

21 Tel: 604-875-2534; Fax: 604-875-2569; Email: Paul.Yong@vch.ca

22

23 Clinical Trial: Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC) Data Registry
24 (ClinicalTrials.gov: NCT02911090).

25 IRB: University of British Columbia: H11-02882 and H16-00264. Date: October 16, 2012
26 and June 13, 2016

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45 **Abstract**

46

47 **Background:** Endometriosis is a complex condition that can negatively affect a woman's
48 quality of life, including her sleep. This study aims to assess the multifactorial variables
49 associated with poorer quality of sleep in women with endometriosis.

50 **Methods:** Data from the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC) data
51 registry were analyzed for women who underwent surgery at the BC Women's Center for
52 Pelvic Pain and Endometriosis with histopathological confirmation of endometriosis
53 (June 2015 to June 2017). The primary outcome was quality of sleep pre-operatively,
54 from the Chronic Pain Sleep Inventory. Bivariate analysis and multivariable linear
55 regression were done to determine any significant associations between pre-operative
56 patient variables and overall quality of sleep, based on p-value of 0.05.

57 **Results:** Two hundred and seventy-five women met the study criteria. Poorer overall
58 quality of sleep was independently associated with poorer functional quality-of-life (EHP-
59 30) ($b = -.18$, $p = .0026$), more depressive symptoms (PHQ-9) ($b = -1.62$, $p < .001$), and
60 painful bladder syndrome ($b = -5.82$, $p = .035$). This indicates that a 1 point increase in
61 the EHP-30 (worsening quality-of-life), a 1 point increase in the PHQ-9 (worsening
62 depression) and the presence of painful bladder syndrome, increased the primary
63 outcome (i.e. towards poorer quality of sleep) by 0.18, 1.62, and 5.82 points.

64 **Conclusion:** Poorer quality of sleep in women with endometriosis is associated with
65 poorer quality-of-life, more depressive symptoms, and bladder pain. Research into
66 interventions that improve sleep is warranted as part of the management of some
67 women with endometriosis.

68 **Key words:** endometriosis, quality of sleep, Chronic Pain Sleep Inventory, pain.

69

70

71 **Introduction**

72 Endometriosis is a complex condition in which endometrial glands and stroma grow
73 outside the uterus, leading to pelvic pain¹, which in turn can negatively impact women's
74 quality of life^{2,3}. Quality of life is poorer in all domains among women with endometriosis
75 compared to controls, including poorer quality of sleep⁴. Sleep plays an essential role in
76 vital functions, such as metabolism, memory and repair, in addition to being important for
77 quality of life and social, emotional and physical well-being⁵. In a large study from the
78 National Health and Nutrition Examination Survey, optimal levels of sleep were
79 associated with a reduced risk of all-cause mortality, as well as higher health-related
80 quality of life⁶. Sleep dysfunction is prevalent in patients with chronic pain conditions⁷,
81 and even more, poor sleep quality is associated with dysmenorrhea (painful
82 menstruation)⁸ and chronic pelvic pain⁹.

83 Emerging research suggests that sleep impairment may not only be a consequence of
84 pain, but can also lead to worse pain¹⁰. Edwards et al revealed that fluctuations in daily
85 sleep patterns influenced the patient's next day subjective pain report¹¹. Additionally,
86 another study showed that insufficient sleep led to higher inflammatory markers and
87 increased pain ratings¹². These findings highlight the importance of targeting sleep as
88 part of the treatment of patients with chronic pain.

89 In a group of pre-menopausal women with noncancerous gynecologic conditions,
90 women scoring higher on the Pelvic Problem Impact Questionnaire had higher odds of
91 experiencing poor sleep quality (adjusted odds ratio 1.59 [1.27-1.98]¹³. In regards to
92 patients with endometriosis, Nunes et al revealed that these women have poorer sleep,

93 as well as reduced pain thresholds, supporting the relationship between poor sleep and
94 endometriosis-associated pain¹⁴. Another study looked specifically at patients with
95 posterior cul-de-sac endometriosis, and showed poorer quality of sleep, excessive
96 daytime sleepiness, and insomnia, compared to a control group¹⁵. However, these
97 studies did not look at quality of life or psychological comorbidities.

98 In this study, we performed a quantitative analysis of sleep quality in women with
99 surgically-confirmed endometriosis, utilizing a comprehensive prospective database, in
100 order to assess the multifactorial variables associated with poorer sleep including the
101 use of validated questionnaires for mental health and functional quality-of-life. The goal
102 was to identify factors independently associated with poorer sleep, which may point to
103 strategies to improve quality of life in this population.

104

105 **Materials and Methods**

106 Setting

107 The data for this study were derived from a prospective data registry (Endometriosis
108 Pelvic Pain Interdisciplinary Cohort (EPPIC), ClinicalTrials.gov: NCT02911090) at a
109 tertiary referral center, the BC Women's Center for Pelvic Pain and Endometriosis. This
110 cohort has been previously described¹⁶, and received institutional research ethics board
111 approval from the University of British Columbia (H11-02882 and H16-00264). After
112 consenting to participation in the registry, patients answered baseline online questions
113 on their severity of pain and past medical history, as well as validated questionnaires
114 including for sleep as described below¹⁷.

115

116 Study criteria

117 For this study, the inclusion criteria were women who a) consented to the registry; b)
118 answered baseline questionnaires including the sleep questions; and c) subsequently
119 underwent surgery at the center between June 2015 to June 2017, with excision of
120 visual disease and histopathological confirmation of endometriosis. Women who
121 indicated “no bleeding” or “never sexually active” were excluded from analysis, to focus
122 on women who were menstruating and were sexually active, such that we could assess
123 dysmenorrhea and dyspareunia.

124

125 Outcome variables

126 The Chronic Pain Sleep Inventory (CPSI) is a 5-item questionnaire that was previously
127 validated in patients undergoing clinical trials for chronic pain¹⁷. CPSI item 5 asks “How
128 would you rate the overall quality of your sleep?”, rated on a 100-mm visual analog scale
129 (VAS) anchored from 0 (very poor) to 100 (excellent). For our primary outcome, we
130 incorporated CPSI item 5 into our online patient registry, by asking patients about overall
131 quality of sleep with an online VAS bar that patients could move from left (anchor = 0 or
132 very poor) to right (anchor = 100 or excellent).

133

134 If significant associations were identified for the primary outcome, sub-analyses were
135 done for CPSI items 1-4, which were incorporated into our online patient registry by
136 asking patients abbreviated questions about trouble falling asleep, needing sleep
137 medication, awakened by pain in the night, or awakened by pain in the morning, each

138 with an online VAS bar that patients from could move left (anchor = 0 or never) to right
139 (anchor = 100 or always) (see Supplementary tables).

140

141 Statistical analysis

142 We tested for associations between the primary outcome and the following pre-operative
143 baseline variables from the data registry: 1) demographic variables (e.g. age, BMI); 2)
144 pain scores on a numeric rating scale (0-10) for dysmenorrhea, dyspareunia, dyschezia,
145 and back pain; 3) functional pain subscale of the validated Endometriosis Health Profile-
146 30 for quality-of-life¹⁸, which assesses impact of endometriosis-associated pain on day-
147 to-day activities; 4) validated psychological questionnaires, Generalized Anxiety
148 Disorder-7 (GAD-7) for anxiety¹⁹, Patient Health Questionnaire-9 (PHQ-9) for
149 depression²⁰, and the Pain Catastrophizing Scale (PCS)²¹; 5) co-morbid diagnoses
150 including irritable bowel syndrome (IBS) using Rome III criteria²² and painful bladder
151 syndrome (PBS) using the criteria of the American Urological Association²³ or
152 International Continence Society²⁴; and 6) endometriosis anatomical variables at the
153 time of surgery (e.g. Stage, superficial endometriosis, ovarian endometrioma cyst, deep
154 infiltrating endometriosis).

155 Bivariate analysis was done to determine any significant associations between these
156 variables and the primary outcome (overall quality of sleep), based on p-value of .05.

157 Bivariate tests included Spearman's rank correlation, Mann-Whitney U Test, or Kruskal-
158 Wallis test, based on the type of variable. Non-parametric testing was used due to non-
159 normality of continuous variable as confirmed by the Kolmogorov-Smirnov and Shapiro-
160 Wilk tests. Variables with a significant association on bivariate analysis with the primary
161 outcome were then entered into a multivariable linear regression model, with the primary

162 outcome (overall quality of sleep) as the dependent variable. This was followed by
163 backward elimination based on p-value of .05 to obtain the final model. The purpose of
164 the regression analysis as to identify variables with an independent association with the
165 primary outcome, rather than confounding adjustment.

166 IBM SPSS Statistics 24 was used for statistical analyses. Means are described +/- one
167 standard deviation for normally distributed variables, with medians and ranges for non-
168 normally distributed variables. Missing variables were excluded. A sample size of ~250
169 is required for valid estimates of correlation coefficients in observational studies²⁵.

170

171 **Results**

172 Descriptive statistics

173 Two-hundred and seventy-five women met study criteria (Figure 1). Demographic data
174 are shown in Table 1. In particular, a slight majority (58.6%; 161/275) had ASRM Stage
175 I-II endometriosis, compared to ASRM Stage III-IV²⁶. Most patients had superficial
176 endometriosis (86.5%, 238/275), but 28.7% (79/275) had an ovarian endometrioma cyst,
177 and 18.5% (51/275) had deep infiltrating endometriosis reported at the time of surgery
178 (noting that multiple types of endometriosis can co-exist in the same patient). The deep
179 infiltrating nodules were located on: the rectum (n = 8), sigmoid (n = 3), rectovaginal
180 septum (n = 10), vagina (n = 5), right uterosacral (n = 20), left uterosacral (n = 25),
181 pouch of Douglas (n = 3), posterior uterus/cervix (n = 2), bladder (n = 2), ureteric (n = 3),
182 or other (n = 5) (note that more than nodule could be present in a patient). More than
183 half of patients had co-morbid IBS or PBS (Table 1). Pain scores were moderate, and
184 mean scores are listed in Table 1.

185 For the primary outcome, overall quality of sleep (0-100) at baseline in the cohort was
186 44.1 ± 25.5 (Table 2). Similar scores were obtained for the secondary outcomes
187 (difficulty falling asleep, awakened by pain in the night, and awakened by pain in the
188 morning), except for needing sleep medication (27.4 ± 34.6) (Table 2).

189

190 Bivariate analyses

191 On bivariate analyses, the primary outcome, i.e. overall quality of sleep at baseline, was
192 poorer in those with (Table 3): 1) higher BMI; 2) more severe pain scores; 3) poorer
193 functional quality of life on the EHP-30; 4) more psychological symptomology (on the
194 PHQ-9 depression scale, GAD-7 anxiety scale, and PCS catastrophizing scale); 5)
195 painful bladder syndrome (but not irritable bowel syndrome); 6) alcohol use; and 7)
196 Stage I/II endometriosis (vs. III/IV). In contrast, overall quality of sleep was better in
197 those with 1) older age, higher education, and currently working; and 2) an ovarian
198 endometrioma cyst (Table 3).

199

200 Regression

201 Variables that had a significant bivariate association with the primary outcome were
202 entered into a multivariable linear regression model, and after backward elimination, six
203 variables remained in the final model (Table 4). Poorer overall quality of sleep was
204 independently associated with poorer functional quality-of-life (EHP-30) ($b = -0.18$), more
205 depression symptoms (PHQ-9) ($b = -1.62$) and Painful Bladder Syndrome ($b = -5.82$).
206 That is, a 1 point increase in the EHP-30 (representing a worsening in quality-of-life), a 1
207 point increase in the PHQ-9 (representing a worsening in depression) and the presence

208 of painful bladder syndrome, increased the primary outcome (i.e. towards poorer quality
209 of sleep) by 0.18, 1.62, and 5.82 points, respectively. In contrast, better overall quality of
210 sleep was independently associated with higher education ($b = 8.33$) and presence of an
211 ovarian endometrioma cyst ($b = 8.31$). This indicates that an increase in one category in
212 education and the presence of an ovarian endometrioma were associated with a
213 decrease in the primary outcome (i.e. towards better quality of sleep) by 8.33 and 8.31
214 points, respectively. Pain catastrophizing was borderline significant and had the
215 opposite expected association ($b = .25$) (Table 4).

216

217 Supplementary tables

218 Sub-analyses for the secondary outcomes are in Supplementary Tables 1-4. For each
219 secondary outcome, a statistically significant association was observed for almost all the
220 variables associated with the primary outcome (i.e. overall quality of sleep).

221

222 **Discussion**

223 In this study of women at a tertiary referral center who were subsequently found to have
224 surgically and histologically confirmed endometriosis, we found that baseline pre-
225 operative poorer quality of sleep was independently associated with poorer quality-of-
226 life, more depression symptoms, and painful bladder syndrome. On the other hand,
227 improved sleep was associated with higher education and the presence of an ovarian
228 endometrioma cyst. These associations point towards the importance of sleep for the
229 quality-of-life of women with endometriosis, and also the specific relationship between

230 sleep and depression (compared to other psychological variables) and painful bladder
231 syndrome (rather than irritable bowel syndrome) in this population.

232 The association between poorer quality of sleep and poorer quality-of-life suggests that
233 sleep can impact the ability to perform day-to-day functional activities in the
234 endometriosis population. For example, previous work has shown that poor sleep can
235 lead to more chronic pain and hyperalgesia^{10, 27, 28}; that is, poorer sleep may exacerbate
236 pelvic pain, which in turn leads to poorer quality-of-life.

237 Psychological comorbidities are common in chronic pain²⁹, and we found an independent
238 relationship between poorer sleep quality and depression (rather than anxiety)³⁰. The
239 specific importance of depression in endometriosis has been recognized³¹, and the
240 association between sleep quality and depression is likely bidirectional, with poor sleep
241 worsening mood and depression in turn affecting sleep^{32, 33}. Previous work has shown
242 that depression leads to hyper-arousal, and alters sleep in many ways, including
243 decreased total sleep time, frequent awakenings, and difficulty falling asleep, among
244 others³³.

245 Painful bladder syndrome, a chronic condition characterized by bladder pain and urinary
246 urgency/frequency³⁴, was found to be independently associated with poorer sleep.

247 Again, this relationship may be bidirectional. Sleep disturbances could be the result of
248 nocturia, which afflicts 87% of patients with painful bladder syndrome³⁴, or positioning
249 during sleep that may activate myofascial trigger points associated with painful bladder
250 syndrome. Alternatively, poor sleep could reduce pain thresholds^{27, 28}, and therefore
251 worsen bladder pain. It is interesting that painful bladder syndrome, but not irritable
252 bowel syndrome, was independently associated with poorer sleep, which suggests the

253 specific relationship between sleep and the bladder (rather than the bowel), at least in
254 our endometriosis population.

255 In our study, women with ovarian endometrioma cyst were found to have better sleep
256 scores, independent of other factors (with a similar finding of better sleep for Stage III/IV
257 vs. Stage I/II endometriosis on bivariate analyses). At our center, the subset of patients
258 with endometriomas and more severe endometriosis generally tend to be referred for
259 infertility and/or surgical management of a pelvic mass found on imaging, rather than for
260 pain symptoms, which may be why these patients had overall better quality of sleep.
261 Additionally, higher education (graduate degree or higher) was associated with better
262 sleep (that is, lower education was associated with poorer sleep). This is consistent with
263 previous research showing that socioeconomic factors, such as lower income and
264 education, have a negative association with sleep as shown with the Pittsburgh Sleep
265 Quality Index³⁵. Lastly, lower scores on the pain catastrophizing scale was associated
266 with worse quality of sleep with borderline significance; this is counterintuitive and is
267 likely an artefact of the more strongly associated variables in the regression model.

268 Strengths of this research are a rigorous definition of endometriosis (surgical and
269 histological confirmation), and a quantitative analysis of sleep using a validated sleep
270 scale. Other strengths include use of a standardized data registry and large sample size.
271 Limitations include no control group of women without endometriosis, although such
272 comparative studies have been previously published^{14, 15}. In addition, further research
273 could utilize an objective measure of sleep, for example by using actigraphy, as well as
274 provide more information on sleep components (sleep latency, wake after sleep onset,
275 efficiency, etc.)¹⁰.

276 Altogether, there is a need for more research on sleep in endometriosis, including
277 studies on treatment of sleep dysfunction and its impact on quality-of-life. Some studies
278 have showed the benefit of treatment with melatonin for primary dysmenorrhea³⁶ and
279 endometriosis³⁷. In an 8-week randomized control trial, 10 mg of melatonin daily
280 improved quality of sleep and reduced pain scores in women with endometriosis³⁷. This
281 could be a promising treatment adjunct for these patients. Another possibility is a
282 multidisciplinary approach, including psychological treatments or physiotherapy, to target
283 depression and painful bladder syndrome³⁸, which may lead to improved sleep in the
284 endometriosis population.

285

286 **Conclusion**

287 Poorer quality of sleep in women with endometriosis was independently associated with
288 worse quality of life, depression, and painful bladder syndrome. Research into
289 interventions that improve sleep is warranted as part of the management of some
290 women with endometriosis.

291

292 **Acknowledgements**

293 This work was supported by grants from the Canadian Institutes of Health Research
294 (MOP-142273 and PJT- 156084). PY is also supported by a Health Professional
295 Investigator Award from the Michael Smith Foundation for Health Research.

296

297 **References**

298 1. Leyland N, Casper R, Laberge P, Singh S. Endometriosis: Diagnosis and
299 Management. SOGC Clinical Practice Guideline. J Obstet Gynecol Can. 2010 July;32(7).

- 300 2. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on
301 women's lives: a qualitative study. BMC Womens Health. 2014 Oct 4;14:123.
- 302 3. De Graaff AA, D'Hooghe TM, Dunselman GA, et al. The significant effect of
303 endometriosis on physical, mental and social wellbeing: results from an international
304 cross-sectional survey. Hum Reprod. 2013 Oct;28(10):2677-85
- 305 4. Marinho MCP, Magalhaes TF, Fernandes LFC, Augusto KL, Brilhante AVM, Bezerra
306 LRPS. Quality of Life in Women with Endometriosis: An Integrative Review. J Womens
307 Health (Larchmt). 2018 Mar;27(3):399-408. Abstract.
- 308 5. Assefa SZ, Diaz-Abad M, Wickwire EM, Scharf SM. The functions of sleep. AIMS
309 Neuroscience. 2015; 2(3): 151-171.
- 310 6. Loprinzi PD, Joyner C. Meeting Sleep Guidelines Is Associated With Better Health-
311 Related Quality of Life and Reduced Premature All-Cause Mortality Risk. Am J Health
312 Promot. 2018 Jan;32(1):68-71.
- 313 7. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-
314 relate? Insights from the longitudinal and cognitive-behavioral clinical trials
315 literature. Sleep Med Rev. 2004 Apr;8(2):119-32. Review.
- 316 8. Baker FC, Driver HS, Rogers GG, Paiker J, Mitchell D. High nocturnal body
317 temperatures and disturbed sleep in women with primary dysmenorrhea. Am J Physiol.
318 1999 Dec;277(6 Pt 1):E1013-21.
- 319 9. Cosar E, Çakır Güngör A, Gencer M, et al. Sleep disturbance among women with
320 chronic pelvic pain. Int J Gynaecol Obstet. 2014 Sep;126(3):232-4.
- 321 10. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and
322 a path forward. J Pain. 2013 Dec;14(12):1539-52.

- 323 11. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep
324 contributes to next-day pain report in the general population. Pain. 2008 Jul;137(1):202-
325 7.
- 326 12. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to
327 prolonged sleep restriction are associated with increased pain experience in healthy
328 volunteers. Sleep. 2007; 30:1145.
- 329 13. Singh JK, Learman LA, Nakagawa S, Gregorich SE, Kuppermann M. Sleep
330 problems among women with noncancerous gynecologic conditions. J Psychosom
331 Obstet Gynaecol. 2014 Mar;35(1):29-35.
- 332 14. Nunes FR, Ferreira JM, Bahamondes L. Pain threshold and sleep quality in women
333 with endometriosis. Eur J Pain. 2015 Jan;19(1):15-20.
- 334 15. Leone Roberti Maggiore U, Bizzarri N, Scala C, Tafi E, Siesto G, Alessandri F,
335 Ferrero S. Symptomatic endometriosis of the posterior cul-de-sac is associated with
336 impaired sleep quality, excessive daytime sleepiness and insomnia: a case-control
337 study.Eur J Obstet Gynecol Reprod Biol. 2017 Feb;209:39-43.
- 338 16. Yosef A, Allaire C, Williams C, et al. Multifactorial contributors to the severity of
339 chronic pelvic pain in women. Am J Obstet Gynaecol. 2016;215:760. e761-760. e714.
- 340 17. Kosinski M, Janagap CC, Gajria K, Schein J. Psychometric testing and validation of
341 the Chronic Pain Sleep Inventory. Clin Ther. 2007;29 Suppl:2562-77.
- 342 18. Jones G, Kennedy S, Barnard A, Wong J, Jenkinson C. Development of an
343 endometriosis quality-of-life instrument: The Endometriosis Health Profile-30. Obstet
344 Gynecol. 2001 Aug;98(2):258-64.

- 345 19. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing
346 generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092-7.
- 347 20. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of
348 PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders.
349 Patient Health Questionnaire. JAMA. 1999 Nov 10;282(18):1737-44.
- 350 21. Darnall BD, Sturgeon JA, Cook KF, et al. Development and Validation of a Daily Pain
351 Catastrophizing Scale. J Pain. 2017 Sep;18(9):1139-1149.
- 352 22. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller
353 RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91. Erratum in:
354 Gastroenterology. 2006 Aug;131(2):688.
- 355 23. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and
356 treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011 Jun;185(6):2162-70.
- 357 24. P. Abrams, L. Cardozo, M. Fall, et al. The standardization of terminology of lower
358 urinary tract function: report from the standardization subcommittee of the International
359 Continence Society. Neurourol Urodyn, 2002;21:167-178.
- 360 25. Schönbrodt, F.D. and Perugini M. At what sample size do correlations stabilize? *J*
361 *Res Pers*. 2013; 47: 609-612.
- 362 26. American Society for Reproductive Medicine. Revised American Society for
363 Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997
364 May;67(5):817-21
- 365 27. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep
366 loss are hyperalgesic. Sleep. 2006 Feb;29(2):145-51.

- 367 28. Roehrs TA, Harris E, Randall S, Roth T. Pain sensitivity and recovery from mild
368 chronic sleep loss. Sleep. 2012 Dec 1;35(12):1667-72.
- 369 29. Woo AK. Depression and Anxiety in Pain. Rev Pain. 2010 Mar;4(1):8-12.
- 370 30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression
371 severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.
- 372 31. Laganà AS, La Rosa VL, Rapisarda AMC, et al. Anxiety and depression in patients
373 with endometriosis: impact and management challenges. Int J Womens Health. 2017
374 May 16;9:323-330.
- 375 32. Roberts RE, Duong HT. The prospective association between sleep deprivation and
376 depression among adolescents. Sleep. 2014 Feb 1;37(2):239-44.
- 377 33. Gupta R, Dahiya S, Bhatia MS. Effect of depression on sleep: Qualitative or
378 quantitative? Indian J Psychiatry. 2009 Apr;51(2):117-21.
- 379 34. Vasudevan V, Moldwin R. Addressing quality of life in the patient with interstitial
380 cystitis/bladder pain syndrome. Asian J Urol. 2017 Jan;4(1):50-54.
- 381 35. Mezick EJ, Matthews KA, Hall M, et al. Influence of race and socioeconomic status
382 on sleep: Pittsburgh SleepSCORE project. Psychosom Med. 2008 May;70(4):410-6.
- 383 36. Keshavarzi F, Mahmoudzadeh F, Brand S, et al. Both melatonin and meloxicam
384 improved sleep and pain in females with primary dysmenorrhea-results from a double-
385 blind cross-over intervention pilot study. Arch Womens Ment Health. 2018 Apr 4.
- 386 37. Schwertner A, Conceição Dos Santos CC, Costa GD, et al. Efficacy of melatonin in
387 the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled
388 trial. Pain. 2013 Jun;154(6):874-81.

389 38. Allaire C, Williams C, Bodmer-Roy S, et al. Chronic pelvic pain in an interdisciplinary
390 setting: 1-year prospective cohort. Am J Obstet Gynecol. 2018 Jan;218(1):114.e1-
391 114.e12.

392

393

394 Reprint address:

395 Paul Yong, MD, PhD, FRCSC

396 Assistant Professor, Department of Obstetrics and Gynecology

397 University of British Columbia;

398 BC Women's Center for Pelvic Pain and Endometriosis

399 F2 – 4500 Oak Street

400 Vancouver, British Columbia

401 Canada V6H 3N1

402

403

404

405

406

407

408

409 **Figure legends**

410 **Figure 1.** Inclusions and exclusions for the final study sample.

411

412

413

414

415

416

417

418

419

420

421

422

423

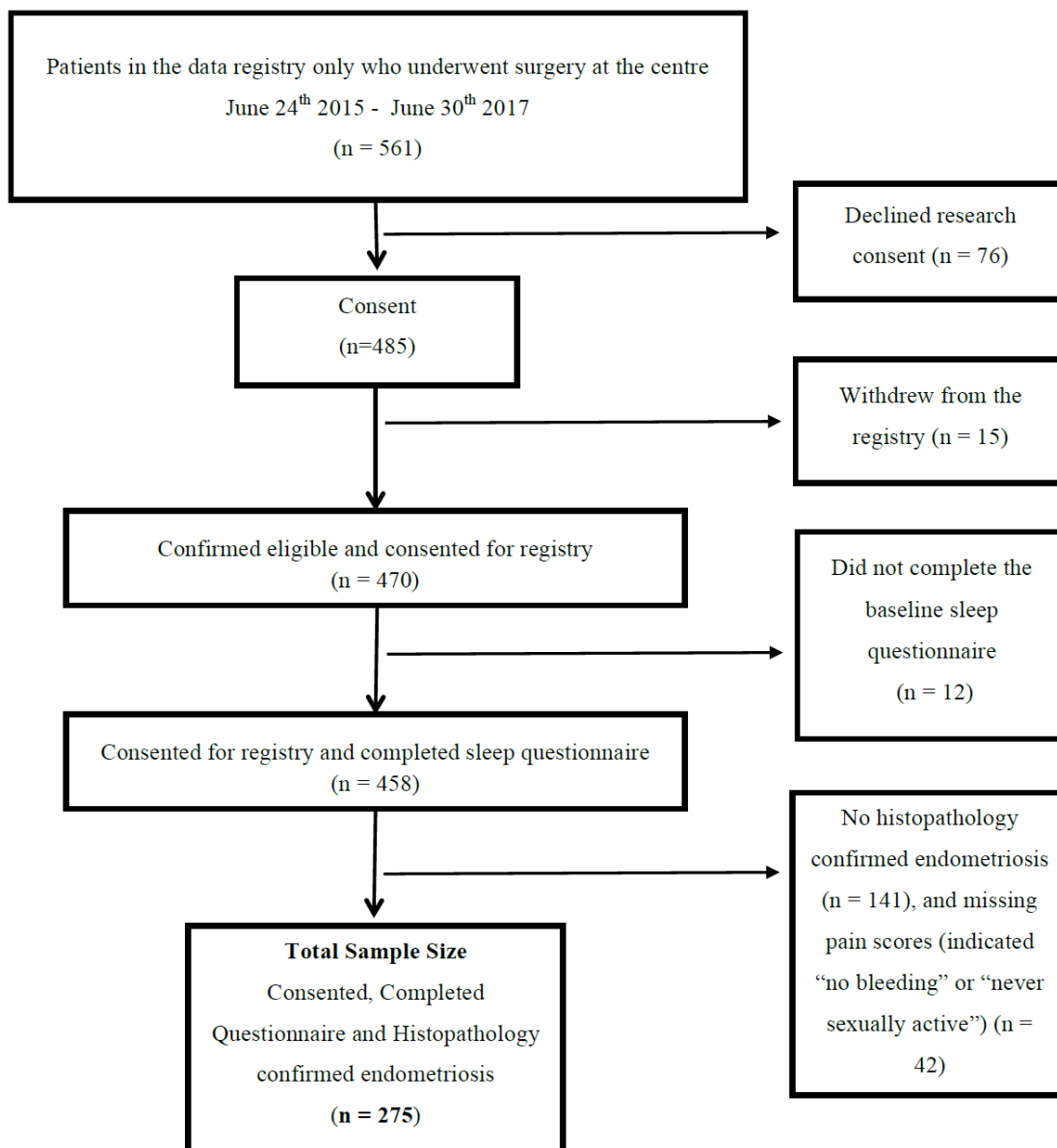
424

425

426

427

Figure 1. Study flowchart.



428
429 Figure 1

430

431

432

433

434 **TABLE 1. Patient characteristics, n = 275.**

Demographic Factors	Median (range) or percentage (frequency)
Age, years	33 (18-52)
Age first experienced pelvic pain, years	16 (0-43)
BMI (n=269)	23.3 (15-46)
Ethnicity	
Caucasian	75.6% (208)
Other	24.4% (67)
Marital Status	
Partnered (married + common-law)	69.5% (191)
Other	30.5% (84)
Previous pregnancy	46.9% (129)
Education	
Graduate degree or higher	60.7% (167)
Other	39.3% (108)
Household income	
<\$20,000	10.9% (30)
\$20,000 - \$39,999	16.4% (45)
\$40,000 - \$59,999	14.5% (40)
\$60,000 - \$79,999	17.1% (47)
\$80,000 - \$99,999	15.6% (43)

\$100,000+	25.5% (70)
Working	
Yes	76.4% (210)
No	23.6% (65)
Because of pelvic pain	46.2% (30/65)
Exercise	
Rarely	24.4% (67)
1-2 times weekly	33.5% (92)
3-5 times weekly	32.4% (89)
Daily	9.8% (27)
Caffeine intake	
No caffeine	9.8% (27)
Not daily	21.8% (60)
1-3 cups daily	63.3% (174)
4-6 cups daily	5.1% (14)
Smoker	
Yes	11.3% (31)
No	88.7% (244)
Alcohol use	
Yes	63.3% (174)
No	36.7% (101)
Recreational drug use	
Never used	52.0% (143)
In past but not now	25.8% (71)
Currently using	14.2% (39)

No answer	8.0% (22)
Daily Opioid Use	
Yes	11.3% (31)
No	88.7% (244)
Infertility	
Yes	38.9% (107)
No	24.4% (67)
Never tried	36.7% (101)
Co-morbid conditions and medications	
Irritable Bowel Syndrome (IBS)	70.9 % (195)
Painful Bladder Syndrome (PBS)	57.1% (157)
Nerve medications (Nortriptyline, Gabapentin/Neurontin, Pregabalin/Lyrica)	
Yes	10.2% (28)
No	82.5% (227)
Don't know	7.3% (20)
Pain scores (0-10)	
Dysmenorrhea	8 (0-10)
Superficial dyspareunia	3 (0-10)
Deep dyspareunia	7 (0-10)
Dyschezia	5 (0-10)
Back pain	6 (0-10)
Chronic Pelvic Pain	7 (0-10)
Validated questionnaires	
Endometriosis Health Profile (EHP-30) functional pain subscale (0-100)	56.8 (0-100)

Patient Health Questionnaire-9 (PHQ-9) depression scale (0-27)	7 (0-27)
Generalized Anxiety Disorder (GAD-7) (0-21)	6 (0-21)
Pain Catastrophizing Scale (PCS) (0-52)	18 (0-52)
Endometriosis characteristics	
Stage	
I	37.5% (103)
II	21.1% (58)
III	17.8% (49)
IV	19.6% (54)
Unknown	4.0% (11)
Pouch of Douglas Obliteration	
Partial	10.9% (30)
Complete	9.5% (26)
No obliteration	79.6 % (219)
Superficial endometriosis	86.5% (238)
Ovarian endometrioma cyst	28.7% (79)
Deep Infiltrating endometriosis	18.5% (51)

435

436

437

438

439

440

441

442 **TABLE 2. Outcomes**

Question	Median	Range
Primary outcome: 0 (very poor) to 100 (excellent)		
Overall quality of sleep	43	(0-100)
Secondary outcomes: 0 (never) to 100 (always)		
Trouble falling asleep	55	(0-100)
Need sleep medication	8	(0-100)
Awakened by pain during the night	50	(0-100)
Awakened by pain in the morning	50	(0-100)

443

444

445

446

447

448

449

450

451

452

453

454

455 **TABLE 3. Bivariate analyses: overall quality of sleep, 0 (very poor) to 100 (excellent)**

Variable	Spearman correlation coefficient; or Median (range)	p-value
Demographic Factors		
Age	r = 0.10	0.09
Age at first pain	r = 0.18	0.002
BMI	r = -0.12	0.045
Ethnicity		0.09
Caucasian	40 (0-100) 50 (0-100)	
Other		
Marital status		0.077
Partner	45 (0-100) 39.5 (0-93)	
No partner		
Previous pregnancy		0.34
Yes	40 (0-100) 45.5 (0-100)	
No		
Education		<0.001
Graduate degree or higher	50 (0-100) 33 (0-94)	
Less than graduate degree		
Household income	r = 0.06	0.35
Currently working		0.019
Yes	45 (0-100) 35 (0-100)	
No		
Exercise	r = 0.05	0.42

Caffeine intake	$r = 0.101$	0.096
Smoker		0.33
Yes	42 (1-76) 43 (0-100)	
No		
Alcohol		0.032
Yes	46 (0-100) 37 (0-100)	
No		
Recreational drug use		0.74
Never used	45 (0-100) 40 (0-90) 40 (2-90)	
In past but not now		
Currently using		
Daily opioid use		0.13
Yes	39 (0-93) 45 (0-100)	
No		
Infertility		0.31
Yes	48 (0-95) 40 (0-100) 40 (0-100)	
No		
Never tried		
Co-morbid conditions and medications		
Irritable bowel syndrome (IBS)		0.065
Yes	40 (0-100) 48.5 (0-100)	
No		
Painful bladder syndrome (PBS)		<0.001

Yes	35 (0-100) 50 (0-100)	
No		
Nerve medications		0.49
Yes	43 (0-100) 41 (0-100)	
No	48.5 ± 24.0	
I don't know what this is		
Pain scores (0-10)		
Dysmenorrhea	r = -0.20	0.001
Deep dyspareunia	r = -0.27	<0.001
Superficial dyspareunia	r = -0.24	<0.001
Dyschezia	r = -0.22	<0.001
Chronic pelvic pain	r = -0.27	<0.001
Back pain	r = -0.26	<0.001
Validated questionnaires		
Endometriosis Health Profile (EHP-30) functional pain subscale (0-100)	r = -0.37	<0.001
Patient Health Questionnaire-9 (PHQ-9) depression scale (0-27)	r = -0.51	<0.001
Generalized Anxiety Disorder (GAD-7) (0-21)	r = -0.40	<0.001
Pain Catastrophizing Scale (PCS) (0-52)	r = -0.23	<0.001
Endometriosis characteristics		
Stage		0.005
I-II	40 (0-100) 50 (0-100)	
III-IV		
Pouch of Douglas Obliteration		0.06
Yes (partial or complete)	48.5 (0-100) 40 (0-100)	

No		
Superficial endometriosis		0.14
Yes	41 (0-100) 50 (12-100)	
No		
Endometrioma		0.002
Yes	50 (0-100) 40 (0-100)	
No		
Deep infiltrating endometriosis		0.13
Yes	50 (2-92) 42 (0-100)	
No		

456

457

458

459

460

461

462

463

464

465

466

467

468 **TABLE 4. Multivariable linear regression: overall quality of sleep, 0 (very poor) to**
 469 **100 (excellent)**

Variable	b coefficient	95% CI for b	p-value
Endometriosis Health Profile (EHP-30)	-0.175	-0.330, -0.021	0.026
Patient Health Questionnaire (PHQ-9) depression scale	-1.624	-2.124, -1.124	<0.001
Painful Bladder Syndrome (PBS)	-5.821	-11.233, -0.409	0.035
Pain Catastrophizing Scale (PCS)	0.247	0.005, 0.490	0.046
Education (graduate degree or higher)	8.329	2.831, 13.828	0.003
Endometrioma	8.307	2.512, 14.101	0.005

470 n=258 due to listwise exclusion of missing values

471

472

473

474

475

476

477

478

479

480

481

482 **Supplementary Tables**483 **TABLE 1. Bivariate analysis: Trouble falling asleep (only variables with significant**
484 **associations with the primary outcome)**

Variable	Spearman correlation coefficient; or Median (range)	p-value
Demographic factors		
Age at first pain	r = -0.044	0.472
Age	r = -0.095	0.118
BMI	r = 0.067	0.277
Ethnicity		0.842
Caucasian	55.5 (0-100)	
Other	52 (0-100)	
Marital status		0.034
Partner	50 (0-100)	
No partner	62 (0-100)	
Previous pregnancy		0.813
Yes	53 (0-100)	
No	55.5 (0-100)	
Education*		0.002
Graduate degree or higher	48 (0-100) 61.5 (0-100)	
Less than graduate degree		
Household income	r = -0.089	0.140
Currently working		0.015
Yes	50.5 (0-100) 65 (0-100)	
No		

Excercise	$r = -0.049$	0.422
Caffeine intake	$r = -0.057$	0.348
Smoker		0.236
Yes	61 (0-100)	
No	51.5 (0-100)	
Alcohol		0.632
Yes	53 (0-100)	
No	60 (0-100)	
Recreational drug use		0.684
Never used	50 (0-100)	
In past but not now	55 (0-100)	
Currently using	60 (0-94)	
Daily opioid use		0.222
Yes	67 (0-100)	
No	51.5 (0-100)	
Infertility		0.342
Yes	55 (0-100)	
No	50 (0-100)	
Never tried	60 (0-100)	
Co-morbid conditions		
Irritable Bowel Syndrome (IBS)		0.020
Yes	58 (0-100)	
No	50 (0-100)	
Painful Bladder Syndrome (PBS)		<0.001
Yes	63 (0-100) 36 (0-100)	

No		
Nerve medications		0.367
Yes	69.5 (0-100)	
No	53 (0-100)	
I don't know what this is	54.5 (6-100)	
Pain scores		
Dysmenorrhea (last 3 months)	r = 0.19	0.001
Deep dyspareunia	r = 0.16	0.006
Superficial dyspareunia	r = 0.28	<0.001
Dyschezia	r = 0.24	<0.001
Chronic pelvic pain	r = 0.26	<0.001
Back pain	r = 0.24	<0.001
Validated questionnaires		
EHP 30	r = 0.32	<0.001
GAD-7	r = 0.45	<0.001
PHQ-9	r = 0.49	<0.001
PCS	r = 0.29	<0.001
Endometriosis characteristics		
Stage		0.003
I-II	62 (0-100) 34 (0-100)	
III-IV		
Superficial endometriosis		0.126
Yes	55.5 (0-100)	
No	40 (0-93)	
Pouch of Douglas Obliteration		0.075

Yes (partial or complete)	44.5 (0-93) 58 (0-100)	
No		
Endometrioma*		0.015
Yes	40 (0-100) 59 (0-100)	
No		
Deep infiltrating endometriosis		0.052
Yes	33 (0-95)	
No	60 (0-100)	

485 *Original wording: "How often have you had trouble falling asleep because of pain?"¹⁷

486

487

488 **TABLE 2. Bivariate analyses: Need sleep medication (only variables with significant**
 489 **associations with the primary outcome)**

Variable	Spearman correlation coefficient; or Mean \pm SD	p-value
Demographic factors		
Age at first pain	r = 0.074	0.224
Age	r = -0.059	0.332
BMI	r = 0.005	0.933
Ethnicity		0.098
Caucasian	11.5 (0-100)	
Other	2 (0-100)	
Marital status		0.045
Partner	4 (0-100)	
No partner	19.5 (0-100)	

Previous pregnancy		0.597
Yes	9 (0-100)	
No	6 (0-100)	
Education*		<0.001
Graduate degree or higher	3 (0-100)	
Less than graduate degree	24.5 (0-100)	
Household income	r = -0.110	0.070
Currently working		0.894
Yes	7.5 (0-100) 8 (0-100)	
No		
Exercise	r = -0.068	0.262
Caffeine intake	r = 0.010	0.875
Smoker		0.482
Yes	10 (0-100)	
No	6 (0-100)	
Alcohol		0.813
Yes	11 (0-100)	
No	5 (0-100)	
Recreational drug use		0.056
Never used	3 (0-100)	
In past but not now	23 (0-100)	
Currently using	29 (0-99)	
Daily opioid use		0.157
Yes	28 (0-100)	
No	6 (0-100)	

Infertility		0.627
Yes	4 (0-100)	
No	9 (0-100)	
Never tried	10 (0-100)	
Co-morbid conditions		
IBS		0.152
Yes	11 (0-100)	
No	3 (0-100)	
PBS		0.048
Yes	13 (0-100) 3 (0-100)	
No		
Nerve medications		0.004
Yes	43.5 (0-100)	
No	4 (0-100)	
I don't know what this is	20 (0-100)	
Pain scores		
Dysmenorrhea (last 3 months)	r = 0.054	0.375
Deep dyspareunia	r = 0.12	0.044
Superficial dyspareunia	r = 0.18	0.003
Dyschezia	r = 0.15	0.012
Chronic pelvic pain	r = 0.24	<0.001
Back pain	r = 0.133	0.027
Validated questionnaires		
EHP 30	r = 0.19	0.001
GAD-7	r = 0.42	<0.001

PHQ-9	r = 0.37	<0.001
PCS	r = 0.24	<0.001
Endometriosis characteristics		
Stage		0.034
I-II	15 (0-100) 3 (0-100)	
III-IV		
Superficial endometriosis		0.205
Yes	9 (0-100)	
No	1 (0-100)	
Pouch of Douglas Obliteration		0.240
Yes (partial or complete)	3 (0-100) 10 (0-100)	
No		
Endometrioma		0.011
Yes	2 (0-100) 12.5 (0-100)	
No		
Deep infiltrating endometriosis		0.465
Yes	7 (0-98)	
No	8 (0-100)	

490 *Original wording: "How often have you needed sleeping medication to help you fall
491 asleep?"¹⁷

492

493

494

495 **TABLE 3. Bivariate analyses: awakened by pain during the night (only variables with**
496 **significant associations with the primary outcome)**

Variable	Spearman correlation	p-value
-----------------	-----------------------------	----------------

	coefficient; or Mean \pm SD	
Demographic factors		
Age at first pain	r = -0.13	0.037
Age	r = 0.030	0.624
BMI	r = 0.055	0.371
Ethnicity		0.686
Caucasian	50 (0-100)	
Other	50 (0-100)	
Marital status		0.236
Partner	50 (0-100)	
No partner	51 (0-100)	
Previous pregnancy		0.534
Yes	51 (0-100)	
No	49.5 (0-100)	
Education*		0.063
Graduate degree or higher	47 (0-100) 51 (0-100)	
Less than graduate degree		
Household income	r = -0.064	0.290
Currently working		0.003
Yes	44 (0-100) 60 (0-100)	
No		
Exercise	r = -0.043	0.476
Caffeine intake	r = -0.167	0.006
Smoker		0.770
Yes	47 (0-100)	

No	50 (0-100)	
Alcohol		0.066
Yes	48 (0-100)	
No	55 (0-100)	
Recreational drug use		0.363
Never used	50 (0-100)	
In past but not now	50 (0-100)	
Currently using	55 (0-100)	
Daily opioid use		0.001
Yes	70 (2-100)	
No	48.5 (0-100)	
Infertility		0.879
Yes	50 (0-100)	
No	50 (0-100)	
Never tried	49 (0-100)	
Comorbid conditions		
IBS		0.009
Yes	51 (0-100)	
No	33 (0-100)	
PBS		<0.001
Yes	54 (0-100) 31.5 (0-100)	
No		
Nerve medications		0.674
Yes	46 (0-100)	
No	50 (0-100)	

I don't know what this is	51.5 (0-98)	
Pain scores		
Dysmenorrhea (3 months)	r = 0.28	<0.001
Deep dyspareunia	r = 0.19	0.002
Superficial dyspareunia	r = 0.26	<0.001
Dyschezia	r = 0.25	<0.001
Chronic pelvic pain	r = 0.44	<0.001
Back pain	r = 0.40	<0.001
Validated questionnaires		
EHP 30	r = 0.57	<0.001
GAD-7	r = 0.32	<0.001
PHQ-9	r = 0.46	<0.001
PCS	r = 0.45	<0.001
Endometriosis Characteristics		
Stage		0.066
I-II	51 (0-100) 44 (0-97)	
III-IV		
Superficial endometriosis		0.446
Yes	50 (0-100)	
No	32 (0-96)	
Pouch of Douglas Obliteration		0.720
Yes (partial or complete)	50.5 (0-96) 50 (0-100)	
No		
Endometrioma*		0.110
Yes	40 (0-100) 51 (0-100)	

No		
Deep infiltrating endometriosis		0.518
Yes	48 (0-98)	
No	50.5 (0-100)	

497 *Original wording: "How often have you been awakened by pain during the night?"¹⁷

498

499

500

501 **TABLE 4. Bivariate analyses: awakened by pain in the morning (only variables with**
502 **significant associations with the primary outcome)**

Variable	Spearman correlation coefficient; or Mean \pm SD	p-value
Demographic factors		
Age at first pain	r = -0.17	0.005
Age	r = -0.046	0.450
BMI	r = 0.063	0.307
Ethnicity		0.915
Caucasian	50 (0-100)	
Other	50 (0-100)	
Marital status		0.148
Partner	46 (0-100)	
No partner	52.5 (0-100)	
Previous pregnancy		0.852
Yes	50 (0-100)	
No	50 (0-100)	

Education		0.048
Graduate degree or higher	41 (0-100) 54 (0-100)	
Less than graduate degree		
Household income	r = -0.070	0.248
Currently working		0.009
Yes	47 (0-100) 60 (0-100)	
No		
Exercise	r = -0.037	0.539
Caffeine intake	r = -0.137	0.023
Smoker		0.365
Yes	51 (0-100)	
No	50 (0-100)	
Alcohol		0.004
Yes	47 (0-100)	
No	60 (0-100)	
Recreational drug use		0.145
Never used	43 (0-100)	
In past but not now	50 (0-100)	
Currently using	60 (0-100)	
Daily opioid use		<0.001
Yes	82 (0-100)	
No	50 (0-100)	
Infertility		0.837
Yes	50 (0-100)	
No	46 (0-100)	

Never tried	51 (0-100)	
Comorbid conditions		
IBS		0.002
Yes	53 (0-100)	
No	26.5 (0-100)	
PBS		<0.001
Yes	56 (0-100) 31.5 (0-100)	
No		
Nerve medications		0.074
Yes	54 (0-100)	
No	46 (0-100)	
I don't know what this is	62.5 (1-100)	
Pain scores		
Dysmenorrhea (3 months)	r = 0.32	<0.001
Deep dyspareunia	r = 0.23	<0.001
Superficial dyspareunia	r = 0.27	<0.001
Dyschezia	r = 0.26	<0.001
Chronic pelvic pain	r = 0.37	<0.001
Back pain	r = 0.35	<0.001
Validated questionnaires		
EHP 30	r = 0.59	<0.001
GAD-7	r = 0.32	<0.001
PHQ-9	r = 0.48	<0.001
PCS	r = 0.45	<0.001
Endometriosis characteristics		

Stage		0.001
I-II	54 (0-100) 33 (0-100)	
III-IV		
Superficial endometriosis		0.025
Yes	51 (0-100)	
No	19 (0-100)	
Pouch of Douglas Obliteration		0.464
Yes (partial or complete)	40.5 (0-100) 50 (0-100)	
No		
Endometrioma		0.001
Yes	28 (0-100) 54 (0-100)	
No		
Deep infiltrating endometriosis		0.781
Yes	50 (0-100)	
No	50 (0-100)	

503 *Original wording: "How often have you been awakened by pain in the morning?"¹⁷

504

505