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Diagnostic performance of human epididymis protein 4 compared to a combination of biophysical and biochemical markers to differentiate ovarian endometriosis from epithelial ovarian cancer in premenopausal women

Tanja Nikolova[1], Radomir Zivadinovic[2], Nina Evtimovska[3], Violeta Klisarovska[4], Marko Stanojevic[2], Jadranka Georgievska[5] and Natasha Nikolova[1]

Departments for [1]Gynecological Oncology, [5]Urgent Gynecology, University Clinic of Obstetrics and Gynecology, [3]Biochemical Laboratory, [4]Department for Gynecological Oncology, University Clinic of Oncology and Radiotherapy, Skopje, Macedonia; and [2]Department for Gynecological Oncology, Clinic of Obstetrics and Gynecology, University Clinical Center, Nis, Serbia

Abstract

Aim: This study is a comparison of human epididymis protein 4 (HE4) with cancer antigen 125 (CA125), using the Risk of Ovarian Malignancy Algorithm (ROMA), Copenhagen Index (CPH-I), Risk of Malignancy Index (RMI) and Morphology Index (MI) to differentiate ovarian endometriosis from epithelial ovarian cancer (EOC) in premenopausal women.

Methods: The study was performed at the University Clinic of Obstetrics and Gynecology in Skopje. One hundred and sixty-four premenopausal patients were divided into three study groups, including ovarian endometriosis (37), other benign pelvic masses (57) and EOCs (11), and a control group (59). After ultrasonography, all subjects underwent blood sampling. Surgery and histological verification was performed. Pelvic masses were classified based on histological findings. Mann–Whitney, receiver operating characteristic-area under the curve (AUC), sensitivity, specificity and Kruskal–Wallis tests were used for statistical analysis. The level of significance α was set at 5%.

Results: For each of the tested markers, sensitivity, specificity and accuracy to distinguish ovarian endometriosis from EOC were as follows: HE4 (81.82%, 100%, 95.83%); CA125 (81.82%, 48.65%, 56.25%); ROMA (90.91%, 83.78%, 85.42%); CPH-I (81.82%, 97.30%, 93.75%); RMI (90.91%, 35.14%, 47.92%); and MI (100%, 75.68%, 81.25%), respectively. The AUC for ovarian endometriosis compared to EOC for tested markers was as follows: HE4 (AUC = 0.934), CA125 (AUC = 0.821), ROMA (AUC = 0.929), CPH-I (AUC = 0.924) and RMI (AUC = 0.880), respectively.

Conclusion: HE4 and CPH-I perform best to discriminate ovarian endometriosis from EOC in premenopausal women. MI has maximal sensitivity to detect EOC.

Key words: CA125, endometriosis, HE4, ovarian cancer, ultrasonography.

Introduction

Ovarian endometriosis affects up to 10% of the female population of reproductive age, representing one of the most common benign gynecological conditions.[1] Ovarian endometriosis increases the risk of ovarian cancer, particularly endometrioid and clear cell carcinoma. Around 40% of endometrioid ovarian cancers and 50% of clear cell ovarian carcinomas are associated with ovarian endometriosis.[2]

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Correspondence: Dr Tanja Nikolova, University Clinic of Obstetrics and Gynecology, Mother Teresa 17, 1000 Skopje, Macedonia.
Email: nikolovatanja@gmail.com

Failure to recognize ovarian malignancy and apply surgical treatment in non-specialized centers significantly impacts patient survival.[3] However, inappropriate referral of patients with benign pathology to oncology centers may lead to unnecessary overly radical interventions that may affect future fertility. Prompt preoperative triage and adequate referral of cases of ovarian endometriosis is not possible when based only on ultrasonography and cancer antigen (CA) 125 levels. Although CA125 is elevated above a normal level in cases of ovarian endometriosis, inflammation, follicular cysts and cystadenomas, as a marker, CA125 cannot always differentiate ovarian endometriosis as a benign mass and can yield false positive results.[4–6] CA125 is also elevated in cases of pancreatic and gastrointestinal cancers, particularly when widespread.[7]

The novel biomarker HE4 (human epididymis protein 4), a member of the Whey acidic proteins, is among the most frequently upregulated genes in epithelial ovarian cancers (EOC) based on gene expression profiles.[8,9] The use of HE4 has been intensively studied. HE4 has been shown to overcome the discriminate power of CA125, either alone or incorporated in logistic regression models.[10–13] HE4 is reported to have increased sensitivity for detecting early stage epithelial ovarian cancer.[14] Age and renal function may influence its levels.[15]

A number of biophysical or both biophysical and biochemical markers in the form of ultrasound morphologic scores, multimodal scoring systems and biomarker algorithms have been developed to predict the nature of a detected ovarian mass.

The primary aim of this study was to compare the diagnostic performance of the novel tumor marker HE4 with the performance of CA125 alone and in Risk of Ovarian Malignancy Algorithm (ROMA) and Copenhagen Index (CPH-I) logistic regression models in premenopausal women. Furthermore, we compared the diagnostic performance of HE4 with the modified Jacobs's Risk of Malignancy Index (RMI) and Ueland's Morphology Index (MI) in premenopausal women.

Methods

A prospective, comparative study was conducted at the University Clinic of Obstetrics and Gynecology in Skopje. The ethical committee at the Macedonian Ministry of Health approved the study. Only patients who agreed to sign informed consent were included in the trial.

We consecutively recruited 164 premenopausal women and divided them into three study groups including ovarian endometriosis, other benign pelvic masses and EOCs, and a control group. Patients were required to be aged ≥18 years to have an ultrasonography scan confirming an ovarian cyst/mass and to be scheduled for surgical intervention to be eligible for enrollment in the study. Patients aged <18 years, who had undergone prior bilateral oophorectomies, had current or past malignancy, renal failure or pathology, were undergoing current hormonal therapy or pregnant were excluded from the study. Healthy subjects for the control group were recruited after visiting our department for a routine PAP smear. Ultrasonography was performed and only women with normal scans were included. Other inclusive and exclusive criteria were the same as for the study groups.

Classification of the pelvic masses into groups was based on the findings of histological analysis.

Ultrasound investigation

Ultrasound investigation was performed using a Voluson E8, 4–9 MHz RIC5-9D vaginal transducer with the patient in a supine position. Ultrasonography was performed no later than six weeks prior to the surgical intervention.

Morphology index (MI)

The MI was calculated according to Ueland's equation. The details have been published previously.[16]

Blood collection and analysis

Within 2 h of collection, blood was centrifuged and sera collected and dispensed into 5 cm^3 Eppendorf cryo tubes that were subsequently frozen to −20°C. Sera samples were analyzed using Architect CA125 II and Architect HE4 reagents on an Abbott Platform, following the manufacturer's instructions.

Risk of malignancy index (RMI)

The RMI was calculated according to Jacobs's equation. The details have been published previously.[17] We modified this score by raising the upper cut-off limit from 200 to 250, because of the best individual differentiation reported.[18,19] We used cut-offs as recommended by the Royal College of Obstetrics and Gynecology: <25 low risk, 25–150 moderate risk and 150–250 high risk.

Table 1 Descriptive statistics, HE4 marker for other benign ovarian masses by type of benign ovarian tumors

Tumor	Mean	SD	Median	Min	Max	Range
Epithelial	62.18	44.20	42.50	28.4	163.9	135.5
Functional cysts	40.02	14.63	38.90	15.4	68.9	53.5
Germinative	33.98	8.75	36.95	21.7	40.3	18.6
Inflammatory	51.62	19.10	59.20	27.3	91.9	64.6
Myoma (uterus)	73.40	27.44	73.40	54.0	92.8	38.8
Paraovarian cysts	49.50	13.51	43.30	40.2	65.0	24.8
Stromal	33.00		33.00	33.0	33.0	0

HE4, human epididymis protein 4; SD, standard deviation.

Risk of ovarian malignancy algorithm (ROMA)

To calculate ROMA we employed the equation used by Moore *et al.*[11] As recommended by the manufacturer, a ROMA score of ≥7.4% for premenopausal women was considered a high risk for malignancy.

Copenhagen index (CPH-I)

For CPH-I we employed the equation used by Karlsen *et al.*[13]

As recommended by the manufacturer, HE4 values ≥70 pmol/L in premenopausal women represented a high risk for malignancy. The cut-off for CA125 was set at 35 U/mL.

All patients underwent surgical removal of the ovarian mass. All analyses were performed by technicians blinded to the laboratory results and histological outcomes of the investigated biomarkers.

Women were considered premenopausal if their last menstrual bleeding was within the last 12 months prior to blood sampling. In cases of prior hysterectomy, women were tested for plasma follicle stimulating hormone and were treated as premenopausal if follicle stimulating hormone <22 mIU/mL.

Mann–Whitney *U*, receiver operating characteristic-area under the curve (ROC-AUC) sensitivity, specificity (SPC), positive and negative predictive values for all tested parameters and Kruskal–Wallis tests were performed. The level of significance α was set at 5%.

Results

Of a total of 164 premenopausal patients, the ovarian endometriosis group included 37 (22.6%) patients. The other benign pelvic masses group included 57 (34.7%) patients with: epithelial tumors (15, 26.3%); functional cysts (19, 33.3%); germinative tumors (4, 7.0%); inflammatory tumors (13, 22.8%); uterine myomas (2, 3.5%); paraovarian cysts (3, 5.3%); and a stromal tumor (1, 1.8%). The EOC group included 11 (6.7%) patients and the control 59 (36.0%) healthy subjects. Descriptive statistics of HE4 and CA125 for the other benign pelvic mass group, which included all benign tumors except ovarian endometriosis, differentiated by type of tumor, are listed in Tables 1 and 2. Descriptive statistics of the three study groups and control are listed in Table 3.

A scatter plot shows the correlation between HE4 and CA125 marker concentrations presented in $\log_2$ transformation in patients with ovarian endometriosis and EOC (lines represent cut-off values) (Fig. 1).

Malignancy classifications based on the cut-off values determined above for all analyzed parameters (HE4, CA125, ROMA, CPH-I, RMI and MI) in premenopausal patients in the three study groups are presented in Table 4, and Figures 2 and 3.

Human epididymis protein 4 performed best in differentiating ovarian endometriosis from EOC (SPC = 100%, accuracy [ACC] = 95.83%), while CPH-I

Table 2 Descriptive statistics, CA125 marker for other benign pelvic masses by type of benign ovarian tumors

Tumor	Mean	SD	Median	Min	Max	Range
Epithelial tumors	112.73	250.19	31.90	12.0	1000.0	988.0
Functional cysts	49.46	54.05	23.70	5.4	154.1	148.7
Germinative tumors	28.22	31.11	16.10	7.3	73.4	66.1
Inflammatory	95.29	128.58	34.20	8.7	457.8	449.1
Myoma (uterus)	674.65	921.71	674.65	22.9	1326.4	1303.5
Paraovarian cysts	15.43	6.81	13.50	9.8	23.0	13.2
Stromal tumors	44.60		44.60	44.6	44.6	0

CA125, cancer antigen 125; SD, standard deviation.

performed well in differentiating ovarian endometriosis from EOC, predicting only one false positive case (SPC = 97.30%, ACC = 93.75%). RMI was the poorest predictor, with 24 false positive cases (SPC = 35.14%, ACC = 47.92%). These results suggest that HE4 and CPH-I are superior for discriminating ovarian endometriosis from EOC in women at premenopausal stage (Table 5, Fig. 4).

The HE4 and CA125 levels between the groups were tested. The HE4 level in the other benign pelvic masses group (Mdn = 40.3 pmol/L) was greater than in the control subjects (Mdn = 34.4 pmol/L)

Table 3 Descriptive statistics of the study and control groups

ENDOMETRIOSIS							
		Age (years)		Non-smoker	Smoker	Follicular phase	Luteal phase
	Range	M	SD	N (%)	N (%)	N (%)	N (%)
	19–49	34.70	8.58	24 (64.9)	13 (35.1)	14 (37.8)	23 (62.2)
		Range	M	SD	Mdn	Skewness (SE)	Kurtosis (SE)
HE4	pmol/L	14.4–56.8	37.12	10.00	35.50	0.16 (0.39)	−0.03 (0.76)
CA125	U/mL	10.2–172.4	57.89	47.18	35.40	1.01 (0.39)	−0.12 (0.76)
ROMA	%	0.44–11.16	4.46	2.70	3.71	1.05 (0.39)	0.58 (0.76).
CPH-I	%	0.0021–0.0703	0.018	0.018	0.010	1.56 (0.39)	1.81 (0.76)
RMI		0–486.9	78.09	102.29	35.40	2.41 (0.39)	6.95 (0.76)
9 (24.4%) as ASRM stage III							
28 (75.6%) cases were intraoperatively staged as ASRM stage IV.							
OTHER BENIGN PELVIC MASSES							
		Age (years)		Non-smoker	Smoker	Follicular phase	Luteal phase
	Range	M	SD	N (%)	N (%)	N (%)	N (%)
	18–50	36.90	10.12	33 (57.9)	24 (42.1)	26 (45.6)	31 (54.4)
		Range	M	SD	Mdn	Skewness (SE)	Kurtosis (SE)
HE4	pmol/L	15.4–163.9	49.62	27.87	40.30	2.51 (0.32)	7.73 (0.62)
CA125	U/mL	5.4–1326.4	95.13	221.01	27.50	4.53 (0.32)	21.73 (0.62)
ROMA	%	0.47–61.74	9.37	12.15	5.15	3.16 (0.32)	11.03 (0.62)
CPH-I	%	0.0013–0.7303	0.052	0.133	0.0137	4.21 (0.32)	18.03 (0.62)
RMI		0–3979.2	238.30	670.55	38.40	4.58 (0.32)	21.98 (0.62)
EPITHELIAL OVARIAN CANCERS							
		Age (years)		Non-smoker	Smoker	Follicular phase†	Luteal phase†
	Range	M	SD	N (%)	N (%)	N (%)	N (%)
	30–50	42.46	8.21	9 (81.8)	2 (18.2)	2 (18.2)	9 (81.8)
		Range	M	SD	Mdn	Skewness (SE)	Kurtosis (SE)
HE4	pmol/L	31.2–6488.0	1279.56	1839.93	997.00	2.64 (0.66)	7.74 (1.28)
CA125	U/mL	12.0–3220.7	1088.24	1189.27	556.50	0.74 (0.66)	−1.07 (1.28)
ROMA	%	2.66–99.99	76.25	37.08	99.27	−1.46 (0.66)	0.64 (1.28)
CPH-I	%	0.0077–0.9954	0.708	0.433	0.942	−1.16 (0.66)	−0.77 (1.28)
RMI		12–9662.1	2873.44	3421.6	1669.5	1.16 (0.66)	0.02 (1.28)
HEALTHY SUBJECTS							
		Age (years)		Non-smoker	Smoker	Follicular phase	Luteal phase
	Range	M	SD	N (%)	N (%)	N (%)	N (%)
	21–53	39.95	8.35	41 (69.5)	18 (30.5)	32 (54.2)	25 (42.4)
		Range	M	SD	Mdn	Skewness (SE)	Kurtosis (SE)
HE4	pmol/L	13.3–64.4	35.00	14.42	34.40	0.34 (0.31)	−0.93 (0.61)
CA125	U/mL	5.6–59.0	17.73	12.29	13.40	1.85 (0.31)	3.19 (0.63)
ROMA	%	0.35–12.07	4.13	3.44	3.33	0.86 (0.31)	−0.34 (0.61)
CPH-I	%	0.0009–0.0349	0.007	0.007	0.006	1.95 (0.31)	4.81 (0.61)

†Cases missing; CA125, cancer antigen 125; CPH-I, Copenhagen Index; M, mean; Mdn, median; ROMA, Risk of Ovarian Malignancy Algorithm; RMI, Risk of Malignancy Index; SD, standard deviation; SE, standard error; ASRM, American society of reproductive medicine.

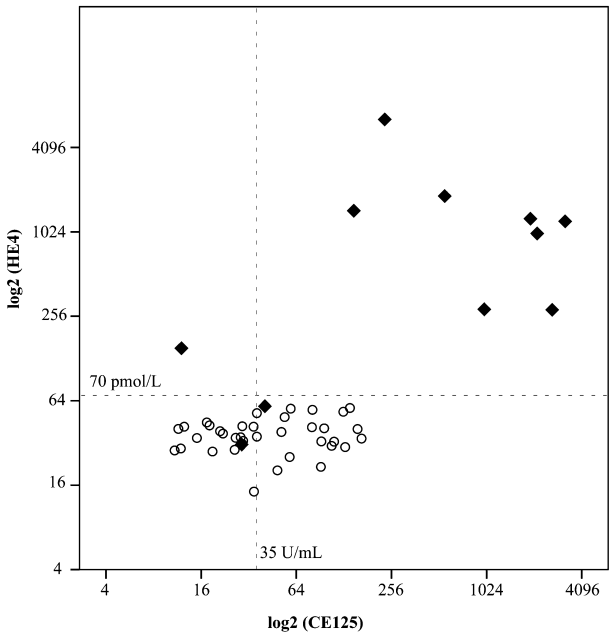

Figure 1 Scatter plot showing the correlation between human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) concentrations presented in $\log_2$ transformation in patients with ovarian endometriosis and epithelial ovarian cancers. Lines show the cut-off values: 70 pmol/L for HE4 and 35 U/mL for CA125. (○) Ovarian endometriosis (n = 37) and (◆) Epithelial ovarian cancers (n = 11).

(U = 1066.5; two-tailed P = 0.016; Glass rank biserial correlation = 0.128, a small effect in Cohen's 1988 classification). The median of ovarian endometriosis (Mdn = 35.5 pmol/L) was significantly lower than median of the other benign pelvic masses (Mdn = 40.30 pmol/L) (U = 752.5; one-tailed P = 0.016). For CA125, the median level in ovarian endometriosis (Mdn = 35.4) was significantly higher than the median level in control subjects (Mdn = 13.4) (U = 355.0; two-tailed P = 0.016; Glass rank biserial correlation = 0.675, a large effect in Cohen's 1988 classification). In addition, there was a significance between the median for other benign pelvic masses (Mdn = 27.5 U/mL), which was higher than the median level in control subjects (Mdn = 13.4 U/mL) (U = 925.5; two-tailed P = 0.016; Glass rank biserial correlation = 0.449, a large effect in Cohen's 1988 classification) (Table 6).

Analysis of the ROC-AUC curves showed that HE4 has the highest discriminant power (AUC = 0.934) followed by ROMA (AUC = 0.929) for ovarian endometriosis compared to EOCs, while CPH-I has the highest discriminant power (AUC = 0.911), followed by ROMA (AUC = 0.900) for other benign pelvic masses compared to EOCs (Figs 5–6; Table 7).

Discussion

In a group of women with stage III–IV ovarian endometriosis, no cases presented with a HE4 level > 70 pmol/L, while 19 (51.4%) cases presented with CA125 levels >35 U/mL. CPH-I showed one and ROMA six false positive results (Table 4). Using ultrasound-based investigation parameters, RMI and MI

Table 4 Malignancy classification based on the cut-off values for HE4, CA125, ROMA, CPH-I, RMI and MI in the study groups

Marker/Index/Score		Ovarian endometriosis		Patients with other benign pelvic masses		Epithelial ovarian cancers	
		N	(%)	N	(%)	N	(%)
HE4	*Positive*	0	(0%)	5	(8.8%)	9	(81.8%)
	Negative	37	(100%)	52	(91.2%)	2	(18.2%)
CA125	*Positive*	19	(51.4%)	22	(38.6%)	9	(81.8%)
	Negative	18	(48.6%)	35	(61.4%)	2	(18.2%)
ROMA	*Positive*	6	(16.2%)	21	(36.8%)	10	(9.1%)
	Negative	31	(83.8%)	36	(63.2%)	1	(90.9%)
CPH-I	*Positive*	1	(2.7%)	7	(12.3%)	9	(81.8%)
	Negative	36	(97.3%)	50	(87.7%)	2	(18.2%)
RMI	*Low*	13	(35.1%)	23	(40.4%)	1	9.1%
	Moderate	22	(59.5%)	24	(42.1%)	2	18.2%
	High	2	(5.4%)	10	(17.5%)	8	72.7%
Morphology index	*Positive*	9	(24.3%)	27	(52.6%)	11	(100%)
	Negative	28	(75.7%)	30	(47.4%)	0	(0%)

Human epididymis protein 4 (HE4) cut-off value = 70; cancer antigen 125 (CA125) cut-off value = 35; Risk of Ovarian Malignancy Algorithm (ROMA) cut-off value = 7.4; Copenhagen Index (CPH-I) cut-off value = 0.07; Risk of Malignancy Index (RMI) score cut-off value <25 (low), 25–250 (moderate), >250 (high); Morphology Index (MI) cut-off value = 5.

performed far worse than biochemical markers, which can be explained with the bizarre tumor patterns that ovarian endometriosis may acquire in advanced stages in premenopausal women.

In our statistical analysis of CA125, significantly lower SPC and ACC were found in comparison to HE4 and the logistic regression models CPH-I and ROMA (Table 5). HE4 showed the highest SPC and ACC in distinguishing ovarian endometriosis from all other ECOs. To our knowledge, our study is one of the first to report the diagnostic performance of RMI and MI for the differentiation of ovarian endometriosis from malign ovarian tumors. RMI performed worst in the differentiation, with the lowest SPC and ACC in comparison to the other investigated parameters (Table 5).

Analysis of ROC-AUC curves showed that HE4 has the highest discriminant power for ovarian endometriosis compared to EOCs, followed by ROMA. CPH-I has the highest discriminant power, followed by ROMA for other benign pelvic masses compared to EOC (Table 7).

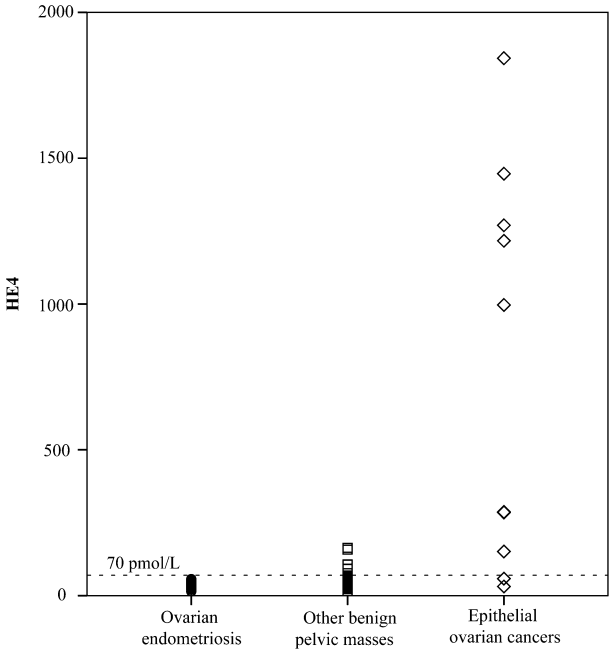

Figure 2 Scatter plot of human epididymis protein 4 (HE4) classification for patients with ovarian endometriosis, other benign pelvic masses and epithelial ovarian cancers (the sample with a max limit for HE4 = 6488 pmol/L for epithelial ovarian cancers was excluded from the plot). Line shows the cut-off value for HE4 70 pmol/L. (○) Ovarian endometriosis, (□) "Other benign pelvic masses", and (◇) Epithelial ovarian cancers.

When analyzing sensitivity, we found that MI showed maximal sensitivity, detecting all cancer cases.

Human epididymis protein 4 showed same sensitivity as the widely used CA125, and the logistic regression model CPH-I, and HE4 sensitivity was lower than ROMA and RMI sensitivity (Table 5).

Our results for the HE4 differentiation of ovarian endometriosis from EOCs are in line with results already reported by Huhtinen et al.[20] The difference between our study and the cited study is that the previous study included both premenopausal and postmenopausal women.

Our ROMA result showed a higher SPC compared to the original study conducted by Moore *et al.* (74.8%),[12] but there was a difference in the nature of benign ovarian tumors included. Unlike our study, Moore *et al.* analyzed ovarian endometriosis cases together with other benign ovarian tumors, which might have affected SPC.

Our results suggest that HE4 alone is the best tool to differentiate between ovarian endometriosis and EOCs in premenopausal women. CA125 has a tendency to be elevated in many benign gynecological tumors (Table 6), particularly in ovarian endometriosis.[21] Consequently, it should not be used as a standalone

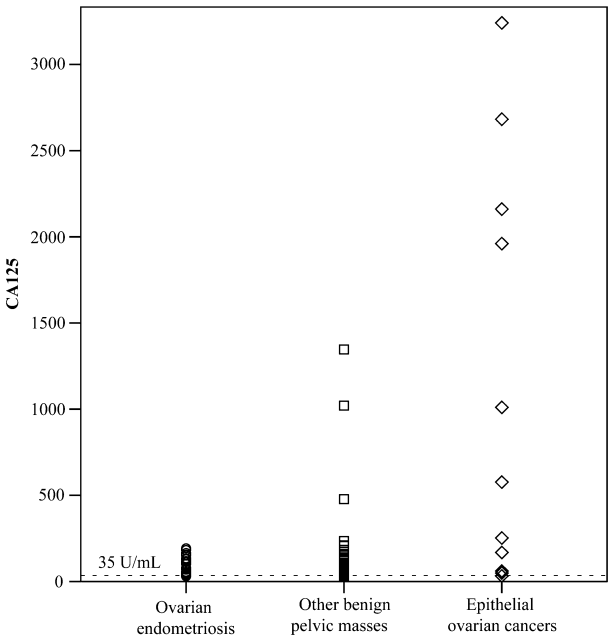

Figure 3 Scatter plot of cancer antigen 125 (CA125) classification for patients with ovarian endometriosis, other benign pelvic masses and epithelial ovarian cancers. Line shows the cut-off value for CA125 35 U/mL. (○) Ovarian endometriosis, (□) "Other benign pelvic masses", and (◇) Epithelial ovarian cancers.

Table 5 Sensitivity, specificity, predictive value and accuracy of biomarkers and parameters investigated

	Cut-off	SEN (%) (95% CI)	SPC (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ACC (%)
Ovarian endometriosis compared to epithelial ovarian cancers						
HE4	*70*	81.82 (48.22–97.72)	100.00 (90.51–100)	100.00 (66.37–100)	94.87 (82.68–99.37)	95.83
CA125	35	81.82 (48.22–97.72)	48.65 (31.92–65.60)	32.14 (15.88–52.35)	90.00 (68.30–98.77)	56.25
ROMA	*7.4*	90.91 (58.72–99.77)	83.78 (67.99–93.81)	62.50 (35.43–84.80)	96.88 (83.78–99.92)	85.42
CPH-I	*0.07*	81.82 (48.22–97.72)	97.30 (85.84–99.93)	90.00 (55.50–99.75)	94.74 (82.25–99.36)	93.75
RMI Score	*25*	90.91 (58.72–99.77)	35.14 (20.21–52.54)	29.41 (15.10–47.48)	92.86 (66.13–99.82)	47.92
Morphology index	5	100.00 (71.51–100)	75.68 (58.80–88.23)	55.00 (31.53–76.94)	100.00 (87.66–100)	81.25

ACC, accuracy; CA125, cancer antigen 125; CI, confidence interval; CPH-I, Copenhagen Index; HE4, human epididymis protein 4; MI, Morphology Index; NPV, negative predictive value; PPV, positive predictive value; RMI, Risk of Malignancy Index; ROMA, Risk of Ovarian Malignancy Algorithm; SEN, Sensitivity; SPC, specificity.

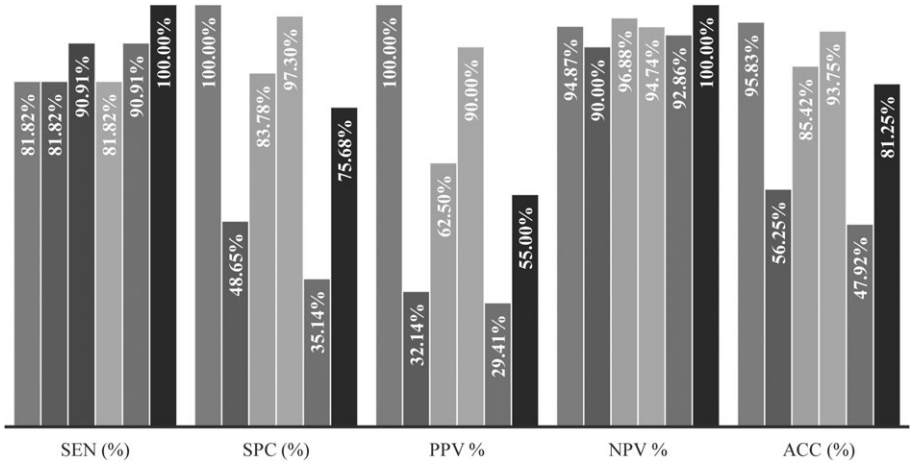

Figure 4 Bar chart showing sensitivity (SEN), specificity (SPC), positive predictive value (PPV), negative predictive value (NPV) and accuracy (ACC) for (■) human epididymis protein 4 (HE4), (■) cancer antigen 125 (CA125), (■) Risk of Ovarian Malignancy Algorithm (ROMA), (■) Copenhagen Index (CPH-I), (■) Risk of Malignancy Index (RMI) Score and (■) Morphology Index (MI).

biochemical tumor marker to distinguish ovarian endometriosis from ovarian malignancy.

Unlike our RMI results (Table 5), Enakpene *et al.* reported a SPC of 74.3%.[19] The SPC of MI in our study was lower than reported by Ueland *et al.*, at 80.7%.[16] Both studies analyzed ovarian endometriosis together with other benign ovarian tumors compared to EOCs in premenopausal and postmenopausal women.

The HE4 AUC result in our study corresponded with results reported by Anastasi *et al.*;[22] however, they also included both postmenopausal and premenopausal women in their analysis.

Table 6 Statistical significance of HE4 and CA125 medians between groups

	Control subjects	Ovarian endometriosis	Other benign pelvic masses	Kruskal–Wallis *P*
HE4	34.40 (13.3–64.4)	35.50 (14.4–56.8)	40.30*,** (15.4–163.9)	0.002
CA125	13.40 (5.6–59)	35.40* (10.2–172.4)	27.50* (5.4–1326.4)	0.0005

*$P < 0.016$ significant versus controls; **$P < 0.016$ significant versus ednometriosis. Human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) reported as median (min-max); *P* values between groups were evaluated by Mann–Whitney *U* test modified with bonferroni correction $P = 0.05/3 = 0.016$.

Table 7 Area under the curve analysis of biomarkers and parameters investigated between the study groups

Markers	Ovarian endometriosis versus epithelial ovarian cancers Area under curve	Other benign pelvic masses versus epithelial ovarian cancers Area under curve
HE4	0.934	0.898
CA125	0.821	0.828
ROMA	0.929	0.900
CPH-I	0.924	0.911
RMI	0.880	0.851

CA125 cancer antigen 125; CPH-I, Copenhagen Index; HE4, human epididymis protein 4; RMI, Risk of Malignancy Index; ROMA, Risk of Ovarian Malignancy Algorithm.

Because the same pathophysiology may orchestrate the progression of ovarian endometriosis and its transformation to endometrioid and clear cell ovarian neoplasms,[23] a highly sensitive and specific tool to properly discriminate ovarian masses is of vital importance.

Tissue sparing surgery in cases of ovarian endometriosis results in better ovarian reserve in young women who wish to preserve their fertility, indicating the critical need for proper ovarian tumor differentiation.

The usefulness of HE4 and its superiority in differentiation to CA125 has previously been reported.[24,25] Our findings are consistent with the majority of published research. HE4 achieved the maximal SPC (100%) and had the same sensitivity (82.1%) as CA125. Keeping in mind that 20% of all EOCs remain undetected, we suggest testing HE4 and CA125 levels in every premenopausal woman with an ovarian mass to ensure more precise differential diagnosis between patients with EOCs from ovarian endometriosis, especially in its advanced forms. Ultrasonography using MI as a solid diagnostic tool can drastically improve the detection of EOCs from benign ovarian masses and ensure better discriminating power for

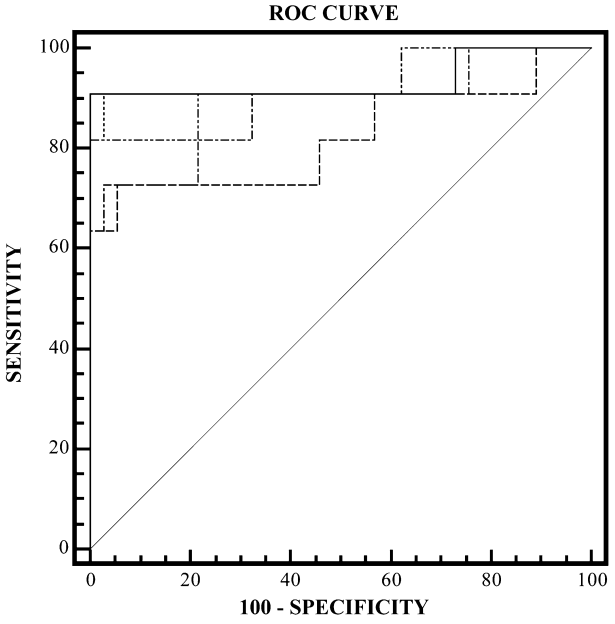

Figure 5 Receiver operating characteristic-area under the curve (ROC-AUC) curves of patients with ovarian endometriosis versus patients with epithelial ovarian cancers for: (——) human epididymis protein 4 (HE4), (– – – –) cancer antigen 125 (CA125), (·····) Risk of Malignancy Algorithm (ROMA), (–·–·–) Copenhagen Index (CPH-I) and (–··–··–) Risk of Malignancy Index (RMI) (Jacobs).

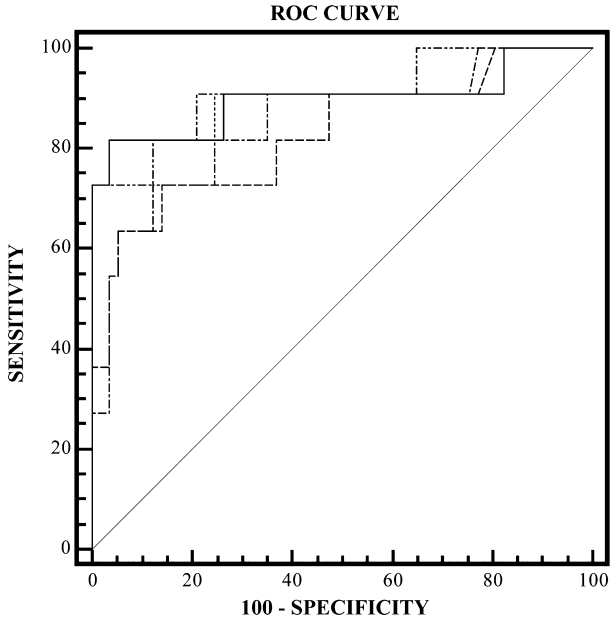

Figure 6 Receiver operating characteristic-area under the curve (ROC-AUC) of patients with other benign pelvic masses versus patients with epithelial ovarian cancers for: (——) human epididymis protein 4 (HE4), (– – – –) cancer antigen 125 (CA125), (·····) Risk of Ovarian Malignancy Algorithm (ROMA), (–·–·–) Copenhagen Index (CPH-I) and (–··–··–) Risk of Malignancy Index (RMI) (Jacobs).

the classification of ovarian tumors; however, a larger study group is needed to confirm our findings.

Conclusion

The HE4 tumor marker is of crucial importance in the differentiation of ovarian endometriosis from ovarian cancer. Although a subjective method, MI is the most sensitive for the evaluation of premenopausal women with a pelvic mass.

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Disclosure

The authors report no conflict of interest.

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