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ORIGINAL ARTICLE

Comparison between Serum HE4 and CA125 as Tumor Markers in Premenopausal Women with Benign Pelvic Mass

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SUMMARY

Background: **The aim of the study was to evaluate the role of human epididymal secretory protein (HE4), cancer antigen 125 (CA125), and the Risk of Ovarian Malignancy Algorithm (ROMA) in diagnosing benign pelvic masses in premenopausal women.**
Methods: **Serum was collected from 391 premenopausal women with benign pelvic mass prior to surgery and from 45 healthy individuals. Serum HE4 and CA125 levels and ROMA scores were evaluated separately.**
Results: **Among the 391 women with benign pelvic mass, 2.3% (9/391) had elevated HE4 levels (> 70 pmol/L), while 37.1% (145/391) had elevated CA125 levels (> 35 U/mL) (p < 0001). Endometriosis provided false-positive results for CA125 levels in more than half of the cases but resulted in no significant change for HE4 level. In 13 gravid women with a mass, 30.8% (4/13) and 38.5% (5/13) had elevated HE4 and CA125 levels, respectively; however, the difference was not significant (p > 0.05). Moreover, serum levels and patient percentages for CA125 elevation significantly increased with increase in mass diameter, whereas those for HE4 did not.**
Conclusions: **CA125 elevation showed random results for benign pelvic masses, while HE4 elevation showed a higher specificity. Thus, serum HE4 testing is a better approach than CA125 testing for diagnosing benign pelvic masses in premenopausal women.**
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human epididymal secretory protein 4, cancer antigen 125, Risk of Ovarian Malignancy Algorithm (ROMA), benign pelvic mass

INTRODUCTION

Ovarian cancer has been the leading cause of death among gynecologic malignancies. Due to the lack of a diagnostic tool for early detection of ovarian cancer, most patients remain undiagnosed until an advanced stage of the disease. The 5-year survival rate is > 70% in stage I disease, but dramatically decreases to 0% - 20% in stage III or IV [1,2]. Therefore, accurately discriminating ovarian cancer from benign pelvic mass is crucial for determining the appropriate therapeutic regimen and evaluating prognosis.

Tumor markers are widely used to help distinguish malignant ovarian tumors from benign pelvic masses. Serum cancer antigen 125 (CA125) is the most widely accepted tumor marker to discriminate ovarian cancer from benign neoplasm in patients with pelvic masses [3]; however, it is also present in some benign gynecologic disorders such as endometriosis, pelvic inflammatory disease (PID), and benign neoplasms of the ovaries and uterus, which significantly decreases its specificity. Therefore, many studies are dedicated to finding new markers for early detection and differential diagnosis of ovarian cancer. Experimental studies have shown that HE4 shows a specific increase in the distinction between ovarian cancer and benign ovarian tumors compared to CA125 [4,5]. Human epididymal secretory protein E4 (HE4) has a higher sensitivity and specificity as a separate marker or in combination with CA125 compared to various serum biomarkers for detecting epithelial ovarian cancer, especially in the early stages of disease [4,6].

The Risk Algorithm for Ovarian Malignancy (ROMA) uses both serum HE4 and CA125 levels during menopause to estimate the malignant probability of ovarian cysts or pelvic masses [3,7]. In current clinical practice, CA125 and HE4 combined with pelvic ultrasound are widely used for improving the diagnostic sensitivity for ovarian carcinoma in patients with pelvic mass [2,8]. Although HE4 has been shown to be a sensitive biomarker for epithelial ovarian cancer, specificity is higher than CA125 and there is very limited research regarding HE4 expression in benign gynecologic tumors and diseases. So far, there is limited research on assessing the diagnostic performance of serum HE4 levels in healthy premenopausal and postmenopausal women with benign gynecologic diseases.

This study aimed to evaluate and compare the role of HE4, CA125, and ROMA in the differential diagnosis of benign pelvic masses in premenopausal women.

MATERIALS AND METHODS

Study population

All patients who presented with a pelvic mass and underwent surgery at Xiamen Maternity and Child Care Hospital from February 2015 to March 2016 were enrolled in the study. Nine postmenopausal women and 22 subjects diagnosed with malignant gynecologic diseases by histopathological results were excluded. The medical records of the remaining 391 patients were retrospectively reviewed for diagnostic information, mass diameter, and histopathological results. The women were stratified by age, benign disease classification, and cyst diameter through ultrasound. Diagnosis was made by interpreting imaging results, including gynecologic sonography and abdomen-pelvis computerized tomography, and available surgical biopsy results. All surgical tissues were examined by specialized gynecologic pathologists.

Forty-five healthy premenopausal women served as the control group of this study. All women provided written informed consent, including self-descriptions regarding their medical status. The study was approved by the ethics committee of Xiamen Maternity and Child Care Hospital.

Serum analysis

All serum samples from patients were collected preoperatively from patients with an ovarian cyst or pelvic mass. Blood samples were collected into non-heparinized tubes and kept for 30 minutes at room temperature before centrifugation for 10 minutes at 3,000 rpm. Serum HE4 and CA125 levels were measured on an ARCHITECT *i*2000 assay platform (Abbott, Abbott Park, IL, USA) according to manufacturer instructions. Normal levels were set to < 35 U/mL for CA125 and < 70 pmol/L for HE4. Serum HE4 levels in premenopausal women with benign gynecological pelvic mass were compared with CA125 levels in the same samples. To assess the diagnostic value of HE4 and CA125 in combination, the final ROMA score was calculated using the following equations: [9]

Premenopausal women:

Predictive index

(PI) = -12.0 + [2.38 x ln(HE4)] + [0.0626 x ln(CA125)]

Postmenopausal women:

PI = -8.09 + [1.04 x ln(HE4)] + [0.732 x ln(CA125)]

Risk of malignancy = exp(PI)/[1 + exp(PI)] x 100

The cutoff values for premenopausal women were set at 7.4%.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (IBM-SPSS, version 22.0). The Kolmogorov-Smirnov test was used to define distributions of marker levels in the healthy population and the group with benign pelvic disease. Data were presented as means, medians ± standard error, and ranges. Tumor marker concentrations between the study groups were compared

Table 1. Characteristics of healthy women and patients with benign pelvic mass.

Patients	Age in years: median ± SE (range)	Diagnosis	n (%)	Mass diameter (n) [a]		
				< 3 cm	3 - 5 cm	> 5 cm
Healthy women	32.0 ± 6.9 (25.0 - 50.0)			45		
Women with benign pelvic mass	31.0 ± 7.9 [b] (14.0 - 55.0)		391 (100)	52 (13.9)	114 (30.4)	209 (55.7)
		Endometriosis/endometrioma	134 (34.3)	13 (10)	39 (30)	78 (60)
		Mature teratoma	100 (25.6)	14 (14.6)	33 (34.4)	49 (51)
		Serous cystadenoma	18 (4.6)	1 (5.6)	9 (50)	8 (44.4)
		Mucinous cystadenoma	22 (5.6)	2 (9.1)	3 (13.6)	17 (77.3)
		PID/hydrosalpinx	23 (5.9)	4 (18.2)	6 (27.3)	12 (54.5)
		Leiomyoma	21 (5.4)	6 (28.6)	6 (28.6)	9 (42.8)
		Pregnant with mass	13 (3.3)	3 (30.0)	2 (20.0)	5 (50.0)
		Other benign mass [c]	60 (15.3)	9 (16.1)	16 (28.6)	31 (55.3)

[a] 16 cases had no data on mass diameter.
[b] The ages of the patients were compared to those of the healthy subjects (p = 0.056).
[c] Includes 3 granulosa cell tumors of the ovary, 1 thecoma, 1 fibrothecoma, 16 parovarian cysts, and 30 simple cysts.
SE - standard error, PID - pelvic inflammatory disease.

Table 2. Serum HE4 and CA125 levels and ROMA scores in each subgroup.

	n	HE4 (pmol/L)			p	CA125 (U/mL)			p	ROMA	p
		Mean	Median ± SE	Range		Mean	Median ± SE	Range		Median ± SE	
Age group					0.507				0.024		0.024
< 30 years	159	37.6	36.7 ± 0.7	23.1 - 80.7		40.8	21.9 ± 4.1	6.8 - 356.5		3.8 ± 0.2	
30 - 39 years	147	39.9	37 ± 1.6	18.6 - 224.6		60.3	30.3 ± 6.4	4.9 - 446.7	0.043	4.0 ± 0.6	0.043
≥ 40 years	85	38.8	35 ± 1.6	22.5 - 117.2		55.5	18.8 ± 11.8	6.3 - 859.7		3.5 ± 0.6	
Healthy women	45	29.5	29.3 ± 1.0	17.7 - 48.5		14.9	14.1 ± 1.0	5.7 - 35.6		2.3 ± 0.2	
Benign classification	391	38.7	36.7 ± 0.7	18.6 - 224.6	0.000	51.3	23.9 ± 3.9	4.9 - 859.7	0.000	3.8 ± 0.3	0.000
Endometriosis/ endometrioma	134	38.2	37.4 ± 0.7	18.6 - 66.1	0.000	82.6	64.7 ± 6.4	8.8 - 385	0.000	4.1 ± 0.2	0.000
Mature teratoma	100	35.2	35.1 ± 0.8	21.9 - 54.7	0.000	20.1	15.3 ± 1.8	6.8 - 113	0.087	3.4 ± 0.2	0.000
Serous cystadenoma	18	47.1	39.4 ± 10.6	22.8 - 224.6	0.000	60	20.5 ± 24.9	9.2 - 446.7	0.016	4.4 ± 4.1	0.000
Mucinous cystadenoma	22	36.6	35.2 ± 1.8	27.5 - 64.6	0.002	33.2	19.5 ± 6.5	7.6 - 114.4	0.004	3.4 ± 0.6	0.002
PID/hydrosalpinx	23	36.2	36.7 ± 1.8	23.1 - 51.4	0.003	95.3	14.7 ± 42.1	4.9 - 859.7	0.521	4.2 ± 0.4	0.002
Leiomyoma	21	35.1	33.7 ± 1.3	22.5 - 44.7	0.006	24.3	16.5 ± 5.5	8.2 - 116.3	0.128	3.1 ± 0.3	0.010
Pregnant with mass	13	53.5	48.1 ± 6.9	23.4 - 103.4	0.001	35.6	30.8 ± 6.3	9.8 - 80.1	0.000	7.5 ± 2.6	0.001
Other benign mass	60	42.2	40.0 ± 2.2	24.8 - 117.2	0.000	33.3	19.1 ± 5.6	5.4 - 276.6	0.001	4.6 ± 0.9	0.000
Group by mass diameter					0.587				0.000		0.307
< 3 cm	52	36.7	36.2 ± 1.2	22.5 - 66.5		27.3	16.9 ± 3.8	5.4 - 147.2		3.6 ± 0.3	
3 - 5 cm	114	38.0	36.0 ± 1.1	22.8 - 91.6		41.5	22.3 ± 4.3	4.9 - 276.6		3.7 ± 0.4	
> 5 cm	209	39.5	36.9 ± 1.0	18.6 - 224.6		60.1	26.6 ± 6.3	7.1 - 859.7	0.000	4.0 ± 0.5	

HE4 - human epididymal secretory protein E4, CA125 - cancer antigen 125, ROMA - Risk of Ovarian Malignancy Algorithm, SE - standard error, PID - pelvic inflammatory disease.

Table 3. Percentage of patients with elevations in HE4, CA125, and ROMA values, according to histological type and diameter of mass.

	n	HE4		CA125		p	ROMA			
		n	%	n	%		n	%	p vs. HE4	p vs. CA125
Benign classification										
Endometriosis/endometrioma	134	0	0	98	72.4	0.000	17	12.7	0.000	0.000
Mature teratoma	100	0	0	8	8.0	0.000	5	5.0	0.074	0.390
Serous cystadenoma	18	1	5.6	5	27.8	0.089	3	16.7	0.603	0.691
Mucinous cystadenoma	22	0	0	8	31.8	0.004	3	13.6	0.232	0.280
PID/hydrosalpinx	23	0	0	6	26.1	0.011	2	8.7	0.470	0.240
Leiomyoma	21	0	0	3	14.3	0.232	0	0		0.232
Pregnant with mass	13	4	30.8	5	38.5	1.00	7	53.8	0.428	0.695
Other benign mass	60	4	6.7	12	20	0.03	11	18.3	0.053	0.817
Total	391	9	2.3	145	37.1	0.000	48	12.3	0.000	0.000
Group by mass diameter										
< 3 cm	52	0	0	10	19.2	0.001	4	7.7	0.126	0.085
3 - 5cm	114	3	2.6	37	32.5	0.000	10	8.8	0.046	0.000
> 5 cm	209	5	2.4	89	42.6	0.000	30	14.4	0.000	0.000

HE4 > 70 pmol/L, CA125 > 35 U/mL, ROMA ≥ 7.4.
HE4 - human epididymal secretory protein E4, CA125 - cancer antigen 125, ROMA - Risk of Ovarian Malignancy Algorithm, PID - pelvic inflammatory disease.

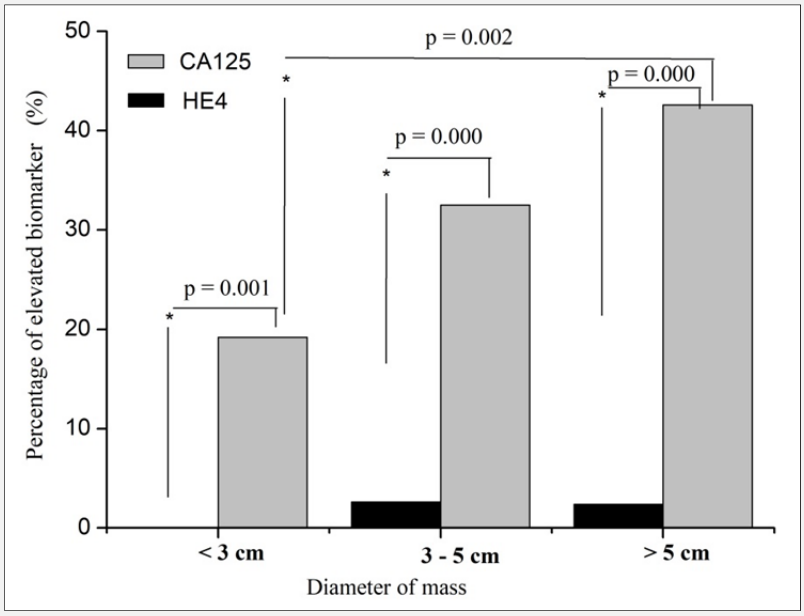

Figure 1. Percentage of patients with elevated HE4 and CA125 levels by mass diameter.

CA125 - cancer antigen 125, HE4 - human epididymal secretory protein E4.

using the Kruskal-Wallis and Mann-Whitney *U* tests. The p-values for comparing patient percentages with elevations in HE4 vs. CA125 vs. ROMA in the different patient stratifications were determined using Pearson's Chi-squared test. p-values < 0.05 were considered statistically significant throughout all analyses.

RESULTS

Characteristics of study groups

A total of 436 patients (45 healthy subjects and 391 women with benign gynecologic pelvic mass) were enrolled. Age was not significantly different between both groups ($p > 0.05$). The cases were categorized into eight groups based on histopathological results. All 375 cases were grouped into three according to mass diameter (16 cases had no data on mass diameter). The distribution of cases according to benign conditions is summarized in Table 1. Endometriosis/endometrioma, present in 34.3% (134/391) of women with benign pelvic disease, was found to be the most common pelvic mass, followed by mature teratoma at 25.6% (100/391). Patients with a mass diameter of > 5 cm accounted for 55.7% of the group with benign pelvic disease.

Serum HE4 and CA125 levels and ROMA scores

The serum HE4 and CA125 concentrations and ROMA scores of each group are presented in Table 2. The median serum HE4 and CA125 levels increased consistently in women aged < 40 years. Interestingly, lower HE4 and CA125 serum concentrations were found in women aged ≥ 40 years. Serum HE4 levels showed no significant difference in all age groups, while serum CA125 levels showed significantly higher elevation in the group aged 30 - 39 years than in the group aged < 30 years ($p = 0.043$).

The median ROMA score and HE4 and CA125 levels of the healthy subjects were 2.3, 29.3 pmol/L, and 14.1 U/mL, respectively, and those of patients with benign pelvic mass were 3.8, 36.7 pmol/L, and 23.9 U/mL. The levels of HE4 and CA125 in patients with pelvic mass were higher than those of the healthy group. Comparison of serum HE4 and CA125 levels for subcategories revealed an elevation in both HE4 and CA125 levels. Moreover, significant differences were observed with HE4 levels ($p < 0.01$); significant differences were also observed with CA125 levels ($p < 0.02$), except for mature teratoma, PID/hydrosalpinx, and leiomyoma ($p > 0.05$).

Regarding mass diameter, comparison of the median values between ROMA, HE4, and CA125 showed that the median values increased consistently with an increase in mass diameter. However, no significant differences were observed between HE4 and ROMA.

Percentage of elevated biomarker levels in all subclassifications of benign pelvic disorders

We set 35 U/mL and 70 pmol/L as the upper normal limits for CA125 and HE4, respectively. The ROMA score was calculated according to the formulae described previously. We considered ≥ 7.4 as a positive PI score (risk of malignancy) for premenopausal women. Among 391 women with benign pelvic mass, serum HE4 levels (2.3%, 9/391) showed less frequent elevations in benign disease than did CA125 levels (37.1%, 145/391) ($p < 0001$). Examination of all subclassifications of benign pelvic disorders revealed a significant difference between the proportions of patients with elevated CA125 and HE4 levels, except for serous cystadenoma, leiomyoma, and pregnant women with a mass. Additionally, for CA125, the most common cause of elevated levels was endometriosis, accounting for 72.4% (98/134) of cases; however, only 12.7% of the 134 patients with endometriosis showed a risk of malignancy based on the ROMA score, and none of them had elevated HE4 levels (Table 3).

Figure 1 illustrates the percentage of elevated biomarker levels by mass diameter. Compared with CA125, HE4 was less often elevated in patients in all groups, and a significant difference was observed in the different subgroups. A linear increase in CA125 occurred in the three groups by mass diameter, and the population with > 5 cm (42.6%) was significantly higher than with < 3 cm (19.2%).

DISCUSSION

Previous studies have suggested the use of serum CA125 level in association with ultrasonography were helpful for early diagnosis of ovarian cancer in asymptomatic women [2,8-14]. While CA125 measurement is a useful tumor marker in the diagnosis of a woman with pelvic masses, its utility is limited by lack of specificity. Increased values of CA125 were seen in ovarian cancer as well as several benign and malignant diseases [15, 16]. This lack of specificity has particular implications in some benign gynecological diseases such as endometriosis and pelvic inflammatory diseases which we could often observe in premenopausal women.

The WAP four-disulfide core domain 2 (WFDC2) gene that encodes the HE4 protein usually over expresses in ovarian cancers [17]. The HE4 gene product is N-glycosylated and secreted into the extracellular environment, which can be detected in the bloodstream of patients with ovarian carcinoma via an enzyme immunoassay [18,19]. Published results of studies on serum HE4 and CA125 indicate that the diagnostic sensitivity and specificity of HE4 in gynecological diseases are better than those of CA125 and that both tumor markers are complementary [3,4,9,20-23].

Benign ovarian neoplasms can lead to elevated serum CA125 levels in > 20% of patients [24], which is consistent with the results of our study. We found that only

2.3% of premenopausal women had elevated serum HE4 levels, while 37.1% had elevated CA125 levels. Our results are also consistent with the findings of Moore et al. [15]. In their study, 29% of patients had elevated CA125 levels in contrast to 8% having elevated HE4 levels. A slight difference in the results between the studies could be due to different sample volumes and histologic types in each study.

Endometriosis is a well-known gynecological disease that causes elevations in serum CA125. One previous study evaluated HE4 levels in 129 women with endometriosis. Huhtinen et al. [23] demonstrated that HE4 level did not increase in any stage of endometriosis, with a median serum concentration of 43.5 pM (range, 15 - 111 pM), well within the normal reference limit for HE4. Similarly, in a retrospective review of 182 women who underwent laparotomy for adnexal mass, Holcomb et al. reported that 85% of benign pelvic masses in women aged ≤ 50 years were associated with a serum CA125 level of > 35 U/mL [25]. In comparison, in this study, we found that although CA125 showed greater sensitivity for malignancy, it was still elevated in 72.4% of premenopausal women with benign mass. In contrast, serum HE4 levels showed almost no elevation in all patients with endometriosis. These studies have led researchers to question the relevance of CA125 in the preoperative evaluation of premenopausal women with pelvic mass.

Besides endometriosis, two common pelvic masses found in both premenopausal and postmenopausal women are serous cystadenoma and cystadenofibroma. These neoplasms typically present as cystic and solid ovarian masses that are difficult to distinguish from ovarian malignancies using standard imaging techniques. Results in our study indicated that the three most common diseases were endometriosis, mature teratomas, and PID in premenopausal women, which is in agreement with studies by Zheng [16]. Meanwhile, their studies also demonstrated that the most common diseases during the postmenopausal period were mucinous cystadenomas and fibromas. Only a very small number of patients had elevated HE4 levels compared with patients with elevated levels of CA125 (5.6% vs. 27.8% for serous cystadenoma and 0% vs. 31.8% for mucinous cystadenoma) in our study. However, in serous tumors, both HE4 and CA125 levels increased, with no significant difference in the proportion of patients with elevated levels. Other subgroups such as PID, mature teratoma, and leiomyoma also showed a lower proportion of cases with elevated HE4 levels than with elevated CA125 levels. Significant differences between the HE4 and CA125 groups were observed, except for the leiomyoma groups.

CA125 can be elevated in a third of cases of cervical or endometrial cancer, in a quarter of cases of pregnancy, and in a third of cases of PID [26]. Sarandakou et al. reported that maternal serum CA125 levels increased to > 35 U/mL only in 10% of pregnant women [27]; likewise, Yong et al. [28] reported that a CA125 concentration in pregnant women was 55.3% higher than in the healthy population. These variations in CA125 elevation limit the application of CA125 in diagnosing pelvic masses in gravid women. A recent study by Moore et al. [29] demonstrated that HE4 showed no elevation in gravid women and even showed a decrease during pregnancy, suggesting its potential role as a more accurate tool for distinguishing pregnant women with an ovarian cyst or mass. Notably, in our study, analysis of gravid women with mass revealed elevated HE4 and CA125 levels in 30.8% and 38.5% of cases, respectively, although the difference was not significant. Our findings further confirm the performance of HE4 as a more powerful biomarker than CA125 for the differential diagnosis between gravid women with mass and those without mass. However, the number of cases of gravid women with mass was limited in this study; thus, a larger sample cohort is required to investigate whether HE4 should be preferentially considered for the differential diagnosis of mass in pregnant women. Further studies about the relationship between HE4 concentration and pelvic masses in pregnant women are also highly needed.

In terms of mass diameter, we found that > 60% of benign pelvic masses measured > 5 cm in diameter. Interestingly, the serum concentration and the proportion of patients for CA125 elevation significantly increased with an increase in mass diameter, whereas those for HE4 elevation did not. To our knowledge, there has been no research on the relationship between HE4 and CA125 expression patterns and different diameters of masses. Elevations of CA125 levels in these cases might due to the expression of the protein.

Thus, a differential diagnosis between patients with ovarian cancer and ovarian endometriotic cysts and healthy patients can be achieved more precisely by combining HE4 and CA125 testing as well as pelvic ultrasonography. This may also help clinicians in the follow-up of patients with advanced endometriosis, when considering the possibility of malignant transformation of the lesions. In patients with an ultrasound-detected pelvic mass and elevation in both HE4 and CA125 levels, the diameter of the tumor was < 5 cm, suggesting a greater likelihood of ovarian cancer; whereas if HE4 is not elevated and only CA125 is elevated, and if the mass diameter is < 5 cm, it indicates advanced or ovarian endometrioma. However, if the mass diameter is > 5 cm, other benign conditions are more likely. In addition, elevated serum HE4 levels but normal CA125 concentrations may indicate the presence of ovarian or other types of cancer, such as endometrial cancer [23]. Although the present study is promising for the early differential diagnosis of benign pelvic masses, there are certain limitations. Our study lacks follow-up and has a small amount of data. Thus, large-scale and multicenter studies are required to overcome these limitations.

Previous studies developed ROMA to estimate the probability of a pelvic mass based on both tumor markers and menopausal status. This method represents

greater sensitivity and specificity than each individual tumor marker in terms of malignancy evaluation. In addition, it is important to mention that in our findings, a ROMA score led to more false-positive results in premenopausal women than HE4 alone. This suggests that in young patients, it is better to only test HE4 and not CA125. HE4 alone is effective for making a diagnosis of a benign pelvic mass. These results agree with those published by Rafael et al. [30], suggesting that the false-positive results associated with CA125 decrease the positive predictive value of ROMA, especially in premenopausal women.

CONCLUSION

In summary, the investigation presented above demonstrated that as a tumor marker for detecting pelvic masses, HE4 shows diagnostic performances comparable to CA125. HE4 provided a more effective specificity and less false-positive results. HE4 alone also performed slightly better than ROMA in detecting benign pelvic masses. Thus, indistinguishing premenopausal women with benign pelvic mass, HE4 performed better than CA125.

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Declaration of Interest:
The authors declare that there is no conflict of interest.

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