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Long-term follow-up after laparoscopic treatment for endometriosis: multivariate analysis of predictive factors for recurrence of endometriotic lesions and pain

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ABSTRACT

Objective: To investigate factors that might influence the recurrence of both painful symptoms and endometriotic lesions following laparoscopic treatment of endometriosis.
Study design: Retrospective cohort study in a University teaching hospital. We reviewed data from patients referred for laparoscopy between March 1993 and November 2007. We selected women who were followed up throughout Transvaginal-ultrasound (TV-US) after a first conservative laparoscopy for endometriosis. After laparoscopy, all patients were followed up according to an internal protocol: a standard gynaecologic examination, the assessment of painful symptoms and a TV-US scan that were repeated at 3, 6, and 12 months, and subsequently on a yearly basis. Sixteen factors were assessed by univariable and multivariable Cox proportional hazards models to evaluate their associations with recurrence of endometriotic lesions and pain related-endometriosis.
Results: 401 women were enrolled. A total of 154 (38.4%) experienced moderate or severe pain after laparoscopy; endometriotic lesions were observed by TV-US in 74 (18.4%) patients. In the multivariable model, age at menarche, severity of chronic pelvic pain (CPP) and dysmenorrhoea prior to surgery were significant risk factors for recurrence/occurrence of pain. Age at the first laparoscopy, stage of disease, pre-operative severity of CPP, and pregnancy were predictive factors of the recurrence for such lesions.
Conclusion: The severity of CPP prior to the first laparoscopy showed the only significant factor in the overall prediction of recurrence of pain and endometriotic lesions. Patients with severe CPP at the time of their first surgery might represent a sub-group of women with a more aggressive form of endometriosis.

1. Introduction

The existence of a relationship between pain and endometriosis is widely accepted by gynaecologists [1,2]. Laparoscopic excision of endometriosis results in pain relief, improved reproductive outcomes, and increased quality of life. Unfortunately, even with surgeons experienced in laparoscopy, 6–51% of women will have a recurrence of endometriosis within 5 years of surgery [3,4].

Few studies have analysed the determinants of recurrence rate in endometriosis, and the available data are controversial. The inconsistencies found in literature may be due to the complexity of endometriosis itself or to widespread methodological problems in the current studies: (i) limited and/or heterogeneous samples, (ii) few studies conducted with a second-look surgery, (iii) failure to control for endometriosis stage and symptomatology, as well as (iv) use of improper statistical analyses. Although some authors have considered recurrence of pain (dysmenorrhoea, dyspareunia or chronic pelvic pain) [3,5] ultrasound findings [3,5–7] or increased CA125 levels [3,5] to be the definition of endometriosis recurrence, there is still absence of a standardised definition.

The aim of this study was to analyse the effectiveness of laparoscopic treatment of endometriosis and to assess prognostic factors that might influence the recurrence rate for pain and endometriosis.

In a further analysis, we hypothesised that patients with recurrence/occurrence of pelvic pain may be at increased risk for the recurrence of endometriosis and sought to investigate this relationship.

2. Materials and methods

We reviewed the medical records of 593 consecutive patients who underwent laparoscopy for endometriosis between March 1993 and November 2007 in the Department of Gynaecology, Perinatology and Human Reproduction at the University of Florence, Italy. Inclusion criteria were: first conservative laparoscopy for endometriosis, diagnosis of endometriosis histologically

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confirmed, Transvaginal-ultrasound (TV-US) follow-up after laparoscopy. Following these criteria, 401 women were included in our study.

All surgeries were performed by three expert laparoscopists. In all cases, the surgical procedures aimed to remove all visible implants of endometriosis. During surgery, disease staging was assigned according to the American Society for Reproductive Medicine (ASRM) classification system [8]. The presence, localization, and extent of typical powder-burn and subtle lesions, adhesions, and deep infiltrating implants were recorded. After adhesiolysis, endometriomas were removed by stripping, excision of deep endometriosis was performed, and peritoneal implants were coagulated with bipolar forceps. Specimens underwent thorough histological analysis. When complications occurred, laparoscopy was converted into laparotomy. Laparotomic conversions were not included in the study.

In our centre, all patients are followed up according to an internal protocol. A standard gynaecologic examination and a TV-US scan are performed before surgery and at 3, 6, and 12 months, and then yearly after surgery. Menstrual-reproductive factors and painful symptoms are also evaluated.

During follow-up visits, patients were asked whether dysmenorrhoea, pelvic pain or dyspareunia occurred during the follow-up period. The time of their first appearance and the intensity of pain symptoms after laparoscopy were also documented.

Chronic pelvic pain (CPP) was defined as noncyclic pelvic pain of at least 3 months' duration or cyclic pain of 6 months' duration, which interferes with one's normal daily living activities [2].

Pain was rated on the basis of a 10-cm visual analogue scale (VAS), and the intensity was divided into none (0), mild (1–4), moderate (5–7), or severe (8–10). Presence of pain before surgery and pain recurrence/occurrence were defined on the basis of a VAS pain score of >5. Threshold points defining different severity of pain were chosen based on previous correlation analysis [7].

Persistent pain was defined as pain still present 2 or 3 months after surgery. Pain recurrence was defined on the basis of a postoperative VAS pain score of >5 in women with preoperative pain symptoms after a period of at least 3 months of relief. Pain occurrence was defined as symptoms presenting after surgery in patients who were asymptomatic at the time of laparoscopy.

Ultrasound recurrence was defined as the presence of an endometriotic cyst or nodule observed during a TV-US. In particular, an ovarian endometrioma was identified by the presence of a cystic ovarian mass characterised by persistent circular, homogeneous, hypoechoic "tissue" without papillary proliferations that had a clear demarcation from the ovarian parenchyma [9–12] and a diameter of more than 2 cm. Ovarian nodules were defined lesions smaller than 20 mm in mean diameter. Deep endometriosis implants, particularly those with rectosigmoid and rectovaginal septum involvement, were suspected from the presence of hypoechoic linear thickening or nodules/masses, with or without regular contours, that had thin band-like echoes departing from the centre of the mass that were described as 'Indian head dress' type [13].

Approval for the study was obtained by the local Institution review board.

2.1. Statistical analysis

The normality of the distribution of data was tested by Kolmogorov–Smirnov test. Student's *t*-test was used to compare continuous variables and Fisher's exact test or the chi-square test to compare categorical variables.

The Kaplan–Meier method was used to calculate the cumulative probability of women presenting with recurrence/occurrence of pain and recurrent endometriosis at TV-US. Patients entered the study either the date of their first laparoscopy for endometriosis or after the end of post-operative medication, if any. When GNRH analogues were prescribed, they entered the study 1 month after the last injection. The events under study were recurrence of endometriosis diagnosed by TV-US and recurrence/occurrence of pain. Cases were considered censored if, at the end of the study, the event under observation had not occurred or the patient was lost to follow-up. The statistical significance for the survival curves obtained was assessed by the Mantel–Cox log rank test.

The following characteristics were analysed: age at the time of surgery, age at menarche, body mass index (BMI), presence of painful symptoms before surgery, infertility as indication for surgery, duration of infertility, primary/secondary infertility, ASRM stages, tubal patency, post-operative medication, attempts at assisted reproductive technology (ART), number of in vitro fertilisation (IVF)/intra cytoplasmic sperm injection (ICSI) cycles, number of intrauterine insemination (IUI) cycles, and occurrence of pregnancy after surgery.

We identified potential risk factors ($p < 0.1$) for recurrence/occurrence of pelvic pain and TV-US recurrence of endometriosis using univariable Cox proportional hazards models and entered them into the multivariable Cox proportional hazards models.

We defined significance as $p < 0.05$ and conducted the statistical analysis using SPSS 13.0 (SPSS, Inc., Chicago, IL).

3. Results

Among 593 consecutive patients submitted to laparoscopy for endometriosis, 401 (67.6%) underwent periodic TV-US after surgery (114 with stage I or II endometriosis; 287 with stage III or IV endometriosis). The mean duration of observation per patient was 6.2 ± 4.1 years (median time 6 years, range 2–11 years). Table 1 shows the general features of the sample that received TV-US after surgery (Table 1).

3.1. Pain recurrence

Of the 401 patients, a total of 154 (38.4%) women experienced at least one period of moderate or severe pain after laparoscopy. Of 278 women suffering from painful symptoms before surgery, 140 (50.3%) did not experience such symptoms after laparoscopic treatment, 138 (49.6%) lamented pain after surgery.

Table 1
Characteristics of 401 selected patients.

	Mean ± SD/Num. (%)
Age (years) (mean ± SD) at the time of surgery	32.3 ± 6.1
Menarche (years) (mean ± SD)	12.4 ± 1.4
BMI (kg/m^2 ± SD)	22.2 ± 3.7
Mean follow-up duration (years) (mean ± SD)	6.2 ± 4.1
Pain before surgery	278 (69.3%)
Dysmenorrhea	271
Dyspareunia	144
Chronic pelvic pain	181
Infertility before surgery	216 (53.8%)
Duration of infertility (years) (mean ± SD) before surgery	3.6 ± 2.6
Stages I–II (Num)	114 (28.4%)
Stages III–IV (Num)	287 (71.6%)
Pregnancies after surgery	174 (43.4%)
Post-operative medication	261 (65.1%)
GnRHa only	199 (76.2%) (3–9 months)
GnRHa and add-back	25 (9.6%) (3–24 months)
Oral contraceptives	31 (11.9%) (3–36 months)
Danatrol	6 (2.3%) (2–6 months)
Women submitted to ART after surgery	90 (22.4%)

SD, standard deviation; GnRHa, Gonadotropin-releasing hormone analogues; ART, assisted reproductive technology.

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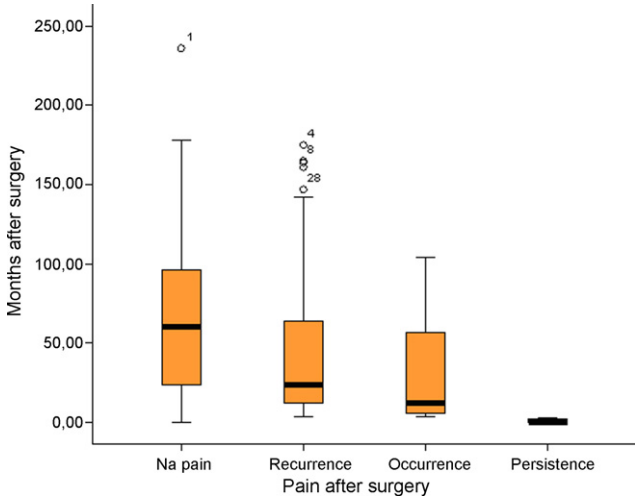

Fig. 1. Box-plots with distribution of pain recurrence, occurrence and persistence after surgery and the time to the onset of pain or censoring. Each bar denotes the median value as a horizontal line, and the box itself represents the area containing the top and the bottom quartile. Outliers (greater than 1.5 times the interquartile range) are represented outside the boxes. The bars indicate the time to the onset of pain or censor.

In 43 patients, pelvic pain persisted after surgery; these women were excluded from the analysis. Patients with persistent pain were mainly diagnosed with a more severe disease (30, 69.8%, patients with persistent pain were diagnosed III–IV stages). The study of the pattern of pain-recurrences after laparoscopy revealed 5 cases of recurrence occurring 145 months after surgery (Fig. 1); these cases were also excluded in order to remove clinical and statistical outliers. Thus, analysis was conducted on the remaining 106 patients with pain after surgery.

In 90 (84.9%), pain recurred after a period of at least 3 months of pain relief after surgery (pain recurrence). Twenty-one (23.3%) of them with minimal-mild endometriosis, 69 (76.7%) moderate-severe stage. For 16 patients (15.1%), pelvic pain was experienced, for the first time, after surgery (pain occurrence), 6 in patients with stages I–II, 10 in stages III–IV. The median time to the onset of pain recurrence was 24 months and 12 months for pain occurrence.

The graph shows the results of Kaplan–Meier analysis of time to pain recurrence. Cumulative recurrence rate at the end of the study was 42.5% for stages I–II and 46.5% for stages III–IV (Log Rank, Mantel–Cox chi square 1832; $p = 0.176$). Cumulative recurrence rate after 60 months were 22.7% for stages I–II, 29.8% for stages III–IV, after 120 months 34.6% for stages I–II, 42.5% for stages III–IV (Fig. 2a and b).

Menarche, severity of CPP and dysmenorrhoea before surgery remained significant risk factors for recurrence/occurrence of pain in the multivariable Cox proportional hazards model (Hazard ratio: 0.645, 95% CI: 0.496–0.838, p: 0.001; Hazard ratio: 1.128, 95% CI: 1.024–1.242, p: 0.014; Hazard ratio: 1. 236, 95% CI: 1.035–1.476, p: 0.019, respectively) (Tables 2 and 3).

The risk of pain recurrence was significantly higher for women who had early menarche (11.9 ± 1.5 years versus 12.7 ± 1.3 years) as well as for those who reported more severe CPP and dysmenorrhoea before laparoscopic treatment.

3.2. TV-US endometriosis recurrence

Of the 401 patients who received the TV-US follow-up, endometriotic lesions were observed in 74 women (18.4%). In 9 cases, endometriotic lesions were observed in the first follow-up visit, which occurred within the 3rd month. Thus, they were considered persistent lesions and excluded from the analysis.

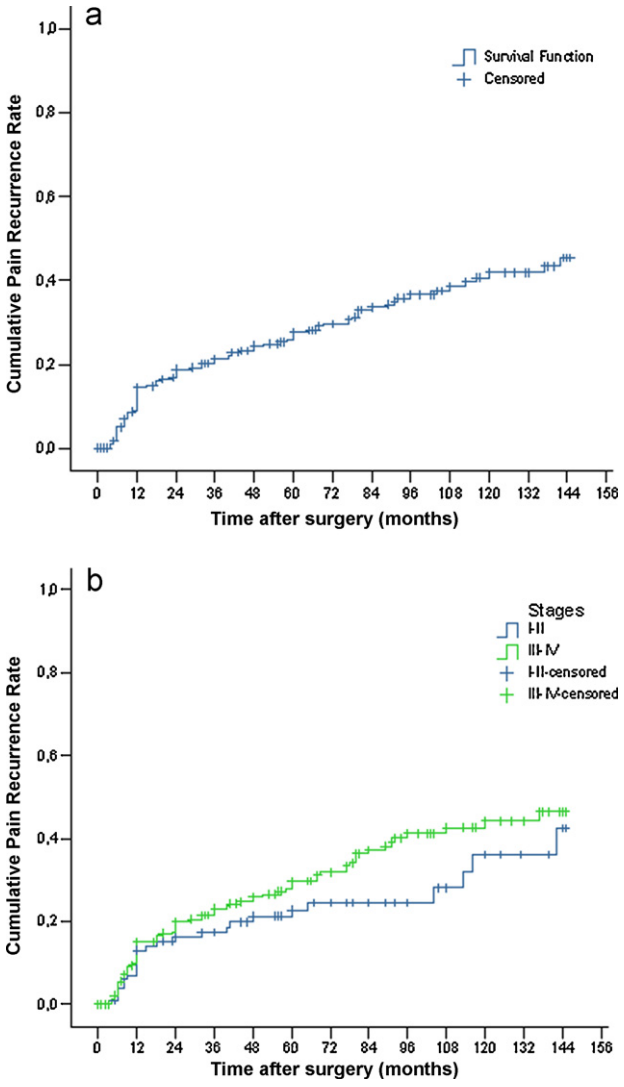

Fig. 2. Cumulative recurrence rate of pelvic pain. (A) All patients; (B) stratified according to stages (Log Rank (Mantel–Cox chi square 1832; $p = 0.176$).

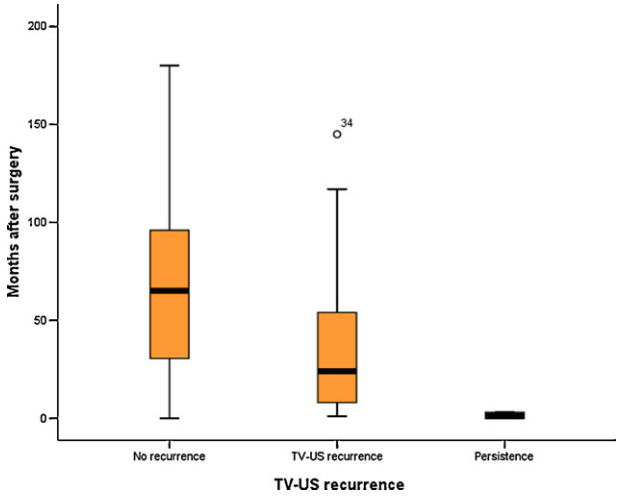

Fig. 3. Box-plots showing distribution of TV-US recurrence and persistence after surgery.

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Table 2
Univariable Cox proportional Hazard models of potential risk factors for recurrence/occurrence of pain after laparoscopy for endometriosis.

	Recurrence/occurrence of pain 106	No recurrence/occurrence of pain 247	Hazard ratio	95% CI	*p*-Value
Age at surgery (years)	31.3 ± 5	32.8 ± 6.4	0.966	0.934–0.999	0.041
Menarche (years)	11.9 ± 1.5	12.7 ± 1.3	0.657	0.528–0.818	0.001
BMI (kg/m^2)	22.7 ± 3.8	21.9 ± 3.9	0.883	0.895–1.100	0.883
Painful symptoms before surgery (Num. of patients)	90 (84.9%)	146 (59.1%)	4.013	2.353–6.845	0.001
CPP (VAS)	6.4 ± 2.5	4.3 ± 2.4	1.167	1.107–1.230	0.001
Dysmenorrhoea (VAS)	8.3 ± 1.7	6.5 ± 1.9	1.158	1.095–1.224	0.001
Dyspareunia (VAS)	5.1 ± 2.3	3.7 ± 2.3	1.120	1.052–1.193	0.001
Infertility as indication for surgery (Num.)	59 (55.7%)	137 (55.5%)	0.596	0.392–0.908	0.016
Duration of infertility (years ± SD)	3.6 ± 2.8	3.8 ± 2.6	1.003	0.874–1.153	0.961
Primary infertility (Num.)	36 (33.9%)	97 (39.3%)	0.816	0.320–2.082	0.671
Stages, I–II, III–IV	27 (25.5%), 79 (74.5%)	71 (28.7%), 176 (71.2%)	1.353	0.868–2.107	0.182
Post-operative medication	68 (64.1%)	172 (69.6%)	1.305	0.819–2.079	0.129
Monolateral or Bilateral Tubal patency (in 311 patients performing laparoscopic dye)	89/92 (96.7%)	212/219 (96.8%)	1.055	0.334–3.335	0.928
ART attempts after surgery (yes/no)	26 (24.5%)	62 (25.1%)	1.141	0.694–1.878	0.603
IVF-ICSI cycles after surgery (Num.)	1.8 ± 0.8	2.2 ± 1.1	0.897	0.734–1.095	0.285
IUI cycles after surgery (Num.)	2.7 ± 1.1	3 ± 1.5	1.031	0.852–1.248	0.454
Pregnancy after surgery (Num. of patients)	41 (38.7%)	101 (40.9%)	0.776	0.523–1.150	0.206

CI, confidence interval; BMI, body mass index; CPP, chronic pelvic pain; VAS, Visual Analogue Scale; SD, standard deviation; ART, assisted reproductive technology; IVF-ICSI, in vitro fertilisation/intra cytoplasmic sperm injection; IUI, intrauterine insemination.
All values are expressed as mean ± SD for continuous variables, for categorial variables the number (percentage) of subjects are given.

Moreover we excluded one case of recurrence, which occurred 145 months after surgery in order to remove statistical outliers (Fig. 3).

Among the remaining patients, 64 recurrences were observed in a median time of 24 months. More than half of all recurrences (37, 56.9%) were observed within 3 years after the first laparoscopy. According to the Kaplan–Meier analysis, the cumulative recurrence rate was 12.5% for stages I–II, and 33.7% for stages III–IV. Cumulative recurrence rates after 60 months were 6.3% for stages I–II, and 19% for stages III–IV; after 120 months 12.5% for I–II stages, 32.7% III–IV stages. Women with minimal-mild disease at surgery showed a significantly lower recurrence rate when compared with those with more severe stages (Log Rank, Mantel–Cox chi square 11,976; $p = 0.001$). (Fig. 4a and b).

In the multivariable analysis, age at first laparoscopy, stage of disease, pre-operative severity of CPP, and pregnancy after surgery showed statistically significant as independent predictors of recurrence (Hazard ratio: 0.935, 95% CI: 0.895–0.977, p: 0.003; Hazard ratio: 3.105, 95% CI: 1.452–6.640, p: 0.003; Hazard ratio: 1.101, 95% CI: 1.101–1.200, p: 0.028; Hazard ratio: 0.529, 95% CI: 0.304–0.921, p: 0.024, respectively; Tables 4 and 5).

The 64 patients who experienced a recurrence of endometriosis underwent the first surgery for endometriosis at a mean age significantly lower than those who did not (mean age 30.6 ± 5.3 years versus 32.6 ± 6.3 years, $p = 0.019$, respectively), had a more severe stage of the disease (55, 19.8% recurrences among 278 stages III–IV versus 9, 7.9%, among 114 stages I–II; $p = 0.004$), and had more severe CPP, as scored by VAS before the first laparoscopy.

Table 3
Multivariable Cox proportional Hazard models of risk factors associated with recurrence of pain after laparoscopy.

	Hazard ratio	95% CI	P Value
Age at surgery (years)	1.023	0.971–1.078	0.388
Menarche (years)	0.645	0.496–0.838	0.001
Painful symptoms before surgery (Num. of patients)	0.821	0.171–3.945	0.806
CPP (VAS)	1.128	1.024–1.242	0.014
Dysmenorrhoea (VAS)	1.236	1.035–1.476	0.019
Dyspareunia (VAS)	0.980	0.872–1.101	0.738
Infertility as indication for surgery (Num.)	1.069	0.554–2.063	0.843

CI, confidence interval; CPP, chronic pelvic pain; VAS, Visual Analogue Scale; SD, standard deviation.

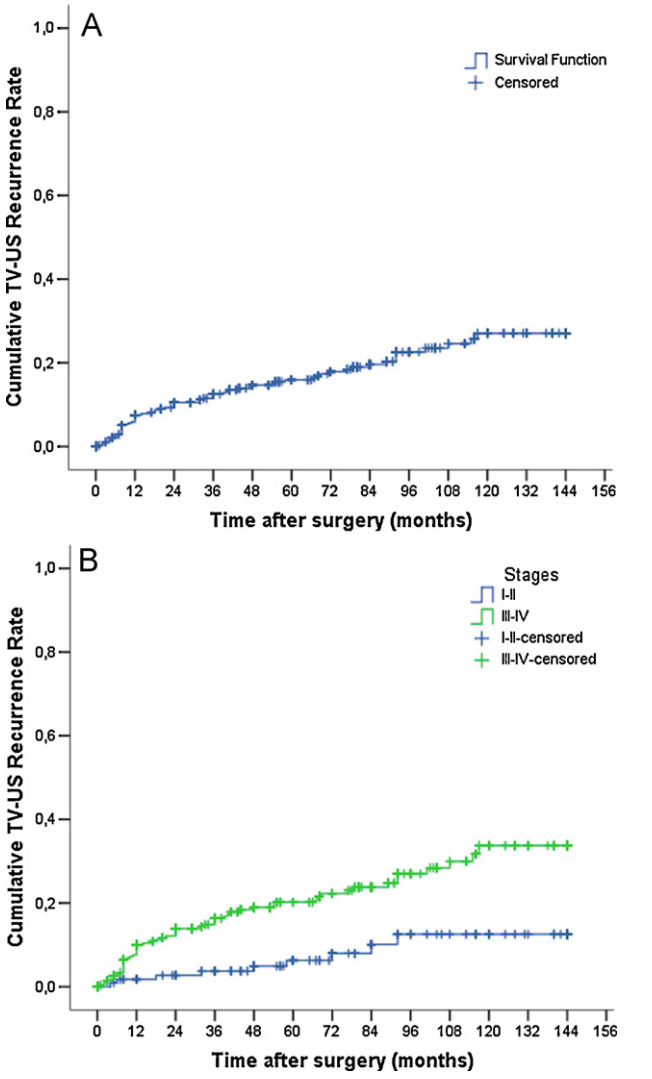

Fig. 4. Cumulative recurrence rate of endometriosis detected by ultrasound: (A) all patients; (B) stratified according to stage of disease (Log Rank Mantel–Cox chi square 11,976; $p = 0.001$).

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Table 4
Univariable Cox proportional Hazard models of potential risk factors for recurrence of endometriosis diagnosed by TV-US.

	Recurrence endometriosis diagnosed by TV-US 64	No recurrence endometriosis diagnosed by TV-US 327	Hazard ratio	95% CI	*p*-Value
Age at surgery (years)	30.6 ± 5.3	32.6 ± 6.3	0.943	0.904–0.985	0.008
Menarche (years)	12.4 ± 1.4	12.5 ± 1.4	0.970	0.770–1.223	0.799
BMI (Kg/m^2)	21.8 ± 2.5	22.3 ± 4.1	0.927	0.822–1.047	0.223
Painful symptoms before surgery (Num. of patients)	48 (75%)	224 (68.5%)	1.657	0.940–2.920	0.081
CPP (VAS)	6.6 ± 2.4	5.9 ± 2.5	1.125	1.052–1.203	0.001
Dysmenorrhoea (VAS)	8.2 ± 1.5	7.8 ± 1.9	1.042	0.977–1.111	0.214
Dyspareunia (VAS)	5.7 ± 1.9	4.9 ± 2.4	1.108	1.022–1.201	0.012
Infertility as indication for surgery (Num.)	31 (48.4%)	178 (54.4%)	0.957	0.560–1.638	0.874
Duration of infertility (years ± SD)	3.6 ± 2.8	3.8 ± 2.7	0.933	0.793–1.097	0.399
Primary Infertility (Num.)	28 (43.7%)	116 (35.5%)	0.408	0.097–1.714	0.221
Stages					
I–II	9 (14.1%)	105 (32.1%)	3.025	1.494–6.123	0.002
III–IV	55 (85.9%)	222 (67.9%)			
Monolateral or Bilateral Tubal patency (in 311 patients performing laparoscopic dye)	52 (81.2%)	279 (85.3%)	0.652	0.159–2.685	0.554
Post-operative medication	48 (75%)	205 (62.7%)	1.213	0.714–2.058	0.131
ART attempts after surgery (yes/no)	17 (26.6%)	72(22%)	0.995	0.552–1.792	0.985
IVF-ICSI cycles after surgery (Num.)	1.7 ± 0.9	2.1 ± 1.1	1.017	0.820–1.261	0.878
IUI cycles after surgery (Num.)	2.5 ± 0.8	3.1 ± 1.5	1.073	0.862–1.335	0.530
Pregnancy after surgery (Num. of patients)	20 (31.2%)	149 (45.6%)	0.513	0.298–0.880	0.015

CI, confidence interval; BMI, body mass index; CPP, chronic pelvic pain; VAS, Visual Analogue Scale; SD, standard deviation; ART, assisted reproductive technology; IVF-ICSI, in vitro fertilisation/intra cytoplasmic sperm injection; IUI, intrauterine insemination.
All values are expressed as mean ± SD for continuous variables, for categorial variables the number (percentage) of subjects are given.

Pregnancy occurred in 169 cases and was associated with a reduced risk of recurrence. Twenty pregnancies were observed among patients with TV-US recurrences (20/64, 31.2%), and 149 in patients who did not experience a recurrence (149/327, 45.6%) ($p = 0.048$).

3.3. Pelvic pain and TV-US findings

The results concerning the number of recurrences observed during the TV-US follow-up were compared with subjective symptomatology. Of the 74 women with endometriotic lesions detected during ultrasonographic follow-up, the majority ($n = 51$, 68.9%) showed recurrence of pain ($p = 0.001$). Symptomatic recurrences showed similar prevalence in women with recurrent ovarian endometrioma and those with other recurrent lesions (nodule, deep lesions) (respectively 29/43, 67.4% and 22/31, 70.9%; $p = 0.945$). On the other hand, pelvic pain was observed in 154 cases after the first surgery; of those cases, only 51 (33.1%) had endometriosis as detected by TV-US, and only 24 (15.6%) required further laparoscopy.

Patients showing both a painful and a TV-US recurrence were significantly younger when compared to the rest of patients (29.9 ± 5.4 years versus 32.6 ± 6.1 years, $p = 0.003$), had earlier menarche (11.7 ± 12.6 versus 12.6 ± 1.4, $p = 0.006$), and recurrence occurred earlier (mean time of pain recurrence 31.4 ± 42 months versus 54.8 ± 46 months, $p = 0.001$; mean time of TV-US recurrence 33.6 ± 31.8 months versus 64.9 ± 43.7 months, $p = 0.001$).

Table 5
Multivariable Cox proportional Hazard models of risk factors associated with recurrence of endometriosis diagnosed by TV-US.

	Hazard ratio	95% CI	P Value
Age at surgery (years)	0.935	0.895–0.977	0.003
Stages (I and II versus III and IV)	3.105	1.452–6.640	0.003
Painful symptoms before surgery (Num. of patients)	0.820	0.388–1.734	0.603
CPP (VAS)	1.101	1.101–1.200	0.028
Dyspareunia (VAS)	1.008	0.914–1.113	0.867
Pregnancy after surgery (Num. of patients)	0.529	0.304–0.921	0.024

CI, confidence interval; BMI, body mass index; CPP, chronic pelvic pain; VAS, Visual Analogue Scale; SD, standard deviation; ART, assisted reproductive technology; IVF-ICSI, in vitro fertilisation/intra cytoplasmic sperm injection; IUI, intrauterine insemination.

4. Comments

Our study confirms the effectiveness of treating endometriosis with laparoscopic excision in order to reduce patients' pain, a finding also reported by others [14–17]. Of 278 women suffering from painful symptoms before surgery, 140 (50.3%) did not experience such symptoms after laparoscopic treatment. Of the 216 infertile women in our sample, 117 (54.2%) were able to achieve pregnancy after surgery.

A younger age at menarche and dysmenorrhoea severity demonstrated risk factors for pain recurrence. This is not so for the recurrence of disease at TV-US. These findings show that the presence of dysmenorrhoea is not a reliable predictor for the diagnosis of endometriosis. In most studies of women with dysmenorrhoea, the prevalence of endometriosis ranged between 30% and 40% [18]. However, the pain felt by women during menstruation may be no less severe than the pain experienced by women with endometriosis. Even though pain is a very subjective matter, it is possible to hypothesise the relationship between precocity and severity of dysmenorrhoea before surgery with pain recurrence. This might be ascribed to the phenomenon often referred to as "pain memory" [19,20]. It has been widely demonstrated that both acute and chronic pain, when severe enough or associated with inflammation, are able to produce the phenomena of spinal memory. In other words, longer periods of pain during menstruation might be related to a higher likelihood of pain recurrence after surgery. This is probably due to several psychological or neurologic components, whereas it is not necessarily due to a recurrence of endometriotic lesions.

ASRM staging system showed a prognostic value in predicting the risk of endometriosis recurrence during TV-US follow-up. It may arguable that incomplete surgery occurs in advanced endometriosis due to access difficulties.In agreement with other authors [5,6], we also identified a younger age at surgery as a risk factor for endometriosis' recurrence. This may be related to an

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aggressive form of endometriosis present in younger women or to higher estrogen levels.

The benefits of pregnancy on endometriosis' progression and recurrence were also confirmed. Some evidence suggested that early pregnancy may be prophylactic against the development of endometriosis and could actually cause the regression of established lesions [5,7,21]. The mechanisms postulated include production of anovulation and amenorrhea, decidual change and eventual necrosis induced within the lesions. Moreover, vaginal parturition enlarges the internal ostium of the uterine cervix and might decrease recurrences by reducing tubal transportation of endometrial debris [22].

In our study, severe CPP was the only significant risk factor for the recurrence of both painful symptoms and endometriotic lesions after laparoscopy. Endometriosis is one of the most prevalent gynaecologic diagnoses among women with recurrent and progressive CPP. A previous study showed that out of 58 patients who presented to a pelvic pain centre for treatment, 48 (83%) had biopsy-confirmed active endometriosis [23].

Patients with severe CPP at the time of their first surgery might represent a sub-group of women with an aggressive form of endometriosis, that manifest a more sudden growth of lesions.

The occurrence of pain after surgery in previously asymptomatic patients might further support this hypothesis. Moen [24] conducted a study in 39 asymptomatic women with endometriosis, diagnosed in conjunction with tubal sterilization, and observed that pelvic pain after surgery was reported by 6% of them. In our study, the occurrence of pelvic pain was observed in a higher number of women (16/123, 13%), probably due to the larger sample size. A valid explanation for pain occurrence after conservative surgery for endometriosis might be the progressive growth and inflammation of microscopic lesions remaining after surgery.

Recent studies suggest that, in women with endometriosis, mechanisms underlying pain and sensitivity to estrogen involve the growth into the ectopic endometrial tissue of a nerve supply, which could have a varied and widespread influence on the activity of neurons throughout the central nervous system [25,26]. Higher endogenous estrogens production in young women is not only critical for developing endometriosis but also modulate CPP through a neuropathic mechanism involving changes in the peripheral nervous system that sensitize the central response. The presence of pain in women without visualized lesions at TV-US might suggests a neuropathic mechanism involving changes in the peripheral nervous system that sensitize the central response.

Our study's power was limited by its retrospective analysis, the self-selected control sub-group of patients choosing to have TV-US follow-up, and the lack of second-look surgery. The strength of our current study is (i) the long-term follow-up, (ii) the measurement of 16 potential risk factors, and (iii) a careful statistical analysis with survival analysis methodology. In addition, we have examined our findings throughout TV-US which is the most objective, non-invasive, and reproducible index of recurrence, with a reported diagnostic accuracy for endometriomas >90% [27].

Additional research is needed in order to understand why endometriosis associates so variably with pain symptoms and why these symptoms are ameliorated by a hypoestrogenic state. Our findings show that there is a significantly higher recurrence rate of endometriotic lesions detected by TV-US in women suffering of painful symptoms after conservative laparoscopy for endometriosis. With the exception of CPP, significant predictors of both pain and ultrasonographic recurrence were different.

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