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Diagnosis of endometriosis in women with chronic pelvic pain

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Summary

Purpose of investigation: To assess the accuracy of CA-125 determination associated with clinical history and of the neutrophil/lymphocyte (N/L) ratio for a presumptive diagnosis of endometriosis in women with chronic pelvic pain (CPP). *Materials and Methods:* This was a cross-sectional study of data from the medical records of women with CPP submitted to laparoscopy from August 1999 to January 2009 at the University Hospital. The performance of the evaluation of CA-125 and of the N/L ratio for the prediction of endometriosis was compared based on the corresponding ROC curves and their 95% confidence intervals. *Results:* CA-125 levels were significantly higher in women with CPP and endometriosis and their association with a complaint of dysmenorrhea improved their sensitivity. For a cut-off of 20 IU/ml, the predictive value for a diagnosis of endometriosis in women with CPP was 97.6%. Dyspareunia, subfertility, and N/L ratio were not useful for a diagnosis of endometriosis in women with CPP. *Conclusion:* The association of elevated CA-125 levels with a complaint of dysmenorrhea is adequate in a presumptive and accurate diagnosis of endometriosis in this specific group of women with CPP, permitting an early institution of clinical treatment without the need of previous laparoscopic confirmation.

Key words: CA-125; Diagnosis; Endometriosis; Dysmenorrhea; Chronic pelvic pain.

Introduction

Endometriosis is a chronic and recurrent disease characterized by the presence of endometrial tissue outside the uterine cavity, mainly identified in the pelvic peritoneum and in the ovaries, leading to an inflammatory process, cicatricial reaction, and formation of adhesions associated with clinical signs and symptoms of dysmenorrhea, dyspareunia, chronic pelvic pain (CPP), and subfertility [1-4]. The prevalence of CPP in Brazil is 15.1% among women in menacme [5], and about 30% of these women are estimated to have endometriosis [6].

The gold standard for the diagnosis of endometriosis is laparoscopy, an invasive procedure involving costs and risks [7]. Thus, the time between the onset of symptoms and the indication of laparoscopy is often quite long, 7.4 years on average [8]. The delay of the diagnosis of patients with endometriosis and CPP impairs the treatment of pain. The prolonged time of symptoms, especially pain, causes the onset of events that may impair the diagnosis and limit the therapeutic proposals, such as peripheral sensitization secondary to neurogenic inflammation, central sensitization with a consequent reduction of thresholds to potentially painful stimuli (hyperalgesia) or potentially not painful ones (allodynia), changes in mood such as anxiety and depression, and a difficult doctor-patient relationship [9-12].

Tumor markers, particularly CA-125, represent an important research line for the diagnosis and follow-up of endometriosis [13], although with limited sensitivity and specificity [14, 15]. In view of the inflammatory state inherent to endometriosis, the neutrophil/lymphocyte (N/L) ratio has been studied in the search for a diagnostic test of low cost and easy application. The N/L ratio can increase the sensitivity of CA-125 for the diagnosis of minimal and mild endometriosis in premenopausal women with no myomas or adenomyosis when a cut-off value of 20.1 is considered, with 59.7% sensitivity and 60.1% specificity [16]. Currently, it is not possible to say whether this association can improve the sensitivity and specificity of CA-125 in diagnosis of endometriosis among the population of women with CPP. Thus, the objective of the present study was to assess the accuracy of CA-125 determination in combination with clinical history and of the N/L ratio for a presumptive diagnosis of endometriosis in women with CPP, in order to begin an early clinical treatment without the need for previous laparoscopic confirmation.

Materials and Methods

This was a cross-sectional study based on the analysis of the medical records of 208 women with CPP submitted to laparoscopy between August 1999 and January 2009 at the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil. A total of 168 medical records containing complete data were included in the study. The data considered were: a clinical history with quantification of pain using a visual analogue scale (VAS), preoperative determination of CA-125 by chemiluminescence at the beginning of the menstrual period, and hematologic examination for the determination of the N/L ratio. The sample was divided into two groups: with endometriosis (vi-

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Table 1. — *Clinical and laboratory characteristics of the women with chronic pelvic pain with and without endometrosis (controls)*

Variables	Endometriosis n=111	Controls n=57	*p*
Age (years)*	32.9±7.45	35.6±8.82	0.04
Visual analogue pain scale*	7.14±2,20	7.11±2.21	0.94
Dyspareunia	54.9%	75.4%	<0.001
Dysmenorrhea	80.1%	47.3%	<0.001
Infertility	23.4%	17.5%	0.43
CA-125*	25.96±37.24	9.42±5.27	<0.001
N/L ratio*	2.31±1.48	2.28±1.25	0.75

*Mean ± SD

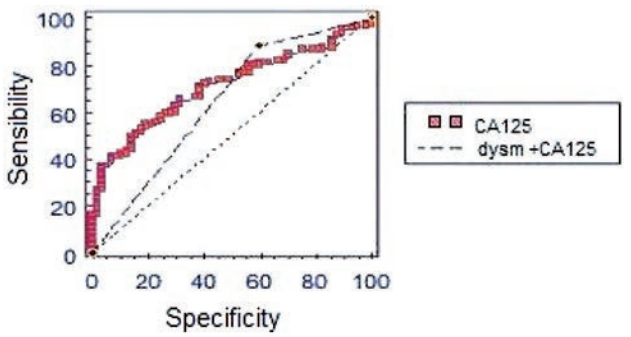

Figure 1. — ROC curves for CA-125 and CA-125 + dysmenorrhea in the diagnosis of endometriosis in a sample of 168 women with chronic pelvic pain. When the complaint of dysmenorrhea is associated with CA-125, an area under the curve of 0.64 - 95% CI (0.56-0.71) is observed, with 88.3% sensitivity and 40.4% specificity (cut-off of 11.4).

sual diagnosis when typical lesions were present and with the aid of anatomopathological examination when lesions were atypical), and without endometriosis. Endometriosis was staged according to the classification of the American Society for Reproductive Medicine (ASRM) 1996 [17]. CPP was defined as pelvic pain not exclusively menstrual, lasting six months or more and sufficiently intense to interfere with habitual activities and to require medical, clinical or surgical, treatment [18].

Statistical analysis

Data were analyzed for normal distribution by the D'Agostino Pearson test. Quantitative variables were compared between groups by the unpaired *t*-test or Mann-Whitney test. The proportions observed for dyspareunia, dysmenorrhea, and previous abdominal surgeries were compared between groups by the Fisher exact test. To compare the performance of the evaluation of CA-125 and of the N/L ratio for the prediction of endometriosis, the corresponding ROC curves and their 95% confidence limits (95% CI) were calculated.

Results

The mean age of the women with endometriosis was lower (32.9 ± 7.45 years) than that of the control group (35.6 ± 8.82 years) ($p = 0.04$). CA-125 levels and the proportion of women with dysmenorrhea were significantly higher in women with endometriosis compared to control. In contrast, the N/l ratio, the rates of infertility and the intensity of pain according to the VAS did not differ between groups (Table 1).

Table 2. — *Frequency (n, %) of the laparoscopic findings of women with chronic pelvic pain with and without endometriosis (controls)*

Laparoscopic findings		Endometriosis n=111 n (%)	Controls n=57, n (%)
Endometriosis	Grade 1	24 (21.6)	
	Grade 2	18 (16.2)	
	Grade 3	31 (27.9)	
	Grade 4	38 (34.2)	
Sequels of DIP			25 (43.8)
Benign cystic lesion			14 (24.5)
No changes			11 (19.2)
Teratoma			3 (5.2)
Benign cystic lesions and myomas			2 (3.5)
Pelvic varices			2 (3.5)

The evaluation of the accuracy of CA-125 as a diagnostic test for endometriosis in women with CPP based on the ROC curve revealed an area under the curve of 0.71 (95% CI 0.63-0.77, $p < 0.001$), with 55% sensitivity and 80.7% specificity, for a cut-off value of 11.4 IU/ml. In contrast, for the N/L ratio, the area under the curve was only 0.51 (95% CI 0.43-0.59, $p = 0.75$).

When a complaint of dysmenorrhea was associated with CA-125, a curve significantly different from random occurrence was observed, with an area under the curve of 0.64 and a 95% CI = 0.56-0.71; ($p < 0.0001$), with 88.3% sensitivity and 40.4% specificity, for a cut-off of 11.4 IU/ml (Figure 1). For a cut-off of 20 IU/ml, specificity was 98.2% and the positive predictive value was 97.6%. When a cut-off of 20 IU/ml was used for CA 125, a total of 41 patients were detected: 40 with a diagnosis of endometriosis and only one without endometriosis (97.6% positive predictive value).

In the group of women with CPP and without endometriosis, there was a higher proportion of dyspareunia (Table 1) and a high incidence of possible sequels of inflammatory pelvic disease (43.85%), especially bilateral tubal-ovarian adhesions and varying degrees of hydrosalpinx (Table 2).

Discussion

The mean age at diagnosis of endometriosis of the women with CPP in the present study was similar to that reported by Arruda *et al.* [8], who observed a mean age of 33 years for this diagnosis among Brazilian women with endometriosis. The difference in age observed between the groups with and without endometriosis may

be explained by the lower frequency of severe dysmenorrhea in the group without endometriosis, a fact that may delay the indication of laparoscopy for these patients. Ballard *et al.* [4] demonstrated that the symptoms associated with endometriosis are relatively uncommon in women without endometriosis. On the other hand, women with abdominal-pelvic pain, menstrual-related symptoms (mainly dysmenorrhea), dyspareunia, and subfertility are at high risk to have endometriosis [4].

The high prevalence of dyspareunia observed in women with CPP in the present study has also been reported by Verit *et al.* [19]. Dyspareunia and subfertility are symptoms frequently used for the diagnosis of pelvic endometriosis. However, considering their high frequency in this specific population, the presence or absence of dyspareunia and subfertility are of no value for a differential diagnosis. In women with CPP, dyspareunia is frequently associated with possible sequels of inflammatory pelvic disease, with painful spasms of pelvic floor muscles, and with bladder pain syndrome, exacerbated by the chronic pain situation itself, with a reduction of sensitive and painful thresholds. In contrast to dyspareunia and subfertility, dysmenorrhea was significantly more prevalent among women with endometriosis and CPP, as also reported by others in patients with endometriosis [4, 20, 21].

CA-125 levels were significantly higher in women with CPP and endometriosis than in women without endometriosis, also showing association with disease severity, in agreement with literature data [21]. The evaluation of its accuracy as a diagnostic test by the ROC curve resulted in a curve significantly differing from a random occurrence, but still showed a moderate efficacy as a diagnostic test. The association of a complaint of dysmenorrhea with CA-125 led to improved sensitivity with a cut-off of 11.4, for a better prediction of endometriosis in this group of patients. When the authors used a cut-off of 20 IU/ml for CA 125, a value already previously used in the authors' service for the diagnosis of endometriosis [22], this value proved to be more accurate for the diagnosis of endometriosis among patients with CPP because of its high predictive value (97.6%).

The N/L ratio was not useful for the diagnosis of endometriosis in these women with CPP. This result agrees with the theory that there is a potential inflammatory state in patients with CPP, regardless of the etiology of the condition [23]. Thus, the N/L ratio could not contribute to the diagnosis of endometriosis in this specific group of patients.

Conclusion

The association of CA-125 levels higher than 20 IU/ml with a clinical complaint of dysmenorrhea was adequate for a presumptive and accurate diagnosis of endometriosis in women with CPP, permitting an early institution of clinical treatment without the need for previous laparoscopic confirmation.

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