



Functional somatic syndromes as risk factors for hysterectomy in early bladder pain syndrome/interstitial cystitis



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ABSTRACT

Objective: We tested the hypothesis that functional somatic syndromes (FSSs) are risk factors for hysterectomy in early bladder pain syndrome/interstitial cystitis (BPS/IC).

Methods: In 312 women with incident BPS/IC, we diagnosed seven pre-BPS/IC syndromes: chronic pelvic pain (CPP), fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome (IBS), sicca syndrome, migraine, and panic disorder. Each was defined as present *before* 12 months (existing syndrome) or onset *within* 12 months (new syndrome) prior to BPS/IC onset. Retrospectively, we sought associations between prior hysterectomy and existing FSSs. Prospectively, we studied associations of existing and new syndromes with subsequent hysterectomy. Logistic regression analyses adjusted for age, race, menopause and education.

Results: The retrospective study showed prior hysterectomy ($N = 63$) to be associated with existing CPP and the presence of multiple existing FSSs. The prospective study revealed that 30/249 women with a uterus at baseline (12%) underwent hysterectomy in early BPS/IC. This procedure was associated with new CPP (OR 6.0; CI 2.0, 18.2), new IBS (OR 5.4; CI 1.3, 22.3), and ≥ 3 existing FSSs (OR 3.9; CI 1.1, 13.9).

Conclusion: Accounting for CPP and IBS, the presence of multiple FSSs (most without pelvic pain) was a separate, independent risk factor for hysterectomy in early BPS/IC. This suggests that patient features in addition to abdominopelvic abnormalities led to this procedure. Until other populations are assessed, a prudent approach to patients who are contemplating hysterectomy (and possibly other surgeries) for pain and who have IBS or numerous FSSs is first to try alternative therapies including treatment of the FSSs.

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Introduction

Recently, investigators have shown that patients with each of several functional somatic syndromes (FSSs) were significantly more likely than those without to have a history of surgery. Fibromyalgia (FM) [1] was linked to appendectomy, back and neck surgery, and gynecologic procedures including hysterectomy [2]; chronic fatigue syndrome (CFS) to gynecologic surgery [3]; and irritable bowel syndrome (IBS) to cholecystectomy, appendectomy, back surgery, and hysterectomy [4]. However, these studies generally had two weaknesses.

The first was the possibility of confounding by other syndromes. A person with one FSS is likely to have additional FSSs as well as other conditions such as depression, anxiety, migraine, and chronic pelvic pain (CPP) [5]. Confounding would be present if an FSS not linked to a surgery appeared to be so because it was associated with another syndrome that itself was linked to the surgery. We demonstrated this concept in a study of women with bladder pain syndrome/interstitial cystitis (BPS/IC) [6], a chronic condition of unknown etiology that comprises pain perceived to be from the bladder plus urinary urgency, frequency, and nocturia. Our study showed that before the onset of BPS/IC, a lifetime history of multiple surgeries was associated by bivariable analyses with each of FM, CFS, CPP and other syndromes. However, when these conditions were studied together in multivariable analyses, only CPP was linked to multiple surgeries. An interpretation of these findings was that the other syndromes were associated with

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surgeries because each was linked to CPP, a common indication for several gynecologic procedures.

Our study, however, could not avoid the second weakness of prior reports, i.e., ignorance of the temporal relationship between FSSs and surgeries. Temporality is the most important hint to causality. If the surgical operation were first, the investigator would be prompted to explore something about the surgery such as anesthesia, peri-operative medications, or tissue damage as a cause of the FSS. If the FSS were first, the hypothesis would be generated that something about the FSS led to the surgical procedure. A preceding process leading to both the FSS and the surgery might yield either chronology, or no consistent sequence.

Our study was of recent-onset BPS/IC. As we followed these patients forward in time, we observed in the early years of BPS/IC a very high incidence of a specific surgical procedure, i.e., hysterectomy [7]. Because we already had determined the presence of FSSs and other syndromes before the onset of BPS/IC [8], we could address temporality by observing whether these preceding syndromes were associated with this subsequent procedure.

Methods

Methods for a case–control study seeking risk factors for BPS/IC have been presented [7,8]. Websites; postal and electronic mailings to patient support groups, urologists, and gynecologists; and solicitations at medical and support group meetings between 2004 and 2008 attracted 1177 women from across the United States who were screened to enroll 312 incident BPS/IC cases (≤ 12 months of BPS/IC symptoms). Inclusion criteria were ≥ 4 weeks of perceived bladder pain plus ≥ 2 of the symptoms of urgency, frequency and nocturia; exclusion criteria were known diseases with similar symptoms. A systematic process identified the BPS/IC onset date (index date). The study size was determined by power analysis for the parent study seeking risk factors for BPS/IC. The mean age of the 312 women on the index date was 42.3 years, 96% were white, 68% were married, 57% had at least a college education, and 39% had an income of $> \$75,000/\text{year}$ [9].

All were interviewed by telephone about pre-index date medical history. For chronic pelvic pain (CPP), fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), sicca syndrome, migraine, and panic disorder, we used published symptom-based consensus diagnoses constructed by experts [8]. A screening question for each syndrome was “At any time in your life before your index date, have you had (cardinal symptom) for (time or number of episodes)”. A “yes” led to a series of questions that included criteria for syndrome diagnosis and this query: “Did this (symptom) begin within 12 months before your index date?” Each syndrome was thus dichotomized: 1) existing syndrome—present *before* 12 months prior to BPS/IC onset; and 2) new syndrome—onset *within* 12 months prior to BPS/IC onset. To ease discussion, these FSSs and associated syndromes all will be called FSSs.

At another part of the interview, each participant was asked: “At any time before your index date of _____, did you have any type of surgery that required anesthesia ...?” [9] If yes, she was asked about hysterectomy and whether it was within 12 months or 1 month before her BPS/IC onset date. For women with both a new FSS and a hysterectomy within 1 month before BPS/IC onset, medical records were reviewed to assess the chronology of the FSS and the surgical procedure. To confirm reports of associations between *history* of FSSs and *history* of hysterectomy, we analyzed these retrospective data.

The prospective study of hysterectomy employed the interview at baseline plus at each follow-up 6, 12, 18, 24, 36 and 48 months later. The median length of follow-up was 33 months after IC/PBS onset; 304 cases (97%) participated in at least one follow-up. The 57 withdrawals (18%) did not differ substantively from cases who maintained follow-up [10]. The investigators had no role in patient management. At each follow-up, each case was asked: “Since _____ (the last contact),

have you had any of the following surgical procedures?” which included hysterectomy.

Similar statistics were applied to the retrospective and prospective studies. Bivariable comparisons of women with and without hysterectomy were conducted using Pearson's chi square or Fisher's exact tests. Analyses by number of FSSs were by non-parametric test of trend. From these assessments, variables significantly associated with hysterectomy ($p \leq 0.05$) were included in logistic regression models with these demographic variables: index date age, race, education and natural menopause. This study was approved by the University of Maryland School of Medicine Institutional Review Board and all participants provided written informed consent.

Results

Retrospective study

By one month before BPS/IC onset, 63 of the 312 cases had already had a hysterectomy and we sought its association with existing FSSs. Bivariable analyses of the seven FSSs showed that a greater proportion of women with a prior hysterectomy than without had each of existing CPP, CFS, and FM ($p \leq 0.013$ for each). Logistic regression analysis adjusted for age, race, menopause and education diminished CFS and FM to non-significance but revealed existing CPP to be associated with prior hysterectomy [odds ratio (OR) of 3.0] (Table 1). We performed a separate logistic regression analysis using the *number* of existing FSSs per person: patients with a history of two (OR 3.1) or ≥ 3 existing FSSs (OR 2.9) were each more likely to have had a prior hysterectomy than those with no FSSs (Table 1).

Prospective study

Of the 249 women who had not yet had a hysterectomy, 30 (12%) underwent this procedure in early BPS/IC. Most of the hysterectomies were clustered around BPS/IC onset: 8 in the month before and another 18 by the 12 month follow-up; the other 4 were reported by the 36 month follow-up [7]. In this report, the term “early BPS/IC” will mean the time from one month before BPS/IC onset through the 36 month follow-up.

New FSSs, i.e., with onset within 12 months before the index date, were examined as risk factors for hysterectomy in early BPS/IC. Among the 249 women with a uterus, 193 did not have existing CPP and so were at risk to develop new CPP. Twenty-two reported new CPP and of these, 8 (36%) underwent hysterectomy in early BPS/IC, vs. 13/171 (8%) without new CPP ($p < 0.001$). Of 188 women at risk for new IBS, 5/11 (45%) with new IBS had a hysterectomy in early BPS/IC vs. 16/177 (9%) who did not have new IBS ($p < 0.001$). Other new FSSs were not associated with hysterectomy in early BPS/IC.

We then looked at the role of existing FSSs, i.e., those present prior to 12 months before BPS/IC onset. On bivariable analyses, CFS was the only existing FSS significantly associated with hysterectomy in early BPS/IC, but this linkage disappeared on logistic regression analysis adjusted for age, race, menopause and education (data not shown). However, the *number* of existing FSSs was associated with hysterectomy in early BPS/IC (Table 2) and remained so in a similar logistic regression analysis (Table 3).

Of the 9 women with ≥ 3 existing FSSs who underwent hysterectomy in early BPS/IC, six had 3, two had 4, and one had 6 existing FSSs. These were IBS in 7, CFS 7, FM 6, migraine 4, panic disorder 4, CPP 3, and sicca syndrome 1. Regarding the FSSs defined by abdominopelvic pain, two of these women had neither existing CPP nor IBS, 4 had only IBS, and three had both. However, the appearance of *new* FSSs resulted in all 9 women reporting CPP and/or IBS by the time of hysterectomy: CPP alone in one, IBS alone in 4, and both CPP and IBS in another 4.

Table 4 integrates these findings: hysterectomy in early BPS/IC was significantly associated with ≥ 3 existing FSSs [OR 3.9; 95% confidence intervals 1.1, 13.9] and with new CPP (OR 6.0; 2.0, 18.2) and new IBS (OR 5.4; 1.3, 22.3). We repeated the logistic regression

Table 1

Logistic regression analyses for prior hysterectomy using existing^a functional somatic syndromes (FSSs) as either 1) individual syndromes or 2) number of syndromes

Variable	Odds ratio	95% confidence interval
1) Using individual existing FSSs		
CFS	2.1	.83 to 5.5
FM	1.2	.52 to 2.8
CPP	3.0	1.5 to 6.1
2) Using the number of existing FSSs		
One FSS	1.1	.44 to 2.8
Two FSSs	3.1	1.3 to 7.5
Three or more FSSs	2.9	1.2 to 7.0

Each analysis was adjusted for index date age, race, education, and natural menopause.

^a Existing = present before 12 months prior to BPS/IC onset.

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