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A Comparative Study of Serum Levels of HE4 and CA125 in Women with Ovarian Masses

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A B S T R A C T

Currently there is no appropriate clinical algorithm to prioritize and triage patients with malignant tumors to the medical centers for surgery. Studies have shown that HE4 alone has higher specificity than CA125 in diagnosis of ovarian tumors and the combination of these two tumor markers has higher accuracy in detecting malignancies than each one alone. The aim of this study was to find a tumor marker that could be used alone or in combination with other markers for the early detection of ovarian cancers especially the epithelial type as well as their differentiation from benign masses and therefore appropriate triage of patients with malignant masses to medical equipped centers for surgery. In this descriptive – retrospective study 86 patients with ovarian masses hospitalized in Ahwaz Imam Khomeini Hospital for surgery were studied. The records of the patients who had been hospitalized within the years of 2011-2013 was analyzed and the HE4 and CA125 serum levels were measured by ELISA method and also the information in the patient records were recorded in demographic questionnaire and compared. SPSS version 18 was used for statistical analysis. Levels of both markers CA125 and HE4 were significantly higher in epithelial cases ($P=0.0001$). CA125 marker frequency distribution based on benign or malignant tumor was not significantly different in patients under study ($P>0.05$) but the marker HE4 was significantly different based on the type of tumor (benign or malignant) in patients under study and its level was higher in malignant cases ($P=0.002$). Based on the results obtained in the study it is concluded that HE4 is a better marker with better efficiency for the differentiation of benign and malignant ovarian tumors and also in malignant cases it is applied in epithelial and Germ cell differentiation but it has no use in the diagnosis of sex cord tumor and germ cell and thus it is recommended to apply it in patients with a diagnosis of ovarian tumors.

Introduction

One of the problems in today's healthcare is cancer that is dramatically increasing in the world (Rahmani *et al.*, 2016; Firoozabadi *et al.*, 2015; Mohammad *et al.*, 2015). Investigating the causes of death among women has shown that ovarian cancers are the second leading cause of death and among the reproductive system cancers ovarian cancer is the fourth leading cause of death in women (Bowtell *et al.*, 2015). In Arab *et al* the rate of ovarian cancer in Iran is reported as 2.3 per hundred thousand women in 2005-2004 (Arab *et al.*, 2010). The average age of developing ovarian cancer in Iran is 46.7 for the epithelial ovarian tumors and the age of 34.3 has been reported for the non-epithelial tumors (Khodabakhshi *et al.*, 2007). Almost 90% of ovarian cancers are associated with epithelial ovarian cancer that is heterogeneous and it is classified based on the type of cell that is involved that includes serous, mucinous, endometrial, clear cell and Brenner and it matches with different types of ovarian epithelial cells in female reproductive system. These tumors are classified into three groups: benign, borderline and malignant. Mucinous and endometrial tumors are usually malignant and invasive carcinoma. But serous tumors are not usually invasive.

In 75% of cases due to late diagnosis of the illness, in spite of extensive surgery and chemotherapy, patients' survival is poor and patients with high-stage ovarian cancer are treated with surgery and chemotherapy but despite great advances in the field of cancer, only 5% of women with stage IV of the disease survive for 5 years and thus the early diagnosis is very critical (Lurie *et al.*, 2007; Horne *et al.*, 2014). It should be noted that the use of specific tumor markers that have the diagnosis power in the early stages is an extremely effective action in improving

health outcomes. It should be noted that currently there is no appropriate clinical algorithm to prioritize and triage patients with malignant tumors to the medical centers for surgery. That is why different cancer markers are introduced for screening and diagnosis of cancer types that CA125 (carcinoembryonic antigen 125) is one of the oldest of these markers and used to predict the risk of malignancy in a pelvic mass but there are shortcomings in the field of working with these cancer markers including the low level of specificity and sensitivity of this marker in many benign diseases in women as well as many other malignancies such as lung cancer and lymphoma (Lu *et al.*, 2004). One of the new markers of ovarian cancer is human epididymis protein 4 or HE4. This marker is discovered by expression rows RNA in normal and malignant ovarian epithelial cells. Studies have shown that HE4 alone has higher specificity than CA125 in diagnosis of ovarian tumors and the combination of these two tumor markers has higher accuracy in detecting malignancies than each one alone. The aim of this study was to find a tumor marker that could be used alone or in combination with other markers for the early detection of ovarian cancers especially the epithelial type as well as their differentiation from benign masses and therefore appropriate triage of patients with malignant masses to medical equipped centers for surgery.

Materials and Methods

After obtaining permission from Ethics Committee of the University, a descriptive – retrospective study was conducted on 86 patients with ovarian masses hospitalized in Ahwaz Imam Khomeini Hospital for surgery. The records of the patients who had been hospitalized within the years of 2011-2013 was analyzed and the HE4 and CA125 serum levels were measured by ELISA

method and also the information in the patient records were recorded in demographic questionnaire and compared. The cut-off levels of He4 were considered as 70 Pmol/Lit and 200 U/mL.

After collecting the required data using SPSS version 18 software the collected data was analyzed and for the qualitative variables the frequency and frequency percentage and for quantitative variables the mean and standard deviations were calculated. In order to evaluate hypotheses the independent t-test and ANOVA were used and the level of significance for the interpretation of the results was considered as 0.05.

Results and Discussion

In this study, 86 patients with ovarian tumors were studied. The average age distribution based on the tumor in patients shows that the benign masses include 46.51% and malignant masses include 53.48% of the total samples under study. The average age in benign cases was 45.31 and 43.28 in malignant cases. Epithelial tumors include 72%, germ cell tumors form

22% and sex cord tumors (granulosa cell tumor) include 6% of the total samples. The amount of both markers CA125 (619.41 + 898.98 versus 105.73+ 87.45) was significantly higher in cases of epithelial (P = 0.0001). The level of CA125 marker was significantly higher in Sex Cord patients (233.98+104.58 versus 491.01+819.18). The level of HE4 was significantly lower in Sex Cord patients (50.98+24.13 versus 220.66+293.93) (P = 0.0001). The level of CA125 was significantly lower in Germ Cell groups that the rest of cases (71.99 + 39.64 versus 590.65+870.64 and P = 0.0001). Also the level of HE4 was significantly lower in Germ Cell groups that the rest of cases (39.93 + 20.01 versus 259.25+ 309.69 and P = 0.0001). The frequency distribution of the marker CA125 based on the benign or malignant tumor had no significant difference in patients (403.07 + 579.01 versus 539.53 + 949.45 P> 0.05), but the marker HE4 based on the type of tumor (benign or malignant) had a significant difference in patients and its value was higher in malignant cases (111.85 + 368.59 versus 296.84+ 72.255 P = 0.002).

Table.1 Age frequency distribution based on tumor type in patients under study

Tumor type	Total	Pathology	No	%	Age
Benign	40	Dermoid	12	13/95	(60-18) 39/45
		Serous cyst adenoma	15	17/44	(61-19) 42/4
		Mucinous cyst adenoma	11	12/79	(62-22) 45/4
		Adeno-fibroma cyst	2	2/32	(50-28) 54
Malignant	46	Immature Tratomia	2	2/32	(58-45) 51/5
		Dysgerminoma	2	2/32	(58-14) 36
		Yolk Sac Tumor	3	3/48	(41-17) 29/3
		Granulosa tumor	5	5/81	(60-43) 51/4
		Serous cyst carcinoma	17	19/76	(82-24) 47/9
		Mucinous cyst carcinoma	15	17/44	(68-20) 44/4
		Endometrioid tumor	2	2/32	(50-30) 42/5

Table.2 CA125 and HE4 Level in Patient sort by epithelial status, Sex cord status, Germ cell status and Type

variable	Sub-Variable	Ca125		HE4		P-Value
		Mean	SD	Mean	SD	
Epithelial	Positive	619.41	898.98	276.05	316.06	0.0001
	Negative	105.73	87.45	42.23	20.87	
Sex cord	Positive	233.98	104.58	50.98	24.13	0.0001
	Negative	491.01	819.18	220.66	293.93	
Germ cell	Positive	71.99	39.64	39.93	20.01	0.0001
	Negative	590.65	870.64	259.25	309.69	
Type	Benign	403.07	579.01	111.85	72.255	0.002
	Malignant	539.53	949.45	296.84	368.59	

HE4 is a secreted protein the expression of which is increased in certain cancers thus this marker could play an important role in the diagnosis and follow up in these patients. Studies have particularly shown that this marker has diagnosis ability alone and can diagnose with high sensitivity in combination with CA125 (Kondalsamy *et al.*, 2013; O’Shannessy *et al.*, 2013). As previously stated the aim of this study was to find a tumor marker that could be used alone or in combination with other markers for the early detection of ovarian cancers especially the epithelial type as well as their differentiation from benign masses and therefore appropriate triage of patients with malignant masses to medical equipped centers for surgery. In this study it became clear that out of 86 patients with ovarian tumors 40 cases (46.51%) were associated with benign masses and 46 cases (53.48%) were associated with malignant masses that the benign masses contained 12 cases of mature teratoma (13.95%), 15 cases of serous cyst adenoma (17.44%), 11 cases of mucinous cyst adenoma (12.79%) and 2 cases of adeno-fibroma cyst (2.23%) and malignant masses contained 2 cases of immature teratoma (2.32%), 2 cases of dysgerminoma (2.32%), 3 cases of Yolk Sac Tumor (3.48%), 5 cases of granulosa tumor

(5.81%), 17 cases of serous cyst carcinoma (19.76%), 15 cases of mucinous cyst carcinoma (17.44%) and 2 cases of endometrioid tumor (2.32%). The results obtained in this study showed that the value of both markers was significantly higher in epithelial cases and it was significantly lower in Germ cell cases; but there was no significant difference between Sex cord and the rest of tumors. Meanwhile, the frequency distribution of marker CA125 based on the type of tumor was not significantly different in patients but the marker HE4 was significantly different in terms of tumor type and its value was higher in malignant cases. Ghasemi *et al.*, (2014) in Yazd concluded that in order to predict the advanced stage of the disease the combination of HE4 and CA125 was more appropriate to predict cancer but this was not investigated in the present study. A cohort study in 2013-2010 in China by Wen-Ting Chen *et al.*, showed that HE4 serum level was closely related to surgical outcome. Of course the present study was cross-sectional and patients’ prognosis was not analyzed. Grigorios Kalapotharakos *et al.*, (2012) in Sweden concluded that the high plasma levels of HE4 was a marker independent of poor prognosis in non-ovarian cancers that is not consistent with the results of the present

study. Cristina Anton & Partners (2011) compared the diagnostic accuracy of CA125 and HE4 in ovarian masses and concluded that there was no difference between the accuracy of CA125 and HE4 to differentiate types of ovarian tumors that is not consistent with the results of the present study. Rafael Molina *et al.*, (2011) in Spain by comparing HE4 with CA125 concluded that HE4 alone could be used for ovarian tumor diagnosis and has higher specificity than CA125 and it is consistent with the results of the present study. In Hala A Abdel-Azeez *et al.*, (2010) it was concluded that HE4 has the highest sensitivity in ovarian tumor diagnosis especially in the early stages of the disease which confirms the results of the present study. Richard G. Moore *et al.*, (2007) concluded that HE4 alone has the highest sensitivity in ovarian tumor diagnosis, which is consistent with the results of the present study. Valsive *et al.*, in the USA observed that increased level of CA-125 alone is not sufficient to differentiate benign and malignant pelvic masses that the results of the present study also indicate the same result. Rustin *et al.*, (2000) in a cohort study stated that increasing CA-125 to more than 30 units per ml is associated with the disease progression and recurrence of epithelial ovarian cancer which is not discussed in the present study. Kim *et al.*, conducted a cohort study and in South Korea that its results were published in 2008 and it was concluded that by measuring CA-125 level it is possible to predict the results of surgery and chemotherapy in patients with epithelial ovarian cancer which can be addressed in future studies of the Iranian patients as well.

In general based on the results of this study it can be concluded that HE4 is a better marker with higher efficiency to differentiate the benign and malignant ovarian tumors and also is useful in malignant cases in the differentiation of

epithelial and Germ cell types but it cannot be applied in sex cord tumor and germ cell differentiation and thus it is recommended to apply it in patients with a diagnosis of ovarian tumors. In the end it is proposed to conduct the future multi-center studies with higher sample volume and to confirm these results.

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