment of CPP in the gynecologic setting (Figure 1).

PELVIC FLOOR INNERVATION

The neurologic mechanisms involved in chronic pain are not clearly understood, thus making selective treatment difficult. Incompletely treated CPP may lead to progressive neurologic changes, essentially making it a disease state.[7]

From the Center for Advanced Pelvic Surgery and Medicine, Belleville Memorial Hospital, Belleville, Illinois, USA (EJS); the Institute for Female Pelvic Medicine, Urogynecology and Reconstructive Pelvic Surgery, Knoxville, Tennessee, USA (JRD); and the Department of Surgery/Urology, University of California San Diego Medical Center, University of California San Diego, San Diego, California, USA (CLP)

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Requests for reprints should be addressed to: Edward J. Stanford, MD, MS, Center for Advanced Pelvic Surgery, Belleville Memorial Hospital, 432 North Pleasant Avenue, Belleville, Illinois 62801. E-mail: ejs222@aol.com

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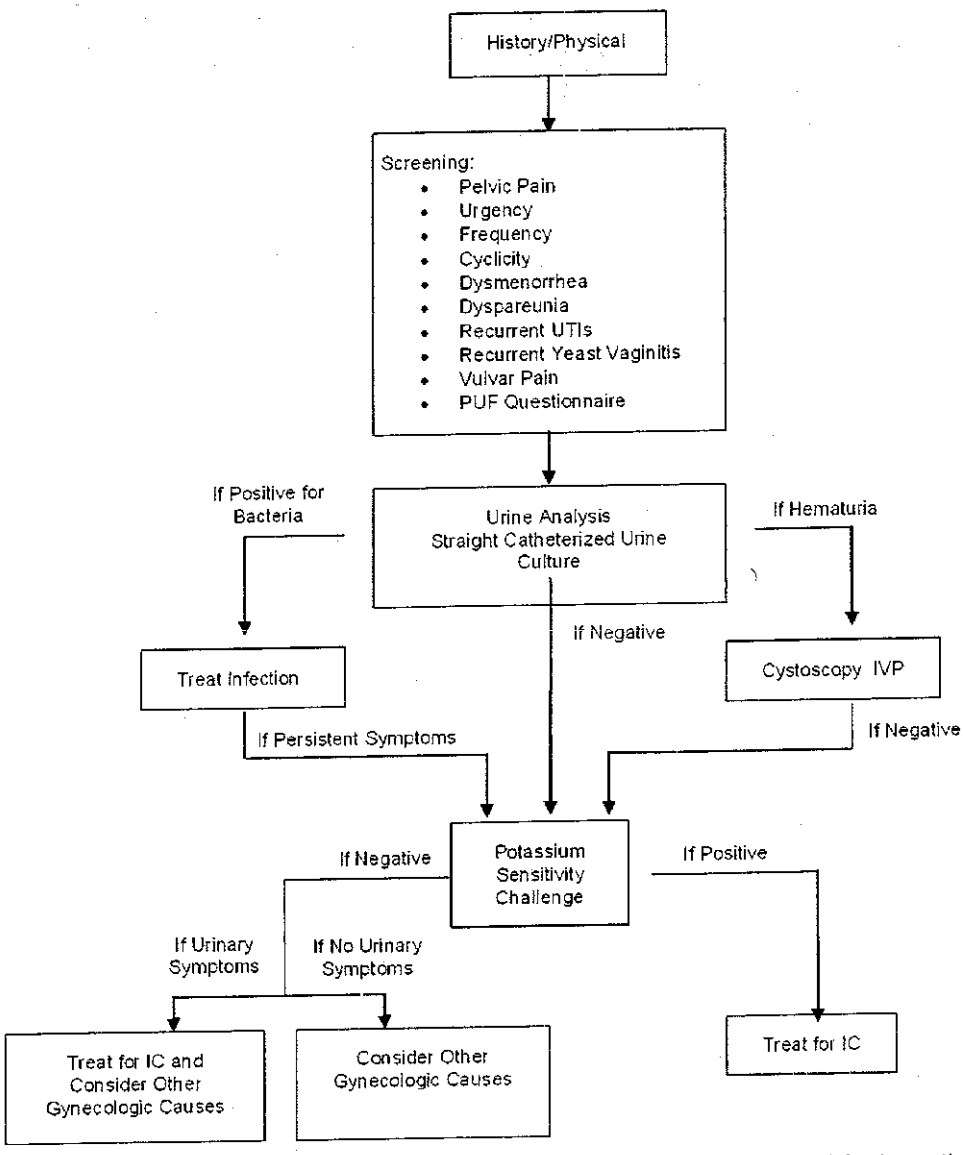

Figure 1. Algorithmic synopsis of the diagnostic approach to ruling out interstitial cystitis (IC) in the patient with chronic pelvic pain. IC should be considered a possible diagnosis early in the patient's evaluation. IVP = intravenous pyelogram; PUF = Pelvic Pain and Urgency/Frequency; UTIs = urinary tract infections.

Briefly summarized, neural signals travel from the pelvis along sympathetic and parasympathetic nerves and merge in the pelvic ganglia.[8] Nociceptive and sensory stimuli are carried by sympathetic (T10–T12) and parasympathetic fibers along S2, S3, and S4 fibers. These visceral afferent nerves ultimately travel to the spinal cord and synapse with many spinal cord segments in the dorsal horn. Signals from multiple organs (eg, muscle, skin, uterus, peritoneum, bladder, adnexa) may converge on a single dorsal horn neuron. Unfortunately, this "normal" intermingling of neural signals in the dorsal horn also means that supraspinal second-order neurons receive conflicting signals. Persistent stimuli may cause biochemical changes that alter the normal sensory processing functions in the dorsal horn. This phenomenon is referred to as neural upregulation. Therefore, normal nonpainful stimuli may be perceived as painful and a hyperalgesic state, referred to as viscerovisceral hyperalgesia,[9] may develop in which stimuli from one organ are perceived as pain and dysfunction in another. The signals in CPP appear to be carried by unmyelinated C-fibers and not by larger myelinated fibers.[10]

The gate control theory has been the theory most accepted to explain the mechanisms of CPP. This theory holds that the afferent neural impulses from peripheral nerves are modulated by spinal and cortical signals, which serve as "gates." The signals act to enhance or decrease afferent impulses by altering the level of firing of the visceral afferent nerves, altering afferent input from cutaneous and deep somatic structures, altering endogenous opioid and nonopioid systems, or altering various central excitatory and inhibitory influences from the brainstem, hypothalamus, and cortex.

Pain impulses emitted by the urinary bladder travel to the spinal cord and can result in pain at any location in the pelvis. As a result, it often is not obvious that the bladder is the source of the pain.[11,12]

Understanding these less-than-perfect and evolving theories, physicians who care for patients with CPP cannot limit their diagnosis or treatment to a single cause. They must consider and be prepared to treat any of the possible "pain generators."

DEFINITION AND DIFFERENTIAL DIAGNOSIS OF CHRONIC PELVIC PAIN

CPP has been characterized in many ways, including somatic versus nonsomatic and cyclic versus noncyclic. To date, a consensus on how to define CPP does not exist. The American College of Obstetricians and Gynecologists (ACOG) has defined CPP as localized noncyclic pain of >6 months' duration that causes a loss of function.[13] Some clinicians consider 3 months of chronic pain, particularly constant rather than cyclic pain, to be consistent with a diagnosis of CPP.

The differential diagnosis of CPP in women is extensive, involving all of the structures of the lower abdomen and pelvic floor including the bladder (Table 1).[14–16] Historically, a woman presenting to a gynecologist with symptoms of CPP was most likely to receive a presumptive diagnosis of endometriosis and undergo laparoscopy for surgical confirmation. This was particularly true if the initial medical treatment was unsuccessful. However, biopsy-confirmed endometriosis is found in only 28%[17] to 33%[4] of women with CPP. Even then, its presence does not mean it is the cause of pain, only that there is an "association." Other common diagnoses include adhesions, vulvar pain, and irritable bowel syndrome (IBS). Here, too, the presence of these findings does not mean that they are the cause of pain, only that there is an "association."

In a study reported in 2002, Clemons *et al*[18] administered an IC symptom questionnaire and performed cystoscopy with hydrodistention in 48 women who were scheduled to undergo laparoscopy for CPP. Of these women, 38% were found to have IC on the basis of symptoms and cystoscopy results, indicating that the bladder was the likely source of pelvic pain.[18] As discussed below, the percentage may have been even higher in this population because cystoscopy is known to underdiagnose IC.[17]

Recently, 2 large multicenter, controlled trials demonstrated that the bladder is the most common pain-generating organ in the pelvis, causing pain alone or in combination with other disorders of the pelvis in 80% to 85% of symptomatic patients.[6,19] In another controlled trial, Chung *et al*[20] reported a positive potassium sensitivity test (PST) rate in 146 of 178 (82%) women with CPP. The importance of these studies is that the patients with CPP had intravesical potassium sensitivity, demonstrating the presence of an abnormal bladder. Fortunately, the traditional approach to the diagnosis (as well as the treatment) of female patients with CPP is undergoing substantial change as a result of more recent findings such as these.

Table 1. Differential diagnosis of chronic pelvic pain

- Gastrointestinal
  - Diverticulitis
  - Inflammatory bowel disease
  - Irritable bowel syndrome
  - Proctalgia fugax
  - Proctodynia
- Gynecologic
  - Adenomyosis
  - Adhesions[14]
  - Chronic pelvic infection
  - Degenerative leiomyomata
  - Endometriosis
  - Hydrosalpinx
  - Neuroma
  - Posterior fornix syndrome[15]
- Musculoskeletal
  - Arthritis
  - Coccygodynia
  - Disc disease
  - Fibromyalgia
  - Hernia[16]
  - Piriformis syndrome
  - Scoliosis
- Perineum
  - Neuroleptic drug exposure
  - Peripheral neuropathy
  - Pudendal nerve entrapment
- Psychiatric
  - Depression
  - Factitious
  - Hypochondriasis
  - Opioid seeking
  - Physical or sexual abuse
  - Somatization
- Urinary
  - Chronic calculi
  - Detrusor dyssynergia
  - Interstitial cystitis
  - Urethral syndrome
- Vaginal
  - Neuroma
  - Scarring
- Vulvar
  - Essential vulvodynia
  - Vulvar dermatoses
  - Vulvar vestibulitis

It is essential to consider the interplay between the multiple organ systems potentially involved, the role of the neural pathways, and the symptom-complex overlap of the various disease entities responsible for CPP. Also, alterations in normal neurologic, immunologic, and endocrinologic responses must also be considered. For example, recent data show that mast cell infiltration and degranulation are found in IC as well as in endometriosis[21] and other chronic pain disorders (Table 2). Mast cell secretion can be stimulated by acetylcholine, stress, and hormone fluctuations, and the resulting mast cell activation can provoke CPP. Clinically this is seen during

allergy seasons with IC flares due to increased mast cell activity.

ENDOMETRIOSIS

As mentioned earlier, endometriosis is a common diagnosis in women with CPP, but has not been proved to be a cause for symptoms. Several pitfalls are also encountered in diagnosing and treating endometriosis. For example, the appearance of endometriosis is variable. Lesions may be clear, tan, red, brown, or black. Recent studies have suggested that the degree of mast cell involvement may vary depending on the appearance of the lesion. Clear lesions appear to have fewer mast cells and minimal degranulation compared with more pigmented lesions.[21] Studies have also shown that only 28%[17] to 33%[4] of women with CPP have biopsy-confirmed endometriosis; therefore, visual confirmation is unreliable and diagnostic biopsies are required. Surprisingly, diagnostic biopsies are not a universal practice in gynecology, and laparoscopic treatment of presumed endometriosis without biopsy confirmation is common.

The mechanism by which endometriosis causes pain is not well understood and there appears to be little correlation between the extent of disease and the amount of pain. For example, endometriosis has been found in patients who are asymptomatic[22] and minimal disease has been found in patients with debilitating pain. But here, too, the key word is "associated," because the endometriosis may not be generating pelvic pain.[6,18–20] The role of laparoscopy should not be minimized because it is the only method available to accurately diagnose endometriosis and because in >60% of those affected, the disease may be progressive.[23] Even so, the need for surgical confirmation has been questioned.[4,24] Treatment with gonadotropin-releasing hormone (GnRH) agonists without laparoscopic confirmation of endometriosis is now considered acceptable. Endometriosis was found at laparoscopy in 98% of patients who had a history of moderate to severe CPP lasting for ≥6 months and a lack of response to nonsteroidal anti-inflammatory drugs or oral contraceptives.[25] The caveat with empiric therapy underscores the need to rule out the bladder as the source of pain. It is important to remember that IC causes painful sex[12,26–31] and that it is affected by the menstrual cycle (ie, premenstrual flares), which are the symptoms that may have been, in part, the basis for the diagnosis of endometriosis.[27,32,33]

It is difficult to reconcile which approach to take when endometriosis is considered because there are few randomized, controlled trials and no consensus on treatment. Further, whether the implants or scarring found at surgery are the specific cause of the patient's pain may not be substantiated. What is known is that pain recurrence and reoperation are common after medical, surgical, and combined treatment. Therefore, even in the presence of endometriosis, suspicion of other CPP etiologies is warranted, particularly in patients who do not respond adequately to treatment.

INTERSTITIAL CYSTITIS

Although endometriosis is common and should be considered in patients with cyclic CPP, IC is emerging as the most common cause of CPP in women. In the past, IC has been considerably underdiagnosed. It is estimated that as many as 1 in 4–5 women in the United States may have IC.[6,34] As presented elsewhere in this supplement, Rosenberg *et al*.[35] recently reported a prevalence of probable IC in women of 17.5% in a large primary care population.

Patients with endometriosis, vulvar vestibulitis (VV), IBS, and IC complain of similar symptoms. These patients typically complain of cyclic pain associated with hormone fluctuation; perimenstrual or postcoital flaring; referred pain throughout the lower abdomen, genital area, and thighs; and, very often, voiding symptoms. Interestingly, 75% of men as well as 75% of women have symptom flares associated with sexual activity.[12,26–30] It has been known for >60 years that IC is affected by the menstrual cycle,[32] and more recent studies have confirmed the presence of symptom flares during the week before menses in approximately 75% of patients.[27,33] Usually the patient is most affected by pelvic pain, which is the principal iatrogenic stimulus. Consequently, the patient perceives that she has a gynecologic problem and seeks help from a gynecologist and, as a result, genitourinary symptoms may be missed.

Only recently has the diagnosis of bladder-origin pain been simplified, allowing for office-based diagnosis. Previous criteria for diagnosing bladder pain required cystoscopy to confirm vascular changes or ulcers in the bladder. However, use of cystoscopy results in underdiagnosis of pain of bladder origin, because patients may have painful symptoms yet have normal cystoscopic findings.[32,36–40] Additionally, in a population of 20 healthy women undergoing tubal ligation, a study found cystoscopic changes that historically were considered characteristic of IC.[41] The PST is more sensitive and specific (80% vs 50%) compared with cystoscopy, leading to the recognition and treatment of patients who might otherwise have been neglected. Although there has been a reluctance to accept the PST as the best test for diagnosis of bladder-origin pain, it has demonstrated a positive result in up to 96% of patients.[6,11,12,19,20,42] Currently, the PST is the most widely reported diagnostic test for IC and has the highest sensitivity. It has been shown that as many as 89% of patients with CPP presumed to have endometriosis have a positive PST.[19] This finding underscores the point that endometriosis may not be the cause of the pain symptoms.

In addition, laparoscopic confirmation of endometriosis does not rule out IC. In a prospective study using laparoscopy, cystoscopy, and PST in 178 women with CPP, Chung *et al*.[20] found both endometriosis and IC in

Table 2. Conditions associated with mast cell infiltration and degranulation

- Chronic fatigue syndrome
- Depression
- Fibromyalgia
- Interstitial cystitis
- Irritable bowel syndrome
- Somatization

Table 3. Conditions associated with vulvar dermatoses

- Chronic contact dermatosis
- Herpetic infections
- Inflammatory dermatoses
- Lichen planus
- Lichen sclerosis
- Lichen simplex chronicus
- Psoriasis
- Seborrheic dermatitis
- Systemic autoimmune diseases (Behçet syndrome or systemic lupus erythematosus)

78 of 115 (65%) patients, endometriosis in 134 of 178 (75%) patients, and IC in 159 of 178 (89%) patients. The PST was positive in 146 of 178 (82%) patients overall, and cystoscopy confirmed the presence of IC in 140 of 146 (96%) women who were PST positive.[20] These results indicate the high accuracy of the PST in detecting IC and demonstrate the importance of considering IC in the diagnosis of gynecologic CPP. Again, although endometriosis and IC may coexist, it is entirely possible that the bladder is the main generator of symptoms.

Treatment for patients with IC begins with recognizing that the bladder is the source of the patient's symptoms. Moldwin *et al* [43] discuss the treatment of patients with IC in an article elsewhere in this supplement.

VULVAR PAIN

Vulvar pain, particularly VV, should be considered in any patient with CPP. The incidence of vulvar pain in patients with CPP is estimated to be approximately 20%.[17] It is important to recall that pelvic nerves innervate the vulvar skin and that symptoms expressed by the patient may be the result of referred pain. In VV, the patient complains of severe sensitivity to touch at the introitus as well as postcoital discomfort. Constant discomfort or cyclic flaring may be reported. Here, too, as with endometriosis, IC needs to be ruled out. In a study on patients with vulvovaginitis, 80% were shown to have IC.[19] As is obvious, the cyclic pain and association with sexual activity are well-known symptoms of IC. Male symptoms are a great analogue to the female ones, because 40% to 50% of men with IC have scrotal pain.[12] Various inciting causes have been attributed to VV—such as increased alkalinity of the vaginal fluids, topical irritants, birth trauma to pelvic nerves, early use of hormone therapy, and urinary calcium oxalate—but none are well substantiated. In most patients, however, biopsies show an increased infiltration of mast cells similar to that seen in patients with IC and endometriosis.[44] Before embarking on treatment of VV, it may be advisable to rule out IC, because the therapies are quite different. If the patient has not responded to traditional therapy, then IC should be considered the more likely cause of symptoms. Therapy for IC is currently quite successful and is reviewed by Moldwin *et al* [43] in this supplement.

Traditional empiric treatments for VV include topical analgesia, topical corticosteroids, biofeedback, and surgical excision. Experimental therapies include intralesional α-interferon and botulinum toxin. In some cases, it appears that patients undergo spontaneous remission. In refractory patients, vestibulectomy has a reported cure rate of up to 90%.[45]

Essential vulvodynia is also constant or cyclic and has been suggested to be caused by pudendal neuralgia. Initial treatment with a long course of amitriptyline is recommended. Vulvar dermatoses should be considered in patients with CPP (Table 3). Cyclic vulvovaginitis may flare after sex or during the luteal phase of the menstrual cycle. In some it may be owing to hypersensitivity to *Candida* antigen or to an immunoglobulin A deficiency. This entity is probably not as prominent as previously thought, and symptoms may more often be related to referred pain. Treatment for cyclic vulvovaginitis with prolonged antimycotics has been recommended. In all cases of vulvar pain, one should consider the possibility that it may be referred pain and IC should be ruled out. The Pelvic Pain and Urgency/Frequency (PUF) questionnaire,[6] and perhaps the PST, can help determine the true source of the pain.

IRRITABLE BOWEL SYNDROME

The criteria for IBS as the cause of CPP include continuous or recurrent abdominal pain or discomfort relieved with defecation, a change in stool consistency, altered stool frequency or form, passage of mucus, and bloating.[46] One mechanism to describe the pain from IBS is inappropriate activation of hormone-dependent descending pain inhibition systems seen in those with dysmenorrhea or IBS. This may be responsible for a greater development of central (spinal) sensitization in response to visceral events (uterine or intestinal contractions or distentions).[47] It has been shown that, in general, women have lower thresholds, higher intensity ratings, and less tolerance to somatic pain stimuli compared with men.[48] Also, a decline in estrogen or progesterone is associated with hyperalgesia and may explain why IBS responds to GnRH agonist therapy.[49]

PELVIC CONGESTION

The chronic pain symptoms of pelvic congestion include postcoital aching, avoidance of sex, ovarian point tenderness, long duration of symptoms, dull ache with acute

episodes, and bilateral or unilateral symptoms; worsening of symptoms with prolonged standing; dysmenorrhea; and menorrhagia. Many patients with a diagnosis of pelvic congestion ultimately undergo hysterectomy. Here, too, IC should be ruled out as the cause of symptoms because these symptoms are generated by the bladder.

ADHESIONS

The role of abdominopelvic adhesions as the cause of CPP is controversial when they are the only operative finding, although adhesiolysis is reported to have a high rate of success in controlling CPP.[50] As discussed earlier, previous CPP and the presence of adhesions is an "associated" but not necessarily causal relation. Essentially, there is a lack of scientific evidence to document that adhesions cause pain or CPP.

NEW FINDINGS ON PREVALENCE OF INTERSTITIAL CYSTITIS IN GYNECOLOGIC PATIENTS

To determine whether IC is as prevalent as is suggested in the literature (ie, 1 in 4-5 women), a study was undertaken to screen all consecutive gynecologic patients in an 8-physician gynecologic practice.[51] Patients were screened with the newly developed and validated PUF questionnaire.[6] The questionnaire, which was validated jointly by urologists and gynecologists, devotes approximately one third of its questions to urgency, one third to frequency, and one third to pelvic pain. In addition, it contains 2 questions concerning sexually-associated symptom flares. It combines the urologic and gynecologic symptoms in a simple 1-page questionnaire that is quite specific for IC complaints. The prevalence of IC was then estimated on the basis of a previously published study by Parsons *et al*.,[6] in which PUF scores were demonstrated to correlate with the likelihood of a positive PST both in gynecologic patients with CPP and in urologic patients.

A total of 1066 gynecologic patients in the 8 practices completed the PUF questionnaire. The data were pooled and the patients' predicted likelihood of a positive PST was calculated. As shown in Table 4,[6] the prevalence of IC in this population, as reflected in the predicted rate of a positive PST, was 25.7%. The results of this study lend support to the notion that IC may be present in as many as 1 in 4 women and agree with the data from a primary care practice presented by Rosenberg *et al*.[35]

CONCLUSION

Recent evidence indicates that the clinician who approaches the diagnosis and treatment of a patient with CPP must bear in mind that the traditional view of a gynecologic problem as the cause of symptoms may not be true. Before proceeding to assign a gynecologic cause or to treat the patient for a gynecologic problem, the clinician must first rule out the bladder as the cause of the patient's symptoms. In particular, if the patient has been treated with traditional methods and has not responded to therapy, it is important to rule out the bladder as the source of the symptoms. To do so, the clinician can now use a symptom questionnaire that is specific for IC (the PUF questionnaire) and an office-based test (the PST) to show that the bladder epithelium is abnormal. If these tools detect the presence of IC, then the patient can be treated for CPP of bladder origin. Therapy for IC has a high rate of success. If these tools fail to document the bladder as the cause of the symptoms, then traditional gynecologic approaches to CPP should be undertaken. The major changes in the CPP paradigm are that IC appears to be far more common and is more frequently the cause of the pelvic pain seen in gynecologic patients than has been thought traditionally.

Table 4. Estimated prevalence of interstitial cystitis (IC) determined from Pelvic Pain and Urgency/Frequency questionnaire (PUF) scores

PUF Score Range	Patients (n)	Predicted Rate of Positive PST (%)	Estimated Patients with Probable IC* (n)
0–4	527	0	0
5–9	332	37.5	124
10–14	144	68	98
15–19	37	73	27
20–24	18	86	15
≥25	8	93	7
All	1066	25.7	271

PST = potassium sensitivity test.
* Based on predicted rate of positive PST from Parsons et al.[6]
Adapted from Urology.[6]

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