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Original Article

Combining CA125 and VEGF-C serum markers for diagnosis endometriosis

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Abstract: The most accurate procedure for diagnosis of endometriosis is laparoscopy. The identification of less invasive and more accessible markers of the disease is needed. Angiogenesis is an important pathogenesis of endometriosis. Vascular endothelial growth factor C (VEGF-C) is one of the most important factors in the regulation of both normal and abnormal angiogenesis. In this study, we measured the serum values of VEGF-C and CA125 in patients with endometriosis, benign ovarian cyst and healthy people respectively. We found that soluble VEGF-C concentrations were significantly higher in endometriosis patients when compared to benign ovarian cyst patients and healthy people. ROC curves showed that the specificity of VEGF-C test was 92.11%, the sensitivity of VEGF-C combined CA125 was 95.35%. Soluble VEGF-C may be a new serum marker for diagnosis endometriosis with high specificity. Combining CA125 and VEGF-C has higher sensitivity compared to VEGF-C alone, which has the value for diagnosis endometriosis.

Keywords: Endometriosis, VEGF-C, CA125, diagnosis

Introduction

Endometriosis is a chronic estrogen-dependent disease, affecting 5-10% of women in reproductive age [1, 2]. The pathogenesis of endometriosis is very complex and it has a high recurrence rate. The reported recurrence rate was high, estimated as 21.5% at 2 years and 40-50% at 5 years including dysmenorrhea and lesions reproduction [3]. Recent studies show that endometriosis is an angiogenesis-dependent disease [4]. The increasing of angiogenic factor activity or decreasing of angiogenesis inhibitor activity is an important factor in the process of the formation of endometriosis [5]. Soluble vascular endothelial growth factor C (VEGF-C), a member of VEGF family, promote angiogenesis and endothelial cell growth, influence the permeability of blood vessels maybe a target of anti-angiogenesis therapy for endometriosis [6].

CA125 is best known as a biomarker to monitor epithelial ovarian cancer. Serum CA125 levels increase in women with endometriosis. However, compared to laparoscopy, measuring serum CA125 levels has no value as a diagnostic tool [7].

In this study, we measured the serum values of VEGF-C and CA125 in patients with endometriosis, benign ovarian cyst and healthy people respectively to explore the potential value of VEGF-C combined CA125 as a diagnostic marker for endometriosis.

Materials and methods

Patients

86 patients with a surgery and histological diagnosis of endometriosis were selected. The subjects were 21 to 56 years old, had no other reproductive disorders or any tumors and had

Table 1. Serum VEGF-C and CA125 valure

	Endometriosis	Benign ovarian cyst	Healthy people
VEGF-C (pg/ml)	64.25±57.20 pg/ml	37.03±24.08 pg/ml	35.79±15.07 pg/ml
CA125 (u/ml)	138.41±177.49 u/ml	49.79±54.50 u/ml	12.93±4.25 u/ml

Table 2. ROC related parameters for VEGF-C, CA125 and VEGF-C combined CA125

	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	Youden index
VEGF-C	62.89	0.634±0.0437	39.53%	92.11%	35.8%	93.2%	0.3164
CA125	22.63	0.894±0.0268	95.35%	76.32%	30.9%	99.3%	0.7166
VEGF-C+CA125	0.49	0.937±0.0248	95.35%	90.79%	53.5%	99.4%	0.8614

not been taking any hormone therapy for at least 3 months before sample collection.

36 women of reproductive age without endometriosis, fibrosis, pelvic adhesions, or infertility, aged 18 to 52 years old were selected. These women were subjected to surgery for simple ovarian cyst removal, with surgery confirmation of the absence of endometriotic lesions and had not been taking hormone medication for at least 3 months before biopsy collection. Another 40 healthy people also investigated in the study with ultrasound and medical history confirmation of the absence of endometriotic lesions and had not been taking hormone medication for at least 3 months before biopsy collection. All tissue samples were obtained with informed consent and all procedures were performed in accordance with the Human Investigation Ethical Committee of Fengxian Hospital, Southern Medical University.

ELISA

The determination of serum CA125 valure was performed using a sandwich technique of a commercial ELISA kit (Cusabio Biotech Co. Ltd) and the dosage of serum soluble VEGF-C was also performed with an ELISA kit (Cusabio Biotech Co. Ltd) according to manufacturers instructions.

Statistical analyses

Data were presented as the means ± standard error of the mean (SEM). Continuous variables were compared by *t*-test. The accuracy of VEGF-C, CA125, and VEGF-C combined CA125 was evaluated by using the receiver operating characteristics (ROC) curve analysis. For all statistical tests, *P* value less than 0.05 was considered significant. Statistical analyses were performed using SPSS 17.0 for Windows (IBM) and Medcalc 15.2.2.

Results

Serum VEGF-C valure

Our data showed the serum VEGF-C valures of women with endometriosis (86 cases), benign ovarian cyst (36 cases) and healthy people (40 cases) were 64.25±57.20 pg/ml (99-287.95 pg/ml), 37.03±24.08 pg/ml (10.14-111.88 pg/ml) and 35.79±15.07 pg/ml (14.05-69.57 pg/ml), respectively (**Table 1**). We found that soluble VEGF-C concentrations were significantly higher in endometriosis patients when compared to benign ovarian cyst patients (P<0.001) and healthy people (P<0.001). Soluble VEGF-C concentrations of benign ovarian cyst cases were higher when compared to the healthy people group, but it did not reach statistical significance (P=0.7949).

Serum CA125 valure

Serum CA125 valure in endometriosis group, benign ovarian cyst group and healthy people group were 138.41±177.49 u/ml (14.02-1217.0 u/ml), 49.79±54.50 u/ml (8.62-230.3 u/ml) and 12.93±4.25 u/ml (5.64-21.6 u/ml), respectively (**Table 1**).

Diagnostic accuracy of VEGF-C/combing CA125 and VEGF-C

ROC curves showed that AUC of VEGF-C, CA125 and VEGF-C combined CA125 was 0.634, 0.894 and 0.937, respectively. The specificity of VEGF-C was 92.11% while the sensitivity of CA125 was 95.35%. In addition, the sensitivity

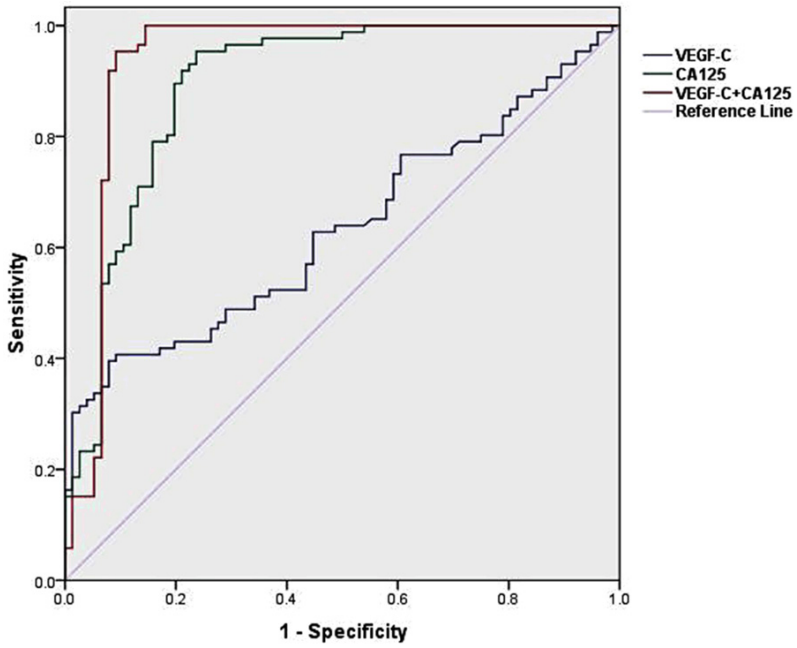

Figure 1. ROC curves for VEGF-C,CA125, and VEGF-C combined CA125.

and specificity were 95.35% and 90.79% when VEGF-C combined CA125 (**Table 2**; **Figure 1**).

Discussion

Endometriosis is a disorder in which the tissue that lines the uterus grows somewhere else, such as on the ovaries, behind the uterus, or on the bowels or bladder. This can cause cysts to form, eventually leading to the development of scar tissue and adhesions. This trapped tissue can cause extreme pain [8], very heavy periods, and infertility, though some women may present no symptoms at all [9]. The cause of endometriosis is not known. The most accurate procedure for diagnosis of endometriosis is laparoscopy [10], 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 needed.

A biomarker of interest to this study was soluble vascular endothelial growth factor C(VEGF-C), a protein that can promote angiogenesis and endothelial cell growth, influence the permeability of blood vessels. Vascular endothelial growth factor C(VEGF-C) is one of the members of the VEGF family [11, 12]. In recent years, studies have shown that angiogenesis is an important pathological process in the pathogenesis of endometriosis. Endometriotic lesions require neovascularization to deliver essential oxygen and nutrient supply for the development and progression of the disease [13]. Endometrial angiogenic disorders may be the basis of pathogenesis. Overexpression of VEGF has been reported to correlate with the pathogenesis of endomertriosis by regulating the angiogenesis [14]. In this study, we collected the serum of endometriosis patients, benign ovarian cyst patients and healthy people respectively and measured the serum levels of VEGF-C by ELISA. Analyzing our results, we found that the concentrations of VEGF-C in the endometriosis patients were higher than in the benign ovarian cyst patients and healthy people. There are no significant differences between the benign ovarian cyst group and healthy people group. Furthermore, we made the ROC curves for VEGF-C for distinguishing endometriosis cases from healthy controls and the AUC was 0.634. The sensitivity and specificity were 39.53% and 92.11%. It is suggested soluble VEGF-C is a potential detection biomarker of endometriosis.

Cancer antigen 125 (CA125) is a glycoprotein found on the surface of cells originating from embryonic coelomic epithelium, including epithelium of the fallopian tubes, endometrium, and endocervix. The CA125 level of endometriosis patients significantly increases and is positively correlated with the progression of the disease. And the more serious the endometriosis was, the higher the CA125 content would be [15, 16]. After active treatment, the CA125 level is significantly reduced, which can be used as contrast index of the clinical effect of endometriosis [17-19]. In present study, we wrote the ROC curves for VEGF-C, CA125 and VEGF-C combined CA125. The AUC of VEGF-C combined CA125 was 0.937±0.0248, the sen-

sitivity and specificity were 95.35% and 90.79%. The specificity (90.79%) was lower than VEGF-C (92.11%), however the sensitivity (95.35%) was great higher than VEGF-C (39.53%). Combining CA125 and VEGF-C has the value for diagnosis endometriosis.

In conclusion, soluble VEGF-C may be a new serum marker for diagnosis endometriosis with high specificity. Combining CA125 and VEGF-C has higher sensitivity for diagnosis endometriosis.

Disclosure of conflict of interest

None.

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