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Serum CEA, CA-125, CA-15-3 and CA19-9 Levels as A Diagnostic Test for Endometriosis

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Abstract

Objectives

The aim of this study was to evaluate the clinical utility of serum CEA, CA-125, CA15-3 and CA19-9 levels in the diagnosis of endometriosis.

Methods

58 infertile women, 38 of whom exhibited endometriosis, underwent laparoscopy. Patients were divided into three groups: group (A) consisted of 20 patients with stage I or II endometriosis; group (B) consisted of 18 patients with stage III or IV endometriosis and group (C) consisted of 20 patients who were the control group. All patients were submitted to serum determination of CEA, CA-125, CA15-3 and CA19-9. Results: CA-125 serum concentrations were significantly increased in the group B ($p<0.05$), while the levels of the other serum markers did not show any statistically significant difference.

Conclusion

In patients with advanced endometriosis, there is an increase of CA- 125 levels compared with minor endometriosis and control women. On the contrary, neither CEA, nor CA15-3 and CA19-9 may serve as an indicator of the disease.

Keywords: Endometriosis; Laparoscopy; CEA; CA-125; CA15-3; CA19-9

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus and is a common benign but aggressive disease affecting 7% [1] of women in reproductive age, while it is detected in 38.5% [2] of infertile women. Despite a long history of clinical experience and experimental research, it remains an enigmatic disease because its etiology is unclear until now and more than a single theory have been proposed to explain the pathogenesis of endometriosis. The transplantation theory, proposed by Sampson is widely accepted compared to coelomic metaplasiatheory which was proposed by Meyer, but cannot justify the location of endometriosis in all cases [3]. It is frequently associated with dysmenorrhoea, chronic pelvic pain, infertility or it may be asymptomatic. Laparoscopy is the gold standard for the diagnosis of endometriosis and histological confirmation is essential to establish it [4].

Although many attempts have been made to use clinical, imaging and serum markers to reach a diagnosis without surgery, a non-invasive method to diagnose endometriosis is not available. An ideal serum marker should exhibit high sensitivity and specificity with excellent prognostic value and good correlation with the stage of disease. Also, it could be used not only for diagnosing endometriosis, but also for monitoring disease progression and responding to medical and surgical treatment [5].

CA-125 is a high molecular weight glycoprotein that is expressed on the cell surface of some derivatives of embryonic coelomic epithelium including endometrium, endocervix, fallopian tubes, peritoneum, pleura and pericardium. Serum levels of CA-125 have been found to be elevated not only in moderate and severe endometriosis but also in ovarian epithelial cancers and other benign gynaecological conditions such as leiomyomas, pelvic inflammatory disease, ovarian hyperstimulation syndrome, in which the associated inflammation could lead to an increased shedding of CA-125 [6]. Despite many studies have assessed the performance of serum CA-125 measurement in the detection of endometriosis, the specificity of CA-125 is reported to be higher than 80% with a sensitivity rate between 20-50%.This fact poses limitation for its clinical use as a single blood test for the diagnosis of endometriosis [7].

Furthermore, CA 19-9 is a high molecular weight glycoprotein that was initially thought to be an oncofetal antigen. Serum CA 19-9 is found elevated in patients with a certain type of malignant tumor, such as gastrointestinal adenocarcinoma, pancreatic carcinoma or lung carcinoma; thus the measurement of serum CA 19-9 levels is useful in the diagnosis of these tumors. In gynaecology, the serum CA 19-9 is elevated in patients with malignant and benign ovarian tumors. Also, it was demonstrated that CA19-9 levels in patients with endometriosis are significantly higher than those in patients without endometriosis. Furthermore, serum CA19-9 levels increase in accordance with the advancement of the clinical stage of endometriosis. CA 19-9 levels was detected in the endometrial glandular epithelium in ovarian chocolate cysts by immunohistochemistry [8-12].

Moreover the value of CEA oncofetal antigen was evaluated in combination with CA-125 and CA 19-9 in patients with endometriosis and was found informative to differentiate endometriosis from malignant tumors [13] CA 15-3, another oncofetal antigen is routinely determined for the follow up of breast carcinoma. The combination of CA15-3, CA-125 and CA19-9 serum markers concentrations were found elevated in patients with endometriosis [14-16].

The objective of this study was to evaluate the clinical utility of serum levels of, CEA, CA-125, CA15-3 and CA19-9, in the diagnosis of endometriosis, as there is no similar study in the literature with regard to the combination of all above serum markers.

Materials and Methods

Patients

The study was conducted in the First Department of Obstetrics and Gynaecology of Aristotle University of Thessaloniki, at "Papageorgiou" General Hospital with the approval of its internal Committee and informed consent was obtained from each patient. A total of 58 patients participated in this study and underwent laparoscopy as part of the diagnostic work-up for infertility or as therapeutic approach in cases of endometriotic cysts in a period of two years (January 2011 until December 2012). Out of the 58 infertile patients enrolled, 38 exhibited endometriosis, and 20 did not, as confirmed by laparoscopy. Patients were classified into three groups; group A: 20 women had stage I/II endometriosis; group B consisted of 18 patients with III/IV stage of endometriosis and group C included 20 patients, who were the control group and underwent laparoscopy during the diagnostic workup for infertility. Exclusion criteria were: hormonal treatment during a 6 month period prior to surgery; clinical and or echographic indications of polycystic ovarian disease; diabetes; systemic, hepatic, renal disease and any pelvic disease (myomas, adenomyosis, hydrosalpinges, pelvic inflammatory disease) other than endometriosis diagnosed at the time of laparoscopy.

Methods

In all patients of group A and B, endometriosis was classified into four stages according to a modification of the revised American Fertility Society (r-AFS) staging system. The diagnosis of endometriosis, both peritoneal and endometriotic cysts, was confirmed by histology in all cases. All patients were submitted to serum determination of CEA, CA-125, CA15-3, CA19-9. The blood samples were obtained during the early prolifirative phase of the menstrual cycle at the beginning of laparoscopy. Then blood samples were centrifuged at 4000 g for 5 min and the supernatant was stored at less than 20°C. Serum CEA, CA-125, CA19-9 were measured by Immunoenzyme method (Abbott, IMX System) and 15-3 was measured also by Immunoenzyme method (Abbott, AXFYM System). The normal values for these substances are: up to 35 U/ml for CA 125; up to 31.3 for CA 15-3; up to 37 U/ml for CA19-9; up to 5ng/ml for CEA among non-smokers and up to 10ng/ml among smokers;. For Ca-125, concentration ranged from 0 to 600 U/ml and sensitivity was ⟨ 0.2 U/ml. For CA 19-9, concentration ranged from 0 to 500 U/ml and sensitivity was ⟨2 U/ml. For CEA, concentration ranged from 0 to 500U/ml and sensitivity was ⟨ 0.5 ng/ml and finally, for CA 15-3, concentration ranged from 3 to 250 U/ml and sensitivity was ⟨ 0.2 U/ml. Statistical analysis was carried out using the non-parametric test Mann-Whitney test. A $p<0.05$ was considered statistically significant. All results are reported as mean ± SD.

Results

The mean age of the patients was 30.9 (± 4) years (mean value x±SD) in group A, 30.2 (± 3.9) years in group B and 32 (± 3.4) years in the control group. It is obvious that there was no significant difference in age among these three groups and the estimated concentrations of tumor markers were not correlated to their age. Table 1 provides the mean and standard deviations (± SD) of serum concentrations of CEA, CA125, CA15-3 and CA19-9 measured in groups A, B and C. The concentration of all tumor markers in group A and B were correlated among them as well as they were compared to the estimated concentrations of group C. The mean concentrations of CEA in group A was found similar to group B, but significantly lower than in control group C, but it did not reach statistical significance. The mean levels of CA 125 were markedly elevated in group B, in comparison to that of patients in group A ($p<0.01$), as well as, to that of patients group C ($p<0.05$). As far as the cut-off value of Ca-125 for the diagnosis of endometriosis, this has a variation among authors, which ranges from 16 U/ml to 35 U/ml. In our

study, the cut-off value was defined at 16 U/ml. Therefore, in endometriosis stage I-II, we did not have any value equal or higher than the above, while in endometriosis stage III-IV, we had 11 cases with higher than the above mentioned value. So, for the advanced-stage endometriosis (stage III-IV), the sensitivity of Ca-125 in the serum was 42% and the specificity 95%. For the total number of patients with endometriosis, the overall sensitivity was 21% and the specificity 92%. The mean serum values of all the other serum markers were within the normal range, without any significant difference among the three groups.

Table I. Serum concentrations of CEA, CA-125, CA 15-3 and CEA for patients with endometriosis stage I/II (Group A), stage III/IV (Group B), and without endometriosis (Group C) (mean ±SD).

	CEA	CA 125	CA15-3	CA 19-9
Group A	0.5±0.4	6.6±3*	12.6±6.7	6.5±6.7
Group B	0.6±0.5	18.5±18.6*,**	12±7.4	7.4±8.7
Group C	1.0±0.9	8.9±7.9**	13±5.9	4.2±5.4

CEA: A versus B, P: NS; A versus C, P: NS ; B versus C, P: NS.

CA 125 : A versus B, P<0.01 (*); A versus C, P:NS ; B versus C, P< 0.05 (**).

CA 15-3 : A versus B, P : NS ; A versus C, P:NS ; B versus C, P:NS.

CA 19-9 : A versus B, P : NS ; A versus C, P:NS ; B versus C, P:NS.

NS = not significant

Discussion

It is known that endometriosis is an enigmatic disease and despite the fact that a number of serum markers have been proposed in the literature, as a diagnostic tool for the detection of endometriosis, there is no ideal non-invasive method to diagnose it [1]. Among these, only serum CA 125 has been one of the most extensively studied and elevated levels of this marker are often found in the serum of patients with endometriosis [7]. However, this marker detects endometriosis with high specificity but with low sensitivity, especially in minimal or mild endometriosis and it has been abandoned as a non useful diagnostic tool for the definitive diagnosis of endometriosis. So until now, a definite diagnosis of endometriosis can be made only by submitting a patient to laparoscopy in order to visualise endometriotic lesions and take a representative biopsy for histological examination [17-19].

The purpose of our study was to investigate whether endometriosis belongs to the pathologic condition which induce a concomitant increase in the values of CEA, CA 125, CA 15-3 and CA19-9 at the beginning of the menstrual cycle, as up to date, no data are available concerning the simultaneous investigation of the above serum markers that reliably could replace laparoscopy in the investigation of this common gynaecologic disease [12]. We evaluated these oncofetal antigens in the early prolifirative phase in all patients with and without endometriosis. Unfortunately, in the present study, no significant variations in the values of the serum markers were found among the three groups, except for CA-125, which was significantly elevated only in patients with moderate or advanced endometriosis and this finding was in agreement with the results of other studies [7,11,12]. Surprisingly, in Group C, the mean value of Ca-125 was higher compared with Group A, but it can be explained, at least partly, by the fact that the SD in this group was almost similar to the measured mean value. To be more specific, we couldn't demonstrate the clinical utility of serum levels CA19-9 to discriminate patients with advanced endometriosis as other studies have reported [10,11,13]. Furthermore, no significant increase was found in the simultaneous measured levels of CA 125, CA 19-9, and CA15-3 between patients with endometriosis and normal controls and these findings were contradictory to the results of other studies [18]. Moreover there was only one investigation in the literature, which demonstrated high levels of CA125, CA15-3 and CA19-9 in the peritoneal fluid of women with and without endometriosis suggesting a possible role of these oncofetal antigens in the pathophysiology of this disease, but without being a sufficient diagnostic tool that could be used for detecting women with endometriosis [16]. This significant difference in the concentration of oncofetal antigens in the serum compared to those in the peritoneal fluid can be attributed to the local production of these antigens in the peritoneal cavity and the slow absorption in the pounch of douglas due to the high molecular weight. Also, our study differs from others, as it was found a significant lower concentration of CEA between women with and without endometriosis, but within the normal range. Another possible reason for the contradictory results of our study in comparison to those of others is the fact the currents staging system does not represent the exact dynamic of the disease, rather than an overestimation of the adhesions scores in these patients A limitation of our study is the small number of patients in each group, as well as its association with the achievement of pregnancy or the postsurgical prognosis.

In conclusion, women with advanced endometriosis, there is an increase of CA- 125 levels compared with minor endometriosis and control women. On the contrary, neither CEA, nor CA 15-3 and CA 19-9 may serve as an indicator of the disease.

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