

# Chronic Pelvic Pain: Endometriosis and Interstitial Cystitis

MAURICE K. CHUNG, MD, RPH

## INTRODUCTION

The more common gynecologic diagnoses of chronic pelvic pain (CPP) are pelvic adhesions, adnexal cysts, endometriosis, endosalpingiosis, ovarian remnant syndrome, pelvic congestion syndrome, residual ovarian syndrome, pelvic inflammatory disease, adenomyosis, and uterine leiomyomas.<sup>1,2</sup> Often, management of women with CPP involves invasive procedures or surgical interventions. In fact, more than 40% of laparoscopies and 10% to 12% of all hysterectomies are performed as a result of CPP, which contributes to its significant economic burden.<sup>3,4</sup> Endometriosis is one of the more prevalent gynecologic diagnoses among women with recurrent and progressive CPP.<sup>1</sup> Among 58 patients who presented to a pelvic pain center for treatment, 48 (83%) had biopsy confirmed active endometriosis.<sup>3</sup> This finding is consistent with findings in the current literature.<sup>3,6-10</sup> Endometriosis is the presence of ectopic endometrial glandular tissue outside of the endometrial cavity. Symptoms include dyspareunia; cyclic premenstrual, menstrual, or both, low abdominal pelvic pain; irritative voiding; and flares after sexual intimacy.<sup>11</sup> Ideally, the diagnosis of endometriosis involves visual confirmation of the lesion during laparoscopy and histologic confirmation of the presence of both ectopic endometrial glands and stroma.<sup>11</sup>

## INTERSTITIAL CYSTITIS

### PAINFUL BLADDER SYNDROME

Interstitial cystitis (IC), or pelvic pain of bladder origin, occurs predominantly in women 30 to 59 years of age,<sup>12</sup> with up to 85% of reported cases in those 40 to 45 years of age.<sup>13,14</sup> Along with endometriosis, IC is considered one of the more

common disorders associated with CPP.<sup>15</sup> Yet, only 500,000 patients with debilitating bladder problems have been diagnosed with IC, while the number of those with undiagnosed IC has been estimated to be more than 8 million.<sup>16</sup> Still, some estimates range up to 28 million, with the overwhelming majority of these individuals incorrectly diagnosed or undiagnosed.<sup>17</sup>

Symptoms include urinary urgency, frequency and/or pelvic pain in the absence of urinary tract infection. Although these symptoms represent the classic triad of IC, some patients have no pain and present with symptoms of overactive bladder. In addition, 15% of patients present with chronic pain and no urologic symptoms.<sup>16</sup> Furthermore, many patients have dyspareunia and cyclic premenstrual, menstrual, or both, low abdominal pain exacerbated by sexual intimacy.<sup>16,18</sup>

In the mid-1980s, the National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK) established clinical and cystoscopic diagnostic criteria for research studies of IC (Table 1).<sup>19,20</sup> The consensus criteria for diagnosis of IC, including



MAURICE K. CHUNG, MD, RPH

**POSITIVE POTASSIUM SENSITIVITY TEST RESULTS CORRELATE WITH CYSTOSCOPIC DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS\* IN PATIENTS WITH CHRONIC PELVIC PAIN**

CPP + Cystoscopic Evidence of IC n=159/178 (89%)	CPP + Positive PST n=146/178 (82%)
+ Positive PST n=140/159 (88%)	+ Cystoscopic Evidence of IC n=140/146 (96%)

TABLE 1

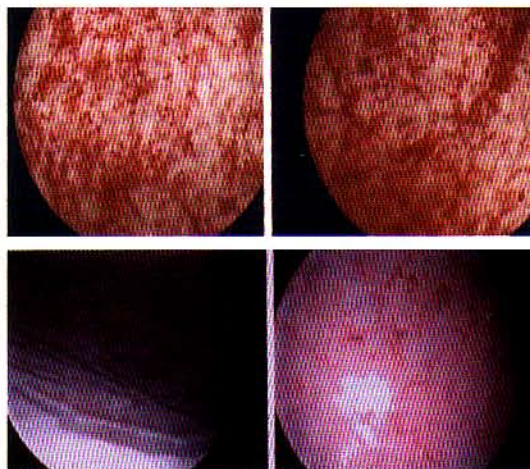
\*Glomerulations and hematuria according to the National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases guidelines.

†PST=Potassium Sensitivity Test; IC=interstitial cystitis; CPP=chronic pelvic pain.

\*N=178.



exclusions and cystoscopic evidence of ulcers and glomerulations, were widely accepted for both clinical and research purposes and thereafter became the de facto criteria for establishing a clinical diagnosis.<sup>30,21</sup> Glomerulations, however, are not pathognomonic of IC (Figure 1).<sup>19,21</sup> A recent study reported glomerulations in about 45% of “normal” women undergoing tubal ligation.<sup>22</sup> Unfortunately, the women were not specifically questioned about urinary or gynecologic symptoms, such as CPP, and were not asked to complete voiding logs or pain questionnaires. Some of these women may have had occult IC characterized by pelvic pain, irritative voiding symptoms, or both of these.<sup>21</sup>



**Figure 1.** LEFT LOWER CORNER SHOWS MUCOSAL CRACKS, WHICH ARE FREQUENTLY FOUND IN PATIENTS WITH IC. ALL THE OTHERS SHOW GLOMERULATIONS.<sup>19,21</sup>

The NIH-NIDDK criteria were found to be too restrictive for clinical use based on results of the Interstitial Cystitis Database Study because more than 60% of patients evaluated by experienced clinicians and thought to have or to definitely have IC did not meet the NIH-NIDDK criteria.<sup>19</sup>

Similar to the diagnostic criteria for IC, the pathogenesis and cause of IC remain incompletely defined. A consensus is emerging, however, regarding the central role of bladder epithelial dysfunction, bladder sensory nerve upregulation, and mast-cell activation in the genesis of IC.<sup>16,23</sup> The urothelial surface is lined by impermeable bladder surface mucin composed of sulfonated

glycosaminoglycans and glycoproteins. Injury to this surface can cause changes in permeability that allow potassium ions to traverse the urothelium, depolarize sensory and motor nerves, and activate mast cells.<sup>18,23,24</sup>

On the basis of this hypothesis, Parsons et al<sup>25</sup> developed the Potassium Sensitivity Test (PST) to indicate abnormal permeability of the epithelium, which may be used to support a diagnosis of IC. The use of PST has been validated in several studies. Over 80% of CPP patients demonstrated positive potassium sensitivity, suggesting a bladder component to their pain (IC).<sup>18,26</sup>

Parsons et al<sup>25</sup> also designed a Pelvic Pain and Urgency/Frequency (PUF) symptom scale that provides balanced attention to bladder-origin pelvic pain (IC) and to pelvic pain or dyspareunia. The severity of IC symptoms and the extent to which the patient is bothered by each symptom are measured on a scale of 0 (no symptoms) to 35 (most severe). PST was used to validate PUF as a diagnostic tool. In patients suspected of having IC with a PUF score of 10 to 14 (moderate symptoms), 74% showed positive potassium sensitivity.<sup>17</sup> Furthermore, it was shown that a PUF score of 15 or higher is associated with an 84% chance of a positive PST, which provides strong evidence for the presence of IC.<sup>17</sup>

## ENDOMETRIOSIS

Endometriosis is considered one of the 4 most common diagnoses in women with CPP.<sup>15</sup> Based on findings from many studies, at least 80% of patients with CPP have endometriosis.<sup>5-8,10,26,27</sup>

To establish a definitive diagnosis of endometriosis, many opinion leaders still believe that laparoscopy is necessary.<sup>11</sup> However, diagnosing endometriosis during laparoscopy can be difficult and is dependent on the surgeon's level of experience. An inexperienced surgeon may miss the diagnosis of endometriosis because its appearance can vary widely.<sup>11,28</sup> Diagnosis also presents other challenges. Although surgeons are urged to obtain



histologic confirmation of endometriosis, it is often uncertain whether endometriotic implants or adhesions found during surgery are the source of the patient's pain. Although pelvic adhesions are diagnosed in approximately 25% of women with CPP or without endometriosis, their relationship to CPP is still controversial.<sup>15</sup> It is prudent, therefore, to consider other possible causes of CPP even in the presence of endometriosis, especially in patients whose symptoms persist despite therapy.

Although endometriosis has been recognized as a major cause of CPP, the treatment of endometriosis is often not successful. Due to a lack of adequate randomized controlled trials, evidence is insufficient to support the efficacy of medical therapy, surgical therapy, or both, for CPP and endometriosis. As a result, management of women with CPP considered secondary to endometriosis includes a vast range of therapeutic approaches that are often suboptimal and costly.<sup>29</sup> To complicate management even further, endometriosis has been found in more than 60% of asymptomatic patients and progressive disease exists in close to 60% of patients overall.<sup>5,30,31</sup>

When endometriosis is found at the time of surgery, destruction of the lesions by fulguration, excision, or both, is recommended. Although excisional surgery offers a better success rate in treating endometriosis in patients with CPP, it also requires a higher level of surgical skill.<sup>29</sup> Many patients, therefore, may receive inadequate treatment for their endometriosis by less experienced surgeons, which, in turn, can lead to persistent and recurrent disease. Furthermore patients have undergone numerous laparoscopies and have had a hysterectomy and still suffer from CPP.

Interestingly, endometriosis has been found to involve the urinary tract and has been reported in at least 16% of women undergoing a laparotomy for the condition.<sup>32</sup> Recently, there was a report on a small series of patients with bladder endometriosis.<sup>33</sup> In addition, it has been demon-

strated that 79% of patients with persistent chronic pelvic pain after a hysterectomy have IC.<sup>34</sup> It is advisable, therefore, to evaluate urinary symptoms in patients with CPP and endometriosis. Strict adherence to this principle has led to the discovery that IC and endometriosis, the evil twins, can coexist in women with CPP.

## **ENDOMETRIOSIS AND INTERSTITIAL CYSTITIS THE EVIL TWINS STUDY**

Results of recently published papers<sup>5,26,27,35</sup> demonstrate the presence of endometriosis and IC, the "Evil Twins," in 38% to 80% of patients with chronic pelvic pain based on the potassium sensitivity test and laparoscopic and cystoscopic evaluation.

In our recent "The Evil Twins" study<sup>26</sup> of 178 patients, 159 (89%) were diagnosed with interstitial cystitis by cystoscopic evidence. A positive potassium sensitivity test was achieved in 146 patients (82%). Both IC and PST were found in 140 (78.6%) patients. Biopsy confirmed endometriosis was found in 134 patients (75.2%). Both IC and endometriosis were found in 115 patients (65%). In the positive PST group of 146 patients, 140 (96%) were diagnosed with IC by cystoscopy. Irritable urinary symptoms occurred in 145 of 178 patients (81.5%) with chronic pelvic pain. Urinary incontinence was present in 77 (43.3%) patients. The average pelvic pain (PUF) score was 14 of 35. An average of 20% of the study patients had no urinary symptoms. Painful overactive bladder symptoms were complaints among not only patients with endometriosis but also those with negative findings following laparoscopic evaluation. In fact, the 44 patients with no endometriosis showed significant improvement in their symptoms of CPP, including their painful overactive bladder symptoms after cystoscopic hydrodistention, indicating that IC could be the cause of their CPP. It was concluded, therefore, that patients with CPP (80%) with or without urologic symptoms of urgency/frequency (20%) may in



fact have IC as a component of their pelvic pain.<sup>26</sup>

If cystoscopy had been performed only in patients with irritative voiding symptoms/overactive bladder, a diagnosis of IC would have been missed in approximately 20% of patients. Furthermore, cystoscopy/hydrodistention is often performed only in patients with a negative laparoscopic evaluation. Consequently, patients are required to undergo 2 separate procedures while under general anesthesia, and the diagnosis of IC is delayed in approximately 80% of patients. Cystoscopy/hydrodistention should be considered as an integral part of the surgical evaluation of patients with CPP.

Several modalities are used to diagnose IC. Cystoscopic hydrodistention and clinical presentation remain the "gold standard." However, this gold standard is not ideal and is considered controversial by many.<sup>21,22</sup> In addition, the stringent diagnostic criteria for IC developed by the NIH-NIDDK and the controversy concerning the accuracy of less stringent criteria have interfered with recognition of IC as a major cause of CPP. To make the problem worse, gynecologists in general are not accustomed to addressing irritable urinary symptoms in patients with CPP, thus making the diagnosis of IC less common.

The PUF questionnaire and the PST as advocated by Parsons and colleagues have emerged as a simple office screening tool and diagnostic procedure, respectively, for patients with symptoms of CPP and IC. These tests have been recently validated as diagnostic approaches for IC.<sup>17,36</sup> In this study, the diagnostic accuracy of PST increased when performed in conjunction with cystoscopic hydrodistention. Notably, it has been shown that a PUF score of 15 or higher is associated with an 84% chance of a positive PST, which provides strong evidence for the presence of IC.

It is very important to use all existing screening and diagnostic modalities to establish an early diagnosis of IC. When surgery is indicated, cysto-

scopic hydrodistention in conjunction with laparoscopy is recommended to establish an earlier diagnosis of endometriosis and IC/ CPP of bladder origin,<sup>5,26,27,33,37</sup> the evil twins of CPP.

Simple conservative methods exist for treating IC, including diet, pelvic floor physical therapy, and medications, such as hydroxyzine and pentosan polysulfate sodium (Elmiron, Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ). Recent published articles have indicated the efficacy of oral contraceptives in treating CPP and IC.<sup>33,38</sup> We have presented a clinical study of using intravesical instillation of anesthetic in patients with chronic pelvic pain resulting in close to a 40% reduction in pain symptoms in 8 to 10 weeks.<sup>39</sup>

Many thought leaders believe that the treatment of women with CPP has been ineffective because the underlying cause is actually urologic rather than gynecologic.<sup>40</sup> Therefore, it is reasonable to conclude that ineffective management of CPP and treatment failures may be in part the result of missed diagnoses of IC.

In summary, it is desirable to have a urologist perform cystoscopy and hydrodistention, especially when these procedures are new to the gynecologist. If, however, a urologist is not available to assist in the procedure, or alternatively, if the gynecologist does not wish to perform a cystoscopy and hydrodistention, he or she should consider using the PST test. This test has validated the PUF questionnaire, and together the PUF and PST are more than adequate to confirm a diagnosis of IC.

#### OVERLAP OF INTERSTITIAL CYSTITIS AND ENDOMETRIOSIS: THE UNDERLYING NEUROPATHOLOGY

Both endometriosis and IC are CPP syndromes that can be frustrating for patients and physicians alike. These CPP syndromes are associated with other pain syndromes, including irritable bowel syndrome (IBS), fibromyalgia, dyspareunia, and



vulvodynia.<sup>41,42</sup> The association may be as a result of neuro-upregulation, and pain centralization; other neuropathic states are reviewed elsewhere<sup>43,44</sup> and include visceral hyperalgesia (eg, irritable bowel syndrome), viscerosomatic hyperalgesia (eg, essential vulvodynia associated with IC), viscerovisceral hyperalgesia (eg, IBS associated with IC), and abnormal visceromuscular reflexes (eg, pelvic floor tension myalgia).<sup>45-50</sup>

A review of the neuropathology of CPP and multisystem interactions involved in all the above-mentioned clinical pain syndromes demonstrates that the significant overlap of IC and endometriosis observed in our studies is to be expected.<sup>51</sup> A multidisciplinary approach to chronic pain has been repeatedly shown to be highly efficacious.<sup>52-55</sup> The substantial efficacy of this approach can potentially be attributed to down-regulation of the upregulated dorsal horn with resultant relief of chronic pain. This concept of the visceral pain syndrome should encourage clinicians to abandon an organ-specific approach to the evaluation and treatment of their patients with CPP. Instead, they should pursue a more holistic and mechanistic management strategy in this patient population. Our study strongly supports the rationale for this approach.

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Address reprint requests to: Maurice K. Chung, MD, RPh, Midwest Regional Center for Chronic Pelvic Pain and Bladder Control, 310 S Cable Rd, Lima, OH 45805, USA. Telephone: 419 227 3085, Fax: 419 228 1000.

Maurice K. Chung, MD, RPh, is a Clinical Associate Professor at the University of Toledo School of Medicine and an Adjunct Professor of Pharmacy at Ohio Northern University. He is the Director of the Midwest Regional Center for Chronic Pelvic Pain and Bladder Control. Dr

Chung is also in private practice in Lima, Ohio. He has published in *JSLs*, *Journal of the Society of Laparoendoscopic Surgeons* and other journals as well as presented his clinical studies in national and international conferences. Dr Chung sits on the boards of the International Pelvic Pain Society and the International Society of Gynecologic Endoscopy.

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