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Research Article

A prospective study to evaluate the role of serum vascular endothelial growth factor levels and color Doppler indices in prediction of malignancy in adnexal masses

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ABSTRACT

Background: Several markers have been used for predicting malignancy in adnexal masses. Objectives were to measure preoperative serum vascular endothelial growth factor (VEGF) and to determine its value in predicting risk of malignancy in adnexal masses, in combination with colour Doppler indices (resistance index, RI; pulsatility index, PI).

Methods: A hospital based prospective observational study was conducted in 79 women with 102 adnexal masses, who underwent a preoperative colour doppler ultrasound and CA-125 and VEGF levels were estimated. Cut-off levels for suspicion of malignancy were taken at CA-125>35IU/ml, RI<0.56, PI<1.0. Study variables were correlated with the histopathological diagnosis and their sensitivity, specificity, predictive values and accuracy for detecting malignancy were computed. Receiver operating characteristic (ROC) curve analysis was performed to assess serum VEGF and Doppler indices as markers for detection of malignant masses.

Results: Among 96 adnexal masses studied, ten (10.4%) were malignant, 33 (34.4%) benign, one (1%) borderline and remaining were non-neoplastic. RI and PI accurately predicted malignancy in 93.75% and 88.54% cases respectively, while CA-125 was 64.58% accurate. The mean VEGF level in malignant was significantly higher than that in benign cases (1761±1381.7pg/ml, 429.8±501.9 pg/ml respectively, p-value < 0.001). Combination of VEGF, RI and PI was 96% accurate in detecting malignancy in adnexal masses.

Conclusions: Serum VEGF may be a useful marker to screen for malignancy in an adnexal mass, at a cut-off of ≥1080pg/ml. Addition of RI and PI to VEGF increased the specificity and diagnostic accuracy, performing better than CA-125, RI and PI, when used independently or together.

Keywords: Adnexal masses, Doppler ultrasonography, Malignancy, Serum VEGF

INTRODUCTION

Adnexal masses may be found incidentally on ultrasonography or present with non-specific clinical signs and symptoms, posing a diagnostic challenge to the clinician. Although the majority of adnexal masses are benign, the primary goal of diagnostic evaluation is exclusion of malignancy. A thorough clinical examination, morphological analysis using ultrasonography, Colour Doppler imaging and serum tumor marker assays are used to detect malignant masses at an early stage.[1-3] Differences in Doppler parameters, such as the pulsatility index (PI) or the resistance index (RI), can help in differentiating between benign and malignant lesions.[4-7]

Preoperative evaluation of patients with suspected ovarian carcinoma usually includes a serum CA-125 determination, which is limited by false-positive results

due to other conditions. Vascular endothelial growth factor (VEGF), a proangiogenic molecule, has been shown to parallel tumor growth and maybe of value in identifying the nature of the tumor.[8-10]

In this study, we evaluated the nature of adnexal masses with colour Doppler, measured the serum VEGF levels in these patients preoperatively and related these with the histopathologic diagnosis, in an attempt to determine the role of Doppler indices in combination with serum VEGF levels in predicting the nature of adnexal masses.

METHODS

A prospective observational study was conducted at a tertiary care teaching hospital over a period of 18 months, after institutional ethics committee approval. Study population included women with symptomatic adnexal masses and asymptomatic patients with adnexal masses detected incidentally, either on per vaginal examination or on ultrasonography. Patients, who were already on treatment or follow up of diagnosed adnexal masses, were excluded. After obtaining written informed consent, patients were enrolled into the study and demographic data regarding age, occupation, educational status, presenting complaints, obstetric history, menstrual history, past history of surgical or medical ailments, past history of tuberculosis, and family history of gynaecological cancer were noted. Relevant physical examinations were performed. All routine investigations were carried out including CA-125.

Conventional gray scale ultrasonography and colour Doppler was performed using a Philips HDI 5000 ATL (Advanced Technologies Laboratories, Bothell, Washington USA) or Toshiba Nemio XG (Toshiba Medical Systems Corporation) machine. Transabdominal or transvaginal ultrasonography was performed in the patients within one week prior to surgery. Sassone's morphological scoring, based on conventional ultrasound parameters, was used for defining the nature of the adnexal masses.[1] This scoring system is based on the inner wall structure, wall thickness, presence of septa and echogenicity of the adnexal masses, rated between 1-5 points for each variable (Table 1), and a total score above nine was considered to be a predictor of malignancy.

Colour doppler study of the masses was also undertaken to assess the vascularity of the tumor within the solid areas and to determine RI, PI and PSV. When no blood flow was detectable within the tumor, a signal was recorded by the adnexal branch of the uterine artery or the ovarian artery. The filter level was set at 100 MHz in order to eliminate low frequency signals occurring from vessel wall motion and flow velocity waveforms were displayed and measured. Signals from various areas within the tumor were recorded and measured thrice; the lowest PI and RI values were considered for data analysis (Figure 1). Vessels with PI $\geq$ 1.0 or RI $\geq$ 0.56 were considered predictive of benignity, based on previous studies done by several authors.[11–14] The waveforms without end diastolic flow were assumed to be of benign origin.

The patient's blood was obtained 24-48 hours preoperatively by venous puncture and after clotting, the sample was centrifuged at 5000rpm for 10 min. A commercially available ELISA kit was used (Human VEGF-A BIOLISA; Diaclone, Gen Probe, France) for the measurement of VEGF in serum. The limit of detection of VEGF-A defined as the analyte concentration resulting in absorption significantly higher than that of the dilution medium (mean plus 2 standard deviations) was given as 7.9 pg/ml by the manufacturer.

Based on the clinical and investigative findings, a provisional diagnosis was made and the patient was managed according to standard protocol. Patients with simple cysts were first managed conservatively and repeat ultrasound was done after six weeks. In patients with persistent cysts, laparotomy or laparoscopy was undertaken and tissue sent for histopathological examination. The histopathologic diagnosis being considered as the gold standard, was used to make a final diagnosis.

Descriptive statistical analysis was carried out. Student t test (two tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (inter group analysis) on metric parameters. Diagnostic statistics i.e. sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were computed to find the correlation of study variables such as CA-125, VEGF, sassone score, PI and RI with final diagnosis for detecting malignant cases. Receiver operator characteristic (ROC) curve analysis was performed to assess the variables under study as markers for detection of malignant masses. Descriptive and inferential statistics were carried out using statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1 and R environment ver.2.11.1 and Microsoft Word and Excelwere used to generate graphs and tables.

RESULTS

A total of 79 patients with 102 adnexal masses were enrolled in the study. Of these, 3 patients were lost to follow up and in 3 patients, the adnexal masses resolved with conservative or medical management. The final data analysis was done for 74 patients, who underwent laparoscopy or laparotomy and tissue was obtained for histopathological diagnosis. The adnexal masses were bilateral in 22 patients, making a total of 96 adnexal masses.

Patients aged under 40 years constituted 81.1%, while 18.9% were over 40 years of age (Mean±SD: 31.30±12.50). 37.8% of the patients studied were nulliparous. Majority of patients (74.3%) presented with

abdominal pain. Menstrual abnormality was the second most common complaint, seen in 28.4% of patients. Abdominal distension, dyspareunia, urinary retention and lump abdomen were other complaints.

Table 1: Sassone Score.[1]

Morphology	1	2	3	4	5
Inner wall structure	Smooth	Irregularities ≤ 3mm	Papillarities > 3mm	Not applicable, mostly solid	----
Wall thickness (mm)	Thin (≤ 3)	Thick (>3)	Not applicable, mostly solid	----	----
Septa (mm)	None	Thin (≤3)	Thick (>3)	----	----
Echogenicity	Sonolucent	Low echogenicity	Low echogenicity with echogenic core; mixed echogenicity	----	High echogenicity

Table 2: Nature of adnexal masses (n=96) based on histopathology.

Final diagnosis		No. of masses
Malignant masses	Serous cystadenocarcinoma of ovary	6
	Endodermal sinus tumor of ovary	1
	Dermoid cyst- immature cystic teratoma	1
Benign neoplastic masses	Serous cystadenoma ovary	16
	Mucinous cystadenoma ovary	2
	Dermoid cyst-mature cystic teratoma	9
Borderline masses	Borderline papillary serous cystadenoma	1
Non neoplastic masses	Simple ovarian cyst	4
	Hemorrhagic cyst	15
	Corpus luteal cyst	4
	Follicular cyst	1
	Endometriotic cyst	12
	Hydrosalpinx	21
	Pyosalpinx	1
	Appendicular mucinous cystadenoma	1
	Leiomyoma of uterus	1

Table 3: Performance of CA125, VEGF, Sassone score, PI and RI in screening for malignancy in adnexal masses based on their ROC curve analysis.

Parameters	AUC*	95%CI	Result
CA-125 IU/ml	0.722	0.62-0.81	Fair test
VEGF pg/ml	0.835	0.74-0.90	Good test
Sassone score	0.862	0.77-0.92	Good test
PI	0.869	0.78-0.93	Good test
RI	0.846	0.76-0.91	Good test

*AUC- area under the ROC curve, Diagnostic values based on AUC: 0.9-1.0: Excellent test; 0.8-0.9: Good test; 0.7-0.8: Fair test, 0.6-0.7: Poor test, 0.5-0.6: Fail.

The serum CA-125 levels in the patients were found to be elevated at ≥ 35 IU/ml in 29 (39.18%) patients. Sassone score was ≥ 9 in 21.9% of adnexal masses. On spectral Doppler analysis of the adnexal masses, the RI was suspicious of malignancy in 12.5% of the adnexal masses and PI was suspicious of malignancy in 14.6% of the adnexal masses.

Among the 96 adnexal masses studied, histopathology revealed that 10 masses (10.4%) were malignant, 33 (34.4%) were benign neoplastic, 1 (1%) was borderline and 52 (54.2%) were non-neoplastic. The non-neoplastic masses consisted of inflammatory tubo-ovarian masses, hydrosalpinges, ectopic pregnancy, endometriotic cysts, simple cysts of ovarian and para-ovarian origin and hemorrhagic cysts (Table 2).

RI and PI accurately predicted malignancy in 93.75% and 88.54% cases respectively, while CA-125 was only 64.58% accurate. The mean serum CA-125 levels in malignant adnexal masses were 151.14±173.00 U/ml and 56.69±99.19 U/ml in non-malignant masses. CA-125 alone is a poor predictor of malignancy, at a cut-off of ≥ 35 U/ml had a sensitivity of 60%, specificity of 61.22% and accuracy of 61.11%.

Table 4: Comparison of type of adnexal masses in various studies.

	Total no. of masses (n)	Benign n (%)	Malignant n (%)	Borderline n (%)
Present study	96	85 (88.6%)	10 (10.4%)	1 (1%)
Riaz et al[15]	150	126 (84%)	20 (13%)	4 (3%)
Leeners et al[6]	103	80 (77.67%)	23 (22.33%)	0
Timmerman et al[16]	1066	800 (75%)	266 (25%)	0
Zanetta et al[13]	80	47 (58.75%)	29 (36.25%)	4 (5%)
Chia et al[17]	204	108 (52.94%)	77 (37.74%)	19 (9.3%)
Mousavi et al[18]	101	48 (47.52%)	53 (52.5%)	0
Terzic et al[28]	609	449 (73.7%)	126 (20.7%)	34 (5.6%)

Table 5: Histopathology of the adnexal masses in various studies.

Histologic type	Present study (%)	Deligeoroglou et al[19] (%)	Riaz et al[15] (%)	Terzic et al[28] (%)
Malignant epithelial ovarian tumors	6.25	2.1	6.67	14.4
Benign epithelial ovarian tumors	18.75	10.6	29.33	12.3
Germ cell tumors	11.46	31.9	7.33	11.5
Borderline papillary serous cystadenoma	1	-	16	-
Simple ovarian cyst	4.16	10.6	-	15.4
Functional cysts	20.83	25.5	14	10
Endometriotic cyst	12.5	12.8	24	19.9
Hydrosalpinx	21.88	-	7	-

Table 6: Performance of combination of parameters to screen malignant cases (positive is defined as all components positive).

Combination	Number of positive masses (n = 96)	% of positive masses	Sensitivity	Specificity	Accuracy	P value
VEGF+Sassone	7	7.3	60.00	98.84	94.29	<0.001**
VEGF+RI	8	8.3	70.00	98.84	95.83	<0.001**
VEGF+PI	8	8.3	70.00	98.84	95.83	<0.001**
VGEF+RI+PI	7	7.3	70.00	100.00	96.00	<0.001**
VGEF+RI+PI+ Sassone	6	6.3	60.00	100.00	95.83	<0.001**

** Highly significant (P value: P ≤ 0.01).

The mean serum levels of VEGF in the malignant masses was 1761 pg/ml, in benign neoplastic masses it was 323.78 pg/ml, in borderline mass it was 790 pg/ml and in non-neoplastic masses it was 490.09pg/ml, with a statistically significant difference between VEGF in malignant and non-malignant masses (P-value < 0.001).

After constructing an ROC curve for serum VEGF for prediction of malignant adnexal masses, it was observed that area under ROC curve was 0.835 (Figure 2). From this curve, a best possible cut-off value was calculated and found to be 1080pg/ml of serum VEGF, which achieved a sensitivity of 80%, specificity of 88.37% and accuracy of 87.50%. ROC curves were plotted for sassone score, CA-125, RI and PI separately, at cut-off values already stated and the area under the curve (AUC) compared for diagnostic efficacy of the tests. All except CA-125 were observed to be good tests, while CA-125 was only a fair test (Table 3, Figure 2). Combination of serum VEGF+RI+PI yielded 70% sensitivity, 100% specificity and 96% accuracy for detection of malignancy in adnexal masses.

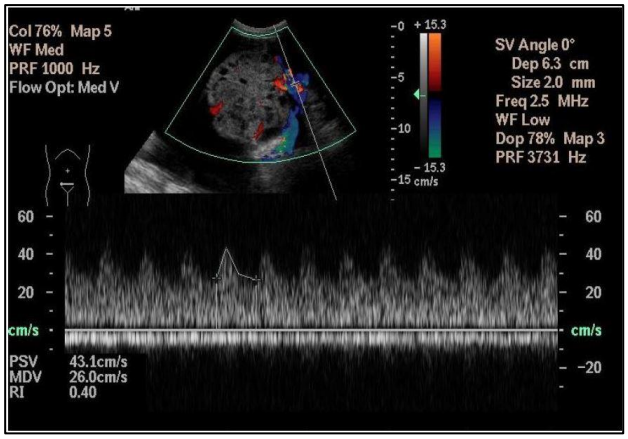

Figure 1: Doppler evaluation revealing evidence of low resistance blood flow (R.I-0.4) within solid portion of adnexal mass.

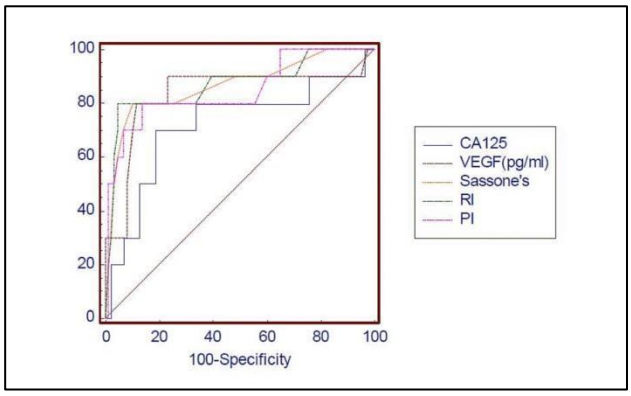

Figure 2: ROC curves for Sassone score, RI, PI and serum VEGF for diagnosing malignancy.

DISCUSSION

Adnexal masses are common in women across all age groups. A woman with an adnexal mass can present a difficult dilemma for the gynaecologist because of the uncertainty in diagnosis, especially when adnexal masses are encountered in younger women. Identification of benign cysts avoids unnecessary surgery. Hence, it is essential to have a good test to differentiate between benign and malignant adnexal masses.

A comparison of the number and type of adnexal masses included in various studies is represented in table 4 and table 5.[6,13,15-18] A higher percentage of malignant masses were reported in studies which included patients with a higher mean age and greater number of post-menopausal women, compared to our study.[13-16] Riaz et al, reported a slightly lower percentage (44%) of non-neoplastic masses than the present study (54.2%), since they excluded simple cysts < 8 cm in their study.[15] In contrast, Deligeoroglou et al, in their study, reported an equal number of benign neoplastic and benign non-neoplastic masses (48.9%) in their study, which could be due to the inclusion of only adolescent population, who have a high incidence of functional cysts.[19]

Multiple scoring systems to improve the preoperative discrimination between benign and malignant masses, include various combinations of parameters including age, menopausal status, gray scale ultrasound morphology. These pose problems in clinical practice as there are often very complex. These scoring systems have been evaluated, but a completely reliable differentiation of malignant masses is not possible by sonography alone.[3,20–27]

The simple rules by the international ovarian tumor analysis group and various modifications of the risk of malignancy index have been evaluated in several studies for differentiating between benign and malignant adnexal masses. Two-step and three step triage strategies have been proposed. These indices have proven useful in defining cut-offs for referral to a gynaecologic oncologist.[22–27]

Lack of any doppler signal is highly indicative of its benign nature, but metabolically active tumors may result in false positive doppler parameters. Absence of vascularity on doppler may be seen in spite of histological evidence of neovascularisation and hence malignant tumors may be missed.[5-7] Many studies have concluded that the addition of doppler parameters increases the confidence with which a malignancy is diagnosed. However, they all used variable cut-off levels (RI 0.50-0.88; PI 0.56-1.0) for diagnosing malignancy.[13,18,28] Terzic et al concluded that RI (cut-off level 0.88) is more reliable than PI (cut-off level 0.56) for predicting malignancy.[28]

Several tumor markers have been evaluated for their ability to identify malignancy. Used individually, neither ultrasonography nor CA-125 estimation provides an adequate positive predictive value.[29,30] The role of VEGF in ovarian pathology has been studied extensively in the past few years, with varying results.[9-11]

Yildrim et al evaluated the role of preoperative VEGF and migration inhibitory factor (MIF) in differentiation of benign and malignant adnexal masses and concluded that both these markers are unsuitable for differentiating between benign and malignant masses.[31] Other markers that have been evaluated in prediction of ovarian cancer in adnexal masses are human epididymis protein 4 (HE4) and cyclo-oxygenase 2 (COX 2).[32,33] A recent study which correlated the VEGF and COX 2 staining with survival in ovarian cancer patients, concluded that patients' whose tumors were positive for both VEGF and COX 2 have a decreased survival and may be useful in selection of patients who will benefit from anti-angiogenic therapy.[34] Vaginal fluid concentrations of CA-125, CA 19-9 and CEA were found to be significantly higher in patients with primary ovarian cancer than to those in patients with benign adnexal masses.[35]

The mean serum VEGF levels in malignant and non-malignant masses were 1761.00±1381.7pg/ml and 429.76±501.96pg/ml respectively, in our study. The higher levels mean of serum VEGF in malignant adnexal masses, may be because of the small number of malignant masses in the study population and a higher histological grade and stage of disease at the time of the VEGF assay. The mean value of serum VEGF was altered by the very high serum VEGF levels in two patients who had bilateral serous cystadenocarcinoma of ovaries with concurrent ascites. Ascites is known to be associated with very high levels of serum VEGF and could be the cause of the overall increase in the mean serum VEGF in these patients and a higher cut-off level obtained, for detection of malignancy. Reasons for varying serum VEGF levels between studies by different authors may also be due to the differences in storage of specimens or assay techniques or use of monoclonal or polyclonal antibodies or cross-reactivity with cytokines or serum proteins.

From the results of the present study, it was found that serum VEGF was a good predictor of malignancy in an adnexal mass, at a cut-off value of ≥1080 pg/ml. Therefore, serum VEGF may be useful in patients with persistent adnexal masses to differentiate malignant masses from benign ones and to decide on the need for referral to a gynaecologic oncologist for further specialised care and management.

Serum VEGF in ovarian cancer has been studied by several researchers, who observed that although correlation of serum VEGF with serum CA-125 levels in patients with ovarian cancer, stage of the disease and histological subtype was statistically significant, VEGF did not represent a useful tool for early diagnosis of ovarian cancer.[8-10] On the other hand, Cooper et al and Tempfer et al observed that VEGF is an independent prognostic factor of overall and disease free survival on multivariate analysis.[10,36] Premalata et al also found that only one third of ovarian carcinomas has a high expression of VEGF-A.[37]

There is limited evidence with use of three dimensional and power Doppler indices for detection of malignancy.[21,38,39] Studies have demonstrated three dimensional power doppler indices to have a positive correlation with serum VEGF levels in ovarian masses.[21,38] Preoperative serum levels of vascular endothelial growth factor (VEGF) were correlated with three dimensional power Doppler indices in ovarian masses and the vascularization index (VI), flow index (FI) and vascularization flow index (VFI), correlated positively with serum VEGF levels, which were higher in malignant ovarian masses than in benign masses.[38] However, another study which evaluated the 3-D power Doppler indices concluded that VI, FI and VFI had a high intra-observer variability and low accuracy for identifying false positive results of IOTA simple rules.[39] Also, the inaccessibility to 3-D power doppler and expertise can be a limitation in low resource settings.

The role of serum VEGF in combination with doppler parameters (RI, PI) for identification of malignancy in adnexal masses had not been evaluated previously. In our study various combinations of serum VEGF with the doppler parameters and sassone score were evaluated (Table 6) in order to find the combination of parameters that would be most useful in predicting the malignant nature of the adnexal masses. For such combinations, it was assumed that only if all the component tests or markers indicated malignancy, then the combination would indicate malignancy. By using a combination of the markers, rather than their independent use, sensitivity of the tests in detecting malignancy was not improved, but the specificity and accuracy improved. The addition of RI and PI to serum VEGF was found to increase the specificity and diagnostic accuracy as compared to either VEGF or PI or RI, when used alone. This combination, performs better than CA-125, RI and PI, when used independently or together**.** Limitations of the study was this; the number of malignant adnexal masses in our study is small to draw any definitive conclusions. Also, the cut-off value of serum VEGF obtained may have been influenced by the advanced tumor stage at diagnosis, as demonstrated in other studies.[8-10,40] Randomized control studies are required to evaluate these results further.

CONCLUSION

Ultrasonography is the most appropriate first line investigation for an adnexal mass. Colour doppler flow imaging aids better characterisation of the masses. Among the various tumor markers that have been studied to date, CA-125 is being extensively used inspite of its several limitations.

The results of our study, point to an important role of serum VEGF combined with doppler parameters in prediction of malignant adnexal masses. The addition of RI and PI to serum VEGF, increases the specificity and diagnostic accuracy as compared to either VEGF or PI or RI, when used alone.

Further studies are required to evaluate and compare their performance with the two dimensional spectral Doppler indices (RI and PI) in predicting malignancy. Future research directed at evaluating the cost-benefit analysis of using VEGF and/or power doppler flow indices in early detection of malignancy may also be useful.

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