Evaluation of CA-125 and soluble CD-23 in patients with pelvic endometriosis: a case-control study

Ivana Maria de Luna Ramos[1], Sérgio Podgaec[2], Maurício Simões Abrão[2], Ricardo de Oliveira[3], Edmund Chada Baracat[2]

[1] MD, Endometriosis Division, Obstetrics and Gynecology Department, Universidade de São Paulo (USP), São Paulo, SP, Brazil
[2] MD, PhD, Endometriosis Division, Obstetrics and Gynecology Department, USP, São Paulo, SP, Brazil
[3] MD, PhD, RDO Clinical Laboratory, São Paulo, SP, Brazil

Summary

Objective: To evaluate serum concentrations of CA-125 and soluble CD-23 and to correlate them with clinical symptoms, localization and stage of pelvic endometriosis and histological classification of the disease. **Methods:** Blood samples were collected from 44 women with endometriosis and 58 without endometriosis, during the first three days (1st sample) and during the 7th, 8th and 9th day (2nd sample) of the menstrual cycle. Measurements of CA-125 and soluble CD-23 were performed by ELISA. Mann-Whitney U test was used for age, pain evaluations (visual analog scale) and biomarkers concentrations. **Results:** Serum levels of CA-125 were higher in endometriosis patients when compared to the control group during both periods of the menstrual cycle evaluated in the study. This marker was also elevated in women with chronic pelvic pain, deep dyspareunia (2nd sample), dysmenorrhea (both samples) and painful defecation during the menstrual flow (2nd sample). CA-125 concentration was higher in advanced stages of the disease in both samples and also in women with ovarian endometrioma. Concerning CD-23, no statistically significant differences were observed between groups. **Conclusion:** The concentrations of CA-125 were higher in patients with endometriosis than in patients without the disease. No significantly differences were observed for soluble CD-23 levels between groups.

Keywords: Endometriosis; biological markers; symptoms; CA-125 antigen.

©2012 Elsevier Editora Ltda. All rights reserved.

Resumo

Avaliação do CA-125 e CD-23 solúvel em pacientes com endometriose pélvica: estudo de caso-controle

Objetivo: Avaliar as concentrações séricas de CA-125 e CD-23 solúvel e correlacioná-los com sintomas clínicos, localização e estádio da endometriose pélvica e classificação histológica da doença. **Métodos:** Amostras de sangue foram coletadas de 44 mulheres com endometriose e 58 sem endometriose durante os primeiros três dias (1ª amostra) e durante o sétimo, o oitavo e o nono dia (2ª amostra) do ciclo menstrual. As dosagens de CA-125 e CD-23 solúvel foram realizadas por ELISA. O teste U de Mann-Whitney foi usado para idade, avaliação de dor (escala analógica visual) e para a concentração dos biomarcadores. **Resultados:** Os níveis séricos de CA-125 foram mais altos nas pacientes com endometriose do que no grupo-controle quando avaliados em ambos os períodos do ciclo menstrual, assim como apresentaram-se elevados nessas mulheres quando referiam dor pélvica crônica, dispareunia de profundidade (coleta na 2ª amostra), dismenorreia (ambas as amostras) e dor ao evacuar durante o fluxo menstrual (coleta na 2ª amostra). A concentração de CA-125 foi mais alta no estádio avançado em ambas as amostras, assim como em mulheres com endometriomas ovarianos. Em relação ao CD-23 solúvel, nenhuma diferença estatisticamente significativa foi observada entre os grupos. **Conclusão:** As concentrações de CA-125 foram mais altas em pacientes com endometriose do que em pacientes sem a doença. Nenhuma diferença estatisticamente significativa foi observada para CD-23 solúvel entre os grupos.

Unitermos: Endometriose; marcadores biológicos; sintomas; antígeno Ca-125.

©2012 Elsevier Editora Ltda. Todos os direitos reservados.

Study conducted at Endometriosis Division, Obstetrics and Gynecology Department, Universidade de São Paulo (USP), São Paulo, SP, Brazil

Submitted on: 06/22/2011
Approved on: 11/01/2011

Correspondence to:
Sérgio Podgaec
Departamento de Ginecologia e Obstetrícia (HC-FMUSP)
Av. Dr. Enéas de Carvalho, 255
(HC-FMUSP), 10° andar
sala 10.166
CEP: 05403-000
São Paulo, SP, Brazil
sergiopodgaec@me.com

Conflict of interest: None.

Introduction

The most accurate procedure for diagnosis of endometriosis is laparoscopy, an invasive surgical method. The definitive diagnosis is based on the visualization of the characteristic lesions and on histological confirmation. The identification of less invasive and more accessible markers of the disease is suitable. Several studies have reported that CA-125, a glycoprotein of epithelial origin found in normal cells, has high serum concentrations in patients with endometriosis, mainly when evaluated during the menstrual flow[1-3].

Another biomarker of interest to this study was soluble CD-23, a protein that is expressed on the surface of cell membrane, commonly identified as the low affinity IgE receptor on B cells, eosinophils, monocytes, dendritic cells, epithelial Langerhans cells and platelets[4].

Based on the evidence of increased concentrations of soluble CD-23 in peritoneal fluid of women with endometriosis, it was suggested that the disease would activate B cells, which would promote the release of higher concentrations of soluble CD-23[5,6]. This hypothesis was strengthened by the identification that women treated with danazol had a greater reduction in the concentration of CD-23 when compared to patients treated with leuprolide acetate. If danazol could suppress humoral and cell-mediated immune responses and could alter macrophage function, by a significant increase of soluble leukocyte antigen class I and class II (HLA-I and HLA-II), due to the release of these antigens from intracellular stores, it could also promote the reduction of inflammatory process in endometriosis. It would activate anti-inflammatory cytokines, similar to what occurs in normal pregnancy, creating an inhospitable environment for the establishment of ectopic endometrium. Based on these arguments, it was suggested that changes in the levels of HLA by danazol may reflect the immune competence and the function of macrophages in endometriosis[7,8]. Thus, the hypothesis stated by Odukoya et al.[9] has reinforced that soluble CD-23 may be involved in the development and maintenance of endometriosis and may serve as a possible biological marker.

The presence of soluble CD-23 in patients with endometriosis could occur because the endometrial cells that, by reflux, reach the peritoneal cavity are presented by macrophages and other antigen presenting cells to CD4+ T cells that become activated by cytokines, as IL-4 and IL-10. Recently, our group reported that these cytokines are increased in patients with endometriosis and promote the release of CD-23 by B cells and monocytes[10]. Thus, CD-23 concentration could also be elevated as a consequence of increased concentration of cytokines.

The aim of this study was to determine serum concentrations of CA-125 and soluble CD-23 in patients with and without endometriosis, in two phases of the menstrual cycle: 1st, 2nd or 3th day and 8th, 9th or 10th day. We also compared the concentrations of CA-125 and CD-23 with clinical symptoms, stage and site of the lesions and histological classification of the disease.

Methods

Patients

This study was approved by the Ethics in Research Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. From June 2007 to October 2010, the following inclusion criteria were applied to 1,920 consecutive patients complaining of infertility, pelvic pain or desire for family planning by tubal ligation: age between 18 and 45 years, absence of hormone therapy within three months prior to consultation, absence of autoimmune diseases confirmed by history and laboratory tests, when necessary; evidence of ovarian function and laparoscopy examination for the investigation of infertility or pelvic pain refractory to clinical therapy, based on complaints and on gynecological examination or imaging findings, consistent with endometriosis.

One hundred and four patients met inclusion criteria and were invited to participate in the study, after having been informed about the research objectives. Patients underwent medical history, to investigate the presence of six symptoms most commonly associated with endometriosis: dysmenorrheal, chronic pelvic pain, deep dyspareunia, infertility, bowel and urinary cyclic symptoms. The intensity of chronic pelvic pain and dyspareunia was evaluated using a visual analogue scale of 10 points. Pelvic examination was the next step, searching for retrouterine nodules, thickening of the uterosacral ligament or pelvic masses. Patients with endometriosis clinical suspicion was submitted to pelvic and transvaginal ultrasound and, when necessary, to pelvic MRI. Laparoscopy was indicated in the presence of pain even after clinical treatment or if the image exams showed ovarian endometrioma and/or deep infiltrative lesions affecting retrocervical region, vagina, bowel, bladder or ureter.

Up to three months before laparoscopy, after eight hours fasting, all patients had a venipuncture to collect 5 mL of blood sample that was stored in a dry tube. The first sampling occurred between the 1st, 2nd or 3th day of the menstrual cycle and the second at the 8th, 9th or 10th day. The samples were sent to a freezer, maintained at –20° C, at the laboratory and the analysis was performed after the collection of all samples.

After laparoscopy, patients were divided into two groups: the first (case group) consisted of 45 patients with a diagnosis of endometriosis confirmed by pathological examination. The second (control group) consisted of 59 women without endometriosis. One patient in the case group and another in the control group left the research. Thus, the case group was composed of 44 patients and the

control group, of 58 patients. In the case group, the disease was classified according to American Society for Reproductive Medicine[11] stages and location of the disease. In the histological analysis of excised tissues, we followed the classification pattern proposed by Abrão et al.[12].

Laboratory analysis

The determination of serum CA-125 levels was performed using a sandwich technique of a commercial ELISA kit (*Elecsys®*, Roche — *NY, USA*) and the dosage of serum soluble CD-23 was also performed with a ELISA kit (*Bender MedSystems, Vienna, Austria)* according to manufacturers instructions. The analyte range of CA-125 and soluble CD-23 is 25-35 IU/mL and 10-91 U/mL, respectively.

Statistical analysis

Statistical analysis was performed to compare Ca-125 and CD-23 concentrations with case and control groups regarding the presence and intensity of clinical complaints related to endometriosis, site of disease, staging according to the ASRM and histopathological analysis. We compared means using a Mann-Whitney U test, with 5% significance level.

Results

We found that CA-125 average concentrations were significantly higher in cases when compared to controls, both at first and second periods of collection, and soluble CD-23 average concentrations of cases were lower when compared to the control group, but it did not reach statistical significance (Table 1). It was identified that the average concentration of CA-125 in the second collection allowed differentiating cases from controls with chronic pelvic pain (VAS > 6), as well as the presence of deep dyspareunia. The differentiation of patients with intense chronic pelvic pain was also possible by CA-125/soluble CD-23 ratios, in the second collection (Table 1).

As for dysmenorrhea, we found that CA-125 average concentrations, in both collections, differentiated cases and controls when the complaint of infertility was absent and when the intensity of dysmenorrhea was high (VAS > 6). This differentiation was also possible by biomarkers ratio, in the second collection (Table 1). Regarding the presence of intestinal symptoms, cases and controls were differentiated by mean concentrations of CA-125, soluble CD-23 and CA-125/soluble CD-23 ratios, also in the second collection (Table 2).

Concerning the lesions sites, it was observed that patients with endometriosis in all sites had higher CA-125 mean concentrations when compared to the control group, in both blood collections. The same was not observed in terms of average concentrations of soluble CD-23 (Table 3).

In advanced endometriosis (stage III or IV), the mean concentrations of CA-125, in both collections, were higher than in initial endometriosis (stage I or II) and in absence of endometriosis (Table 3).

Discussion

In the present study, serum levels of CA-125 were higher in endometriosis patients when compared to the control group during both periods of the menstrual cycle evaluated in the study. CA-125 concentration was higher in advanced stages of the disease in both samples and also in women with ovarian endometrioma. Concerning CD-23, no statistically significant differences were observed between groups.

CA-125 has been extensively studied and is considered a useful tool for clinical diagnosis of endometriosis[2-4,13,14-16]. High CD-23 concentrations have been observed in peritoneal fluid of women with endometriosis, suggesting the activation of B cells and a possible imbalance of humoral immune system in endometriosis[6-8,17].

The decision to evaluate these markers in two stages of the menstrual cycle was taken from studies that showed fluctuations in their concentrations, especially CA-125 during the menstrual cycle. Kafali et al.[2] identified in women without endometriosis an increase of CA-125 concentration of 22% during menstruation, compared to other days of the cycle. Abrão et al.[3] demonstrated that during the first three days of the menstrual cycle, CA-125 concentrations were greater than the eighth and tenth day of the cycle.

Our study is the first one that evaluates both markers (CA-125 and CD-23) in patients with endometriosis. Although there is no direct relationship between markers CA-125 and CD-23, both participate in the pathophysiology of endometriosis (proliferation and epithelial cellular inflammatory response/immune, respectively), justifying the assessment of these two markers in the same cohort of patients with and without endometriosis. Moreover, as panel markers evaluation has been previously published and still no satisfactory results were found, we thought that the association of these two markers could improve the auxiliary value of laboratory tests in predicting endometriosis using a non-invasive diagnosis method.

In the present study, the average concentrations of CA-125, higher in the case group than in the control group, reinforced the assertion that this marker may be useful as an auxiliary diagnosis and management of endometriosis. Analyzing our results, we found that the average concentrations of CA-125 in the first collection (on the first, second or third day of the menstrual cycle) were always higher than in the second (eighth, ninth or tenth day of the cycle), both in cases and controls. Abrão et al.[3,18] reported the same results evaluated in serum samples obtained during the menstrual cycle: on day 1, 2 or 3 of the

Table 1 – CA-125, sCD-23 and CA-125/sCD-23 levels in cases and control samples according to chronic pelvic pain, deep dyspareunia and dysmenorrhea

	CA-125		sCD-23		CA-125/sCD-23	
	Samples		Samples		Samples	
	1st	2nd	1st	2nd	1st	2nd
Cases (n = 44)	51.98 ± 7.88	42.23 ± 5.66	42.85 ± 3.93	52.98 ± 10.58	1.64 ± 0.29	1.32 ± 0.22
Controls (n = 58)	29.19 ± 5.65	21.20 ± 2.78	54.47 ± 7.21	58.08 ± 8.09	0.99 ± 0.18	0.75 ± 0.12
p-value	0.018	0.001	0.132	0.697	0.048	0.017
Chronic pelvic pain						
Absent						
Case (n = 15)	47.01 ± 15.18	39.15 ± 1.8	47.43 ± 6.31	79.01 ± 28.48	0.98 ± 0.27	0.8 ± 0.22
Control (n = 28)	21.28 ± 3.0	19.09 ± 2.89	58.36 ± 11.33	54.37 ± 9.28	0.93 ± 0.25	0.76 ± 0.17
p-value	0.117	0.092	0.504	0.315	0.902	0.897
1 to 5						
Case (n = 11)	78.83 ± 19.40	54.58 ± 12.01	39.27 ± 10.21	34.75 ± 7.74	2.70 ± 0.8	2.04 ± 0.6
Control (n = 18)	38.82 ± 16.29	27.21 ± 7.62	59.28 ± 13.85	68.42 ± 19.61	1.07 ± 0.4	0.87 ± 0.28
p-value	0.132	0.053	0.314	0.125	0.053	0.058
6 to 10						
Case (n = 18)	39.72 ± 7.4	37.26 ± 7.69	41.23 ± 5.39	42.43 ± 7.86	1.54 ± 0.41	1.32 ± 0.33
Control (n = 12)	33.21 ± 10.28	17.10 ± 2.03	47.88 ± 10.67	51.26 ± 15.25	1.0 ± 0.28	0.53 ± 0.11
p-value	0.602	0.02	0.547	0.578	0.339	0.033
Deep dyspareunia						
Absent						
Case (n = 19)	54.74 ± 14.4	37.78 ± 8.2	48.22 ± 8.36	52.87 ± 8.82	1.27 ± 0.31	0.84 ± 0.14
Control (n = 30)	32.95 ± 8.56	21.81 ± 3.86	52.7 ± 8.99	54.86 ± 11.06	1.1 ± 0.25	0.78 ± 0.16
p-value	0.186	0.051	0.768	0.914	0.698	0.845
Present						
Case (n = 25)	41.8 ± 6.92	37.84 ± 5.83	37.17 ± 4.23	51.45 ± 17.65	1.86 ± 0.45	1.59 ± 0.36
Control (n = 18)	24.24 ± 4.47	21.28 ± 4.19	56.04 ± 10.75	59.59 ± 12.02	0.9 ± 0.26	0.75 ± 0.21
p-value	0.058	0.039	0.116	0.728	0.078	0.05
Dysmenorrhea						
Absent						
Case (n = 2)	135.55 ± 102.45	103.35 ± 69.85	41.2 ± 12.6	37.95 ± 9.05	2.79 ± 1.63	2.4 ± 1.26
Control (n = 18)	18.22 ± 2.52	16.25 ± 2.37	59.06 ± 14.09	52.26 ± 12.15	0.65 ± 0.16	0.38 ± 0.18
p-value	0.457	0.430	0.686	0.706	0.414	0.013
1 to 5						
Case (n = 5)	66.24 ± 39.15	35.34 ± 10.26	37.56 ± 6.29	39.62 ± 5.65	1.74 ± 0.91	0.89 ± 0.21
Control (n = 11)	59.76 ± 28.0	34.03 ± 13.02	53.7 ± 19.85	69.97 ± 22.23	1.51 ± 0.64	1.15 ± 0.48
p-value	0.897	0.950	0.538	0.212	0.842	0.726
6 to 10						
Case (n = 37)	45.54 ± 6.09	39.86 ± 5.54	43.66 ± 4.58	55.6 ± 12.53	1.57 ± 0.32	1.32 ± 0.26
Control (n = 29)	24.4 ± 2.3	19.41 ± 1.89	54.79 ± 9.13	57.19 ± 11.88	1.0 ± 0.25	0.63 ± 0.11
p-value	0.002	0.001	0.250	0.928	0.184	0.017

sCD-23, soluble CD-23; case, patients with endometriosis; control, patients without endometriosis; 1st, second or third day of the menstrual cycle; 2nd, eight, ninth or tenth day of the menstrual cycle.

Table 2 – CA-125, sCD-23 and CA-125/sCD-23 levels in cases and control samples according to infertility, urinary and intestinal symptoms

	CA-125		sCD-23		CA-125/sCD-23	
	Samples		Samples		Samples	
	1st	2nd	1st	2nd	1st	2nd
Infertility						
Absent						
Case (n = 18)	45.67 ± 8.07	44.04 ± 7.51	43.8 ± 5.4	42.05 ± 5.75	1.4 ± 0.3	1.42 ± 0.3
Control (n = 30)	21.89 ± 2.11	17.93 ± 1.83	53.94 ± 10.09	54.73 ± 12.92	0.76 ± 0.15	0.64 ± .12
p-value	0.01	0.003	0.464	0.444	0.035	0.028
Present						
Case (n = 16)	46.1 ± 13.59	30.63 ± 7.64	40.38 ± 7.87	65.68 ± 27.41	1.55 ± 0.47	0.8 ± 0.17
Control (n = 17)	29.91 ± 8.15	21.1 ± 4.39	58.18 ± 12.97	66.94 ± 15.92	1.14 ± 0.39	0.74 ± 0.21
p-value	0.308	0.281	0.257	0.968	0.503	0.813
Never tried						
Case (n = 10)	72.78 ± 23.03	57.53 ± 16.61	45.1 ± 7.65	52.34 ± 13.54	20.21 ± 0.89	1.99 ± 0.74
Control (n = 11)	47.97 ± 26.65	30.26 ± 12.14	60.75 ± 18.37	53.54 ± 12.1	1.4 ± 0.64	1.04 ± 0.44
p-value	0.494	0.195	0.457	0.948	0.463	0.275
Cyclical intestinal symptoms						
Absent						
Case (n = 26)	56.71 ± 11.6	43.55 ± 7.66	47.56 ± 4.63	64.69 ± 17.03	1.39 ± 0.27	1.0 ± 0.16
Control (n = 35)	31.32 ± 8.65	23.87 ± 4.38	52.72 ± 9.33	47.50 ± 7.4	1.06 ± 0.24	0.93 ± 0.18
p-value	0.078	0.031	0.657	0.315	0.365	0.790
Present						
Case (n = 18)	45.16 ± 9.67	40.33 ± 8.57	36.04 ± 6.74	36.07 ± 6.88	2.0 ± 0.59	1.79 ± 0.48
Control (n = 23)	25.94 ± 5.65	17.14 ± 2.09	62.19 ± 11.52	74.19 ± 16.7	0.89 ± 0.29	0.46 ± 0.1
p-value	0.079	0.017	0.058	0.044	0.098	0.014
Cyclical urinary symptoms						
Absent						
Case (n = 44)	51.98 ± 7.88	42.23 ± 5.66	42.85 ± 3.93	52.98 ± 10.57	1.64 ± 0.29	1.32 ± 0.22
Control (n = 54)	30.19 ± 6.04	21.82 ± 2.97	54.12 ± 7.2	56.32 ± 8.34	1.02 ± 0.19	0.77 ± 0.13
p-value	0.031	0.002	0.173	0.802	0.065	0.034

sCD-23, soluble CD-23; case, patients with endometriosis; control, patients without endometriosis; 1st, second or third day of the menstrual cycle; 2nd, eight, ninth or tenth day of the menstrual cycle.

cycle and on day 8, 9 or 10 of the cycle and compared to stage of the disease. The advanced stage of the disease was also associated with high levels of CA-125. It could also be noted that the average concentrations of CA-125 differentiate patients with stromal or well differentiated glandular pattern from those without the disease only in the second sampling. This detailed analysis between concentrations of CA-125 and histological classification (stromal and glandular pattern) of pelvic endometriosis was not yet reported in the literature, which hindered the discussion of our findings. Also, in terms of stages of endometriosis, Mihalyi et al.[19] reported differences in the concentration of CA-125 between cases and controls. It is noteworthy that these authors made this statement not only by using the CA-125 as complementary diagnostic biomarker, but they associated it with CA-19-9, IL-6, IL-8, high sensitivity C-reactive protein and tumor necrosis factor alpha, which seems to justify a greater sensitivity and specificity.

The average concentration of CA-125 allowed us to differentiate cases and controls in the second collection, in the presence of chronic pelvic pain and dysmenorrheal, deep dyspareunia and intestinal symptoms as well as intense dysmenorrhea, in the first collection. These findings agreed with Barbosa et al.[14], who reported

Table 3 – CA-125, sCD-23 and CA-125/sCD-23 levels according to the site of the disease, ASRM staging and histolological classification

	CA-125		sCD-23		CA-125/sCD-23	
	Samples		Samples		Samples	
	1st	2nd	1st	2nd	1st	2nd
Localization						
Control (n = 58)	29.19 ± 5.65	21.20 ± 2.78	56.48 ± 7.21	58.08 ± 8.09	0.99 ± 0.18	0.75 ± 0.12
Ovarian (n = 9)	92.37 ± 26.88	64.86 ± 15.40	44.71 ± 5.3	46.31 ± 4.49	2.28 ± 0.63	1.5 ± 0.35
p-value	0.048	0.022	0.528	0.208	0.079	0.029
Control (n = 58)	29.19 ± 5.65	21.20 ± 2.78	56.48 ± 7.21	58.08 ± 8.09	0.99 ± 0.18	0.75 ± 0.12
Peritoneal (n = 20)	41.04 ± 8.52	32.09 ± 6.67	38.02 ± 6.77	59.04 ± 22.5	1.82 ± 0.53	1.48 ± 0.44
p-value	0.278	0.144	0.158	0.960	0.148	0.121
Control (n = 58)	29.19 ± 5.65	21.20 ± 2.78	56.48 ± 7.21	58.08 ± 8.09	0.99 ± 0.18	0.75 ± 0.12
Deep (n = 15)	42.34 ± 9.62	42.18 ± 9.77	48.18 ± 6.5	48.91 ± 8.83	1.02 ± 0.25	1.02 ± 0.23
p-value	0.283	0.055	0.572	0.582	0.939	0.306
p inter-localizations	0.03	0.092	0.518	0.874	0.256	0.628
ASRM classification						
I-II (n = 19)	41.79 ± 8.94	32.59 ± 7.01	37.86 ± 7.13	60.16 ± 23.69	1.89 ± 0.55	1.52 ± .46
III-IV (n = 25)	59.73 ± 12.02	49.56 ± 8.24	46.64 ± 4.28	47.53 ± 5.47	1.46 ± 0.29	1.18 ± 0.19
p-value	0.265	0.14	0.274	0.56	0.468	0.446
Histological classification						
Control (n = 58)	29.19 ± 5.65	21.20 ± 2.78	56.48 ± 7.21	58.08 ± 8.09	0.99 ± 0.18	0.75 ± 0.12
Stromal (n = 11)	55.22 ± 17.94	38.6 ± 7.09	46.72 ± 3.06	47.65 ± 3.36	1.21 ± 0.42	0.82 ± 0.14
Glandular well differentiated (n = 27)	48.66 ± 7.84	41.22 ± 7.11	42.42 ± 6.18	43.73 ± 6.89	1.87 ± 0.42	1.48 ± 0.33
Glandular undifferentiated (n = 2)	35.9 ± 6.8	33.3 ± 10.0	39.05 ± 12.35	32.65 ± 10.85	1.08 ± 0.52	1.26 ± 0.72
Mixed glandular (n = 4)	73.58 ± 54.84	63.52 ± 37.98	37.02 ± 7.7	140.25 ± 109.12	1.57 ± 0.95	1.69 ± 0.84
p-value	0.807	0.692	0.926	0.07	0.78	0.627

sCD-23, soluble CD-23; control, patients without endometriosis; 1st, second or third day of the menstrual cycle; 2nd, eight, ninth or tenth day of the menstrual cycle.

that the presence of endometriotic lesions in symptomatic patients remained correlated with the expression of CA-125. Some authors suggest a correlation between levels of CA-125 and the proliferative activity of epithelial cells in the lesions of endometriosis, because the disease is an inflammatory process associated with a change in immune cell functions[20,21]. For some patients, the gynecologic examination may be normal as well as the symptoms may be absent, especially for those with superficial peritoneal disease[22]. By comparing patients without endometriosis to those with endometriosis according to location of the ectopic implants, we concluded that the concentrations of CA-125 differed from the cases with ovarian endometriosis, which may be due to increased blood supply in that location, which would determine higher expression of the marker by epitheliocytes[23].

Concerning soluble CD-23, there are few studies in the literature which correlate this marker with endometriosis[5-7,9]. The comparison of average concentrations between cases and controls failed to distinguish the presence or absence of endometriosis. By analyzing the relationship between the symptoms of endometriosis and the concentrations of soluble CD-23, our results demonstrated that, in the second collection, there was a significant difference between cases and controls with intestinal symptoms.

The most relevant findings of our study were the confirmation of CA-125 as an auxiliary biological marker able to differentiate cases and controls. High CA-125 levels were associated with clinical symptoms such as chronic pelvic pain, dysmenorrhea, deep dyspareunia, bowel symptoms, and contribute to the diagnosis of ovar-

ian endometriosis. Moreover, it was possible to identify an association between the presence of intestinal symptoms and the average concentration of soluble CD-23 in the second collection.

Furthermore, one limitation of this study is the small number of samples in some of the groups evaluated. It may have contributed to the lack of association between the markers and some parameters analyzed in this study. A greater number of samples could contribute to a better accuracy of the parameters evaluated.

Conclusion

Our results do not invalidate the warning that for some patients physical examination may be normal as well as symptoms may be absent, especially for those with superficial peritoneal disease. The ratio of the markers allows us to differentiate cases and controls with severe chronic pelvic pain (ranging from 6 to 10 – VAS), presence of severe dysmenorrhea, infertility absence, presence and absence of intestinal symptoms of urinary symptoms.

Thus, this study confirms that the noninvasive diagnosis of endometriosis remains a challenge despite the increase in diagnostic possibilities, represented by measurement of CA-125 and soluble CD-23.

References

1. McLeod BS, Retzloff MG. Epidemiology of endometriosis: an assessment of risk factors. Clin Obstet Gynecol. 2010;53:389-96.
2. Kafali H, Artuc H, Demir N. Use of CA-125 fluctuation during the menstrual cycle as a tool in the clinical diagnosis of endometriosis; a preliminary report. Eur J Obstet Gynecol. 2004;116:85-8.
3. Abrão MS, Podgaec S, Martorelli Filho B, Ramos LO, Pinotti JA, Oliveira RM. The use of biochemical markers in the diagnosis of pelvic endometriosis. Human Reprod. 1997;12:2523-7.
4. Hassa H, Tanir MH, Teckin B, Kirilmaz SD, Matlu FS. Cytokine and immune cell levels in peritoneal fluid and peripheral blood of women with early-and late-staged endometriosis. Arch Gynecol Obstet. 2009;279:891-5.
5. Odukoya OA, Bansal A, Wilson P, Lim K, Weetman AP, Cooke ID. Serum soluble CD 23 in patients with endometriosis and the effect of treatment with danazol and leuprolide acetate depot injection. Hum Reprod. 1995;10:942-6.
6. Odukoya OA, Bansal A, Cooke ID. Serum endometrial IgG antibodies and soluble CD 23 concentrations in patients with endometriosis. Acta Obstet Gynecol Scand. 1996;75:927-31.
7. Matalliotakis IM, Neonaki MA, Koumantaki Y, Goumenou AG, Kyriakou DS, Koumantakis EE. A randomized comparison of danazol and leuprolide acetate suppression of serum-soluble CD-23 levels in endometriosis. Obstet Gynecol. 2000;95:810-13.
8. Matalliotakis IM, Athanassakis I, Goumenou AG, Neonaki MA, Koumantakis EE, Vassiliadis S, et al. The possible anti-inflammatory role of circulating human leukocyte antigen levels in women with danazol and leuprorelin acetate depot. Mediators Inflamm. 2001;10:75-80.
9. Odukoya OA, Bansal A, Wilson P, Lim K, Weetman AP, Cooke ID. Soluble CD-23 protein in the peritoneal fluid of patient with endometriosis. Hum Reprod. 1996;11:2018-21.
10. Podgaec S, Abrão MS, Dias Jr JA, Rizzo LV, Oliveira RM, Baracat EC. Endometriosis: an inflammatory disease with a Th2 immune response component. Hum Reprod. 2007;22:1373-9.
11. ASRM. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis**.** Fertil Steril. 1997;67:817-821.
12. Abrão MS, Nerme RM, Carvalho FM, Aldrighi JM, Pinotti JA. Histological classification of endometriosis as a predictor of response to treatment. Int J Gynecol Obstet. 2003;82:31-41.
13. Ghaemmaghami F, Zarchi MK, Hamedi B. High levels of CA125 (over 1,000 IU/ml) in patients with gynecologic disease and no malignant conditions: three cases and literature review. Arch Gynecol Obstet. 2007;276:559-61.
14. Barbosa CP, Souza AMB, Bianco B, Christofolini D, Bach FAM, Lima GR. Frequency of endometriotic lesions in peritoneum samples from asymptomatic fertile women and correlation with CA125 values. São Paulo Med J. 2009;127:342-5.
15. Bellelis P, Dias Jr JA, Podgaec S, Gonzales M, Baracat EC, Abrão MS. Epidemiological and clinical aspects of pelvic endometriosis-a case series. Rev Assoc Med Bras. 2010;56:467-71.
16. Petta CA, Matos AM, Bahamondes L, Faúndes D. Current practice in the management of symptoms of endometriosis: a survey of Brazilian gynecologists. Rev Assoc Med Bras. 2007;53:525-9.
17. Podgaec S, Dias Junior JA, Chapron C, Oliveira RM, Baracat EC, Abrão MS. Th1 and Th2 ummune responses related to pelvic endometriosis. Rev Assoc Med Bras. 2010;56:92-8.
18. Abrão MS, Podgaec S, Pinotti JA, Oliveira RM. Tumor markers in endometriosis. Int J Gynaecol Obstet. 1999;66:19-22.
19. Mihalyi A, Gevaert O, Kyama CM, Simsa P, Pochet N, De Smet F, et al. Noninvasive diagnosis of endometriosis based on a combined analysis of six plasma biomarkers. Hum Reprod. 2010;25:654-64.
20. Agic A, Xu H, Finas D, Banz C, Diedrich K, Hornung D. Is endometriosis associated with systemic subclinical inflammation? Gynecol Obstet Invest. 2006;62:139-47.
21. Cho S, Cho H, Nam A, Kim HY, Choi YS, Park KH, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril 2008;90:2073-9.
22. Abrão MS, Gonçalves MOC, Dias Jr JA, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. Hum Reprod. 2007;22:3092-7.
23. Mikhaleva LM, Vorobeva NN, Samsonova MV. Ovarian endometriosis: characteristics of the blood circulatory bed. Arkh Patol. 2006;68:20-2.