



DIAGNOSTIC VALUE OF CA-125, HE-4 AND RISK OF OVARIAN MALIGNANCY ALGORITHM IN DIAGNOSING OF OVARIAN CANCER IN PRE- AND POSTMENOPAUSAL WOMEN

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ABSTRACT

Ovarian cancer is responsible for the most deaths in the gynecological sphere. The advancements in science and modern diagnostic methods made possible the thorough investigation of this organ but there are still unsolved questions. The aim of this study is to estimate the predictive value of measuring CA-125, HE-4, and Risk of Malignancy Algorithm (ROMA) in the diagnosis of ovarian malignant tumors in pre- and postmenopausal women at the stage of preoperative examination.

Introduction

Ovarian tumors involve a wide range of neoplasms, from innocuous benign tumors to aggressive cancers and they are considered one of the hardest to diagnose diseases in gynecological pathology, often being referred as the silent killer. This “name” was attributed because of the lack of precursor lesions and a specific set of symptoms, the disease being diagnosed in most cases during a routine examination and even then in a late stage. The medical history is very important, and we must be careful not to exclude any risk factors. The correct preoperative diagnosis of cancer is essential, as it allows a prompt referral to a center, where the operations are performed by gynecologic oncologists. In ovarian cancer, effective and correct primary surgery is the most important prognostic

factor. On the other hand, conservative follow-up may be sufficient for benign tumors.

The quest to finding a cause of ovarian cancer, from an epidemiologic standpoint has been hampered by the high number of histological subtypes and the lack of consensus between pathogenic theories. A high risk of disease can be found in women who have never been married. This can be explained through the argument that unmarried women carry the same risk as married women who have never procreated. Worldwide age distribution shows that most cases affect women between the ages of 45 and 74, this being an argument for the high risk in women who have reached menopause.

Currently, tumor markers CA125 is frequently used to detect ovarian cancer before clinical signs appear, but CA125 can increase



in association with some physiological conditions such as in pre-menopausal women and in women having benign diseases. Much effort has been done in order to discover other markers supplementing CA 125 and or marker replacements. In 1999, Human epididymis protein 4 (HE4) gene expression in ovarian cancer has been cited. In several studies conducted for the purpose of determining the risk of cancer algorithm (risk of ovarian malignancy algorithm [ROMA]), combined levels of CA125 and HE4 in patients with ovarian cyst or pelvic mass were used to differentiate patients as low risk and high risk groups for ovarian neoplasm and in this manner, patients will be referred to centers that could offer the best care possible. Considering that referral of patients to a well equipped gynecologic oncology center requires differentiation between benign and malignant ovarian neoplasm, therefore, in this study, the measurements of CA125 and HE4 markers and ROMA values were used in order to diagnose patients with neoplasm of the ovaries and to refer these patients to gynecologic oncology centers.

Materials and Methods: A retrospective study was conducted, which included 50 pre- and postmenopausal patients. The case histories of patients who received treatment at the Tashkent city branch of Republican specialized scientific-practical medical center of oncology and radiology in the period from 2018 to 2021 were studied. CA125, HE4, ROMA were determined in patients with ovarian cancer and benign tumors. CA125, HE4 cut offs were 35 U/ml and 70 pM, respectively. ROMA algorithm cut off was 11.4 % and 29.9 % for pre-menopausal or post-menopausal women, respectively.

Results: In this study, serum level of CA125, HE4 and ROMA were higher in patients with ovarian cancer than benign tumors ($P < 0.001$). CA-125 was 2.7-120

U/mL and 5.33-158.2 U/mL in pre- and postmenopausal women with benign ovarian tumors, respectively, then 10-393.7 U/mL and 27.3-993.22 U/mL in pre- and postmenopausal women with malignant ovarian tumors, respectively ($p = 0.001$). HE-4 was 3.17-68.93 pmol/L and 11.9-206.1 pmol/L in pre- and postmenopausal women with benign ovarian tumors, respectively, then 22-221.6 pmol/L and 74 -764.06 pmol/L in pre- and postmenopausal women with malignant ovarian tumors, respectively ($p = 0.082$). ROMA was 0.3-15.4 % and 1.2 – 55.5 % in pre- and postmenopausal women with benign ovarian tumors, respectively, then 1.1 -96.5 % and 10.9 -98.6 % in pre- and postmenopausal women with malignant ovarian tumors ($p = 0.001$). In this study the sensitivity of CA-125 and HE-4 measurement, and ROMA in postmenopausal women was 75%, 25% and 75%, respectively, and the specificity of these three parameters was 100%.

Conclusion: The median CA125, HE4 and ROMA serum levels didn't differ significantly only between benign and malignant cases, but also between pre- and postmenopausal women. Measurement of HE4 and ROMA increased the detection of malignant diseases compared with CA125 alone. Although the study demonstrated the high sensitivity of CA-125 measurement, and ROMA as diagnostic markers and the high specificity of CA-125 and HE-4 measurement, and ROMA, It should be a choice method of diagnosis for postmenopausal women who has III-IV stage ovarian malignancy.

Materials and Methods

A retrospective study was carried out, which was studied the case histories of 50 patients in the pre- and postmenopausal period who were admitted for the surgical treatment of neoplasms in the ovary at the Tashkent city branch of Republican specialized scientific-



practical medical center of oncology and radiology in the period from 2018 to 2021.

ROMA was calculated using the ROMA calculator to Calculate Risk of Epithelial Ovarian Cancer (http://homatools.he4test.com/calculator_row_en.html) based on menopause status and content of CA-125 tumor markers and HE-4 in serum. In pre- and postmenopausal women, ROMA values equal to or greater than 11.4 % and 29.9 % indicate high risk, respectively, and ROMA values less than 11.4% and 29.9 % indicate low ovarian cancer risk.

A retrospective study was conducted, which included 50 pre- and postmenopausal patients. The case histories of patients who received treatment at the Tashkent city branch of Republican specialized scientific-practical medical center of oncology and radiology in the period from 2018 to 2021 were studied. CA125, HE4, ROMA were determined in patients with ovarian cancer and benign tumors. CA125, HE4 cut offs were 35 U/ml and 70 pM, respectively. ROMA algorithm cut off was 11.4 % and 29.9 % for pre-menopausal or post-menopausal women, respectively based on the study conducted by Moore et al.

Finally, the differentiations of ovarian masses from benign to malignant were based from the pathologist's report. Patients diagnosed with ovarian cancer were differentiated based on the Federation of Obstetrics and Gynecology Guidelines (FIGO) then the type, stage and grade of tumor were determined.

Results: Adenocarcinoma is the most common malignant tumor of the ovary (44% in premenopausal women and 68% in postmenopausal women), III stage (31%) was the most common stage and grade, respectively. Average HE4 in patients with malignant ovarian tumors was 184.5 pmol/L and 231.9 pmol/L in pre- and postmenopausal women and for benign tumors was 34.8 pmol/L and

86.1 pmol/L and the mean HE4 between the benign group and malignant group was $P = 0.001$, which was significant. Average CA125 in patients with malignant ovarian tumors was 150.9 U/ml and 315.9 U/ml in pre- and postmenopausal women and for benign tumors was 47.6 U/ml and 47.97 U/ml respectively and the difference of the CA125 level between benign and malignant groups was considerable ($P \geq 0.001$). Average ROMA in patients with malignant ovarian tumors was 39.43 % and 68.08 % and for patients with benign tumors was 8.04 % and 26.02 % in pre- and postmenopausal women, respectively and the difference of the ROMA level between these 2 groups was statistically significant ($P \geq 0.001$).

The values of ROMA, CA125 and HE4 in patients with malignant tumors based on their different stages. The difference between the average CA125 in patients with stage I-II (early stage) ovarian cancer in comparison to the levels of CA125 in patients with stage III-IV (advanced stage) ovarian cancer were considerable significant. There was significant difference found between the average ROMA in patients with stage I-II in comparison to patients with stage III-IV ovarian cancer.

In patients with benign ovarian mass the mean CA125 in menopausal women was 47.97 U/ml and in pre-menopausal women was 42.6 U/ml. Considering $P=0.058$ there were no significant statistical differences between 2 groups namely menopausal and premenopausal.

The mean HE4 in menopausal women was 86.1 pmol/L and in pre-menopausal women 34.8 pmol/L. Considering $P = 0.04$ there was a meaningful statistical difference between 2 menopausal and premenopausal groups.

The mean ROMA in menopausal women was 26.02 % and in pre-menopausal women was 8.04 %. Considering $P = 0.04$ there were dramatic statistical differences between 2



groups. In patients with malignant ovarian mass the mean CA125 in menopausal women was 315.8 U/ml and in pre-menopausal women was 150.9 U/ml. Considering $P = 17$ the statistical difference between two groups was not meaningful.

The mean HE4 in menopausal women was 231.9 pmol/L and in pre-menopausal women was 184.5 pmol/L. Considering $P = 2$ there was no large statistical difference between two menopausal and non-menopausal groups.

The mean ROMA in menopausal women was 68.08 % and in non menopausal women was 39.43 %. Considering $P = 16$ there were no meaningful statistical differences between two groups.

Finally, based on the ROC curve, ROMA, HE4, and CA125 values for the diagnosis of malignant ovarian tumors were compared and it was observed that they have high diagnostic value in ovarian cancer. The AUC of these 3 methods were calculated and no significant differences were observed (AUC of CA125, HE4 and ROMA were 82.4%, 84.1%, 82.4% respectively).

Discussion

HE4, as a single tumor marker, has the most sensitivity in differentiating ovarian tumors from benign masses and using both HE4 and CA125 has more exact predicting power than each of them alone. In the present study, the mean studied three tumor markers in

patients with grade 1,2 ovarian cancer had difference with grade 3 patients. Also the mean CA125, ROMA between the 2 early stages (I,II) and advanced stage (III,IV) groups were not different but the mean HE4 marker in advanced stage was meaningfully more than early stage (I,II). In this present study, the 3 tumor markers ROMA, HE4 and CA125 in patients with ovarian cancer were highly significant however ROMA and HE4 are not more sensitive in differentiating malignancy before surgery in comparison to CA125. In considering the cost of these tests, it seems that it is more cost effective for patients to undergo a combined CA125 and HF4 test rather than the single CA125 test.

However, in this study the level of the 3 tumor markers mentioned above were significantly higher with increasing stage of the disease process.

Conclusion

In this study, all three tumor marker HE4, CA125 and ROMA were able to distinguish malignant from benign tumors, since the value of ROMA and HE4 in diagnosing ovarian cancer was higher in comparison to CA125 alone. According to the promising results in preliminary studies, in the current study, HE4 and ROMA measurements in comparison to CA125 alone was of much help in diagnosing cancer, especially in postmenopausal women with III-IV stage of ovarian tumor.

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