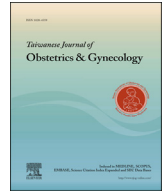




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Original Article

Clinical significance of serum follistatin levels in the diagnosis of ovarian endometrioma and benign ovarian cysts



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ABSTRACT

Objective: To determine the clinical significance of serum follistatin levels in women with an ovarian endometrioma.

Materials and methods: This is a prospective study of 89 women, 56 with an ovarian endometrioma (endometrioma group) and 33 with a benign ovarian cyst (control group) who underwent laparoscopic excision. Age, parity, body mass index, serum CA-125, serum CA 19-9, and serum follistatin levels were determined for all participants and evaluated as potential prognostic factors prior to laparoscopic cystectomy.

Results: There were no significant differences in demographic factors between the endometrioma group and the control group. However, serum follistatin levels were significantly higher in the endometrioma group (9350 ± 895 pg/mL vs. control group 725 ± 72 pg/mL, $p < 0.05$). The optimal diagnostic cut-off values (sensitivity and specificity) of CA-125, CA 19-9, and follistatin for ovarian endometrioma were 23.2 IU/mL (82.14% and 72.73%), 30.14 IU/mL (45.28% and 87.50%), and 2350 pg/mL (53.7% and 60.61%), respectively.

Conclusion: Despite the increased serum follistatin levels in patients with ovarian endometrioma, CA-125 was determined to be a more sensitive and specific marker than follistatin for the diagnosis of ovarian endometrioma and endometriosis.

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Introduction

Endometriosis is a chronic condition characterized by the growth of hormone-responsive endometrial tissue outside the uterine cavity [1]. An ovarian endometrioma is a cyst composed of endometrial tissue detected in 20–40% of women with endometriosis [1,2]. The gold standard for diagnosis of endometriosis is histological examination, which requires an invasive procedure, such as laparoscopy or laparotomy, to obtain tissue samples [3,4]. Many serum biochemical markers, such as cytokines, hormones, and growth factors, which may be released into the bloodstream by ectopic endometrial tissue, have been suggested for noninvasive diagnosis of endometriosis. Although these markers have some clinical value, diagnostic serum markers for endometriosis have not

been identified. CA-125, a transmembrane glycoprotein, is elevated in women with endometriosis [5], and previous studies have reported that ectopic endometrial tissue may release follistatin into the bloodstream [5–8].

Follistatin is an extracellular glycoprotein originally identified as an inhibitor of pituitary follicle-stimulating hormone secretion. The majority of follistatin's physiological effects are due to its ability to neutralize activin [9,10]. Florio et al [11] reported that follistatin is expressed in human endometrium and ectopic endometrial tissue, and is a promising diagnostic marker due to its sensitivity and specificity for ovarian endometriomas.

This study compares the serum levels of follistatin in women with ovarian endometriomas with those with benign ovarian cysts to determine the role of follistatin in the diagnosis of ovarian endometrioma and endometriosis.

Materials and methods

This prospective case control study was conducted between February 2012 and May 2013 at Zekai Tahir Burak Women's Health

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Education and Research Hospital in Ankara, Turkey. The study was performed according to the standards of the Helsinki declaration, and written informed consent was obtained from all participants. The study was approved by our Institutional Ethics Committee (ethical approval no: 22-02-12/20).

Patient characteristics

Eighty-nine women with ovarian masses were enrolled in the study: 56 women with an ovarian endometrioma (endometrioma group) and 33 women with a benign ovarian cyst (control group). Age, parity, body mass index, tobacco use, alcohol use, diameter of the ovarian mass, bilaterality of the mass, platelet count, neutrophil leukocyte ratio, serum follistatin, serum CA-125, and serum CA 19-9 levels were determined for each participant.

All patients in the endometrioma group had Stage 3 or 4 endometriosis according to the revised American Society for Reproductive Medicine classification [12]. Patients in the control group did not have endometriosis but had benign ovarian tumors with histological confirmed final diagnoses, including serous ($n = 18$) and mucinous ($n = 15$) cystadenomas.

Blood samples

Peripheral venous blood samples were collected from all patients prior to laparoscopic cystectomy to measure serum follistatin, CA-125, and CA 19-9 levels. All blood samples were allowed to clot at room temperature. Samples were centrifuged at 300g for 20 minutes at room temperature, and the serum was separated using a disposable pipette, transferred to a cryoresistant tube, and stored at -80°C for 3–15 months (average 9 months).

Laboratory assays

The serum follistatin concentration was measured using a commercially available enzyme-linked immunosorbent assay (ELISA; Eastbiopharm Co., Ltd., Hangzhou, China). For the follistatin ELISA, the intra- and inter-assay coefficients of variation were 3% and 9%, respectively.

The serum concentration of CA-125 was measured using an electrochemiluminescence immunoassay kit (Roche Elecsys Kits, Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation were 3.8% and 1.5%, respectively. The reference range for serum CA-125 was 0–35 IU/mL.

Serum CA 19-9 was measured using an electrochemiluminescence immunoassay (Roche Diagnostics E 170 analyzer). A normal CA 19-9 value was defined as < 27 IU/mL.

Statistical analysis

The means and standard deviations were calculated for continuous variables, and normal distribution was analyzed using the Kolmogorov–Smirnov test. The Chi-square (χ^2) test and Student t test were used to evaluate associations between the categorical and continuous variables. For non-normally distributed categorical variables, the Mann–Whitney U test was used. Receiver operator characteristic (ROC) curve analysis was used to establish the cut-off values for follistatin, CA-125, and CA 19-9. The Youden index (sensitivity + specificity – 1) was also calculated, and the cut-off value with the maximum Youden index was deemed the optimal cut-off value. A p value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient demographic and clinical features are presented in Table 1. The mean age, parity, body mass index, tobacco use, and alcohol use were similar between the endometrioma and the control groups. There were no statistically significant differences between the groups in terms of the mean platelet count or NLR ($p > 0.05$). The mean diameter of the cystic mass was 6.79 ± 1.56 cm in the control group (benign ovarian cyst) and 5.64 ± 2.01 cm in the endometrioma group ($p < 0.05$). Serum CA-125, CA 19-9, and follistatin levels in the endometrioma group versus the control group were 93.45 ± 89.55 IU/mL versus 47.25 ± 72.05 IU/mL, 84.79 ± 93.37 IU/mL versus 34.89 ± 76.9 IU/mL, and 9350 ± 895 pg/mL versus 725 ± 72 pg/mL, respectively.

According to ROC curve analysis, the cut-off values (sensitivity and specificity) for serum CA-125, CA 19-9, and follistatin were 23.2 IU/mL (81.14% and 72.73%), 30.14 IU/mL (45.28% and 87.5%), and 23.5 ng/mL (53.57% and 60.61%), respectively (Fig. 1). The area under the curve values for CA-125, CA 19-9, and follistatin were 0.814, 0.613, and 0.54, respectively (Table 2). Combining CA-125, CA 19-9, and follistatin levels using the cut-off values in Table 2 significantly improved the diagnostic accuracy with a specificity of 93.75% and a sensitivity of 26.8%.

Table 1
The demographic and clinical characteristics of the patients.

	Endometrioma group ($n = 56$)	Benign cyst group ($n = 33$)	p
Age (y) ^a	31.71 ± 7.79	29.06 ± 10.75	0.692
Parity ^b	0.70 (0–3)	1.06 (0–4)	0.788
BMI (kg/cm^2) ^a	2.77 ± 3.71	2.3 ± 3.53	0.532
Smokers ^c	18 (32.14)	12 (36.36)	0.365
Alcohol use ^c	2 (3.5)	1 (3.03)	0.278
Bilaterality ^c	15 (28.57)	9 (27.27)	0.976
Diameter of the mass (cm) ^a	5.64 ± 2.01	6.79 ± 1.56	0.007
NLR ^a	2.36 ± 2.21	2.39 ± 1.86	0.964
CA-125 (IU/mL) ^a	93.45 ± 89.55	47.25 ± 72.05	0.014
CA19-9 (IU/mL) ^a	84.79 ± 93.37	34.89 ± 76.9	0.010
Follistatin (pg/mL) ^a	9350 ± 895	725 ± 72	0.011

BMI = body mass index; NLR = neutrophil lymphocyte ratio.

A p value < 0.05 was considered statistically significant.

^a Data are presented as mean \pm SD.

^b Data are presented as median (min–max).

^c Data are presented as n (%).

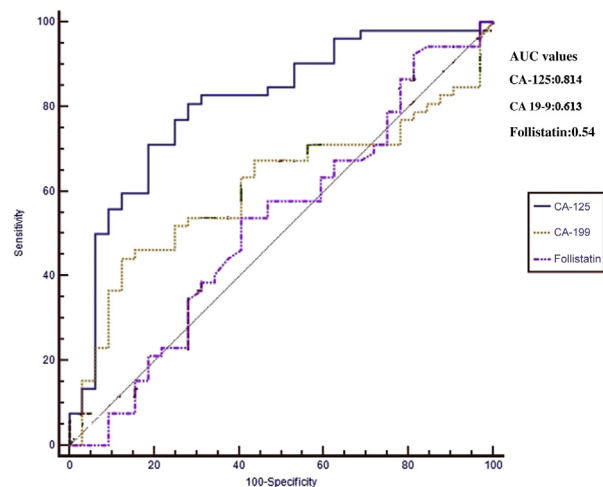


Fig. 1. ROC curve of CA-125, CA 19-9, and follistatin for the discrimination of endometrioma cases from benign cysts. AUC = area under the curve; ROC = receiver operating characteristic.

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