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Prevalence of fibromyalgia among women with deep infiltrating endometriosis

Jose Luis Coloma[1] | Maria-Angeles Martínez-Zamora[1,2,3,*] | Antonio Collado[4] | Meritxell Gràcia[1] | Mariona Rius[1] | Lara Quintas[1] | Francisco Carmona[1,2,3]

[1]Department of Gynecology, Institut Clínic of Gynecology, Obstetrics and Neonatology, Hospital Clínic of Barcelona, Barcelona, Spain

[2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[3]Faculty of Medicine, University of Barcelona, Barcelona, Spain

[4]Service of Rheumatology, Institut Clínic d'Especialitats Mèdiques i Quirúrgiques, Hospital Clínic of Barcelona, Barcelona, Spain

*Correspondence
Maria-Angeles Martínez-Zamora, Department of Gynecology, Institut Clínic of Gynecology, Obstetrics and Neonatology, Hospital Clínic of Barcelona, Barcelona, Spain.
Email: mazamora@clinic.cat

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Abstract

Objective: To estimate the prevalence of fibromyalgia among women with endometriosis and analyze the effect of fibromyalgia on health-related quality of life (HRQoL).

Methods: An observational case–control study conducted at a tertiary hospital in Barcelona between April 2015 and March 2017 among women with deep infiltrating endometriosis (DIE; n=80), women with superficial endometriosis or ovarian endometrioma (non-DIE; n=76), and control women without endometriosis (n=73). Fibromyalgia was assessed via the London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ). HRQoL was evaluated with the 36-Item Short Form (SF-36) questionnaire. The impact of fibromyalgia and other clinical characteristics was assessed by multivariate regression analysis.

Results: More women fulfilled the criteria for fibromyalgia in the DIE group than in the non-DIE and control groups by LFESSQ-4 (31 [39%], 12 [16%], and 6 [8%], respectively; *P*=0.009) and LFESSQ-6 (22 [28%], 8 [11%], and 4 [5%], respectively; *P*=0.008). The DIE group reported significantly poorer HRQoL for all SF-36 dimensions. Women with DIE who fulfilled the criteria for fibromyalgia had lower physical component scores (−31.6; 95% confidence interval, −50.8 to −12.3; *P*=0.003).

Conclusion: The estimated prevalence of fibromyalgia was higher among women with DIE. Women with DIE and positive fibromyalgia screening had lower HRQoL.

KEYWORDS

Deep infiltrating endometriosis; Endometriosis; Fibromyalgia; London Fibromyalgia Epidemiological Study Screening Questionnaire; Pain; Quality of life; SF-36 questionnaire

1 | INTRODUCTION

Endometriosis is a leading cause of pain and infertility among women, and can severely impair quality of life and work productivity across countries and ethnicities.[1] Despite an estimated prevalence of 10% in women[2] and substantial associated costs,[3] the etiology of endometriosis remains largely unknown.

Although little is known about the causes of endometriosis, in recent years, different research studies have associated endometriosis with different types of autoimmune diseases, cancer, cardiovascular diseases, asthma and atopy.[4,5] Therefore, it has been postulated that patients with endometriosis could present a higher risk of developing these chronic diseases.[4,5] A more detailed investigation of these associations could help to advance the knowledge of the causes and consequences of endometriosis. In addition, because endometriosis is very prevalent, it would be expected that the establishment of tools for early detection and specific prevention of these chronic diseases could have an important impact on public health in general.[6]

Recent studies have suggested that there is a high prevalence of fibromyalgia among women with endometriosis,[4,7,8] although another

study reported contradictory results.[9] Furthermore, no data are available on the prevalence of fibromyalgia among women with different types of endometriosis such as deep infiltrating endometriosis (DIE), which is known to cause high levels of pain.[2] Therefore, the aim of the present study was to determine the prevalence of fibromyalgia among women with different types of endometriosis and to assess the effect of fibromyalgia on their health-related quality of life (HRQoL).

2 | MATERIALS AND METHODS

The present preliminary observational case–control study was conducted among women attending Hospital Clínic of Barcelona, a tertiary university teaching hospital in Barcelona, Spain, between April 6, 2015 and March 31, 2017. The study was supported by a "Premi Fi de Residència Emili Letang" grant from the Hospital Clinic of Barcelona and was approved by the local ethics committee in accordance with the relevant regulations (no. 5497). All women gave informed consent before initiation of the study.

The study was designed to examine fibromyalgia screening scores and the estimated point prevalence of fibromyalgia in three groups of women: those with DIE (DIE group); those with ovarian endometrioma or superficial endometriosis, but no DIE (non-DIE group); and those without endometriosis and without any rheumatologic or autoimmune disease (control group). All study participants were premenopausal, aged 18–40 years, and had a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) of less than 30. The exclusion criteria were malignancy or a history of malignancy, endocrine, cardiovascular, rheumatologic, autoimmune or systemic inflammatory diseases, premature ovarian failure, or menopausal status. Women who had been pregnant, had breastfed, or had presented with an infectious disease within 6 months of the study were also excluded.

The DIE group included women suspected to have DIE on the basis of an extensive preoperative protocol described elsewhere.[10] In brief, all women with suspected DIE underwent clinical examination and transvaginal ultrasound (TV-US), and magnetic resonance imaging was performed in selected cases. DIE was diagnosed when the lesions penetrated more than 5 mm under the peritoneal surface and were histologically confirmed after the laparoscopic procedure performed for the surgical management of DIE. The non-DIE group included women undergoing surgery for an ovarian endometrioma of 3 cm or larger (detected by TV-US and confirmed during the surgical procedure). Women with a novel finding of superficial endometriosis and/or ovarian endometrioma (but no DIE) during treatment for a benign adnexal pathology were also included in the non-DIE group. Findings of endometriosis were confirmed by histologic examination. The control group included women without presurgical suspicion of endometriosis (based on clinical or TV-US examination) who underwent laparoscopy for a mild benign adnexal pathology (e.g., adnexectomy, cystectomy, or tubal sterilization) and showed no signs of endometriosis or an inflammatory pelvic condition during surgery. After a woman was enrolled in the DIE group, the next two women without suspicion of DIE undergoing surgery with and without endometriosis were enrolled in the non-DIE group and the control group, respectively.

Operative laparoscopy was performed for all study women. The excised tissue was examined for pathology, and the women were definitively assigned to the DIE, non-DIE, or control group on the basis of the laparoscopy and histologic results.

Clinical and epidemiologic data, including age, BMI, ethnicity, educational level, and smoking status, were collected from all participants. Women were also asked to quantify the severity of dysmenorrhea, dyspareunia, and chronic pelvic pain via a visual analog scale (VAS), a frequently used tool for the measurement of pain associated with endometriosis.[11] Women graded their perception of each type of pain on a 10-cm line from 0 (no pain) to 10 (unbearable pain); a mean VAS score of 7 or higher was considered severe.[12]

Before the surgical procedure, all women were asked to complete the London Fibromyalgia Epidemiological Study Screening Questionnaire (LFESSQ) for fibromyalgia screening, a six-item questionnaire with four items related to widespread pain and two items related to fatigue.[13] The LFESSQ has been translated into Spanish and validated in accordance with international recommendations on the methodology of quality-of-life (QoL) questionnaires.[14] A positive diagnosis of fibromyalgia was considered when either all four pain criteria (LFESSQ-4) or both the four-pain and the two-fatigue criteria (LFESSQ-6) were met.[13] The sensitivity of LFESSQ-4 and LFESSQ-6 for fibromyalgia has been reported to be 100% (95% CI, 90–100) and 93% (95% CI, 84–100), respectively,[13] and the specificity has been reported to be 53% (95% CI, 35–71) and 80% (95% CI, 66–94) for LFESSQ-4 and LFESSQ-6, respectively.[13] The positive predictive value was 56.8% (95% CI, 53.0%–60.6%) using the LFESSQ-4 and 70.6% (95% CI, 55.3%–85.9%) using the LFESSQ-6. For those initially screening negative, the rest-retest reliability was 95.0% (95% CI, 88.8%–100%) for the LFESSQ-4 and 81.0% (95% CI, 69.1%–92.8%) for the LFESSQ-6.[13]

The prevalence of fibromyalgia in the different study groups was calculated as previously described.[15] In brief, the point prevalence of fibromyalgia was determined as the percentage of study women who screened positive for LFESSQ-4 or LFESSQ-6, multiplied by the corresponding positive predictive value (PPV), reported as 0.18 and 0.25 for LFESSQ-4 and LFESSQ-6, respectively, in Spain.[15]

General HRQoL was evaluated by the Medical Outcomes Study 36-Item Short Form (SF-36) questionnaire translated into Spanish. Specifically, the SF-36 version 2 (SF-36v2) Health Survey 2000 adapted by Alonso[16] in 2003 was used. The questionnaire comprised 36 items and assessed eight health concepts: physical functioning, role limitations due to physical health, body pain, energy/fatigue, role limitations due to emotional problems, emotional well-being, social functioning, and general health perception. An aggregate percentage score for a summary of physical QoL (physical component summary; PCS) and emotional QoL (mental component summary; MCS) was obtained via the mean of the respective physically and emotionally relevant items.[16]

Data analyses were performed by using SPSS version 20 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± SD;

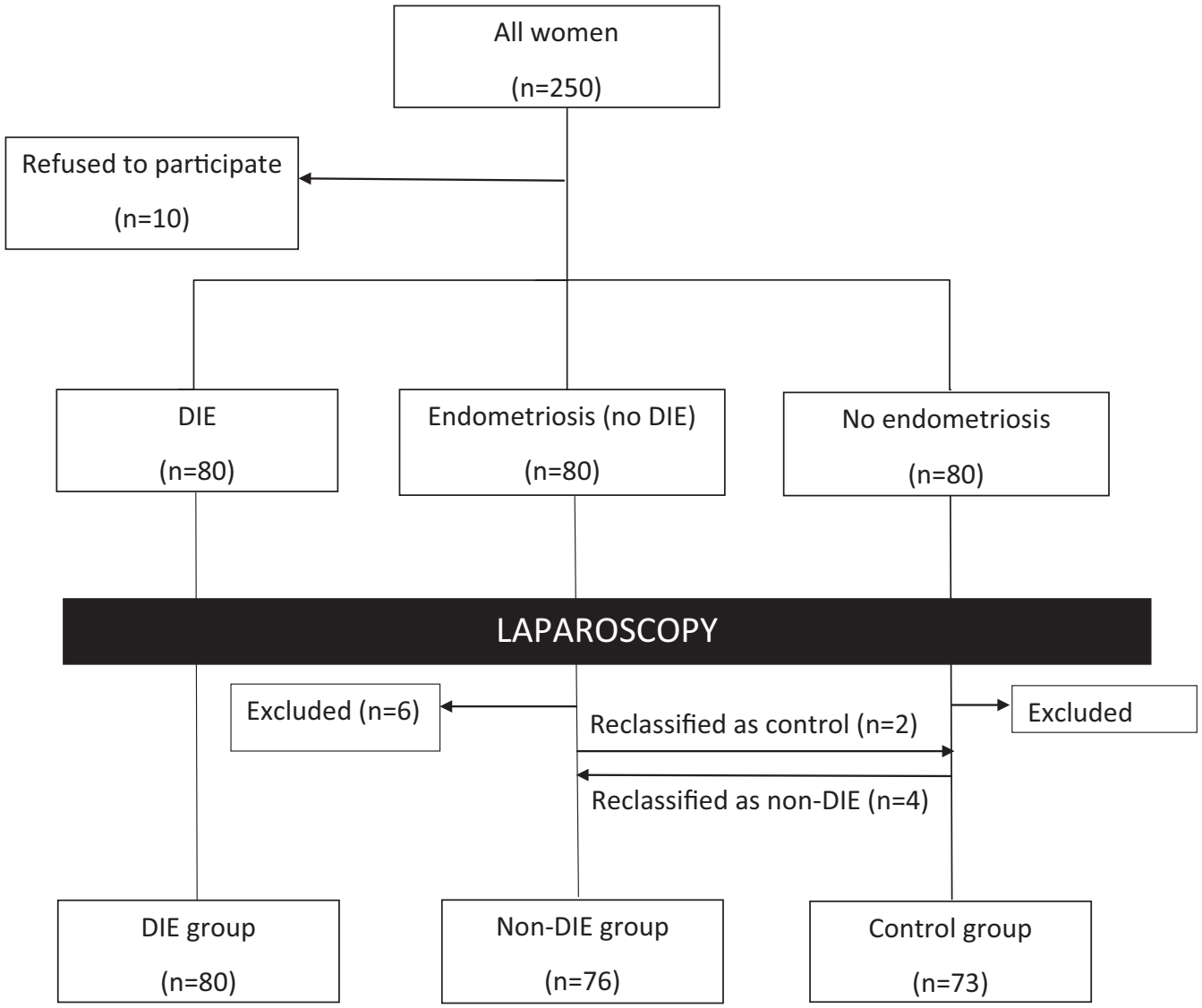

FIGURE 1 Flow chart showing recruitment of the study population. The DIE group included women with deep infiltrating endometriosis; the non-DIE group included women with endometriomas and/or superficial peritoneal endometriosis but without DIE; the control group included women with benign adnexal pathology and without endometriosis. Six women in the non-DIE group were excluded due to the presence of an acute infectious process concomitant with ovarian endometrioma. Five women in the control group did not fulfill the inclusion criteria (three cases of malignancy and two cases of infection) and were excluded.

categoric variables were expressed as number (percentage). The χ^2 test was used for statistical analysis of qualitative data, and one-way analysis of variance was used for quantitative data. Confidence intervals (CIs) for fibromyalgia point prevalence were calculated by using the modified Wald method.[17] A multivariate logistic regression model was constructed via the stepwise method. A *P* value of less than 0.05 was considered to indicate statistical significance.

3 | RESULTS

Among an initial group of 250 women, 10 refused to participate in the study. Thus, 240 women (consecutively recruited and fulfilling the inclusion criteria) were divided among the three study groups. Four patients who were initially assigned to the control group were reallocated to the non-DIE group after the discovery of histologically confirmed superficial endometriosis. Two women in the non-DIE group were reclassified to the control group because the surgical procedure did not show any signs of endometriosis. Six women in the non-DIE group were excluded due to the presence of an acute infectious process concomitant with ovarian endometrioma. Five patients in the control group did not fulfill the inclusion criteria (three cases of malignancy and two of pelvic infection) and were also excluded from the analysis. The final sample of 229 women comprised 80 women in the DIE group, 76 in the non-DIE group, and 73 in the control group (Fig. 1).

Table 1 summarizes the baseline demographic and clinical characteristics of the study women by group. There were significantly more

TABLE 1 Baseline clinical and demographic data of the study women by group.[a]

Characteristic	Control group (n=73)	Non-DIE group (n=76)	DIE group (n=80)	*P* value
Age, y	34.7 ± 6.6	35.8 ± 5.6	35.3 ± 5.7	0.273[b]
BMI	25.2 ± 4.9	23.0 ± 3.8	23.1 ± 3.5	0.864[b]
Current smoker	23 (32)	26 (34)	27 (34)	0.951[c]
Marital status: married	42 (58)	45 (59)	48 (60)	0.920[c]
Educational status				<0.015[c]
Primary	18 (25)	8 (11)	10 (13)	
Secondary	22 (30)	35 (48)	36 (45)	
University	33 (45)	33 (43)	34 (43)	
History of live birth	35 (48)	32 (42)	19 (24)	<0.017[c]
Pain symptoms				
Dysmenorrhea (VAS ≥7)	19 (26)	48 (63)	66 (83)	<0.001[c]
Mean VAS score	3.8 ± 1.2	6.5 ± 2.5	8.8 ± 1.3	<0.001[b]
Dyspareunia (VAS ≥7)	1 (1)	12 (16)	59 (74)	<0.001[c]
Mean VAS score 0–10	0.8 ± 0.2	2.0 ± 0.8	5.0 ± 1.7	<0.001[b]
Chronic pelvic pain (VAS ≥7)	0 (0)	7 (9)	17 (21)	<0.001[b]
Mean VAS score 0–10	0.3 ± 0.0	1.3 ± 0.3	5.3 ± 0.6	<0.001[b]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); VAS, visual analog scale.
[a]Values are given as mean ± SD or number (percentage) unless stated otherwise.
[b]By analysis of variance.
[c]By χ^2 test.

women reporting severe pain symptoms (dysmenorrhea, dyspareunia, and chronic pelvic pain with a mean VAS score ≥7) in the DIE group than in the non-DIE group or the control group (all *P*<0.001).

The characteristics of endometriosis and the medication taken by the women in the DIE and non-DIE groups are summarized in Table 2. The DIE group more frequently underwent previous endometriosis surgical procedures as compared with the other groups. The control group comprised 23 women who requested tubal sterilization and 50 who underwent surgery for a benign adnexal pathology.

TABLE 2 Baseline characteristics of the two groups of endometriosis.[a]

Characteristic	Non-DIE group (n=76)	DIE group (n=80)	*P* value[b]
Ovarian endometrioma[c]	62 (82)	44 (55)	0.013
Left only	34 (55)	22 (50)	
Right only	21 (34)	13 (30)	
Bilateral	7 (11)	9 (21)	
SPE only	13 (17)	0 (0)	<0.001
Adenomyosis	6 (8)	39 (49)	<0.001
Medication	10 (13)	43 (54)	<0.001
Oral contraceptives	10 (13)	24 (30)	
GnRH-a	0 (0)	11 (14)	
Others	0 (0)	8 (10)	
Previous surgery	6 (8)	50 (63)	<0.001

Abbreviations: DIE, deep infiltrating endometriosis; GnRH-a, gonadotropin releasing hormone analog; SPE, superficial peritoneal endometriosis.
[a]Values are given as mean ± SD or number (percentage).
[b]By χ^2 test.
[c]23 women in the DIE group and 29 women in the non-DIE group had SPE in addition to ovarian endometrioma.

A higher frequency of women fulfilled the criteria for fibromyalgia screening in the DIE group than in the non-DIE or control group. For the LFESSQ-4, the values were 31 (39%), 12 (16%), and 6 (8%) for the DIE, non-DIE, and control groups, respectively (*P*=0.009). For the LFESSQ-6, the proportions were 22 (28%), 8 (11%) and 4 (5%), respectively (*P*=0.008). Similarly, the point prevalence for fibromyalgia in the DIE group was 7.0% (95% CI, 1.8–16.0) and 6.7% (95% CI, 1.8–20.5) by the respective LFESSQ-4 and LFESSQ-6 criteria. The estimated prevalence of fibromyalgia was lower in the non-DIE group (2.8% [95% CI, 0–12] and 2.6% [95% CI, 0–12] for LFESSQ-4 and LFESSQ-6, respectively) and in the control group (1.5% [95% CI, 0–10] and 1.4% [95% CI, 0–10], respectively).

Each of the SF-36v2 dimension values were lower for women diagnosed with DIE than for women in the non-DIE or control group (all *P*<0.001), indicating a significant reduction in HRQoL (Fig. 2A). Regarding the percentage scores of the PCS and MCS (Fig. 2B), the PCS score was significantly lower (68.1 ± 18.1) in the DIE group than in the non-DIE and control groups (82.4 ± 9.2 and 88.9 ± 10.3, respectively; *P*<0.001). MCS was also significantly worse for individuals with DIE (68.1 ± 17.7) as compared with the non-DIE and control groups (79.1 ± 11.0 and 81.9 ± 12.3, respectively; *P*<0.001).

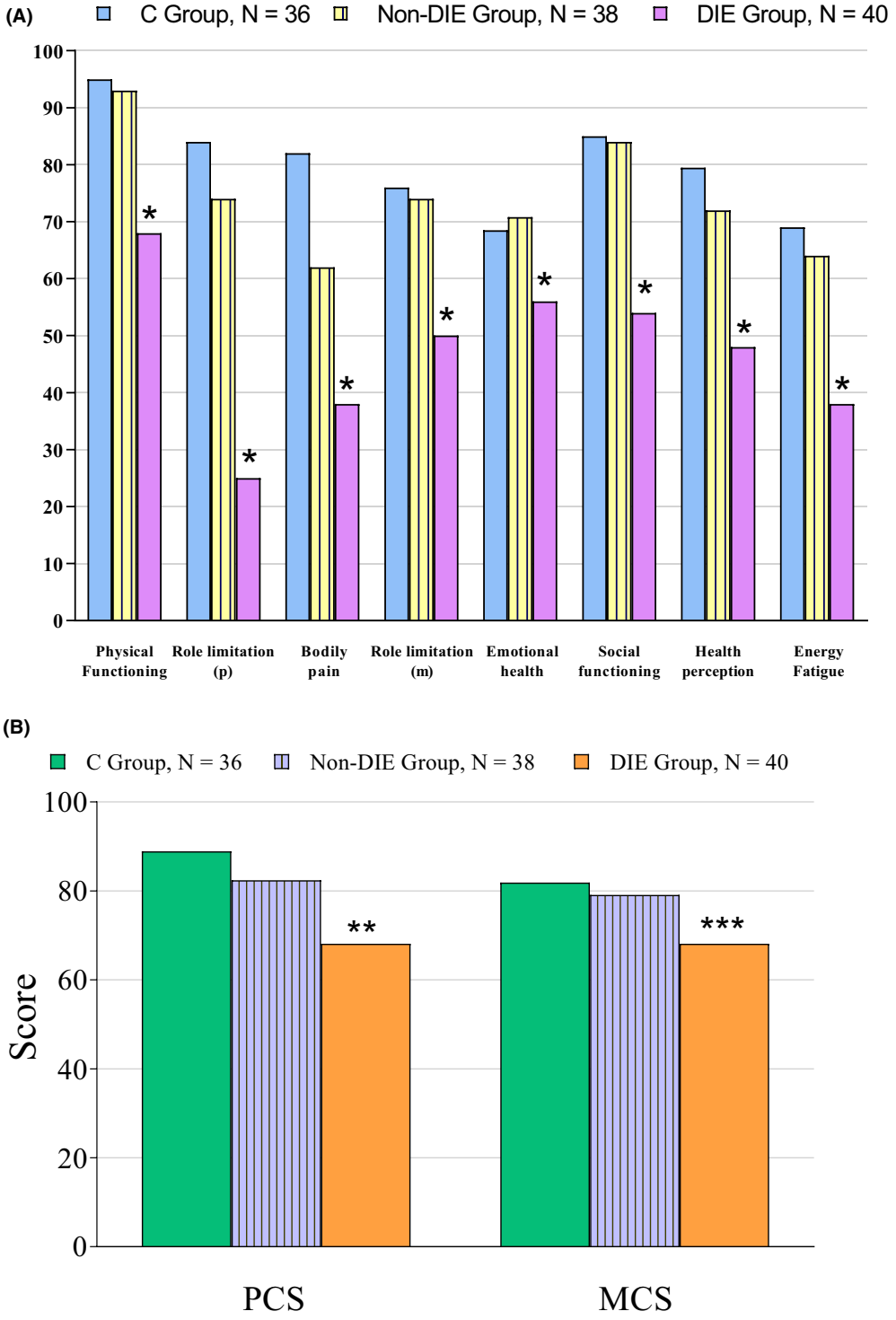

FIGURE 2 SF-36 scores of the study population. (A) Mean scores of all SF-36v2 dimensions. A lower score indicates a lower health-related quality of life (HRQoL). All SF-36v2 dimension values were lower in the deep infiltrating endometriosis (DIE) group than in the non-DIE or control group (C-group) (all $P<0.001$), indicating a significant reduction in HRQoL (B) Mean scores of the physical component summary (PCS) and mental component summary (MCS) of HRQoL. The PCS score was lower (68.1 ± 18.1) in the DIE group than in the non-DIE group or C-group (82.4 ± 9.2 or 88.9 ± 10.3, respectively; $P<0.001$). MCS was also worse in the DIE group (68.1 ± 17.7) than in the non-DIE group or C-group (79.1 ± 11.0 and 81.9 ± 12.3, respectively; $P<0.001$).

In multivariate regression analysis of data for the DIE group, fulfillment of the criteria for fibromyalgia was the only parameter clearly associated with reduced PCS scores (−31.6 [95% CI, −50.8 to −12.3]; $P=0.003$). Furthermore, in the DIE group there was a trend toward an association between screening positive for fibromyalgia and lower MCS scores (−1.7 [95% CI, −3.6 to 0.1]; $P=0.061$).

4 | DISCUSSION

The main finding of the present study was that the point prevalence of fibromyalgia was significantly higher in the group of women who presented with histologically confirmed DIE. By contrast, the frequency of fibromyalgia was similar between women with non-DIE endometriosis and those without endometriosis. Moreover, fulfilling the criteria for fibromyalgia was associated with reduced PCS and MCS scores among women with DIE.

Previous studies have shown that women with endometriosis might have a higher risk of other medical illnesses.[4,5] Together with the present study, these findings suggest that women with endometriosis may require greater medical care because they not only have endometriosis-related health problems, but also have other medical illnesses with a significant impact on public health.[6] Notably, however, previous studies did not assess the risk of chronic diseases by the type of endometriosis, even though DIE is known to cause more severe symptoms as compared with other types of endometriosis.[2]

The exact mechanism by which DIE lesions cause pain remains unknown. Neurogenic mechanisms have been described for endometriotic lesions affecting the peripheral and central nervous system, leading to increased sensitivity to pain and stress reactivity[18] In addition, recent investigations have indicated that several painful disorders might share a common pathologic process of dysregulated nociception called "central sensitization".[19] Peripheral pain is initially produced locally by mechanisms such as inflammation and/or mucosal irritation, but when the nociceptive input becomes persistent or chronic, it leads to changes in the central nociceptive system.

In the case of fibromyalgia, persistent activation of the nociceptive C fibers produces a sustained release of substance P, along with excitatory amino acids (glutamate and aspartate), into the dorsal horn synapse.[20] Sustained release of these neurotransmitters makes the primary afferent neurons hyperexcitable, responding to lower levels of nociceptive stimuli (hyperalgesia) or to stimuli that were not previously painful (allodynia).[21] This might explain why the women with DIE who described persistent severe pain in the present study were more likely to have fibromyalgia. The prevalence of fibromyalgia in the non-DIE group was similar to that in the healthy control group. At present, however, it remains unclear whether DIE and fibromyalgia co-occur, act as risk factors to develop one other, or evolve from localized to widespread pain disorders.

Fibromyalgia is a common condition that is recognized as a major cause of morbidity worldwide.[15] The overall prevalence of fibromyalgia in our Spanish population is estimated to be 2.3%, and 3.3% among women in particular.[15] Nevertheless, it is important to note that prevalence is age-related and widespread pain tends to increase with age. The prevalence of fibromyalgia among women aged 35 years, which was the mean age of the study cohort, is estimated to be approximately 1.5%,[15] in concordance with the present findings. Previous studies have reported a high prevalence of fibromyalgia among women with endometriosis[4,7,8] A large cross-sectional survey of 3680 US Endometriosis Association members with surgically diagnosed endometriosis in 2002 found a prevalence of fibromyalgia of 5.9%.[4] This high prevalence was subsequently confirmed by a prospective controlled study of 45 women with histologically corroborated pelvic endometriosis, where 9% of women fulfilled the 1990 criteria of the American College of Rheumatology (ACR) for fibromyalgia.[7] In contrast, Nunes et al.,[9] who also utilized the 1990 ACR criteria, found that only 2 (0.8%) women had fibromyalgia among 257 Brazilian women with histopathologically confirmed endometriosis. It has been suggested that the clinical presentation of endometriosis and the prevalence of coexisting symptoms (including fibromyalgia) may not be universal, but instead may be subject to population-specific patterns[8] Therefore, as a strength of the present research, the study was designed with strict inclusion and exclusion criteria, whereby the diagnosis of endometriosis was histologically confirmed or excluded, and the incidence of fibromyalgia was assessed in accordance with the presence or absence of DIE.

Multivariate analysis showed that testing positive for fibromyalgia negatively affected the HRQoL of the present study population. As expected, women with DIE had significantly poorer HRQoL (reduced scores in all SF-36v2 dimensions). The physical component was particularly impaired in the DIE group as compared with the non-DIE and control groups. Mabrouk et al.[22] obtained similar data not only for these four dimensions, but also for all the remaining SF-36v2 items, reflecting the impaired general HRQoL of their cohort of women. Furthermore, the present multivariate regression analysis of the DIE group found that fulfillment of the criteria for fibromyalgia was the only parameter associated with lower PCS, and this parameter also showed a trend to lower MCS scores.

The present study has some limitations. First, the sample size was small and arbitrarily chosen on the basis of studies analyzing the prevalence of fibromyalgia in other diseases.[23,24] Second, the diagnosis of fibromyalgia was not based on clinical features at examination, which commonly include widespread musculoskeletal pain, sleep difficulties, neuropsychologic complaints, and tender points[25]; however, the present results were in line with previous reports of fibromyalgia prevalence.[6,8] Third, the study, included all women with endometriosis and control women regardless of intake of hormonal medication, although this treatment might have influenced the results. However, a subanalysis of fibromyalgia prevalence and HRQoL among the endometriosis and control groups stratified by hormonal treatment did not find statistical differences (data not shown).

Fourth, the prevalence of smoking was high in the study population at the time that the study was performed and might have influenced the results. Overall, 34% of smokers in the cohort were considered occasional or social smokers (<5 cigarettes per day; <3 or <7 days per week, respectively). Although a subanalysis of smokers versus non-smokers found no differences with respect to fibromyalgia prevalence and HRQoL, the sample size may have been too small to obtain firm conclusions. Further studies should be performed to evaluate this parameter in other populations with different smoking habits. Fifth, the main indication for surgery among women with endometriosis but without DIE in the study department was

ovarian endometrioma, and the indication for women with isolated peritoneal endometriosis was very low. As a result, the non-DIE group predominantly comprised women with ovarian endometrioma, and only 17% had isolated superficial peritoneal endometriosis, which must be considered a limitation of the study. Last, as expected, a high percentage (63%) of women in the DIE group had previously undergone surgery, which might have biased the results. Nevertheless, a subanalysis of the DIE group with and without previous surgery did not find significant differences with respect to the prevalence of fibromyalgia (data not shown).

In conclusion, the results of the present study suggest that there is an increased prevalence of fibromyalgia among women with surgically and histologically confirmed DIE. Furthermore, multivariate analysis showed that women with DIE and a positive screening for fibromyalgia had a lower HRQoL. Further studies are needed to confirm whether women with DIE have an increased risk of fibromyalgia.

AUTHOR CONTRIBUTIONS

JLC contributed to study design, recruitment of women, questionnaire evaluation, data analysis, and manuscript drafting. M-AM-Z contributed to study design, recruitment of women, data analysis, manuscript preparation, and critical discussion. AC contributed to study design and critical revision. MG, MR, and LQ contributed to recruitment of women, data analysis, and critical revision. FC contributed to study design, data analysis, manuscript drafting, and critical discussion. All authors revised the manuscript critically, provided final approval of the submitted manuscript, and agreed to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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