# *Non-bladder centric interstitial cystitis/bladder pain syndrome phenotype is significantly associated with co-occurring endometriosis*

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***Introduction:*** *Interstitial cystitis/bladder pain syndrome (IC/BPS) and endometriosis are coexistent diagnoses in 48%-65% of women with chronic pelvic pain (CPP), suggesting that dual screening may be warranted. To further investigate the clinical relationship and risk factors between these two conditions, we performed a retrospective review of our large IC/BPS patient data registry.*

***Materials and methods:*** *We evaluated IC/BPS patients who were prospectively enrolled into our registry who completed validated questionnaires and underwent therapeutic hydrodistension, during which anesthetic bladder capacity (BC) and Hunner's lesion (HL) status were recorded. Demographic/medical history were reviewed. IC/BPS patients with co-occurring endometriosis diagnosis versus those without were compared using descriptive statistics as well as multivariate regression analyses to determine predictors of co-occurring disease.*

***Results:*** *Of 431 IC/BPS participants, 82 (19%) were also diagnosed with endometriosis. These women were significantly younger, had increased prevalence of non-low BC (> 400 cc), and decreased prevalence of HL ($p < 0.05$). Patients with co-occurring endometriosis also had increased prevalence of irritable bowel syndrome (IBS), CPP, fibromyalgia, and vulvodynia ($p < 0.05$). On multivariate analysis, non-low BC (OR 4.53, CI 1.004-20.42, $p = 0.049$), CPP (OR 1.84, CI 1.04-3.24, $p = 0.04$), and fibromyalgia (OR 1.80, CI 1.03-3.14, $p < 0.04$) were significantly associated with a diagnosis of endometriosis.*

***Conclusions:*** *Patients with IC/BPS and co-occurring endometriosis were significantly more likely to carry a non-bladder centric IC/BPS phenotype as well as several comorbid, systemic pain diagnoses. This study characterizes features of a target IC/BPS phenotype that could potentially benefit from endometriosis and systemic pain syndrome screening.*

**Key Words:** interstitial cystitis/bladder pain syndrome, endometriosis, chronic pelvic pain, phenotype

## Introduction

Chronic pelvic pain (CPP) can be described as persistent pain related to the pelvic region for at least 6 months duration that affects approximately 9 million women in the United States (US).[1] Patients with CPP require a detailed clinical evaluation and often multidisciplinary approach due to a high prevalence of underlying and comorbid medical conditions that may be contributing to the pain experienced.[1,2] Endometriosis, a benign gynecologic condition characterized by ectopic endometrial tissue outside of the uterine cavity, and interstitial cystitis/bladder pain syndrome (IC/BPS) are two of the most common diagnoses in women with CPP.[2] Several reports in recent literature have suggested that approximately 48%-65% of women with CPP suffer from both endometriosis and IC/BPS.[3-5]

The IC/BPS patient population encompasses a wide array of clinical heterogeneity.[6,7] Previously published reports have suggested at least two

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phenotypic subgroups of disease, with most studies using Hunner's lesion (HL) status, (previously defined as ulcerative disease), as the clinical delineator between the bladder-centric versus non-bladder-centric subgroups.[8-10] Using anesthetic bladder capacity (BC) as a delineator for variation, we have demonstrated significant differences in gene expression between patients with low BC (defined here as ≤ 400 cc) and patients with non-low BC (> 400 cc).[11] Furthermore, we found that patients with low BC were significantly more likely to present with a bladder-centric phenotype, whereas patients with non-low BC were more likely to present with a systemic disease phenotype, encompassing non-urologic symptoms and syndromes such as irritable bowel syndrome and depression.[12] Our published findings, along with other reports in the literature, suggest that there are at least three relevant phenotypic subgroups in IC/BPS characterized by: 1) low BC, 2) low BC with HL, and 3) non-low BC.

Recognizing the high rate of co-existing diagnoses of IC/BPS and endometriosis, we hypothesized that endometriosis would be more common in IC/BPS women who fell within the non-low BC phenotype. To this end, we performed a retrospective review of our large IC/BPS data registry to characterize patients with low versus non-low bladder capacity to investigate for concurrent endometriosis and other co-existing systemic pain syndromes. Identifying the clinical features of IC/BPS patients who are more likely to suffer from concurrent endometriosis would be clinically useful to aid in determining which subtype of IC/BPS patients would benefit from gynecologic investigation.

## Materials and methods

### *Patient recruitment and enrollment*

Institutional Review Board approval (IRB00018552) was obtained prior to study initiation. IC/BPS patients (18-80-years-old) were prospectively enrolled into the data registry prior to undergoing a scheduled therapeutic hydrodistension. Patients with a history of urogenital cancer, urethral diverticulum, neurologic disease (including stroke and neurogenic bladder), cyclophosphamide use, radiation cystitis, bladder tuberculosis, current urethral catheter placement, or active bladder infection were ineligible and excluded from the IC/BPS data registry. Patients with an active bladder infection at the time of hydrodistension were deferred from enrollment into the study. Written informed consent was obtained prior to patient enrollment.

### *IC/BPS registry data collection*

Demographic and medical history data were obtained from each patient via patient self-report as well as a review of diagnoses in the patient's electronic medical record at the time of enrollment, including a history of the following co-morbid medical conditions: endometriosis, CPP, irritable bowel syndrome (IBS), fibromyalgia, depression, panic disorder, vulvodynia, and dyspareunia. We additionally obtained data specifically pertinent to IC/BPS disease symptoms, including scores from two validated questionnaires: 1) The Pelvic Pain Urgency/Frequency (PUF) Patient Symptom and Bother Scales and 2) The Interstitial Cystitis Symptom and Problem Index (ICSI/ICPI). Anesthetic BC and HL status were also determined at the time of hydrodistension (performed at a pressure of 100 mmHg of water for 5 minutes).

### *Statistical comparisons*

We performed a retrospective review of all female patients within the IC/BPS data registry and stratified individuals into two comparison groups: Group 1) IC/BPS patients with known co-occurring endometriosis and Group 2) IC/BPS patients without known co-occurring endometriosis. SPSS 16.0 software was used for all statistical analyses performed. Mann Whitney U tests were performed to compare means for all continuous variables. Chi-squared tests were performed for all categorical variable comparisons. Univariate and multivariate logistic regression analyses were performed to determine independent predictors of concurrent IC/BPS and endometriosis. A $p \leq 0.05$ was used to determine statistical significance for all analyses performed.

## Results

### *Demographic and medical history data*

Of the 431 total female IC/BPS patients reviewed in our data registry, 82 (19.0%) had known co-occurring endometriosis. IC/BPS patients with a co-occurring endometriosis diagnosis were significantly younger in age compared to IC/BPS patients without a co-occurring endometriosis diagnosis (43 ± 11.5 versus 46 ± 14.2 years; Table 1, $p = 0.020$). There was no difference in mean body mass index (BMI) between groups (28.80 ± 8.31 versus 29.70 ± 8.10; Table 1, $p = 0.504$).

IC/BPS patients with a co-occurring endometriosis diagnosis had an increased prevalence of IBS (52.4% versus 38.8%, $p = .020$), CPP (35.4% versus 18.1%; $p = .006$), fibromyalgia (46.3% versus 25.2%; $p < 0.001$), and vulvodynia (23.2% versus 12.9%; $p = .020$) when compared to IC/BPS patients without a co-occurring

TABLE 1. **Demographic and medical history data**

| | IC/BPS with endometriosis | IC/BPS without endometriosis | p value |
|---|---|---|---|
| Total patients | n = 82 | n = 349 | |
| Age (years) | 42.96 ± 11.46 | 46.44 ± 14.17 | 0.02 |
| Body mass index | 28.80 ± 8.32 | 29.70 ± 8.10 | 0.50 |
| Chronic pelvic pain | 29 (35.4%) | 63 (18.1%) | 0.006 |
| Irritable bowel syndrome | 43 (52.4%) | 135 (38.5) | 0.02 |
| Fibromyalgia | 38 (46.3%) | 88 (25.2%) | 0.0002 |
| Depression | 34 (41.5%) | 122 (35.0%) | 0.27 |
| Panic disorder | 29 (35.4%) | 122 (35.0%) | 0.94 |
| Vulvodynia | 19 (23.2%) | 45 (12.9%) | 0.02 |
| Dyspareunia | 37 (45.1%) | 150 (43.0%) | 0.72 |

IC/BPS = interstitial cystitis/bladder pain syndrome

endometriosis diagnosis, Table 1. There was no difference in the prevalence of depression (35.0% versus 41.5%; p = 0.270), panic disorder (35.0% versus 35.4%; p = 0.940), or dyspareunia (43.0% versus 45.1%; p = 0.720) between groups, Table 1.

### *IC/BPS disease characteristic data*

IC/BPS patients with a co-occurring endometriosis diagnosis had an increased prevalence of non-low anesthetic BC during cystoscopic hydrodistension (97.6% versus 85.4%; p = 0.003) and a decreased prevalence of HL (2.4% versus 11.2%; p = .020) when compared to IC/BPS patients without a co-occurring endometriosis diagnosis, Table 2. There was no difference in mean PUF Symptom Index scores (15.33 ± 4.32 versus 16.1 ± 3.04; p = 0.170) and PUF Bother Index Scores (8.24 ± 2.49 versus 8.69 ± 1.83; Table 2, p = 0.180). There was also no difference in mean ICSI scores (11.97 versus 13.97 ± 2.81; p = 0.33) and ICPI scores (12.52 ± 3.18 versus 12.77 ± 2.5; Table 2, p = 0.470).

### *Predictors for concurrent endometriosis in IC/BPS patients*

Univariate logistic regression analyses demonstrated that the non-low anesthetic BC phenotype (OR = 6.85, 95% CI 1.63-28.73, p = 0.01), CPP (OR = 2.48, CI 1.46-4.21, p = 0.001), a co-diagnosis of IBS (OR = 1.77, CI 1.09-2.87, p = 0.021), a co-diagnosis of fibromyalgia (OR = 2.56, CI 1.56-4.21, p < 0.001), and a co-diagnosis of vulvodynia (OR = 2.04, 1.12-3.72, p = 0.02) were predictors of a concurrent diagnosis of endometriosis in IC/BPS patients, Table 3. Increased age (OR = 0.98, CI 0.96-0.99, p = 0.025) and HL presence (OR = 0.20, CI 0.05-0.84, p = 0.028) were significant negative

TABLE 2. **IC/BPS disease characteristics**

| | IC/BPS with endometriosis | IC/BPS without endometriosis | p value |
|---|---|---|---|
| Non-low bladder capacity | 80 (97.6%) | 298 (85.4%) | 0.003 |
| Hunner's lesion presence | 2 (2.4%) | 39 (11.2%) | 0.02 |
| PUF symptom | 16.1 ± 3.04 | 15.33 ± 4.32 | 0.17 |
| PUF problem | 8.69 ± 1.83 | 8.24 ± 2.49 | 0.18 |
| IC symptom index | 13.97 ± 2.81 | 13.57 ± 3.90 | 0.33 |
| IC problem index | 12.77 ± 2.50 | 12.52 ± 3.18 | 0.47 |

IC/BPS = interstitial cystitis/bladder pain syndrome

TABLE 3. **Univariate logistic regression analysis**

| | OR | 95% confidence interval | p value |
|---|---|---|---|
| Age (years) | 0.98 | 0.96-0.99 | 0.03 |
| Body mass index | 0.97 | 0.95-1.02 | 0.40 |
| Non-low bladder capacity | 6.85 | 1.63-28.73 | 0.01 |
| Hunner's lesion | 0.20 | 0.05-0.84 | 0.03 |
| Chronic pelvic pain | 2.48 | 1.46-4.21 | 0.001 |
| Irritable bowel syndrome | 1.77 | 1.09-2.87 | 0.02 |
| Fibromyalgia | 2.56 | 1.56-4.21 | < .001 |
| Depression | 1.32 | 0.81-2.15 | 0.27 |
| Panic disorder | 1.02 | 0.62-1.68 | 0.94 |
| Vulvodynia | 2.04 | 1.12-3.72 | 0.02 |
| Dyspareunia | 1.09 | 0.67-1.77 | 0.73 |

predictors of a concurrent endometriosis diagnosis in IC/BPS patients, Table 3. Depression (OR = 1.32, CI 0.81-2.15, p = 0.27), panic disorder (OR = 1.02, CI 0.62-1.68, p = 0.94), and dyspareunia (OR = 1.09, p = 0.73) were not significantly associated with a concurrent endometriosis diagnosis in IC/BPS patients, Table 3.

Subsequent multivariate logistic regression analysis demonstrated that the non-low anesthetic BC phenotype (OR = 4.53, CI 1.004-20.42, p = 0.049), CPP (OR = 1.84,CI 1.04-3.24, p = 0.04), and a co-diagnosis of fibromyalgia (OR = 1.80,CI 1.03-3.14, p = 0.04) were independent predictors of concurrent diagnosis of endometriosis in IC/BPS patients, Table 4. Increased age (OR = 0.98, CI 0.96-1.01, p = 0.22), HL presence (OR = 0.50, CI 0.11-2.34, p = 0.38), IBS (OR = 1.33, CI 0.77-2.28, p = 0.31), and vulvodynia (OR = 1.63, CI 0.85-3.12, p = 0.14) were not significantly associated with a concurrent diagnosis of endometriosis in IC/BPS on the MV analysis, Table 4.

## Discussion

In this study, we demonstrate that the non-bladder centric IC/BPS phenotype is significantly associated with a comorbid diagnosis of endometriosis. It is possible that the presence of endometriosis lesions in the pelvis cause bladder symptoms that may be incorrectly attributed to a primary bladder diagnosis of IC/BPS. Understanding this association is critical to appropriate gynecologic referral to further investigate IC/BPS patients who have normal bladder findings on hydrodistension.

Age was inversely correlated with a concurrent diagnosis of endometriosis: there was a 0.98-fold

TABLE 4. **Multivariate logistic regression analysis**

| | OR | 95% confidence interval | p value |
|---|---|---|---|
| Age (years) | 0.98 | 0.96-1.01 | 0.22 |
| Non-low bladder capacity | 4.53 | 1.004-20.42 | 0.049 |
| Hunner's lesion | 0.50 | 0.11-3.34 | 0.38 |
| Chronic pelvic pain | 1.84 | 1.04-3.24 | 0.04 |
| Irritable bowel syndrome | 1.33 | 0.77-2.28 | 0.31 |
| Fibromyalgia | 1.80 | 1.03-3.14 | 0.04 |
| Vulvodynia | 1.63 | 0.85-3.12 | 0.14 |

decreased risk of co-occurring endometriosis for every one-year increase in age demonstrated on UV regression analysis. These findings are consistent with what we know about endometriosis pathophysiology, in that it is predominantly considered an estrogen-dependent disease occurring in premenopausal women.[13-15] Several published reports have demonstrated that endometriosis symptoms significantly diminish, and often disappear completely, with natural, pharmacologic, and/or surgical induction of menopause.[15-17] Recent reports in the literature, however, have described the phenomenon of endometriosis symptom recurrence, most notably CPP, following menopause.[18-20] Our findings, as well as what is known in the published literature regarding disease pathophysiology, suggest that patients with CPP-related endometriosis symptom recurrence following menopause should undergo a detailed evaluation for IC/BPS among other medical co-morbid conditions, as they have a higher potential for dual disease.

Non-bladder centric IC/BPS patients with a concurrent diagnosis of endometriosis were significantly more likely to have other systemic pain syndromes including IBS, fibromyalgia, and vulvodynia. This is also consistent with what we know regarding endometriosis pathophysiology in that several inflammatory cytokines, most notably IL-1 beta, IL-6, IL-17, and TNF-alpha, have all been demonstrated to have increased concentrations within endometriosis lesions throughout the peritoneal cavity.[21-23] This intralesional inflammation may account for associations between endometriosis and multiple pain syndromes, including IC/BPS, IBS, fibromyalgia, vulvodynia, and dysmenorrhea. Reports in the literature have demonstrated that endometriosis patients have a highly associated prevalence of both IBS[24] and fibromyalgia.[25] Additionally, Trutnovsky et al showed a significant prevalence of both endometriosis and vulvodynia in CPP patients,[26] further highlighting the association between these medical conditions. Previous reports have also demonstrated an associated prevalence of both IBS and fibromyalgia,[27,28] among other conditions, in patients with IC/BPS. Moreover, UV regression analyses demonstrated that co-diagnoses of IBS (1.77-fold) and vulvodynia (2.04-fold) were predictors for concurrent diagnosis of endometriosis in IC/BPS patients, and a MV regression analysis demonstrated that fibromyalgia was an independent predictor concurrent endometriosis in IC/BPS patients with a 1.80-fold increased risk. IC/BPS patients with fibromyalgia, IBS, and vulvodynia should be considered for endometriosis screening.

Symptom scores obtained from two validated IC/BPS questionnaires (PUF and ICSI/ICPI) did not significantly differ between IC/BPS patients with and without concurrent diagnosis of endometriosis. This finding suggests that symptom severity scores on validated questionnaires are not enough information alone to predict the likelihood of concurrent endometriosis in IC/BPS patients.

The strengths of this study are the large, well-characterized, heterogeneous cohort of women who carried a diagnosis of IC/BPS and all underwent hydrodistension to determine anesthetic bladder capacity. This permitted robust statistical analysis of associated factors with different IC/BPS subtypes. This study was limited by the standard factors associated with a retrospective review including the potential for missed variables in the medical record. It is certainly plausible that a significant portion of women have undiagnosed endometriosis contributing to their CPP. While the incidence of co-occurring endometriosis was high, especially in patients with a systemic IC/BPS phenotype, it was less than the incidence demonstrated in previously published reports.[3-5] This may in part be due to the predominant symptoms present at the time of initial screening as well as the specialty performing screening. Therefore, if IC/BPS patients do not respond to IC/BPS therapies and have any residual pelvic pain, a laparoscopic evaluation and consultation with gynecology should be considered.

In conclusion, from this large retrospective database review, we found that women with non-low BC IC/BPS were significantly more likely to have concurrent endometriosis, IBS, fibromyalgia, and vulvodynia. Significant negative predictors for endometriosis were increased age and absence of HL on cystoscopy. Awareness about these associations will permit appropriate comprehensive assessment for endometriosis in women with non-low bladder capacity. □

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