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Association between chronic pelvic pain symptoms and the presence of endometriosis

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Abstract
Purpose The link between endometriosis and the presence or intensity of pain is controversial. The aim of the present study was to assess the relationship between chronic pelvic pain (CPP) and severity of endometriosis and the effectiveness of laparoscopic treatment in a 6-month follow-up.
Methods Prospective observational study in a referral unit. 144 women had laparoscopy to investigate CPP. Symptoms were assessed by a 10-point visual analog scale. The main outcome measure was the frequency and intensity of CPP.
Results No difference in pain was found between women with and without endometriosis. Advanced endometriosis was associated with dysmenorrhea, deep endometriosis with dyspareunia and rectovaginal disease with dyschezia. Laparoscopic treatment improves symptoms.
Conclusions Women with severe endometriosis are more likely to report severe dysmenorrhoea. Furthermore location of endometriosis in the rectovaginal space is associated with dyschezia and deep endometriosis with dyspareunia. However, the association between presence and stage of endometriosis and severity of symptoms is marginal.

Keywords Endometriosis · Dysmenorrhea · Chronic pelvic pain · Laparoscopy · Dyspareunia

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Introduction

Endometriosis is associated with chronic pelvic pain (CPP); 83 % of women with endometriosis and 29 % without endometriosis reported CPP symptom [1]. Women with endometriosis are not always symptomatic. In a series of 107 asymptomatic women who had sterilization, ten had visually and 14 histologically diagnosed endometriosis [2]. It has been reported that two-thirds of patients who undergo laparoscopy for CPP will not have endometriosis [3]. For the diagnosis of endometriosis, surgical and ideally histological confirmation is required. The link between endometriosis and the presence or intensity of pain is controversial being associated with debilitating symptoms or being an incidental diagnosis. To further explore this issue, we analyzed a series of women who had laparoscopy in the context of investigation of CPP to evaluate whether severity of symptoms was related to the presence and severity of endometriosis as well as to assess the safety and efficacy of laparoscopic treatment at a 6-month follow-up.

Materials and methods

This prospective, observational study took place in a University District General Hospital where a laparoscopic unit is providing a tertiary referral service. Women who underwent diagnostic and when necessary therapeutic laparoscopy for investigation and treatment of CPP were included in the study unless they were less than 16 years old, had history of fibroids, pelvic inflammatory disease (PID) or irritable bowel syndrome (IBS) and treatment with Gonadotropin—Releasing Hormone analogs (GNRHa) in the last 6 months. CPP was defined as the presence of dysmenorrhoea, non-cyclical pelvic pain, dyspareunia or

dyschezia for more than 6 months. The severity of each symptom was graded by visual analog scales (VAS: 0 = no pain to 10 = unbearable pain/need for hospital admission). The VAS was completed in hospital before the laparoscopy and was handed to the surgeons. Endometriosis was staged according to the revised American Fertility Society (rAFS) classification system [4] and was classified to superficial (SE) or deep infiltrating (DIE) and rectovaginal according to Brosens [5].

In the context of treatment, for SE (stage I/II), we used ablation or excision. For the ablation we used the Helica Thermal Coagulator at 6 W or bipolar diathermy at a coagulation current of 50 watts on a pair of 3-mm forceps. Coagulation continued until the peritoneum was destroyed and an eschar could be seen. All visible lesions were coagulated. For moderate and severe cases, we used excision of endometriosis using a 3-mm round-tipped, round-bodied pair of scissors. When necessary to desiccate tissues, monopolar diathermy with a combination of 90 watts cut and 50 watts coagulation was used. All visible lesions were excised. Biopsies from the excised tissues were sent for histology and diagnosis was confirmed if both glands and stroma were present in a sufficient biopsy specimen.

Operative details were collected including the length of procedure after induction of anesthesia, estimated blood loss (calculated by subtracting the volume of the irrigation fluid from the total amount of the fluid in the suction apparatus), length of postoperative stay and complications.

In their follow-up 6 months postoperatively, patients were asked to grade their CPP symptoms using the same VAS. No medical treatment for endometriosis was prescribed during the follow-up period.

The project was registered with the local Research and Development department (i.e., the local institutional ethics committee) as service evaluation.

Statistical analysis

The distribution of normality of continuous variables was assessed by the Kolmogorov–Smirnov test. Comparisons between groups were made by the unpaired t test or the Mann–Whitney U tests for normally or non-normally distributed variables, respectively. Comparisons between groups pre-versus postoperatively were made by the Wilcoxon two-related samples test since the variables were not normally distributed. Correlations between categorical variables were estimated by the Chi-square or Fisher's Exact Test, as appropriate. Odds ratios (OR) and 95 % confidence intervals (CI) for binary outcomes in univariate and multiple logistic models were calculated and reported. Significance level was set to 0.05. Values were presented as mean value ± standard deviation (±SD) when normally distributed and median value (range) when not normally distributed. Statistical analysis was performed using SPSS (Statistical package for the Social Sciences, version 16.01; SPSS, Inc., Chicago, IL) for Windows XP (Microsoft Corp).

Results

During the study period, 144 patients had a diagnostic laparoscopy to investigate CPP and endometriosis was diagnosed visually in 96. The patients' characteristics are presented in Table 1. No significant difference was seen between women with and without endometriosis, apart from previous surgery in the endometriosis group. In this latter group 8 % had previous diagnostic laparoscopy; 16 % cesarean sections; 3 % drainage of Bartholin's abscess; 27 % previous surgery for endometriosis. The staging of endometriosis is presented in Table 2. The preoperative symptoms of patients with stage I/II disease

Table 1 Characteristics and symptoms of women with and without endometriosis

	Endometriosis ($N = 96$)	No-endometriosis ($N = 48$)	p value
Age (mean ± SD) years	33.4 ± 0.9	32.9 ± 1.5	0.78
BMI (mean ± SD) kg/m^2	25.5 ± 0.5	26.3 ± 0.8	0.47
Previous delivery	24 (25 %)	20 (41 %)	0.15
Previous gynecological surgery	52 (54 %)	8 (16 %)	**0.02**
Non-cyclical pain frequency	62.5 %	70.8 %	0.48
Non-cyclical pain intensity	6 (0–10)	6.5 (0–10)	0.94
Dysmenorrhoea frequency	79.1 %	87.5 %	0.37
Dysmenorrhoea intensity	8 (0–9)	7 (0–9)	0.07
Dyspareunia frequency	25 %	33.3 %	0.46
Dyspareunia intensity	3 (0–10)	2 (0–8)	0.45
Dyschezia frequency	25 %	20.8 %	0.69
Dyschezia intensity	2 (0–6)	2 (0–7)	0.61

Mean values ± SD when normally distributed; median values (range) when not normally distributed

$P < 0.05$ is taken as statistically significant, results at this level are indicated in bold

Table 2 Stage of endometriosis in the 96 women with visually diagnosed endometriosis and comparison of preoperative symptoms between women with Stage I and II and women with Stage III and IV

Stage of endometriosis (rAFS): number (%)	Stage I: 18 (18.8 %) Stage II: 24 (25 %) ($N = 42$)	Stage III: 32(33.3 %) Stage IV: 22 (22.9 %) ($N = 54$)	p value
Non-cyclical pain frequency	28/42 (66.7 %)	32/54 (59.3 %)	0.77
Non-cyclical pain intensity	7 (0–10)	6 (0–9)	0.36
Dysmenorrhoea frequency	28/42 (66.7 %)	48/54 (88.9 %)	0.08
Dysmenorrhoea intensity	7 (0–9)	8 (0–9)	**0.02**
Dyspareunia frequency	10/42 (23.8 %)	22/54 (40.7 %)	0.24
Dyspareunia intensity	2 (0–8)	3 (0–10)	0.21
Dyschezia frequency	4/42 (9.5 %)	14/54 (25.9 %)	0.26
Dyschezia intensity	2 (0–6)	2 (0–7)	0.14

Intensity score is presented as median values (range)

$P < 0.05$ is taken as statistically significant, results at this level are indicated in bold

were compared with those of patients with stage III/IV in terms of frequency and intensity (Table 2). Only the intensity of dysmenorrhoea reached statistically significant difference ($p = 0.02$). There was no significant difference in the demographic characteristics in the two groups.

Twelve patients, all with SE, had ablation; the remaining 84 had excision. In 56 (66.6 %) women, endometriosis was confirmed histologically. The mean time of surgery was 63 ± 18 min, the estimated blood loss 185 ± 23 ml and 76 (90.5 %) of the patients were discharged the same day. No patient required blood transfusion and no procedures were converted to laparotomy at the time of surgery; one patient returned to theater at a later stage because of bowel injury. Two women had postoperative cystitis, successfully treated with antibiotics. One patient with stage IV endometriosis, that required entrance in the rectovaginal septum, developed transient postoperative urinary retention. One patient with stage III endometriosis not involving the bowel, presented 5 days later with signs of bowel injury requiring bowel resection and 4 weeks of hospital care.

The positive predictive value (PPV) for laparoscopic diagnosis of endometriosis, based on histological confirmation, was found to be 66.7 %. Patients with a higher stage of endometriosis were more likely to have positive histology (OR = 4.03, CI: 1.52–10.70, $p = 0.005$). Regarding the reported frequency and intensity of symptoms, no association was found except that noncyclical pain was associated with raised body mass index (BMI) (OR = 1.185, CI: 1.002–1.401, $p = 0.047$) in this cohort of marginally overweight women with endometriosis.

The improvement of symptom intensity preoperatively compared with at 6-month follow-up is presented in Table 3. There was significant improvement in all symptoms postoperatively.

Women with DIE not involving the rectovaginal space complained of significantly more severe dysmenorrhoea and dyspareunia preoperatively compared to women with SE. All pain parameters improved in both groups at 6-month postoperative follow-up (Table 4).

Table 3 Preoperatively versus 6 months postoperatively pain intensity in the endometriosis subgroups studied

Pain intensity	Pre-operatively	Post-operatively	p value
Women with endometriosis			
Non-cyclical pain	6.5 (0–10)	0 (0–7)	<0.001
Dysmenorrhoea	8 (0–9)	2 (0–7)	<0.001
Dyspareunia	3 (0–10)	0 (0–7)	<0.001
Dyschezia	2 (0–7)	0 (0–5)	0.002
Women with superficial endometriosis			
Non-cyclical pain	7 (0–10)	0 (0–7)	<0.001
Dysmenorrhoea	8 (0–9)	2 (0–7)	<0.001
Dyspareunia	0 (0–8)	0 (0–7)	<0.001
Dyschezia	0 (0–7)	0 (0–5)	0.008
Women with deep endometriosis			
Non-cyclical pain	6 (0–9)	0 (0–7)	0.006
Dysmenorrhoea	9 (0–9)	2.5 (0–7)	<0.001
Dyspareunia	6 (0–10)	2 (0–5)	0.003
Dyschezia	0 (0–7)	0 (0–5)	0.046
Women without rectovaginal endometriosis			
Non-cyclical pain	6.5 (0–10)	0 (0–7)	<0.001
Dysmenorrhoea	8 (0–9)	2 (0–7)	<0.001
Dyspareunia	0 (0–9)	0 (0–7)	<0.001
Dyschezia	0 (0–6)	0 (0–4)	0.10
Women with rectovaginal endometriosis			
Non-cyclical pain	6.5 (0–9)	0 (0–7)	0.003
Dysmenorrhoea	9 (0–9)	2.5 (0–7)	0.001
Dyspareunia	0 (0–10)	0 (0–5)	0.016
Dyschezia	5.5 (0–7)	4 (0–5)	0.004

Intensity score is presented as median values (range)

Table 4 Comparison of preoperative and postoperative symptoms between women with superficial (SEE) and deep infiltrating endometriosis (DIEE) and between without rectovaginal endometriosis (NRE) and with rectovaginal endometriosis (RE)

	preoperative symptoms			postoperative symptoms			preoperative symptoms			postoperative symptoms		
	SEE ($N = 78$)	DIEE ($N = 18$)	p value	SEE ($N = 78$)	DIEE ($N = 18$)	p value	NRE ($N = 80$)	RE ($N = 16$)	p value	NRE ($N = 80$)	RE ($N = 16$)	p value
Non-cyclical pain frequency	48/78 (61.5)	12/18 (67)	0.68				48/80 (60)	12/16 (75)	0.40			
Non-cyclical pain intensity	7 (0–10)	6 (0–9)	0.96	0 (0–7)	0 (0–7)	0.37	6.5 (0–10)	6.5 (0–9)	0.96	0 (0–7)	0 (0–7)	0.45
Dysmenorrhoea frequency	59/78 (75.6)	17/18 (94)	0.11				61/80 (76)	15/16 (94)	0.18			
Dysmenorrhoea intensity	8 (0–9)	9 (0–9)	**0.001***	2 (0–7)	2.5 (0–7)	**0.04**	8 (0–9)	9 (0–9)	**0.002**	2 (0–7)	2.5 (0–7)	0.09
Dyspareunia frequency	21/78 (26.9)	11/18 (61)	**0.007**				25/80 (31)	7/16 (44)	0.34			
Dyspareunia intensity	0 (0–8)	6 (0–10)	**0.004**	0 (0–7)	2 (0–5)	**0.01**	0 (0–9)	0 (0–10)	0.12	0 (0–7)	0 (0–5)	0.34
Dyschezia frequency	8/78 (15.4)	6/18 (33)	0.26				5/80 (6.3)	13/16 (81)	**0.0001**			
Dyschezia intensity	0 (0–7)	0 (0–7)	0.09	0 (0–5)	0 (0–5)	0.08	0 (0–6)	5.5 (0–7)	**0.0001**	0 (0–4)	4 (0–5)	**0.001**

Intensity score is presented as median values (range)

$P < 0.05$ is taken as statistically significant, results at this level are indicated in bold

Frequency is presented as absolute number and rate (%)

* Interquantile range was 5 for SEE and 1 for DIEE

The group of women with rectovaginal endometriosis reported significantly more dysmenorrhoea and dyschezia. Postoperatively, they reported improvement in all the pain parameters (Table 4). Nine women had both rectovaginal and DIE and reported significant dysmenorrhoea, dyspareunia and dyschezia; all pain parameters had improved at their follow-up ($p = 0.001$).

Discussion

In our population in a high percentage of patients endometriosis was visually diagnosed, probably attributed to the increased number of referrals (35 %) of women already diagnosed with endometriosis; 27 % had been surgically treated in the past similarly to previous reports [6]. Ablation used in 12 cases of SE since equally effective with excision [7, 8], but with the disadvantage that histological confirmation is not possible. Looking at the PPV of laparoscopy in diagnosing histologically confirmed cases of endometriosis, we could suggest that its value is limited, especially in cases of SE, as the majority of false-positive diagnoses involved women with SE. Our findings are in agreement with Wykes who reported that negative diagnostic laparoscopy seems to be accurate for excluding endometriosis as opposed to the limited value of a positive laparoscopy when used in isolation [9]. Whether or not we should replace the gold standard of diagnostic laparoscopy with histology is a matter of debate. The importance of histological confirmation of endometriosis has been stressed in a study of 62 women with CPP irrespective of previous pelvic surgery or history of endometriosis; endometriosis was confirmed in just 73 % [10]. In our study, the disease was confirmed in 96 % of women previously treated for endometriosis. Carbonized peritoneum or scar tissue could confuse the operative findings and justify the negative histology. On the other hand, the high positive percentage suggests a potential high recurrence rate for endometriosis, although not all women previously treated had previously positive histology. As we do not take biopsies from women with negative laparoscopy is impossible to compare the two tests and calculate the true accuracy of visual diagnosis.

At 6-month follow-up, all parameters of CPP had improved significantly. Among the patients who failed to improve, one had bowel injury and seven had SE. We could speculate that either the visually diagnosed endometriosis was not the cause of CPP or that these women did not have endometriosis.

Looking at the endometriosis subgroups, women with DIE reported more intensive and more frequent dyspareunia, while women with rectovaginal endometriosis complained more often of more intensive dyschezia.

Women with SE or DIE reported significant improvement of CPP at the 6-month follow-up as previously reported [11]. A prospective observational study did not confirm improvement after 18-month follow-up in women with SE [12]. The different follow-up period, the shorter duration of the benefits from laparoscopic treatment or the increased presence of the placebo effect of laparoscopy in our group may explain these discrepancies.

Regarding dyspareunia, it appears that DIE in the pelvis is associated with this particular symptom and laparoscopic excision with improvement; additionally excision of rectovaginal endometriosis offers significant improvements in CPP and particularly in dyschezia [13–16]. An alarming finding is the fact that dyschezia symptoms, although significantly improved, were still present in our population at short-term follow-up. Studies with longer follow-up have suggested a high recurrence rate of 25–36 % [17] implying incomplete treatment, new disease or side effects from the surgical manipulation of the rectovaginal space. Additionally, although surgery for deep endometriosis appears effective, it is associated with significant complication rates, particularly when the bowel is involved [18].

Overall, our findings suggest that excision of endometriosis is beneficial and associated with CPP reduction. However, an observational study is subject to bias from the placebo effect of laparoscopy, estimated to be up to 30 % [19]. In our study, we were unable to examine the placebo effect of laparoscopy in our non-blind control group.

In our population, there was no difference in the age of women with and without endometriosis as opposed to Sampson's theory [20] suggesting older women of reproductive age to be diagnosed with more advanced endometriosis as having had more menses. If endometriosis is a progressive disease [21], women with severe endometriosis should be older than women with SE; this was not confirmed in our study. Furthermore, 1000 women with endometriosis reported that severity reduced with advancing age [22]. Decreasing estrogen production with time, or spontaneous regression of the disease may be the cause. However, a retrospective epidemiological study including 42,079 women suggested a relatively high prevalence of the condition in patients aged over 40 [23]. Of note randomized controlled trials (RCT) have shown that spontaneous improvement of endometriosis is possible [19, 25] and women with this chronic disease must be counseled about this before undergoing any treatment.

Regarding symptom intensity, there was no difference between women with and without endometriosis. Women with advanced endometriosis according to the rAFS complained of more severe dysmenorrhea than those with SE [26]. It is unclear whether this finding reflects any relationship between the presence and extension of endometriosis and biological impact, since the other pain markers did not show any difference. As a significant number of women have more than one lesion it would be difficult to identify the exact source of the symptoms [27].

Classifying endometriosis according to the rAFS appears to have limited value. When considering the severity of disease, as measured by the rAFS score, several studies have failed to correlate its extent with the degree of CPP [24, 27, 28]. The staging of endometriosis as SE, DIE and rectovaginal appears to have more clinical relevance when considering preoperative symptoms and the attempt to link those symptoms with the site of endometriosis.

Looking at the evidence, Koninckx retrospectively evaluated the symptoms of 451 women and reported that dysmenorrhoea, dyspareunia and non-cyclical pain are associated with DIE, concluding that endometriosis is a progressive disease as would be predicted by the theory of reflux menstruation [21]. However, RCTs showed that spontaneous regression of the stage and the symptoms of the disease are possible [19]. In an observational, prospective study severity of CPP correlated with the laparoscopic findings of pelvic and adnexal adhesions [27]. Vercellini reported association of dyspareunia with DIE and of dysmenorrhea with the rAFS classification [24]. In 1054 women, only 329 had CPP as a primary symptom; the severity of symptoms was assessed with a pain scale 0–100 that was dichotomized as pain and no pain. The diagnosis of endometriosis was done visually only and a number of cases required restaging in retrospect based on operation notes. Fauconnier in a retrospective case notes review of 225 women with macroscopic DIE and CPP correlated symptoms with particular locations of DIE [29]; symptoms and their severity were assessed in a non-standardized way and mapping of the DIE was done in retrospect using arbitrary criteria. Dyspareunia was found to be associated with DIE in uterosacral ligaments and dyschezia with involvement of the rectovaginal area whether patients' symptoms improved after excision of the relevant DIE is not clear. Ferero in a prospective observational study of 68 women with dyspareunia linked the symptom to DIE of the uterosacral ligaments with contribution from rectovaginal endometriosis and periovarian adhesions reporting improvement after laparoscopic excision [30].

A multicenter cross-sectional observation study did not find any association between location or stage of endometriosis and CPP [31]. Chronic pelvic pain as primary symptom in 469 women was evaluated with multidimensional verbal scales and its severity with a 10-point VAS with the disadvantage that an especially painful incident can skew the response. Women were also self-referred to hospitals because of their symptoms and there was no report of co-morbidities mimicking endometriosis

(IBS, chronic PID) presence. Additionally, as histological confirmation was not reported, it is not possible to exclude misdiagnoses.

A RCT could provide evidence of the association between endometriosis and CPP by comparing the treatment arm with placebo [19]. Although surgical treatment is effective in improving symptoms, its value on the interpretation of the relationship between endometriosis and pain is limited. Placebo effect is strong (30 %), spontaneous remission of symptoms can occur, while complete excision of disease is not reported being often impossible to achieve, implying that the real impact of surgical treatment on pain remains unclear. Indeed in a Cochrane review including 10 RCTs, the authors concluded that there is only moderate quality evidence regarding the effectiveness of surgical treatment of endometriosis [32].

Ballard related the symptoms of CPP to deep and SE while avoiding the rAFS score [33], concluding that, women with endometriosis are more likely to experience throbbing pain and dyschezia.

In conclusion, available evidence has not yet revealed a clear association between endometriosis and CPP. The discrepancies between studies in terms of definition of CPP, non-standardized methods of symptom evaluation, differences in the recruited patients and diagnostic methods are all leading to conflicting conclusions. In isolation, the value of CPP symptoms as prognostic or risk factors for endometriosis is probably limited: endometriosis is a disease notorious for the spectrum and the inconsistency of symptoms and other common gynecological problems can present with similar symptoms. However, the combination of a complete history (i.e., infertility) together with clinical signs (palpable nodules on uterosacral ligaments, retrofixed uterus) could be used to refer patients appropriately, avoiding undue delays [34]. A review paper suggested that surgical resection is most beneficial for women with palpable lesions at the time of clinical examination and this finding correctly correlates to the presence of disease [35].

The method of assessing symptoms is also important, as pain is perceived differently by different people and can fluctuate during a menstrual cycle. A prospective evaluation using a monthly symptom diary may increase the quality and value of the relevant history, highlighting the possibility of endometriosis and offering a base for treatment evaluation. Finally, the staging of endometriosis as SE, DIE and rectovaginal appears to allow greater correlation between laparoscopic findings and preoperative symptoms.

Summarizing, women with DIE not involving the rectovaginal space complain of more severe dyspareunia. The involvement of rectovaginal area is associated with dyschezia. However, the enigmatic pain pathway of this disease remains an obstacle to interpreting symptoms accurately and using them to predict disease severity. Laparoscopic excision of endometriosis appears a safe, well-accepted treatment and in the short term improves symptoms; diagnostic laparoscopy with histological confirmation remains the gold standard for the diagnosis of endometriosis. Long-term studies are needed to provide more reliable information regarding the duration of benefits.

Compliance with ethical standards

Conflict of interest All authors declare that they do not they have a financial relationship with the organization that sponsored the research and they confirm to have full control of all primary data and that they agree to allow the Journal to review their data if requested.

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