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Original Article

Significance of adding progesterone to the Risk of Ovarian Malignancy Algorithm for early stage ovarian cancer detection in patients with a pelvic mass: A single-center case–control study

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ABSTRACT

Objective: To evaluate the clinical significance of the combination of cancer antigen-125 (CA-125), human epididymis protein 4 (HE4), and progesterone for the identification of ovarian masses in patients with suspected early stage ovarian cancer (OC).

Materials and methods: This was a case–control, single-center study of 225 women with a pelvic mass of suspected ovarian origin, including 75 patients with Stage I/II OC and 150 controls. Diagnostic procedures included pelvic and rectal examinations, transvaginal ultrasound, evaluation of CA-125 and HE4 levels alone and in the Risk of Ovarian Malignancy Algorithm (ROMA), and a new algorithm combining ROMA and progesterone.

Results: Median CA-125 and HE4 levels were significantly higher in patients with OC compared with women with benign ovarian tumors, irrespective of menopausal status. The highest median progesterone levels occurred in premenopausal women with benign ovarian tumors, compared with premenopausal women with OC with or without benign ovarian disease. The combination of ROMA and progesterone was significantly more accurate at detecting OC compared with ROMA or CA-125 or HE4 alone, but only in premenopausal patients.

Conclusion: Different algorithms should be used for diagnosing OC, and the addition of progesterone might improve the performance of ROMA for the diagnosis of pelvic masses in premenopausal women.

Introduction

Ovarian masses are regularly detected in many women who then undergo evaluations to determine if these masses are malignant. Imaging techniques and laboratory tests can help primary-care physicians and gynecologists to determine the likelihood of cancer and to decide if the patient should be referred to a gynecologic oncologist. Women with ovarian cancer (OC) who are treated by a gynecologic oncologist tend to have better outcomes than those treated by general gynecologists or surgeons [1].

Transvaginal sonography is currently the most widely used diagnostic tool for detecting and differentiating ovarian masses [2,3]. Computed tomography (CT), magnetic resonance imaging, and positron emission tomography can all be used in the determination and diagnosis of an ovarian mass, and all play pivotal roles in the staging, treatment selection, and follow-up of patients with OC [4,5].

In addition to imaging techniques, laboratory tests are also used extensively in the differential diagnosis and therapy follow-up of patients with OC. The first approved OC marker was the cancer antigen-125 (CA-125), which is elevated in approximately 80% of patients with OC. CA-125 has a sensitivity of 50% in women with Stage I disease and up to 90% in patients with more advanced-stage disease [6,7]. This biomarker is particularly accurate among postmenopausal women, in whom the positive predictive value (PPV) reaches 98%, compared with only 49% in premenopausal patients [8]. However, CA-125 is nonspecific and can be elevated under many other conditions, including benign gynecologic etiologies, nongynecologic diseases, and other malignancies, such as breast or endometrial cancers [9,10].

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The novel tumor marker human epididymis protein 4 (HE4) was recently shown to be a complementary marker to CA-125 for differentiating between benign and malignant diseases in women with an ovarian tumor or pelvic mass [11–13]. HE4 is an 11-kDa protein that is a precursor to the epididymal secretory protein E4, and is overexpressed in OC. Using both CA-125 and HE4 according to the Risk of Ovarian Malignancy Algorithm (ROMA) increased sensitivity and specificity compared with either marker alone [14–16]. At a specificity of 75%, the ROMA cutoff value showed sensitivities of 77–81% for premenopausal women and 90–92% for postmenopausal women [16–20].

However, a panel of complementary biomarkers able to detect early stage OC with satisfactory sensitivity and specificity is still required. Early stage OC can be treated effectively by primary surgery followed by chemotherapy, attaining an 80–90% survival rate, whereas women with advanced disease have much poorer prognoses [21]. Novel biomarkers enabling early stage OC diagnosis will thus markedly improve the clinical treatment of OC.

Evidence suggests that ovarian carcinogenesis is affected by steroid hormones, primarily estrogens, and progesterone. Recent data have indicated that estrogens favor neoplastic transformation within the surface epithelium of the ovary, whereas high progesterone levels seem to protect against the development of OC [22,23].

We therefore determined whether progesterone could act as a subsidiary marker to improve the diagnosis of early stage OC. In this study, we evaluated the clinical significance of ROMA combined with progesterone levels for use as a diagnostic tool to differentiate ovarian masses.

Materials and methods

This single-center case–control study was approved by the Institutional Review Board of Jagiellonian University, Krakow, Poland. All patients provided written informed consent.

Patient population

The primary group comprised 1358 patients diagnosed with a pelvic mass of suspected ovarian origin at the Gynecology and Oncology Department between 2008 and 2012, and who were scheduled for surgical intervention. Exclusion criteria were as follows: (1) OC Stage III/IV, (2) age < 18 years, (3) prior bilateral oophorectomy, (4) pregnancy, (5) history of infertility, (6) chronic liver or (7) renal insufficiency, (8) pulmonary cystic fibrosis or tuberculosis, and (9) hormone treatment. Borderline ovarian tumors were considered cancers according to the International Federation of Gynecology and Obstetrics ovarian tumor classification [24]. Menopause was defined clinically as a lack of menstruation for 12 months or more. Every patient with early stage OC was matched for age, age at menarche, parity, and menopausal status with two control patients diagnosed with benign ovarian masses, identified from among the primary group of patients (Figure 1). Participant allocation was carried out using a computer-generated list of random numbers to select control cases from each group of eligible patients using a block size sequence. After applying the exclusion criteria and randomization, 255 patients were selected for the final analysis.

Diagnostic procedures

After recording their medical histories, all patients underwent bimanual pelvic examination, rectal examination by a gynecologic oncology consultant, and ultrasound imaging to document the presence of an ovarian mass. Ultrasonography was performed using a Voluson 730 Pro equipped with a 6.5-MHz transvaginal probe (General Electric Medical Systems, Kretztechnik, Zipf, Austria). For large tumors, a transabdominal scan was also performed using a 2–5-MHz (transabdominal) transducer (General Electric Medical Systems). Chest X-ray and pelvoabdominal CT scan were performed in selected cases as a part of the preoperative work-up.

Blood analysis

Venous blood samples were analyzed to determine CA-125, HE4, and progesterone levels. Blood samples were centrifuged within 4 hours of collection; serum and plasma were collected and dispensed into multiple 5 cm^3 CryoTubes (Sigma-Aldrich Sp. z.o.o. Poznan, Poland), and all samples were frozen to −80°C. The blood samples were only analyzed if the patient ultimately entered the study. Serum CA-125 concentrations were measured using the Architect CA 125II assay (Abbott Diagnostics, Wiesbaden, Germany) and were expressed as units/milliliter (reference range < 35.0 U/mL). Serum HE4 levels were determined using the Architect HE4 assay (Abbott Diagnostics) and were expressed as picomole/liter (reference range < 90.0 pmol/L). Serum progesterone concentrations in premenopausal patients were determined during the secretory phase of the menstrual cycle (because of irregular periods in some patients, progesterone samples were taken at least 20 days from the last menstrual bleeding) using the AxSYM Progesterone Assay (Abbott Diagnostics) based on microparticle enzyme immunoassay technology, and reported in nanogram/milliliter. In postmenopausal patients, progesterone levels were checked in the same blood sample collected for evaluating CA-125 and HE4 levels. The reference level of serum progesterone in the secretory phase of the menstrual cycle was 5.5–38.0 ng/mL, and the postmenopausal reference range was 0.5–1.0 ng/mL, according to the manufacturer's guidelines. The median time between blood sampling for CA125, HE4, and progesterone and surgery was 17.5 days [interquartile range (IQR) 6.0 days].

ROMA

ROMA is used to assess the risk of epithelial OC in patients with an adnexal mass scheduled for surgical intervention. ROMA classifies patients into low- and high-risk groups for malignant disease using algorithms, as described previously [15,16].

ROMA plus progesterone

We also assessed the risk of OC based on ROMA plus progesterone level. The progesterone concentration was coded as a dichotomous value (i.e., within vs. below normal range). If ROMA indicated a low risk of OC, the patient was described as a low-risk case regardless of the progesterone level. If ROMA indicated a high risk of OC but the progesterone level was within the normal range (premenopausal, 5.5–38.0 ng/mL; postmenopausal, 0.5–1.0 ng/mL), then this case was also coded as having low risk. However, if ROMA indicated a high risk of OC and the progesterone level was below the normal range (i.e., <5.5 ng/mL for premenopausal or <0.5 ng/mL for postmenopausal women), the patient was described as a high-risk case.

Surgical treatment

All patients underwent routine surgical treatment, including laparoscopic ovarian cyst enucleation and laparoscopic unilateral adnexectomy or abdominal hysterectomy with bilateral adnexectomy. In all 75 cases of OC, abdominal hysterectomy with bilateral adnexectomy was followed by a full staging procedure [1,25].

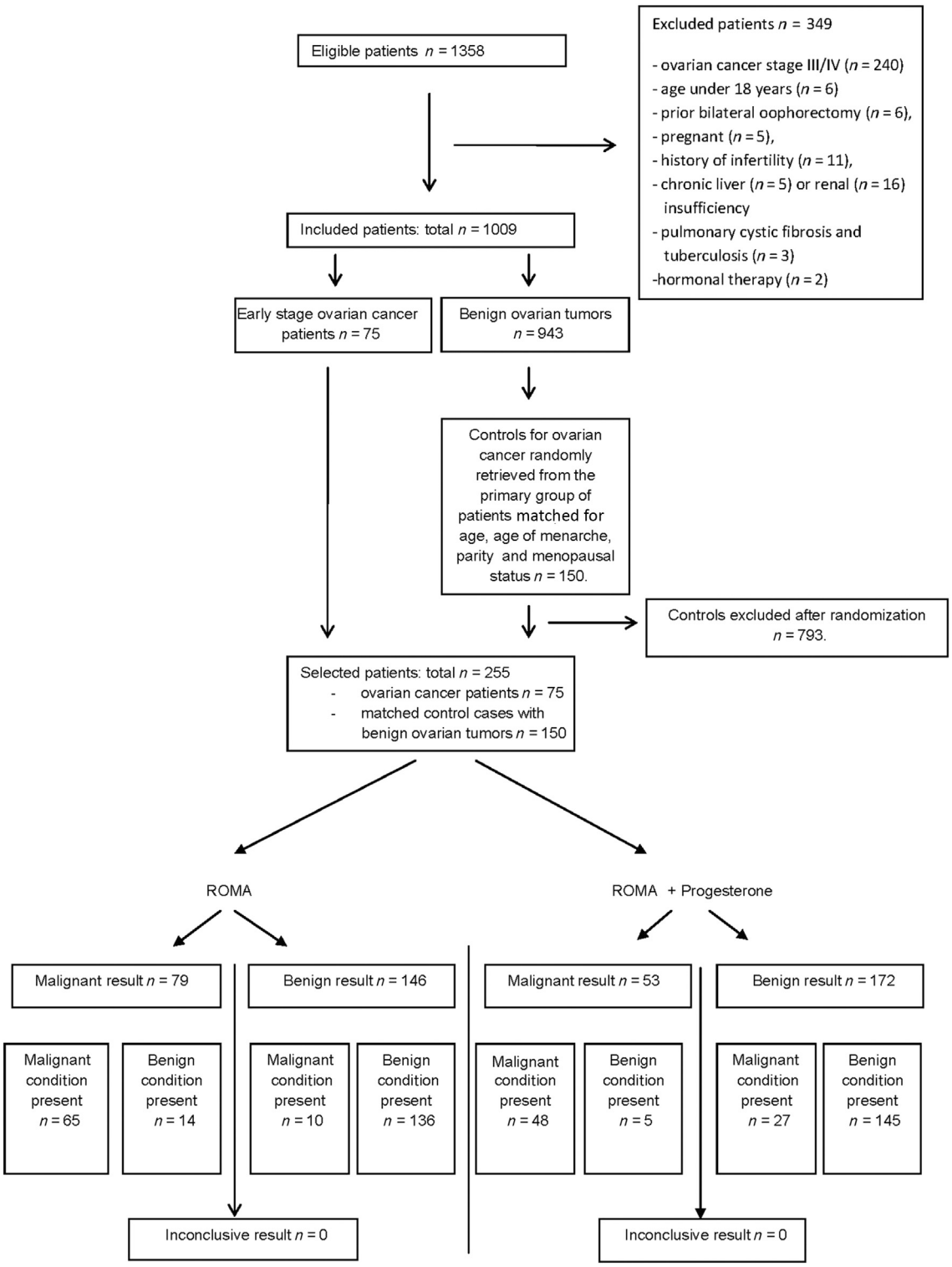

Figure 1. Flow diagram demonstrating the patient-recruitment procedure. ROMA = Risk of Ovarian Malignancy Algorithm.

Histopathological examination

All specimens were examined by hematoxylin–eosin staining and immunohistochemistry, if required. The postoperative diagnosis was based on the final histopathological report. In selected cases, an intraoperative histopathological examination was performed at the surgeon's discretion by a clinical pathology consultant, based on provided frozen sections. However, these results were for clinical use only and were not analyzed further.

Statistical analysis

Distributions of clinical variables were analyzed using Student *t* test or the Mann–Whitney *U* test and the results are presented as

mean ± standard deviation, or median values with the IQR. Differences in median levels of markers among more than two groups were evaluated using Kruskal–Wallis analysis of variance. Fisher exact test (with Yates correction) was used to compare coded clinical data. Diagnostic accuracy, test sensitivity, specificity, PPVs, and negative predictive values (NPVs) were estimated for the entire group of patients and separately for premenopausal and postmenopausal women. A p value of 0.05 or less was deemed to be statistically significant. All calculations were performed using STATISTICA data analysis software, version 9.0 (StatSoft, Tulsa, OK, USA).

Results

The study enrolled 225 patients with adnexal masses, including 162 (72%) postmenopausal and 63 (28%) premenopausal women. Overall, 150 patients (66.67%) had benign ovarian neoplasms and 75 (33.33%) had OC, including 58 Stage I_A–I_C and 17 Stage II_A cases.

Because the OC cases and controls were matched, median age, median age at first period, parity, and menopausal status did not differ significantly between women with benign tumors and those with malignant tumors. The mean age of the patients with OC was 54.8 ± 10.71 years, mean age at first period was 11.6 ± 2.1 years, median age at last period was 52.3 ± 4.8 years, and median parity was 1.0 (IQR 1.5). The respective values in the control group were 55.4 ± 10.9 years, 12.2 ± 2.8 years, 51.5 ± 5.8 years, and 1.5 (IQR 2.0).

The most common benign neoplasm was endometrial cyst, and the predominant diagnosis in patients with malignant disease was serous cystadenocarcinoma (Table 1).

The levels of tumor markers differed significantly between women with benign masses and those diagnosed with OC, in both overall study group and premenopausal and postmenopausal women separately. The median CA-125 concentration was significantly higher in women with OC than in women with benign ovarian tumors [145.7 U/mL (IQR 283.30 U/mL) vs. 13.00 U/mL (IQR 27.00 U/mL), respectively; $p < 0.001$]. The median HE4 level was also significantly higher in patients with OC than in those with benign ovarian masses [123.50 pg/mL (IQR 283.30 pg/mL) vs. 42.10 pg/mL (IQR 19.80 pg/mL), respectively; $p < 0.001$]. By contrast, patients with OC had significantly lower median progesterone levels compared with those with benign ovarian tumors [0.35 ng/mL (IQR 0.68 ng/mL) vs. 0.47 ng/mL (IQR 0.68 ng/mL), respectively; $p < 0.013$].

CA-125, HE4, and progesterone concentrations were further analyzed after stratifying the patients with OC and benign ovarian disease according to menopausal status. The highest median CA-125 concentrations were observed in premenopausal and postmenopausal women with OC [280.30 U/mL (IQR 359.40 U/mL) and 117.75 U/mL (IQR 510.80 U/mL), respectively] compared with premenopausal women with benign ovarian tumors [19.95 U/mL (IQR 39.00 U/mL)] and postmenopausal women with benign ovarian masses, who had the lowest median CA-125 values [12.80 U/mL (IQR 12.70 U/mL)] ($p < 0.001$) (Figure 2).

The highest median HE4 levels were confirmed in postmenopausal patients with OC [145.85 pg/mL (IQR 311.00 pg/mL)], followed by premenopausal women with OC [119.20 pg/mL (IQR 42.50 pg/mL)], postmenopausal women with benign ovarian disease [43.70 pg/mL (IQR 19.80 pg/mL)], and premenopausal patients with benign ovarian disease [37.20 pg/mL (IQR 13.00 pg/mL] ($p < 0.001$) (Figure 3).

By contrast, the median progesterone level was significantly higher in premenopausal women with benign ovarian tumors [10.22 ng/mL (IQR 9.37 ng/mL)] compared with premenopausal patients with OC [0.68 ng/mL (IQR 0.83 ng/mL)], postmenopausal women with OC [0.35 ng/mL (IQR 0.65 ng/mL)], and postmenopausal patients with benign ovarian tumors [0.44 ng/mL (IQR 0.55 ng/mL)] ($p < 00.1$) (Figure 4).

The ROMA uses both CA-125 and HE4 levels to calculate the risk of OC. In this study, we determined whether adding the progesterone level to ROMA would improve the final diagnostic accuracy. In the overall study group, ROMA + progesterone showed significantly lower sensitivity (0.640 vs. 0.867) and NPV (0.843 vs. 0.932) compared with ROMA alone, but slightly better specificity (0.967 vs. 0.907) and PPV (0.906 vs. 0.823). However, ROMA + progesterone significantly outperformed ROMA alone in premenopausal women, showing higher specificity (0.976 vs. 0.769) and NPV (0.976 vs. 0.973), and comparable sensitivity and PPV (0.952 vs. 0.985 and 0.976 vs. 0.973, respectively). In postmenopausal women, ROMA alone was significantly better than the combined method (ROMA + progesterone vs. ROMA; sensitivity 0.519 vs. 0.833; specificity 0.963 vs. 0.926; PPV 0.875 vs. 0.849; NPV 0.800 vs. 0.917). ROMA + progesterone thus had only slightly higher specificity and NPV than ROMA alone, with significantly poorer sensitivity and PPV (Table 2).

Table 1
Histological classification and distribution of ovarian masses [24].

	Malignant	n	%		Benign	n	%
1	Ovarian carcinoma			1	Endometrioma	61	40.67
	Serous	31	41.34	2	Serous cystadenoma/ cystadenofibroma	29	19.34
	Endometrioid	16	21.33				
	Mucinous	12	16.00				
	Clear cell	3	4.00	3	Mucinous cystadenoma/ cystadenofibroma	15	10.00
	Undifferentiated	2	2.67				
	Carcinosarcoma	2	2.67				
	Mixed	1	1.33	4	Mature teratoma	20	13.33
2	Borderline ovarian tumors			5	Brenner tumors	2	1.33
	Serous	4	5.34	6	Functional cyst (corpus luteum, hemorrhagic cyst)	9	6.00
	Mucinous	1	1.33				
	Endometrioid	1	1.33				
3	Sex-cord stromal tumors	1	1.33	7	Fibroma/ fibrothecoma	14	9.33
4	Germ cell tumors	1	1.33				
5	Metastatic tumors	0	0				
Total		75	100	Total		150	100

Discussion

This was the first study to assess the value of including progesterone level in an algorithm for differentiating early stage OC. Our results suggest that the use of progesterone as a marker for the diagnosis of OC should be limited to women of reproductive age. There was no benefit in including progesterone for detecting OC in postmenopausal women, and its addition might even decrease the clinical value of ROMA.

An increasing number of studies had suggested that HE4 is superior to CA-125 for distinguishing between benign and malignant ovarian diseases [10,11,13,26,27]. Kondalsamy-Chennakesavan et al. [28] suggested that HE4 in combination with CA-125 and patient age improved the differential diagnosis of pelvic masses, particularly in postmenopausal women. In addition, a recent meta-analysis including patients with suspicious pelvic masses suggested that adding HE4 to the diagnostic algorithm improved the specificity and sensitivity of OC detection, particularly in postmenopausal women [29,30]. Nevertheless, more detailed studies revealed that neither CA-125 nor HE4 was a reliable biomarker for the diagnosis of borderline ovarian tumors [31].

No detailed studies have investigated the role of progesterone in detecting early stage OC. We therefore compared the diagnostic values of progesterone level with ROMA and ROMA without progesterone for differentiating early OC. OC is diagnosed

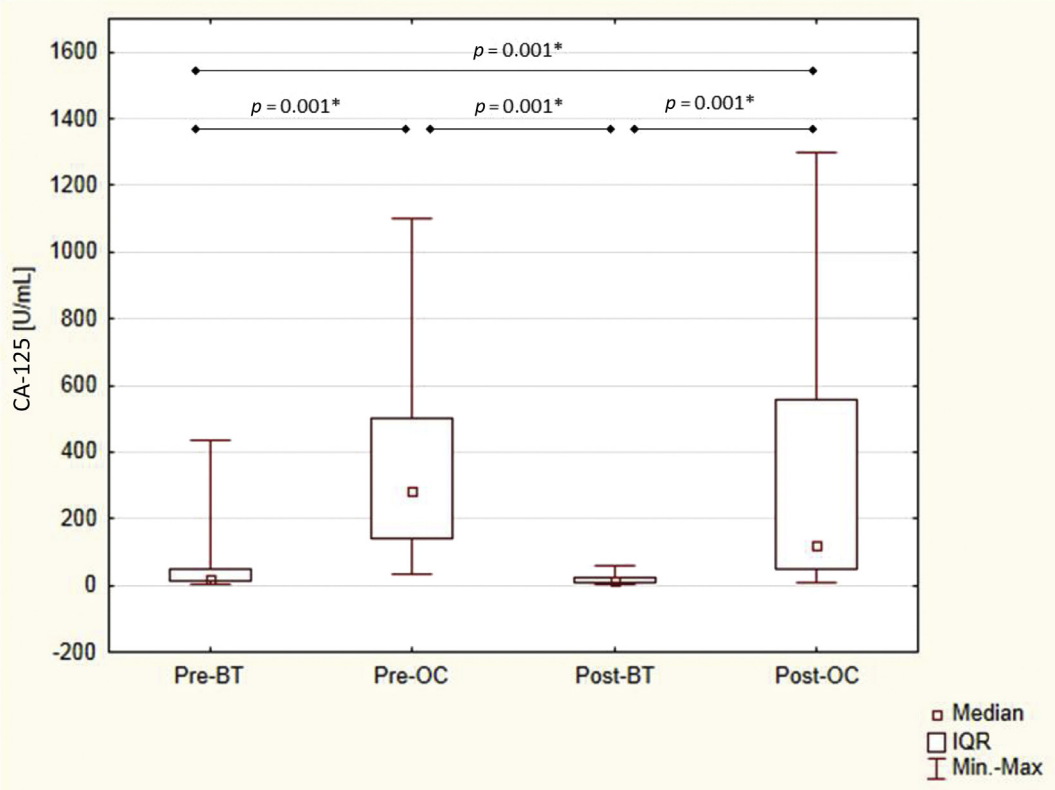

Figure 2. Median cancer antigen-125 (CA-125) concentration in the analyzed subgroup of patients according to final diagnosis and menopausal status. * Statistically significant. IQR = interquartile range; post-BT = postmenopausal with benign tumor; post-OC = postmenopausal with ovarian cancer; Pre-BT = premenopausal with benign tumor; Pre-OC = premenopausal with ovarian cancer.

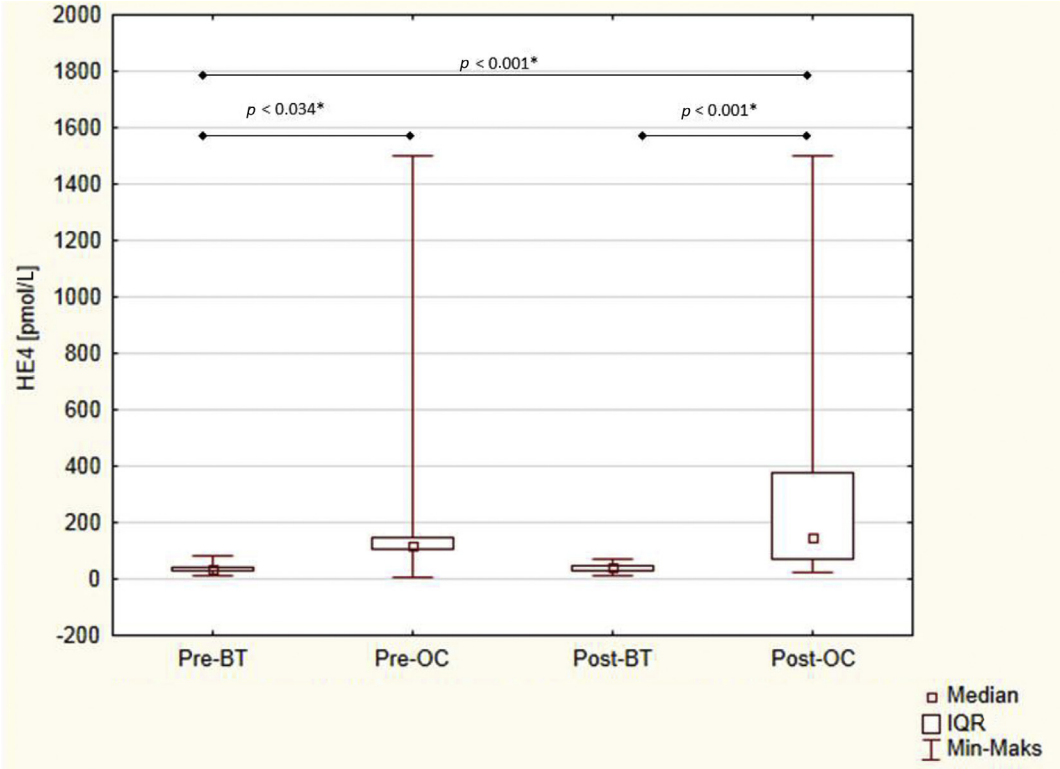

Figure 3. Median HE4 concentration in the analyzed subgroup of patients according to final diagnosis and menopausal status. * Statistically significant. HE4 = human epididymis protein 4; IQR = interquartile range; post-BT = postmenopausal with benign tumor; post-OC = postmenopausal with ovarian cancer; Pre-BT = premenopausal with benign tumor; Pre-OC = premenopausal with ovarian cancer.

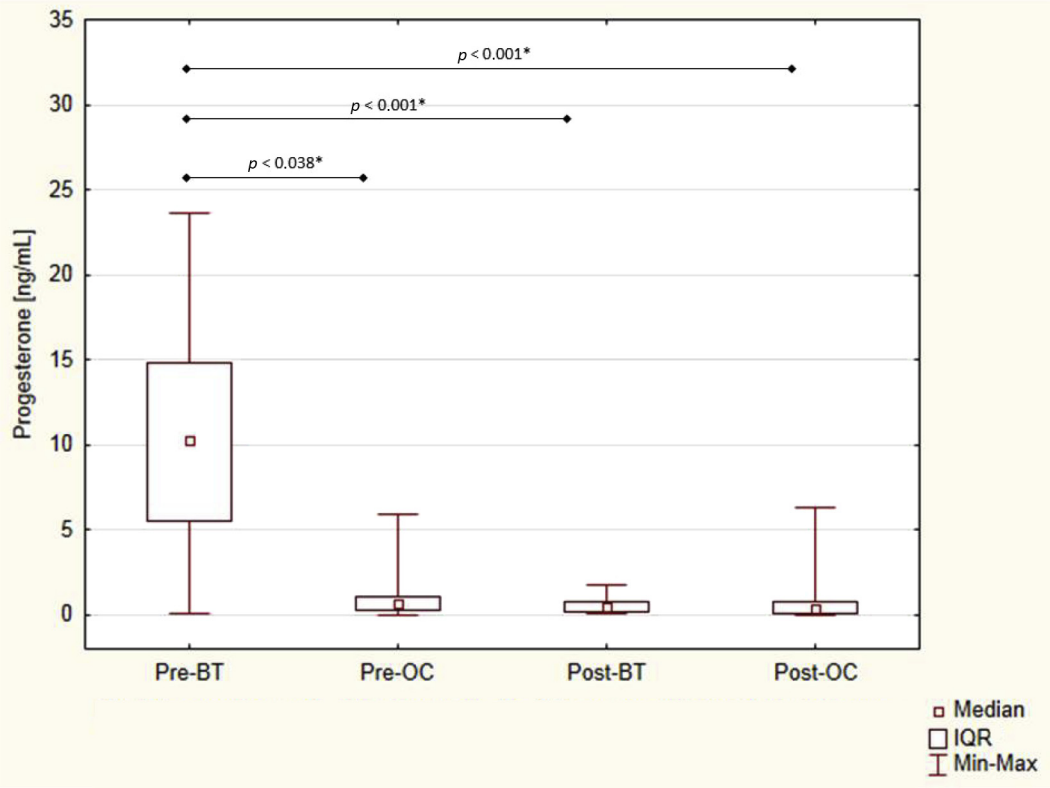

Figure 4. Median progesterone concentration in the analyzed subgroup of patients according to final diagnosis and menopausal status. * Statistically significant. IQR = interquartile range; post-BT = postmenopausal with benign tumor; post-OC = postmenopausal with ovarian cancer; Pre-BT = premenopausal with benign tumor; Pre-OC = premenopausal with ovarian cancer.

Table 2
Clinical value of the Risk of Ovarian Malignancy Algorithm (ROMA) plus progesterone compared with ROMA without progesterone for the diagnosis of ovarian cancer in the overall study population and in premenopausal and postmenopausal patients separately.

	ACC	Sensitivity	Specificity	PPV	NPV	LR+	LR−	DOR
ROMA								
Total sample	0.839	0.867	0.907	0.823	0.932	9.323	0.147	63.576
Premenopausal	0.899	0.952	0.857	0.769	0.973	6.657	0.056	118.861
Postmenopausal	0.895	0.833	0.926	0.849	0.917	11.257	0.180	62.418
ROMA + progesterone								
Total sample	0.858	0.640	0.967	0.906	0.843	19.394	0.372	52.094
Premenopausal	0.968	0.952	0.976	0.952	0.976	39.667	0.049	806.556
Postmenopausal	0.815	0.519	0.963	0.875	0.800	14.027	0.499	28.083

ACC = diagnostic accuracy; DOR = diagnostic odds ratio; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; ROMA = Risk of Ovarian Malignancy Algorithm.

predominantly in postmenopausal women, and ROMA alone showed better sensitivity and specificity for OC diagnosis in postmenopausal patients compared with women of reproductive age [14,27]. The NPV of progesterone for differentiating OC was highest in premenopausal patients, which thus became the target population. The addition of progesterone levels to ROMA reduced the incidence of false-positive cases without affecting the sensitivity of the test.

The main strength of this study was the fact that a final histological diagnosis was obtained for every patient. However, this could also be regarded as a limitation, because the model focused on patients scheduled for surgery. Our study was therefore limited to a strictly selected group of patients with Stage I and Stage II OC, irrespective of tumor histological type or grading. The limited number of cases (OC is usually recognized at an advanced stage) meant that we were unable to analyze the results for serous, mucinous, and endometrial tumors separately, although HE4 secretion has been shown to be associated with OC histotype [32–34]. However, the tumor histopathology was unknown when the ovarian masses were diagnosed in these participants, and the novel diagnostic algorithm was therefore developed irrespective of OC histology.

From a clinical perspective, the optimal point in the menstrual cycle at which to measure progesterone levels to obtain the most reliable results remains unknown. Furthermore, the effect of histological subtype of OC on the diagnostic value of progesterone is unclear. Future research on the usefulness of progesterone in OC diagnostics should therefore focus on these issues in patients with Stage I disease to improve the early diagnosis of OC. Moreover, further studies are needed to compare the role of progesterone in combination with imaging techniques, including the Risk of Malignancy Index, International Ovarian Tumor Analysis, and

Assessment of Different Neoplasms in the Adnexa models in Stage I OC detection. Because this study was limited to early cases of OC, the sample was also too small to perform a statistical analysis according to OC histological subtype.

In conclusion, the results of this study suggest that different algorithms for OC differentiation should be used in premenopausal and postmenopausal patients with adnexal masses. Moreover, while a combination of the tumor markers HE4, CA-125, and progesterone outperforms ROMA alone for the differential diagnosis of pelvic masses in premenopausal women, the addition of progesterone to OC differentiation algorithms does not improve, and may even confuse, well-established diagnostic procedures for postmenopausal women.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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