Title: Chronic pelvic pain in an interdisciplinary setting: 1 year prospective cohort

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Condensation: Chronic pelvic pain, quality-of-life, and healthcare utilization improve in a 1 year prospective cohort at an interdisciplinary center, but catastrophizing is associated with persistent pain.

Short title: Chronic pelvic pain prospective cohort

Abstract

Background: Chronic pelvic pain affects ~15% of women, and presents a challenging problem for gynecologists due to its complex etiology involving multiple comorbidities. Thus an interdisciplinary approach has been proposed for chronic pelvic pain, where these multifactorial comorbidities can be addressed by different interventions at a single integrated center. Moreover, while cross-sectional studies can provide some insight into the association between these comorbidities and chronic pelvic pain severity, prospective longitudinal cohorts can identify comorbidities that are associated with changes in chronic pelvic pain severity over time.

Objective: To describe trends and factors associated with chronic pelvic pain severity over a 1 year prospective cohort at an interdisciplinary center, with a focus on the role of comorbidities and controlling for baseline pain, demographic factors, and treatment effects.

Methods: Prospective 1 year cohort study at an interdisciplinary tertiary referral center for pelvic pain and endometriosis, which provides minimally invasive surgery, medical management, pain education, physiotherapy, and psychological therapies. Exclusion criteria included menopause or age>50. Sample size was 296 (57% response rate at 1 year; 296/525). Primary outcome was CPP severity at 1 year on a 11-point numeric rating scale (0-10), which was categorized for ordinal regression (none-mild 0-3, moderate 4-6, severe 7-10). Secondary outcomes included functional quality-of-life and health utilization. Baseline comorbidities were endometriosis, irritable bowel syndrome, painful bladder syndrome, abdominal wall pain, pelvic floor myalgia, and validated questionnaires for depression, anxiety, and catastrophizing. Multivariable ordinal regression was used to identify baseline comorbidities associated with the primary outcome at 1 year.

Results: Chronic pelvic pain severity decreased by a median 2 points from baseline to 1 year (6/10 to 4/10, p<0.001). There was also an improvement in functional quality-of-life (42% to 29% on the pain subscale of the Endometriosis Health Profile-30, p<0.001), and a reduction in subjects requiring a physician visit (73% to 36%, p<0.001) or emergency visit (24% to 11%, p<0.001) in the last 3 months. On multivariable ordinal regression for the primary outcome, chronic pelvic pain severity at 1 year was independently associated with a higher score on the Pain Catastrophizing Scale at baseline (OR=1.10, 95% CI=1.00-1.21, p=0.04), controlling for baseline pain, treatment effects (surgery), age and referral status.

Conclusion: Improvements in chronic pelvic pain severity, quality-of-life, and health care utilization were observed in a 1 year cohort in an interdisciplinary setting. Higher pain catastrophizing at baseline was associated with greater chronic pelvic pain severity at 1 year. Consideration should be given to stratifying pelvic pain patients by catastrophizing level (rumination, magnification, helplessness) in research studies and in clinical practice.

Keywords: Chronic pelvic pain, endometriosis, interdisciplinary, quality-of-life, prospective cohort, pain catastrophizing

Introduction

Chronic pelvic pain (CPP) is a common clinical problem present in ~15% of women worldwide.[1] CPP is defined as pelvic pain >3-6 months that is not solely related to menstruation, sexual activity, or bowel movements.[2] CPP has a complex etiology arising from an interplay of gynecologic, urologic, gastrointestinal, musculoskeletal, and psychosocial comorbidities,[2] with a potential underlying mechanism being sensitization of the nervous system.[3] CPP can persist even after standard gynecologic management and is amongst the most challenging clinical problems encountered by gynecologists.[4]

Given the multifactorial origins of CPP, a multifaceted care model has been proposed that includes physiotherapy, psychological therapies, and standard gynecologic management.[2,4] This multifaceted care can be multidisciplinary (multiple specialists with independent goals) or interdisciplinary (multiple specialists coordinate to provide a common goal).[5] Several prospective studies have looked at aspects of a multifaceted approach for CPP in women,[6-12] with one study finding that catastrophizing was associated with persistent pain at 1 year.[12]

In 2011, the government of British Columbia funded an interdisciplinary center for pelvic pain and endometriosis, integrating gynecologic management (including advanced laparoscopic surgery with excision of endometriosis of all stages), with pain education, pelvic physiotherapy, and psychological approaches to pain management, all integrated at a single center.[4,13] In a previous baseline cross-sectional study, we observed a strong association between CPP severity at baseline and catastrophizing, in addition to associations with other comorbidities (abdominal wall pain, pelvic floor myalgia, painful bladder syndrome) and several demographic variables.[14]

In contrast, we found no difference in CPP severity between women with and without endometriosis.

In this study, we report on a 1 year prospective observational cohort at this interdisciplinary center. The first aim was to demonstrate the changes in CPP severity, functional quality-of-life, and health utilization, over the 1 year. The second aim was to diagnose comorbidities using rigorous criteria (gynecologic, urologic, gastrointestinal, musculoskeletal, and psychological) and to determine whether they were associated with CPP severity at 1 year, adjusting for baseline pain, demographic factors and treatment effects. Based on our previous baseline cross-sectional study,[14] we hypothesized that catastrophizing, abdominal wall pain, pelvic floor myalgia, and painful bladder syndrome may be associated with CPP severity at 1 year.

Methods

Setting, Cohort, and Study criteria:

This prospective cohort is based at the BC Women's Center for Pelvic Pain and Endometriosis, tertiary referral center for British Columbia.[4,13] The center includes gynecologists with expertise in management of CPP and with advanced training in minimally invasive surgery (e.g. laparoscopic excision of endometriosis). The center also includes a clinical fellow, a registered nurse, a physiotherapist with special interest in pelvic pain, and a clinical counselor with a practice focused on women's reproductive health.

Details of the prospective cohort have been previously published in a baseline cross-sectional study on CPP (December 2013 – April 2015).[14] The cohort was designed to examine variables

associated with baseline and prospective measures of pain and quality-of-life. Subjects gave informed consent for inclusion in the cohort, and the study received institutional research ethics board approval from the University of British Columbia (H11-02882).

For this study of 1 year prospective follow-up, we included new or re-referrals between December 2013 to December 2014. Common reasons for re-referral included recurrent chronic pelvic pain or dysmenorrhea a) after previous conservative surgical treatment at the center (e.g. secondary to myofascial pain or sensitization); b) after the patient chose to stop hormonal suppression (e.g. due to side-effects or to try to conceive); or c) after the patient initially declined recommended treatments, but now wished to return to follow the treatment plan. Exclusion criteria were menopausal or age > 50 (since endometriosis is the major diagnosis at our center), or no follow-up visits at the center (to exclude patients who we referred to another provider, e.g. those with vulvodynia alone).

Interventions:

Interdisciplinary interventions at the center have been previously described.[4] In brief, following discussion with the care providers, patients could choose to undergo minimally invasive surgery (conservative procedures such as excision of endometriosis, or hysterectomy +/- oophorectomy), medical management (hormonal, pain adjuvants, trigger point injections), and/or a pain program (involving a pain education workshop, physiotherapy, and counseling). The pain program was standardized: patients did a group pain workshop, and individual counseling and physiotherapy appointments (typically 2 visits each for counseling and for physiotherapy). Treatments were individualized to each patient. For example, if the pain was primarily non-gynecologic, or if

patients had persistent pain despite previous surgical or medical management, then they may be offered the pain program. In contrast, patients with focal findings on examination (e.g. nodule) may be offered surgery.

For the pain program, the initial pain education workshop involved validation of patients' experiences and discussion of the multifactorial contributors to CPP. Education was also provided on the neurophysiology of pain as an output of the nervous system, such that pain can persist in the central nervous system (sensitization) even after peripheral factors in the "tissue" (e.g. endometriosis) have been addressed.

The physiotherapy component of the pain program involved calm breathing techniques, addressing fear of movement, helpful postural and movement patterns, pacing and grading activity, and exercises to relax identified overactive muscles groups, often including abdominal obliques, rectus abdominus, hip adductors, deep hip rotators and pelvic floor muscles. Manual therapy to address hip and sacroiliac joint asymmetries was performed as needed, and symmetry and gluteal strengthening exercises were given to those with pelvic girdle-related pain.[15] If needed, dietary, behavioral and postural modifications for bladder/bowel function were given. Goals for all treatment were function related, with development of a self-management plan.

Counseling in the pain program included mindfulness-based strategies such as meditation, breathing, guided visualization, body scans and progressive muscle relaxation. Patients were also taught cognitive behavioral therapy strategies whereby they learned how the identification

and modification of thoughts and beliefs can affect emotions. Patients were directed to appropriate community resources and community mental health referrals, as required.

It should be noted that in some cases, patients chose to undergo surgery, physiotherapy, or counselling outside the center, for example due to distance from the center.

Data collection

Data collection was described previously.[14] Prior to the initial consultation, subjects completed an online questionnaire using the Research Electronic Data Capture (REDCap) system. The questionnaire includes ratings of different types of pelvic pain (e.g. CPP) on a 0-10 numeric rating scale in the last 3 months using a series of standardized questions.[14] Functional quality-of-life was also assessed (pain subscale of the Endometriosis Health Profile-30 (EHP-30) that addresses daily activities),[16] as well as physician visits or emergency room visits in the last 3 months via the questionnaire. Comprehensive data from demographics and past history were also collected in the questionnaire, and were supplemented by physical exam findings and review of medical records.

Comorbidities were diagnosed using rigorous criteria from the questionnaire, review of medical records, and/or findings from physical exam.[14] Endometriosis was classified into: present (previous surgical diagnosis or current nodule or endometrioma), clinically suspected (no previous surgery, but suspected based on history and exam tenderness), or absent. A diagnosis of irritable bowel syndrome was made using Rome III criteria,[17] and a diagnosis of painful bladder syndrome using criteria of the American Urological Association[18] or International

Continence Society.[19] For musculoskeletal dysfunction, abdominal wall pain (typically due to myofascial trigger points) was diagnosed by a positive Carnett test, and pelvic floor myalgia diagnosed by tenderness on palpation of the levator ani muscles.[14] Also included were validated questionnaires for depression (Patient Health Questionnaire-9; PHQ-9),[20] anxiety (Generalized Anxiety Disorder-7; GAD-7),[21] and catastrophizing (Pain Catastrophizing Scale; PCS).[22] Finally, we also included a composite variable summing the total number of comorbidities as defined above and using cutoffs for the psychological scales PHQ-9 > 10 (moderate), GAD-7 > 10 (moderate), and PCS > 30 (75^{th} centile).

At 1 year, a follow-up online questionnaire was sent to subjects to assess prospective outcomes. Data on interventions during the 1 year were collected from the follow-up online questionnaire, from review of medical records, and from a surgical database at our center with data entered prospectively as per the Endometriosis Phenome and Biobanking Project (EPHect) of the World Endometriosis Research Foundation.[23]

Data analyses

Comparison of CPP severity between baseline and 1 year follow-up

Primary outcome was CPP severity in the last 3 months (0-10). As previously published, CPP was specifically differentiated from other types of pelvic pain (dysmenorrhea, dyspareunia, dyschezia, back pain).[14] The primary outcome was compared between baseline and 1 year follow-up (Wilcoxon signed rank test or McNemar test when CPP severity was categorized into none-mild 0-3, moderate 4-6, and severe 7-10). Secondary outcomes were functional quality-of-life (EHP-30 pain subscale), and physician visits or emergency room visits in the last 3 months.

For the comorbidities, we also tracked the number of subjects meeting criteria for IBS/PBS and the depression (PHQ-9), anxiety (GAD-7), catastrophizing (PCS) scores over the year.

Factors associated with CPP severity at 1 year

We performed regression between CPP severity at 1 year andcomorbidities, demographic factors and treatments,, controlling for baseline CPP severity due to the risk of regression to the mean in longitudinal observational studies.[24] Ordinal logistic regression was utilized, with CPP severity at 1 year categorized as none-mild 0-3, moderate 4-6, or severe 7-10, because assumptions of linear regression modeling were not met (e.g. normality of residuals, linearity of the relationship, homoscedasticity) when the raw CPP severity (0-10) was used instead. Ordinal logistic regression produces odds ratios (OR) for an increase in CPP severity category (none-mild, moderate, severe). OR values above 1 indicate higher odds of being in a more severe pain category, while OR values below 1 indicate lower odds of being in a severe pain category. For example, an OR of 2.0 indicates a 2-fold higher odds of being in the severe CPP category, compared to the moderate/mild categories; and a 2-fold higher odds of being in the severe/moderate CPP categories compared to the mild category.

Each baseline comorbidity (and demographic factor and treatment) that was significantly associated with CPP severity at 1 year ($p < 0.05$) was then entered into a final multivariable ordinal logistic regression model, again with adjustment for baseline pain. Stepwise modeling was not performed, but all variables were entered simultaneously. . P-values for overall tests of variable significance were calculated via likelihood-ratio tests; 95% CI of the estimates were calculated using likelihood profiling; and the proportional odds assumption was examined for

every model. These regression analyses were done using the Vector Generalized Linear and Additive Models (VGAM) package in R.

Statistics

All statistics were performed using R v3.3.2 or SPSS 22.0™. Statistical significance was $p < 0.05$. Means were provided +/- one standard deviation, and medians were provided with interquartile range. Missing data for demographics and comorbidities were uncommon (0-3%) and were excluded without imputation. For sensitivity analysis, variables were analyzed both as the raw score and with cut-offs to aid in clinical interpretation (e.g. EHP-30 > 59 (75th centile) and PHQ-9 and GAD-7 > 10 (moderate symptoms)).

Pilot study and Sample size

We initially conducted a retrospective pilot study (n = 30) of ~1 year outcomes at our center. CPP severity (0-10) significantly decreased from baseline to follow-up (8.2 +/- 1.4 vs. 5.4 +/- 3.4, $p < 0.001$). Based on these initial findings, we proceeded with this prospective cohort. For the multivariable ordinal regression modeling in the prospective cohort, ~10 "events" for each category of the primary outcome (CPP severity at 1 year: 0-3, 4-6 or 7-10) is needed for each independent variable in the final regression model. In the final regression model, there were 7 independent variables (see Results). Thus, for each category of the primary outcome (0-3, 4-6, 7-10), there should be approximately 70 cases (7 x 10) in each category -- see Table 3.

Results

Study description

Five hundred twenty five patients met the inclusion/exclusion criteria, of which 296 completed the 1 year follow-up (57% response rate; 296/525) (Figure 1). Characteristics of the total sample, with comparison of those who followed-up at 1 year and those who were lost to follow-up, are shown in Table 1. The two groups were similar in baseline CPP severity and the other variables, except those lost to follow-up were on average 1.6 years younger, had depression scores 2 points higher (PHQ-9; out of 27), and anxiety scores 0.5 points higher (GAD-7; out of 21) (Table 1). Median duration of pain was 12 years in the sample. Prevalence of comorbidities at baseline, including endometriosis stage, are shown in Table 1. Interventions during the 1 year are described in Table 2.

Comparison of CPP severity between baseline and 1 year follow-up

Changes in the primary outcome and secondary outcomes from baseline to 1 year are demonstrated in Table 3. On average, CPP severity (0-10) decreased 2 points from baseline to 1 year ($p < 0.001$; Table 3). When CPP severity was categorized (none-mild 0-3, moderate 4-6, severe 7-10), the proportion of individuals in the severe category decreased from baseline to 1 year (49% to 27%), while the proportion in the none-mild category increased (24% to 50%) ($p < 0.001$; Table 3 and Figure 2).

For the secondary outcomes, there was a significant improvement in functional quality-of-life (EHP-30 pain subscale), and there was a significant reduction in the number of subjects with a physician or emergency visit in the last 3 months (Table 3). For comorbidities, the proportion of subjects meeting criteria for IBS and PBS, as well as the depression (PHQ-9), anxiety (GAD-7), and catastrophizing (PCS) scores, all decreased at 1 year (Table 3).

Factors associated with CPP severity at 1 year

To identify factors associated with CPP severity at 1 year, we used ordinal logistic regression with CPP severity at 1 year classified into the three categories (none-mild 0-3, moderate 4-6, severe 7-10), while controlling for baseline CPP severity. Two of the comorbidities at baseline had a significant association with CPP severity at 1 year (Table 4): greater pain catastrophizing ($p = 0.02$) and abdominal wall pain (i.e. positive Carnett test) ($p = 0.02$). There was also a significant relationship between the total number of comorbidities and CPP severity at 1 year ($p = 0.02$). Amongst the demographic variables, re-referral ($p = 0.008$) and history of sexual assault ($p = 0.04$) were associated with CPP severity at 1 year, while older age ($p = 0.006$) was associated with less CPP at 1 year (Table 4). In contrast, other demographic variables such as previous hysterectomy, parity, education, and income were not associated with CPP severity at 1 year (Table 4). Amongst the interventions, surgery at the center was associated with less CPP at 1 year, compared to those who did not undergo surgery ($p = 0.008$) (Table 2). There was no difference between hysterectomy and conservative surgery after adjustment for baseline differences between the two groups, and no significant associations for the other interventions (Table 2).

The final multivariable regression model contained surgery at the clinic, pain catastrophizing, abdominal wall pain, age, re-referral status, and history of sexual assault, again controlling for baseline pain. Total number of comorbidities was not included in this model as it is confounded with pain catastrophizing and abdominal pain. In the final model, greater baseline pain catastrophizing remained significantly associated with CPP severity at 1 year ($p = 0.04$) (Table 5

and Figure 3). Re-referral ($p = 0.01$), older age ($p = 0.02$), and surgery ($p = 0.05$) also remained significantly associated with CPP severity at 1 year, while abdominal wall pain and history of sexual assault did not.

Comment

In this prospective observational 1 year cohort at an interdisciplinary center (which includes laparoscopic surgery, medical management, and a pain program that incorporates pain education, physiotherapy and psychological therapy), we observed improvements in chronic pelvic pain (CPP) severity, functional quality-of-life, and health care utilization. Psychological comorbidities also decreased at 1 year, and interestingly, fewer patients met diagnostic criteria for irritable bowel syndrome (IBS) and painful bladder syndrome (PBS) at 1 year compared to baseline. Moreover, higher pain catastrophizing was the factor at baseline that was associated with CPP severity at 1 year (Figure 3). Other diagnosed comorbidities were not associated, including endometriosis, depression, anxiety, IBS, PBS, and abdominal wall or pelvic floor pain. Other variables associated with CPP severity at 1 year were CPP severity at baseline, younger age and re-referral status; while surgery at the center was associated with less CPP at 1 year (Figure 3).

Strengths of the study include its prospective nature, and its sample size (296 responders) and response rate (57%) that are comparable to other prospective observational cohorts for CPP in women (58-370 responders and response rates of 37.5-67.5%).[9-12] Other strengths are the use of rigorous criteria for diagnosis of comorbidities, including the use of validated questionnaires, published diagnostic criteria, and physical exam findings. The main limitation is the non-

randomized design. Furthermore, patients lost to follow-up were slightly younger and had more depression and anxiety symptoms, which means that improvements observed in the 1 year follow-up cohort may have been overestimated. Also, while the results may be similar for other tertiary referral centers, they may not be generalizable to community settings or to chronic pelvic pain cohorts with lower rates of endometriosis (>50% in our cohort). Another limitation is that outcomes were self-reported symptoms; physical examination (e.g. Carnett test or pelvic floor assessment) was not repeated at follow-up.

The setting of this cohort was an integrated, interdisciplinary center for pelvic pain. Amongst the interdisciplinary treatment components, laparoscopic surgery at the center was associated with less CPP at 1 year compared to having no surgery (Figure 2). However, since treatments were non-randomized and chosen by patient/clinician preference, this could be accounted for by differences between patients undergoing surgery and those that did not. Thus, caution is recommended and further research is needed into the role of minimally invasive surgery in patients with CPP, with follow-up beyond the 1 year period in this study. On the other hand, certain treatments were uncommon (e.g. trigger point injections), while others would be expected to be heterogeneous (e.g. physiotherapy or counseling outside the center), which limits our ability to determine associations with outcome for these interventions.

Several decades ago, a randomized trial was published that showed decreased pain with an integrated approach compared to standard gynecologic surgical/medical treatment,[6] although there have been changes in gynecologic treatments since then (particularly in laparoscopic surgery). Another randomized trial showed benefit for somatocognitive therapy combined with

non-surgical gynecologic management, compared to non-surgical gynecologic management alone.[7] Recently, a randomized trial involving psychotherapy and somatosensory stimulation showed pain reductions compared to wait-list control,[8] although standard gynecologic care was not part of the study design. Although these trials provide evidence for a multifaceted approach, they did not incorporate modern minimally invasive surgery into their treatment or control arms, nor did they include assessments of catastrophizing or health care utilization.

On multivariable regression, re-referral status remained significantly associated with more persistent chronic pelvic pain. It may be that these re-referrals had more central sensitization, which was not measured by or was independent of, at least in part, abdominal wall pain (Carnett test) and catastrophizing. In future work, quantitative sensory testing could be performed to determine whether such re-referrals have more central sensitization as hypothesized.

The magnitudes of the changes in outcomes observed over the 1 year were clinically significant. Subjects described a median 2 point decrease in CPP severity (0-10 scale) and a 13% increase in functional quality-of-life (Endometriosis Health Profile-30 (EHP-30) pain subscale) (Table 3), with a minimal clinically significant difference of 2/10 on the pain numeric rating scale[25] and between 11.5%-24.8% on the EHP-30 pain subscale.[26,27] Notably, there was a 37% and 13% absolute percentage decrease in the number of subjects who had a doctor visit and emergency visit in the last 3 months (Table 3). There was also a 17% and 10% absolute percentage decrease in the number of individuals meeting diagnostic criteria for IBS and PBS (Table 3), which may be evidence of the plasticity underlying viscero-visceral convergence in nervous system sensitization[28]. These observations were noteworthy given the morbidity of the sample: median

duration of pain of 12 years, prevalent comorbidities, and failed management in the community requiring referral to our tertiary center.

Pain catastrophizing is characterized by rumination, magnification, and helplessness.[22] Our finding that baseline pain catastrophizing, controlling for baseline pain severity, was associated with CPP severity at 1 year provides additional evidence for the importance of this psychological factor in women with pelvic pain. Martin et al. also found baseline catastrophizing to be associated with pain measured by the short-form McGill Pain Questionnaire in a 1 year prospective study ($b = 0.18$, $p = 0.04$).[12] In retrospective studies, Carey et al. found that pain catastrophizing at follow-up was associated with persistent pain after endometriosis surgery[29] ($b = 0.66$, $p = 0.01$), while Weijenborg et al. found that a reduction in catastrophizing was associated with an increase in pain control[30] ($r = -0.388$, $p < 0.01$). Catastrophizing may influence 1 year outcomes by ongoing rumination on pain symptoms, which may negatively affect the pain education provided during physician visits or during the formal pain education workshop. Also, even if treatment improves CPP, catastrophizing patients may still magnify pain symptoms, thereby resulting in less improvement in patient-reported CPP severity scores. Helplessness associated with catastrophizing may also antagonize treatment effects: if a patient feels that no treatment will help, then the patient may have less confidence in efficacy even before the treatment has been initiated.We recommend that mental health assessment in women with CPP include catastrophizing in addition to depression and anxiety. Patients with high catastrophizing may be more likely to be treatment resistant, even in an interdisciplinary setting. Consideration should be given to phenotyping or stratifying pelvic pain patients by catastrophizing level in future research and in clinical practice. This study suggests that

psychological treatment of catastrophizing should be considered as part of the management of CPP, in addition to treatments that directly reduce pain (e.g. surgical or hormonal). Such treatments could include cognitive behavioral therapy designed to address catastrophizing[31], mindfulness based stress reduction[31], or strategies to improve sleep[32]. A future clinical trial could examine the synergy between treatments targeted to catastrophizing and those targeted to the pain itself, in order to determine whether they have an additive or multiplicative effect on pain outcomes.

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Tables:

See attached Tables 1-5

Figure titles and legends:

Figure 1. Flow chart. Flow chart of cases who followed-up at 1 year and those who were lost to follow-up

Figure 2. CPP severity at baseline and 1 year. 1 year change in the number of cases within each category of CPP severity (0-3, 4-6, 7-10).

Figure 3. Proportional odds ratios (OR) for variables in the final multivariable regression model for CPP severity at 1 year (three categories: 0-3, 4-6, 7-10). OR > 1 corresponds to higher odds of being in a more severe CPP category at 1 year; while OR < 1 corresponds to lower odds of being in a more severe CPP category at 1 year. All variables are from baseline, except for surgery which was during the 1 year between baseline and follow-up.

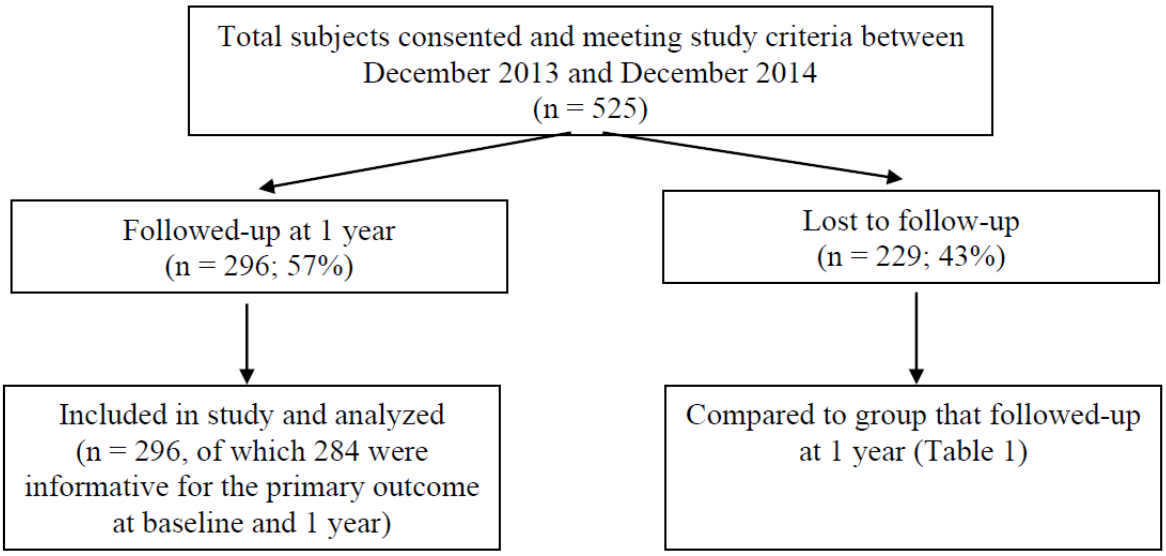
Total subjects consented and meeting study criteria between December 2013 and December 2014 (n = 525)
Followed-up at 1 year (n = 296; 57%)
Lost to follow-up (n = 229; 43%)
Included in study and analyzed (n = 296, of which 284 were informative for the primary outcome at baseline and 1 year)
Compared to group that followed-up at 1 year (Table 1)

Figure 1

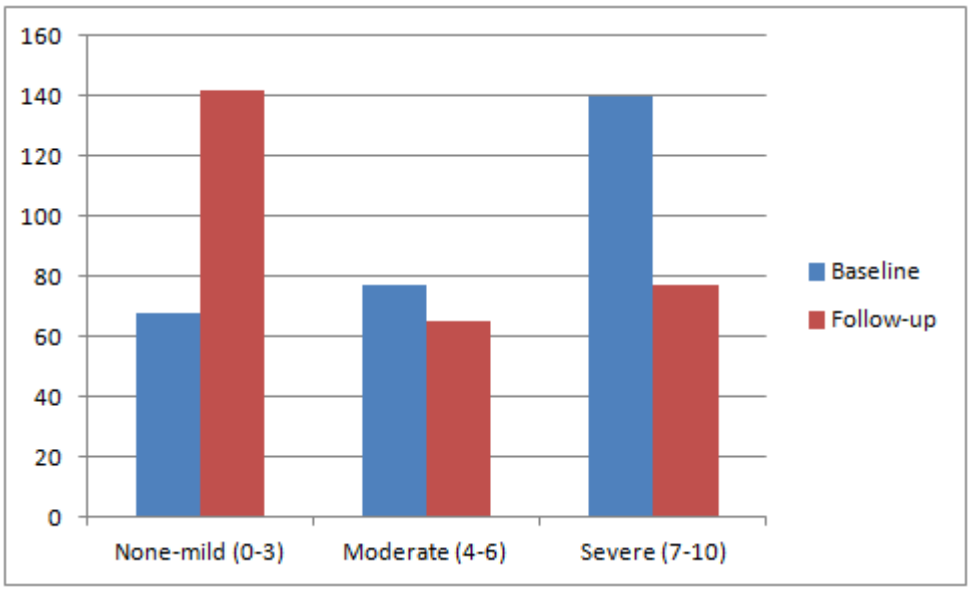
160
140
120
100
80
60
40
20
0
None-mild (0-3)
Moderate (4-6)
Severe (7-10)
Baseline
Follow-up

Figure 2

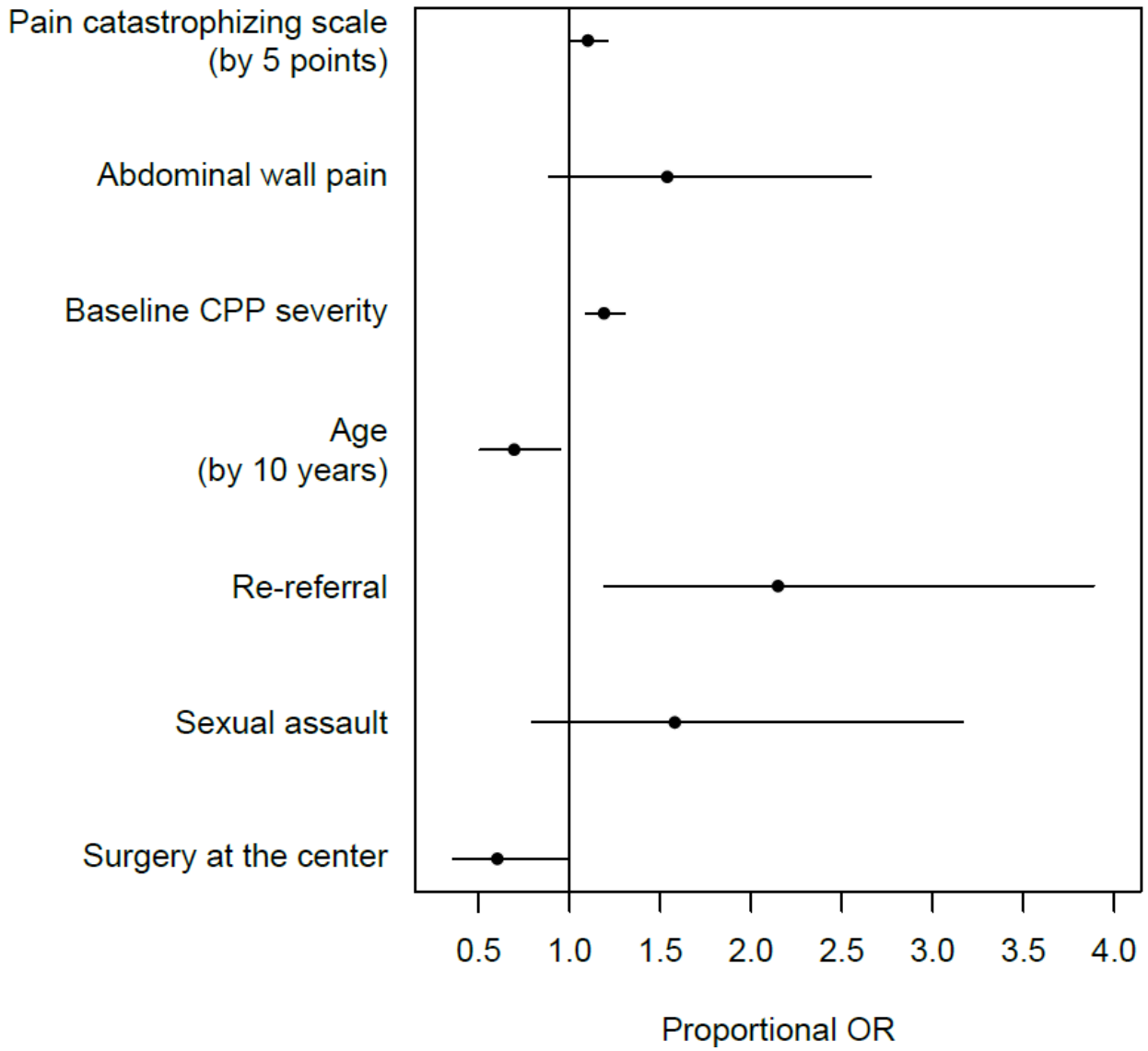
Pain catastrophizing scale
(by 5 points)
Abdominal wall pain
Baseline CPP severity
Age
(by 10 years)
Re-referral
Sexual assault
Surgery at the center
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Proportional OR

Figure 3

Table 1. Clinical characteristics of the study sample.

Baseline variables	Total Sample (n = 525)	1 year follow-up		P-value
		Followed-up (n = 296)	Lost to follow-up (n = 229)	
Demographics				
Age				
Mean (SD)	**34.3 (±7.6)**	**35.0 (±7.8)**	**33.4 (±7.3)**	**0.02**
Parity				
No previous birth	323 (63.2%)	180 (61.9%)	143 (65.0%)	0.52
Previous birth(s)	188 (36.8%)	111 (38.1%)	77 (35.0%)	
BMI				
Mean (SD)	25.3 (±5.6)	25.6 (±5.5)	25.0 (±5.7)	0.13
Smoking				
No	436 (85.3%)	250 (85.9%)	186 (84.5%)	0.71
Yes	75 (14.7%)	41 (14.1%)	34 (15.5%)	
Referral				
New referral	400 (76.2%)	233 (78.7%)	167 (72.9%)	0.15
Re-referral	125 (23.8%)	63 (21.3%)	62 (27.1%)	
Geography				
Metro Vancouver	356 (69.1%)	204 (70.1%)	152 (67.9%)	0.63
Outside	159 (30.9%)	87 (29.9%)	72 (32.1%)	
History of sexual assault				
No or no answer	433 (85.7%)	248 (86.1%)	185 (85.3%)	0.80
Yes	72 (14.3%)	40 (13.9%)	32 (14.7%)	
Family history of chronic pain				
No or Don't know	376 (73.7%)	214 (73.5%)	162 (74.0%)	0.92
Yes	134 (26.3%)	77 (26.5%)	57 (26.0%)	
Duration of pain (years)				
Median (IQR)	12.0 (5.0 - 21.0)	13.0 (5.2 - 21.0)	12.0 (4.0 - 20.0)	0.22
Previous hysterectomy				
No	491 (94.2%)	276 (93.6%)	215 (95.1%)	0.57
Yes	30 (5.8%)	19 (6.4%)	11 (4.9%)	
Education				
High school or less	65 (12.7%)	31 (10.7%)	34 (15.5%)	0.39
Some college	127 (24.9%)	71 (24.4%)	56 (25.6%)	
College graduate	210 (41.2%)	124 (42.6%)	86 (39.3%)	
Post-grad degree	90 (17.6%)	56 (19.2%)	34 (15.5%)	
Other	18 (3.5%)	9 (3.1%)	9 (4.1%)	
Income				
Less than $20,000	61 (12.0%)	28 (9.6%)	33 (15.1%)	0.24
$20,000-$39,999	92 (18.0%)	55 (18.9%)	37 (16.9%)	
$40,000-$59,999	80 (15.7%)	40 (13.7%)	40 (18.3%)	
$60,000-$79,999	85 (16.7%)	51 (17.5%)	34 (15.5%)	
$80,000-$99,999	72 (14.1%)	42 (14.4%)	30 (13.7%)	
$100,000 or more	120 (23.5%)	75 (25.8%)	45 (20.5%)	
Marital Status				
No	283 (55.5%)	155 (53.3%)	128 (58.4%)	0.28
Yes	227 (44.5%)	136 (46.7%)	91 (41.6%)	
Comorbidities				

Table 1. Clinical characteristics of the study sample.

Baseline variables	Total Sample (n = 525)	1 year follow-up		P-value
		Followed-up (n = 296)	Lost to follow-up (n = 229)	
Endometriosis				
None	94 (17.9%)	43 (14.5%)	51 (22.3%)	0.06
Present	304 (57.9%)	175 (59.1%)	129 (56.3%)	
Suspected	127 (24.2%)	78 (26.4%)	49 (21.4%)	
Stage (for endo present)				
I-II	118 (38.8%)	61 (34.9%)	57 (44.2%)	0.24
III-IV	129 (42.4%)	78 (44.6%)	51 (39.5%)	
Unknown	57 (18.8%)	36 (20.5%)	21 (16.3%)	
Abdominal wall pain				
Carnett negative	378 (72.0%)	222 (75.0%)	156 (68.1%)	0.10
Carnett positive	147 (28.0%)	74 (25.0%)	73 (31.9%)	
Pelvic floor myalgia				
Non-tender	350 (68.8%)	209 (71.8%)	141 (64.7%)	0.10
Tender	159 (31.2%)	82 (28.2%)	77 (35.3%)	
Irritable bowel syndrome				
No	242 (46.1%)	131 (44.3%)	111 (48.5%)	0.38
Yes	283 (53.9%)	165 (55.7%)	118 (51.5%)	
Painful bladder syndrome				
No	303 (57.7%)	170 (57.4%)	133 (58.1%)	0.93
Yes	222 (42.3%)	126 (42.6%)	96 (41.9%)	
Depression (PHQ9)				
Median (IQR)	**7.0 (3.0 - 13.0)**	**7.0 (3.0 - 12.0)**	**9.0 (4.0 - 14.0)**	**0.009**
Anxiety (GAD7)				
Median (IQR)	**5.0 (2.0 - 9.0)**	**4.5 (2.0 - 9.0)**	**5.0 (3.0 - 11.0)**	**0.03**
Pain catastrophizing (PCS)				
Median (IQR)	16.0 (8.0 - 30.0)	15.5 (7.0 - 30.0)	16.0 (8.0 - 29.0)	0.84
Total number of comorbidities				
Median (IQR) [range]	2 (1 - 3) [0 - 6]	2 (1 - 3)	2 (1 - 3)	0.46

P-values are from Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for categorical variables

Table 2. Treatment effects on CPP severity at 1 year (categorized into 0-3, 4-6, 7-10)

Intervention	N	OR[a]	95% CI	*P*-value	adjOR[b]	95% CI	*P*-value
Participation in pain program		1.74	0.98-3.12	0.06	1.25	0.65-2.4	0.50
No	233						
Yes	51						
Surgery at the center		**0.53**	**0.33-0.84**	**0.008**	**0.60**	**0.36-0.99**	**0.05**
No	151						
Yes	133						
Hysterectomy	32	**0.36**	**0.14-0.85**	**0.02**	0.52	0.19-1.39	0.61
Conservative	101						
Use of pain adjuvant (baseline, follow-up)				0.29			0.74
None	218	ref	ref		ref	ref	
Started after baseline, and continued to follow-up	15	0.95	0.32-2.65		0.72	0.22-2.18	
Taking at baseline, but discontinued before follow-up	19	1.11	0.47-2.59		0.88	0.33-2.28	
Taking at both baseline and follow-up	30	2.07	0.98-4.45		1.43	0.62-3.32	
Use of hormonal medication (baseline, follow-up)				0.71			0.57
None	169	ref	ref		ref	ref	
Started after baseline, and continued to follow-up	29	0.84	0.38-1.8		0.57	0.23-1.32	
Taking at baseline, but discontinued before follow-up	48	0.81	0.43-1.52		0.79	0.40-1.52	
Taking at both baseline and follow-up	38	1.29	0.56-2.52		0.97	0.46-3.03	
Trigger point injections[c]		1.92	0.65-6.08	0.24	-	-	-
No	269						
Yes	13						
Surgery outside of the center		1.07	0.55-2.06	0.84	1.13	0.55-2.28	0.73
No	243						
Yes	39						
Physiotherapy outside of the center		1.19	0.66-2.13	0.57	0.87	0.46-1.64	0.67
No	232						
Yes	50						
Counselling outside of the center		1.58	0.78-3.19	0.2	1.41	0.69-2.89	0.35
No	248						
Yes	34						

[a]Ordinal regression, adjusted for baseline CPP severity. OR values above 1 indicate higher odds of being in a more severe pain category (0-3 vs. 4-6 vs. 7-10), while OR values below 1 indicate lower odds of being in a severe pain category.
[b]Ordinal regression, adjusted for baseline CPP severity, age, abdominal wall pain (Carnett positive), history of adult sexual assault, pain catastrophizing score, and re-referral status.
[c]No adjusted model due to small sample size in the treatment group

Table 3. Outcome variables at baseline and follow up

Outcomes	**N**	**Baseline**	**Follow up**	**P-value**
Primary[1]	284			
CPP severity (0-10), median (IQR)		6 (4 - 8)	4 (0 - 7)	< 0.0001
CPP severity, severe 7-10, n [%]		140 [49%]	77 [27%]	
CPP severity, moderate 4-6, n [%]		77 [27%]	65 [23%]	
CPP severity, none-mild 0-3, n[%]		68 [24%]	142 [50%]	< 0.0001
Secondary				
Quality-of-life: EHP-30 pain subscale (0-100%), mean (SD)[2]	268	42% (26%)	29% (25%)	< 0.0001
Quality-of-life: EHP-30 pain subscale > 59 (75th centile), n [%][2]	268	90 [34%]	41 [15%]	< 0.0001
Any physician visit in previous 3 months, n [%]	284	206 [73%]	102 [36%]	< 0.0001
Any emergency visit in previous 3 months, n [%]	284	67 [24%]	32 [11%]	< 0.0001
Comorbidities				
Irritable bowel syndrome (IBS), n [%]	284	160 [56%]	110 [39%]	< 0.0001
Painful bladder syndrome (PBS), n [%]	284	121 [43%]	93 [33%]	0.002
Depression: PHQ-9, median (IQR) [2]	268	7 (3 - 13)	4 (1 - 9)	< 0.0001
Depression: PHQ-9, ≥ 10 (moderate), n [%][2]	268	88 [33%]	64 [24%]	0.008
Anxiety: GAD-7, median (IQR) [2]	268	5 (2 - 9)	3 (0 - 7)	< 0.0001
Anxiety: GAD-7 ≥ 10 (moderate), n [%][2]	268	63 [24%]	38 [14%]	0.001
Catastrophizing: PCS, median (IQR) [2]	268	16 (8 - 30)	9 (1 - 20)	< 0.0001
Catastrophizing: PCS > 30 (75th centile), n [%][2]	268	59 [22%]	31 [12%]	0.0002

[1]N = 284 subjects who were informative for chronic pelvic pain (CPP) severity at baseline and follow-up

[2]N = 268 subjects who were informative for the Endometriosis Health Profile-30 (EHP-30) pain subscale at baseline and follow-up. A higher EHP-30 pain subscale indicates a lower quality-of-life (i.e. 100% centile indicative of worst quality-of-life). N = 268 subjects also informative for the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Pain Catastrophizing Scale (PCS) at baseline and follow-up.

P-values are from Wilcoxon signed rank tests for paired numerical data and McNemar tests for paired categorical data

Table 4. Demographics and comorbidities at baseline associated with CPP severity at 1 year (0-3, 4-6, 7-10)

Baseline variables	Proportional OR (95%CI)[a]	p-value
Demographics		
Age	**0.96 (0.93 to 0.99)**	**0.006**
BMI	1.03 (0.99 to 1.08)	0.07
Family history of chronic pain	0.86 (0.52 to 1.44)	0.77
History of sexual assault	**1.98 (1.03 to 3.81)**	**0.04**
Smoking	0.56 (0.28 to 1.11)	0.52
Re-referral	**2.09 (1.22 to 3.61)**	**0.008**
Geography (outside Metro Vancouver)	1.05 (0.64 to 1.71)	0.85
Parous	0.79 (0.49 to 1.26)	0.70
Duration of pain	0.98 (0.96 to 1.01)	0.35
Previous Hysterectomy	0.7 (0.26 to 1.78)	0.46
Education: High school or less	reference	0.53
Education: Some College	0.87 (0.39 to 1.97)	
Education: College graduate	1.02 (0.47 to 2.24)	
Education: Post-grad degree	0.44 (0.18 to 1.09)	
Income: < 20K	reference	0.84
Income: 20-39,999K	0.71 (0.28 to 1.74)	
Income: 40-59,999K	0.53 (0.2 to 1.38)	
Income: 60-79,999K	0.57 (0.22 to 1.45)	
Income:80-99,999K	0.57 (0.22 to 1.45)	
Income: 100K+	0.57 (0.22 to 1.45)	
Married	0.8 (0.51 to 1.27)	0.71
Comorbidities		
Endometriosis present[b]	0.83 (0.42 to 1.66)	0.18
Endometriosis suspected[b]	1.35 (0.64 to 2.89)	
Abdominal wall pain	**1.83 (1.09 to 3.08)**	**0.02**
Pelvic floor myalgia	1.14 (0.69 to 1.88)	0.61
Irritable bowel syndrome (IBS)	1.09 (0.69 to 1.73)	0.71
Painful bladder syndrome (PBS)	1.55 (0.98 to 2.45)	0.06
Depression (PHQ-9)	1.02 (0.99 to 1.33)	0.32
Anxiety (GAD-7)	1.04 (0.99 to 1.08)	0.27
Pain catastrophizing scale (PCS)	**1.02 (1.00 to 1.04)**	**0.02**
Total number of comorbidities	**1.21 (1.03 to 1.41)**	**0.02**

[a]Ordinal regression, adjusting for baseline CPP severity. OR values above 1 indicate higher odds of being in a more severe pain category (0-3 vs. 4-6 vs. 7-10), while OR values below 1 indicate lower odds of being in a severe pain category.

[b]Compared to endometriosis absent

675

Table 5. Multivariable ordinal regression model for CPP severity at 1 year (0-3, 4-6, 7-10)

Independent variables	Proportional OR (95% CI)[a]	p-value
Baseline comorbidities		
Pain catastrophizing scale (PCS)[b]	**1.10 (1.00-1.21)**	**0.04**
Abdominal wall pain	1.54 (0.89-2.66)	0.12
Baseline CPP severity		
CPP severity (0-10)	**1.19 (1.09-1.31)**	**<0.0001**
Baseline demographics		
Age[c]	**0.70 (0.51-0.95)**	**0.02**
Re-referral	**2.15 (1.20-3.89)**	**0.01**
History of sexual assault	1.58 (0.79-3.17)	0.19
Treatment effects		
Surgery at the center	**0.60 (0.36-0.99)**	**0.05**

676 [a]Ordinal regression. OR values above 1 indicate higher odds of being in a more severe pain category (0-3 vs. 4-6 vs.
677 7-10), while OR values below 1 indicate lower odds of being in a severe pain category.
678 [b]5 point increments
679 [c]10 year increments
680