



The relationship between pain intensity and insomnia in women with deep endometriosis, a cross-sectional study

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Abstract

Purpose To investigate the relationship between pain intensity and insomnia frequency in women with a diagnosis of deep endometriosis. The hypothesis is that these patients with moderate or severe pain have a higher frequency of insomnia than those with mild or no pain.

Methods We conducted a cross-sectional study of women with deep endometriosis categorized by pelvic pain intensity based on a numerical scale. Insomnia was assessed through a self-reported questionnaire, and multiple logistic regression was used to control for confounders between pain and insomnia.

Results We included 234 women in the study, 39 (17%) without pelvic pain; 66 (29%) with mild pain; 53 (23%) moderate pain; and 76 (32%) severe pain. Twenty-nine (74%) pain-free women and 50 (75%) with mild pain had no insomnia; only 3 (8%) of the former and 3 (4%) of the latter group had severe insomnia. However, twenty-nine (55%) women with moderate pain and 37 (48%) with severe pain had insomnia. The logistic regression model showed that moderate to severe pain increased insomnia 2.8 times, twice for every 10 years of pain duration, and twice in women with low education levels.

Conclusions Women with moderate or severe pain had a high frequency of insomnia, increasing management complexity in patients with deep endometriosis. Pain intensity, pain duration, and low education level increased the chance of insomnia in those patients.

Keywords Pelvic pain · Endometriosis · Insomnia

Introduction

Endometriosis is an inflammatory disease caused by the development of active endometrial-like tissue outside the uterine cavity. Endometriosis is one of the most frequent causes of chronic pelvic pain (CPP) in women, with a prevalence of

10% of women in menacme [1]. Deep endometriosis is the presence of endometrial implantation 5 mm or more in depth in the pelvic or abdominal sites. Its relationship to CPP is more evident than in superficial endometriosis [2].

The International Association for the Study of Pain defined chronic pain as persistent or recurrent pain lasting more than three months [3]. CPP affects 6 to 27% of women [4], impairs life and sleep quality, increases work absenteeism, and increases health care use [5]. CPP development is multifactorial, and the treatment of endometriosis does not consistently achieve pain relief. In addition, pain may return after surgical treatment or medical treatment interruption, making its management complex [6].

Insomnia is associated with chronic pain, ranging from 40 to 50% in patients with pain [7]. The mechanisms involved are unclear, but sleep deprivation induces inflammatory cytokine activation (interleukin-6 and tumor necrosis factor) [8]; decreases the pain threshold; triggers allodynia and hyperalgesia; reduces the descending inhibitory pain response [8].

Synopsis Women with deep endometriosis experiencing moderate or severe pain have a high frequency of insomnia. Low education level and pain duration also play a role in this relationship.

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The role of insomnia in chronic pain is unclear, but there is evidence that the effect is bidirectional between pain and sleep quality. However, there appears to be a higher effect of pain on sleep than sleep on pain [9]. Also, young adults with obstructive sleep apnea tend to report more severe pain than those without sleep disturbances [10]. Women with CPP have worse sleep quality than healthy women, and women with endometriosis and sleep disorders have a worse quality of life and impaired functional capacity [11].

There is a gap in knowledge regarding the association between sleep quality and pain in women with deep endometriosis. The influence of pain intensity on these women's sleep quality is not clearly understood, primarily because of other comorbidities, such as infertility [12].

Insomnia is the most studied sleep disorder in all kinds of chronic pain [13]. Sleep deprivation impairs the immune system, reducing phagocytosis and CD4+ T lymphocytes levels, increasing inflammatory cytokines, reducing pain threshold, and inducing allodynia [8, 14]. Therefore, investigating insomnia frequency in patients with deep endometriosis may clarify these associations to promote effective management.

Therefore, we conducted a study on women with a diagnosis of deep endometriosis to investigate the relationship between CPP intensity and insomnia frequency. The hypothesis was that these patients with moderate or severe pain complaints have a higher frequency of insomnia than those with mild or without pain.

Materials and methods

This was a cross-sectional study with prospectively collected data, conducted from January 2020 to February 2021, of women referred to a university medical center specializing in endometriosis. The study was approved by the university's research ethics board (The University of the State of Rio de Janeiro—CAAE: 18,261,019.4.0000.5259).

Population

The eligibility criteria were (1) women between 18 and 50 years of age and (2) diagnosis of endometriosis by magnetic resonance (MR), ultrasonography (US), or surgery. For the endometriosis imaging diagnosis, we considered the presence of nodules ≥ 1.5 cm in the pelvis (to increase diagnostic specificity) or surgical report with the histological study. MR and US have a high accuracy in diagnosing deep endometriosis (especially in lesions greater than 10 mm), with a sensitivity of 92% and 79% and specificity of 97% and 94%, respectively [15].

Women were excluded when they had central nervous system diseases, suspected urological and gynecological cancer; natural or surgical menopause; and those unable to understand and answer self-assessment questionnaires. Questionnaires were completed on the same day, in an appropriate place, and without the professionals' interference.

Instruments

Sociodemographic data were collected including age, body mass index (BMI in kg/m^2), race (self-reported), menstrual cycle (present or absent), the main reason for consultation (chief complaint), and pain duration (self-reported, in months). In addition, women who did not feel pain at the time of consultation were also asked about the length of time they experienced pain until the treatment became effective (pain duration).

Pain assessment

Pelvic pain was measured with a Numeric Rating Scale (NRS). Patients were asked to assess the intensity of pelvic pain in the last 4 weeks, assuming a value ranging from 0 to 10 (0 = no pain and 10 = worst imaginable pain). Patients were instructed to report pain outside the menstrual period, not to confuse it with dysmenorrhea. The duration of pain was measured in months, from the moment the patient noticed the first painful symptoms until the date of the examination, or the moment the pain was relieved—by treatment with analgesics, menstruation blockage, and others. We considered CPP in women who experienced more than three months of pelvic pain.

Sleep assessment

The Portuguese version of the Insomnia Severity Index (ISI), a self-administered questionnaire, was used to measure insomnia, and the subject answered it without the researchers' interference. The ISI is an instrument that measures the nature, intensity, and impact of insomnia and has been used very often in assessing insomnia. Easy to apply, it consists of only seven questions, each with a score ranging from 0 to 4 points (0 = no problem and 4 = severe problem), with an excellent correlation with other specific questionnaires for sleep quality, presenting a high sensitivity and specificity in detecting insomnia. The final score is reached with the sum of the seven questions, and the cutoff points are defined in four categories: (1) no insomnia (0–7 points); (2) subthreshold insomnia (8–14 points); (3) moderate insomnia (15–21 points); and (4) severe insomnia (22–28 points) [16].

Sample size

We assumed that 20% of healthy women have insomnia [5, 17]. In women without pain or with mild pain, we assumed that the diagnosis of endometriosis, by itself, can increase insomnia due to the emotional effect of the disease (chronic disease and its association with infertility). We estimated that insomnia would be present in 30% of this group. Studies with women with CPP have shown the prevalence of sleep disorders ranging from 40 to 80% [5, 7]. Therefore, in women with endometriosis and moderate to severe pain, we estimated the prevalence of insomnia to be around 60%.

Forty-two women were needed in each group to detect a 30% difference in insomnia prevalence, with 80% power and alpha of 0.05, between women with endometriosis and moderate to severe pain and women with endometriosis and no or mild pain.

Statistical analysis

Statistical analysis was conducted with R (version 4.1.0) and RStudio (Version 1.4.1717) software. First, data were checked for outliers, excluding extreme observations. Numerical variables were then evaluated for normal distribution, and those without normal distribution were presented using median and interquartile range (IQR). Kruskal–Wallis and Dunn's post hoc tests were used to analyze categories with three or more independent groups and the Wilcoxon test (sum-rank) for two groups. Analysis between categorical variables was performed using the chi-square test.

Formal education was categorized into low (≤ 9 years of study), intermediate (10–12 years of study), and high (> 12 years of study). As the frequency of women with a low level of education was small, it was decided to merge them with the intermediate education level group (low to intermediate).

There is no consensus in the literature regarding the ideal cutoff point to categorize pain intensity. Therefore, the pain groups were categorized according to the NRS intensity into mild (1–4), moderate (5–7), and severe (8–10), as suggested by Dworkin et al. [18].

In the initial analysis, the Kruskal–Wallis test was used to test the differences between the ISI score and pain with four pain intensity categories (including no pain; NRS = 0). Insomnia was categorized into four groups as described in the sleep assessment method. In the final analysis, we grouped women without insomnia and with mild insomnia into a category with “no insomnia” (ISI score ≤ 14) and women with moderate and severe insomnia into another category with “insomnia” (ISI score > 14) [19].

Finally, we grouped women without pain and with mild pain into “group 1” (NRS ≤ 4) and women with moderate or severe pain into “group 2” (NRS > 4) because of their similarity concerning the ISI score.

There were no missing data in pelvic pain, pain duration, and insomnia variables. However, 18 (8%) were missing data in the education variable, and no values were imputed.

After performing univariate analyses and correlation tests, we included in the multivariate analysis only the variables that had a *p*-value higher than 0.20. Therefore, pain intensity, pain duration, and the level of formal education were included in the multiple logistic regression model as independent variables (the final model with the lowest AIC) with insomnia as the dependent variable.

Results

We included 234 women in the study, 39 (17%) without pelvic pain at the time of initial evaluation, 66 (29%) with mild pain, 53 (23%) with moderate pain, and 76 (32%) with severe pain. Table 1 shows a descriptive statistics summary.

The predominant ethnicity was white (146/234). The level of education was proportionally lower in women with moderate or severe pain than in pain-free women or with mild pain. Approximately two-thirds of the women exercised twice or less a week and 1/3 more than three times a week. Less than 4% of women were smokers. More than a half, 140 (60%) women had regular menstrual cycles. The pain was the main reason for the initial consultation, affecting 229 (92%), and, of these, approximately 1/3 had infertility. Only 16 (7%) had an exclusive imaging diagnosis, and 3 (1%) had infertility as an isolated complaint.

Women with moderate or severe pain reported this symptom for 3 years (IQR = 1–8), while for women without pain or with mild pain, the duration of pain was one year (IQR = 0–4) (Kruskal–Wallis; *p*-value < 0.001).

Figure 1 shows the ISI scores distributions according to each group by pain intensity. Women with moderate or severe pain had higher medians than those without or with mild pain. There was a statistical difference between group 1 (no pain or mild pain) and group 2 (moderate or severe pain).

The Kruskal–Wallis test showed a statistically significant difference between the pain group and the insomnia score (chi-squared; *p* < 0.001). Dunn's post hoc test did not show a difference between the medians of the ISI score of women without pain and women with mild pain. There was no significant difference between median sleep scores among moderate or severe pain (*p*-adjusted = 1). After grouping no to mild pain and moderate to severe pain, we found a statistically significant difference between these two groups.

In our sample, twenty-nine (74%) pain-free women and 50 (75%) with mild pain had no or subthreshold insomnia; only 3 (8%) of the former and 3 (4%) of the last group had severe insomnia. However, twenty-nine (55%) women

Table 1 Sample characteristics

Baseline characteristics	Overall N=234 ¹	Pain Intensity				p-value ²
		No pain N=39 ¹	Mild pain N=66 ¹	Moderate pain N=53 ¹	Severe pain N=76 ¹	
Age, years	36 (30, 40)	35 (32, 40)	35 (31, 39)	35 (30, 40)	37 (30, 41)	0.81
BMI	24.6 (21.6, 28.0)	25.1 (23.1, 28.3)	24.4 (21.4, 26.5)	24.5 (21.2, 28.3)	24.6 (21.9, 28.8)	0.59
Ethnicity						0.11
White	146 (64%)	23 (59%)	50 (79%)	32 (62%)	41 (55%)	
Black	33 (14%)	6 (15%)	4 (6.3%)	9 (17%)	14 (19%)	
Brown	50 (22%)	10 (26%)	9 (14%)	11 (21%)	20 (27%)	
Marital status						0.54
Single	85 (37%)	15 (38%)	21 (32%)	16 (30%)	33 (44%)	
Married	132 (57%)	20 (51%)	39 (60%)	34 (64%)	39 (52%)	
Divorced	15 (7%)	4 (10%)	5 (8%)	3 (6%)	3 (4%)	
Education						
Low	19 (9%)	2 (6%)	2 (3%)	1 (2%)	14 (19%)	
Intermediate	98 (45%)	14 (39%)	19 (32%)	28 (57%)	37 (51%)	
High	99 (46%)	20 (56%)	38 (64%)	20 (41%)	21 (29%)	
Exercise						0.26
Rarely	99 (52%)	19 (61%)	23 (42%)	21 (51%)	36 (56%)	
1 to 2 times/week	30 (16%)	3 (10%)	14 (25%)	4 (10%)	9 (14%)	
More than 3 times/week	62 (32%)	9 (29%)	18 (33%)	16 (39%)	19 (30%)	
Smokers	8 (4%)	1 (3%)	2 (3%)	1 (2%)	4 (6%)	0.83
Regular menses	140 (60%)	19 (50%)	43 (65%)	32 (62%)	46 (61%)	0.50
Main complaint						
Image finding	16 (7%)	4 (11%)	9 (14%)	2 (4%)	1 (1%)	
Infertility	3 (1%)	1 (3%)	1 (2%)	1 (2%)	0 (0%)	
Pain	146 (64%)	21 (55%)	35 (56%)	33 (62%)	57 (77%)	
Pain and infertility	63 (28%)	12 (32%)	18 (29%)	17 (32%)	16 (22%)	
Pain duration (years)	2 (1, 5)	1 (0, 4)	1 (0, 3)	3 (1, 8)	3 (2, 5)	0.001

¹Median (IQR); *n* (%); ²Kruskal-Wallis rank-sum test; Pearson's chi-squared test; Fisher's exact test

BMI, body mass index; ethnicity, self-declared; education in years of study (low ≤ 9, intermediate ≤ 12, high > 12); smokers, more than one cigarette/day; regular menses, women with normal menstrual cycles; main complaint, main motive for reference to a tertiary center; pain duration, length of time feeling pain

with moderate pain and 37 (48%) with severe pain had insomnia (Table 2).

A multiple logistic regression model was used to control for confounders in the association between pain and the presence of insomnia. Women with moderate/severe pain (group 2) were 2.8 times more likely to have insomnia than those without or with mild pain (group 1). Likewise, the chance of insomnia increased by approximately two times for every 10 years of pain duration. Women with a lower education level were twice as likely to have insomnia as those with more years of schooling (Table 3).

Discussion

Results confirmed the hypothesis that women with deep endometriosis and moderate/severe pain have higher insomnia prevalence than those with no or mild pain.

Insomnia frequency was similar in women with moderate or severe pain (55% and 49%, respectively). As in previous studies, this evidence reinforces that pain may negatively affect sleep quality, regardless of the underlying disease [7, 20].

Fig. 1 Box plot correlating the ISI score with pain intensity groups. The dotted line marks the ISI score cutoff (14 points). Significance: ns, non-significant; *** $p < 0.001$

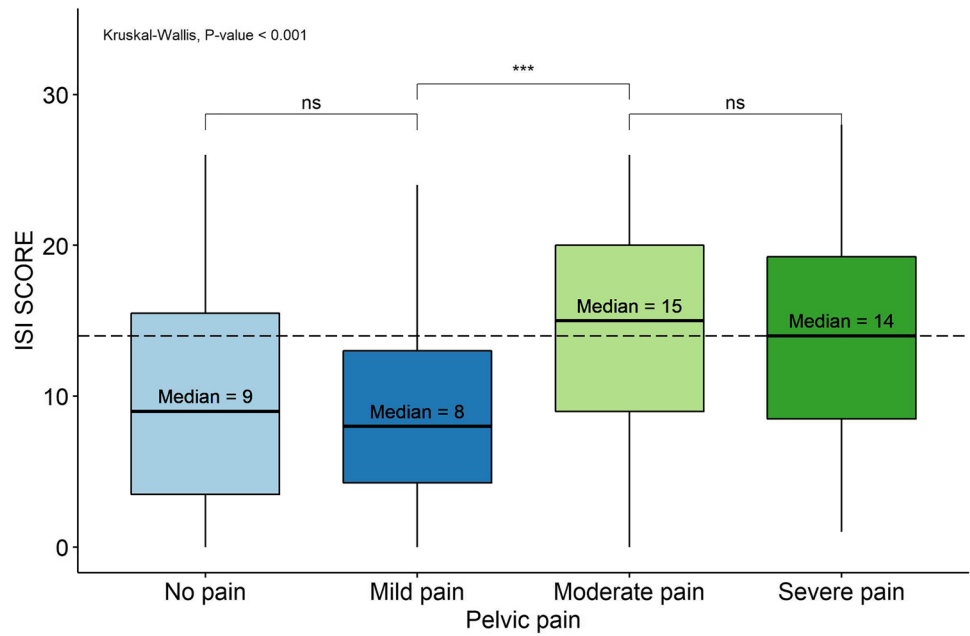


Table 2 Frequency of insomnia according to pain intensity

	Pain Intensity			
	No pain, $N = 39^1$	Mild pain, $N = 66^1$	Moderate pain, $N = 53^1$	Severe pain, $N = 76^1$
Insomnia severity				
No insomnia	15 (38%)	30 (45%)	11 (21%)	19 (25%)
Subthreshold insomnia	14 (36%)	20 (30%)	13 (25%)	20 (26%)
Moderate insomnia	7 (18%)	13 (20%)	19 (36%)	23 (30%)
Severe insomnia	3 (8%)	3 (5%)	10 (19%)	14 (18%)

¹ n (%)

Table 3 Odds ratios of clinically relevant insomnia according to pelvic pain, duration of pain, and education

Insomnia	OR ¹	95% CI ¹	p -value
(Intercept)	0.12	0.06, 0.24	< 0.001
Pelvic pain			
Group 1	1.00	—	
Group 2	2.80	1.41, 5.70	0.004
Pain duration (years)	1.11	1.05, 1.19	< 0.001
Education			
High	1.00	—	
Low/intermediate	2.09	1.06, 4.19	0.035

¹OR, odds ratio; CI, confidence interval

Group 1, no pain or mild pain; group 2, moderate or severe pain; high education > 12 years study; low/intermediate ≤ 12 years study. Insomnia = Insomnia Severity Index score > 14 points

Insomnia is often associated with chronic pain. Mathias et al. reported that this is the most studied sleep disorder in chronic pain, with a prevalence of 72% (95%, CI = 48–88%).

However, this number drops to less than 6% in the presumably healthy general population [13]. Thus, as we hypothesized, women with endometriosis (with no or mild pain) had a higher prevalence of insomnia than healthy women and may be due to other factors involved with the disease, such as stress and infertility, and not necessarily induced by pain [21]. Anxiety, depression, and psychiatric symptoms are also related to endometriosis, impairing quality of life and social function, which may increase insomnia in these patients [22].

Besides pain intensity, the duration of pain symptoms related to insomnia. Women with moderate to severe pain had a duration of pain three times longer than pain-free women or with mild pain. Also, the chance of having insomnia doubled for every ten years of pain duration. Hilda et al. demonstrated that catastrophizing increases with pain duration, which may have been one of the reasons for insomnia in our patients, potentialized by the lack of effective treatments or pain persistence [23]. These findings highlight the importance of pain duration, showing

that studies with CPP should consider pain intensity and the total period during which the patient suffers, especially in endometriosis, as the diagnosis may take up to 10 years after the symptom onset [24].

In addition to pain-related aspects, women with a higher level of formal education had a lower chance of insomnia. Karaman et al. have reported a lower level of education in patients with CPP than in those without CPP [7]. Vulnerability and difficulty in coping with pain may affect more people with a low level of education [25]. Also, this group of patients tend to use less effective strategies to deal with pain. A higher educational level may be related to better access to information and the health system, as well as better interaction with specialized professionals [6]. Education seems to interact with both pain and insomnia, reinforcing the pain-insomnia cycle.

There is evidence that the relation between pain and insomnia is bidirectional, with one increasing the other effect, though insomnia is an independent factor associated with an impairment in quality of life and increased depressive symptoms [11]. In a systematic review, Stroemel-Scheder et al. demonstrated that improved sleep quality could restore pain sensitivity controls, which may also be a target in managing these patients [26].

Limitations of the current study include the use of a self-reported questionnaire to assess insomnia. However, the ISI is widely used, inexpensive, easy to apply, and has high sensitivity (78%) and specificity (100%) to detect insomnia [27].

Histopathological analysis was not obtained for all patients, although several studies have demonstrated high accuracy of imaging tests in diagnosing endometriosis [15] and the specificity of diagnosis was increased by selecting women with nodules larger than 1.5 cm. Furthermore, some patients benefit more from clinical treatment than from surgery, and tissue samples could not be obtained from patients undergoing medical therapy [28].

In conclusion, the prevalence of insomnia in women with deep endometriosis was higher in those with moderate or severe pain than those without pain or mild pain. Furthermore, insomnia was related to pain duration and patients with a lower level of education.

Author contribution De Souza, R. J.: work design; data collection, analysis, and interpretation; draft, discussion, and review.

Oliveira, M.A.P.: work design; data analysis and interpretation; and review.
Vilella, N. R.: results interpretation; discussion; and review.

Data availability The datasets generated during and/or analyzed during the current study are not publicly available due to the sigil's patient information. Still, they are available from the corresponding author on reasonable request.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (The University of the State of Rio de Janeiro—CAAE: 18261019.4.0000.5259) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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