THE DIAGNOSTIC VALIDITY OF PRE-OPERATIVE SERUM CA125 LEVEL IN WOMEN WITH OVARIAN MASSES

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ABSTRACT

Objective: *To determine the validity of serum CA125 levels in differentiating benign and ovarian cancer in patients with ovarian masses, using histopathology as a gold standard.*

Methodology: *In this cross sectional study, blood samples were obtained from 85 women with ovarian masses who fulfilled the inclusion criteria and sent for the assay of serum CA125 levels. They were scheduled for elective surgery at Hayatabad Medical Complex Hospital between 1st April, 2009 and 31st March 2010.*

Results: *Of the 85 women enrolled, ovarian cancer was found in 27 cases (31.8%) and benign ovarian mass in 58 cases (68.2%). The sensitivity, specificity, and accuracy of serum CA125 at the cutoff level of 35 U/mL for prediction of ovarian cancer were 74.14%, 92.5%, 80% respectively; with 95.56% positive predictive value and 62.5% negative predictive value.*

Conclusion: *As stand-alone modality, serum CA125 of more than 35 U/mL in predicting ovarian cancer revealed modest diagnostic accuracy.*

Key Words: *Serum CA125, Ovarian mass, Histopathology.*

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INTRODUCTION

Ovarian cancer is the sixth most common cancer in women worldwide and is the leading cause of death among gynecologic malignancies with more than 190,000 new cases of ovarian cancer each year, accounting for around 4% of all cancer diagnosed in women. Incidence rates vary considerably, with highest rates in USA and Northern Europe (around 43,000 cases occur per year in Europe and 22,000 in USA) and lowest rates in Africa and Asia[1].

In Pakistan, ovarian cancer is the fourth prevalent cause of ovarian cancer[2]. A women has a life time risk of ovarian cancer of 1.5%[3], so there exists a need for tumor marker, which can help in screening, early diagnosis, staging, assessment of treatment response and follow up. At present CA125 is the tumor marker seen in 80% of epithelial ovarian cancer. CA125 is a glycoprotein with a high molecular weight and is recognized by a monoclonal antibody (OC-125) .It is expressed in the amnion and embryonic coelomoc epithelium[4].

A large component of the problem remains a lack of early diagnostic testing specific to discern cancer from benign mass. Early detection is crucial for improving patient survival because of lack of acceptable screening test for ovarian cancer. It is essential to discriminate preoperatively between possible early malignant versus benign ovarian tumors for an appropriate at the time of initial exploration, eliminating the morbidity and expense of a second procedure. Thus this study was conducted to determine the validity of serum CA125 levels in differentiating benign and ovarian cancer in patients with ovarian masses, using histopathology as a gold standard.

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METHODOLOGY

This cross sectional study was conducted after taking permission from the Hospital Ethical Committee. Eighty five women with an ovarian mass were recruited in the present study. A total of 98 patients presented with ovarian masses of which 13 were excluded. Women with Complex

ovarian mass; Symptomatic cysts and; Postmenopausal women with ovarian cysts >5cm were included in the study while patients with adnexal mass other than ovarian mass; pregnant women with ovarian mass; known case of prior malignancy; ovarian ectopic and recurrent ovarian cancer were excluded.

Informed written consent was taken and they were included in the study. Detailed history regarding symptoms and clinical data like abdominal and vaginal examination of ovarian mass size, consistency, mobility and tenderness was obtained and recorded for each individual. The records were reviewed for the age at presentation, presenting symptoms, diagnostic studies, operative approach, surgical procedure and pathology finding. Peripheral venous blood sample was drawn for CA125 levels performed by Architect 125 2nd generation Chemluminescent Microparticle Immunoassay (CMIA) from a private medical laboratory of Peshawar within 1 week before the operation. All women who entered into the present study underwent exploratory laparotomy and were followed up post operatively by histopathological analysis of all surgical specimens for the gold standard or definite diagnosis of each case. The histopathology of all retrieved samples was performed by a single gynecologic pathologist.

The accuracy of CA125 levels was assessed at levels more than 35U/ml in preoperative differentiation of ovarian cancer from benign ovarian disease in women who presented with an ovarian mass. The sensitivity, specificity, positive and negative predictive values were analyzed at 95% confidence interval. False positive and negative rates, accuracy, and prevalence were calculated.

RESULTS

In this study, out of 85 women with ovarian mass, 68.2% (58) had benign while 31.8% (27) had a malignant ovarian tumor (Table 1).

With a cutoff level of 35 U/ml of serum CA125 as the discriminator between benign and malignant ovarian masses, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate of serum CA125 was determined by using open-epi screening test as shown in Table 2.

The study included age ranged from 13 up to 75 years with a mean of 39.98 $\pm$ 18.52 years. Patients' age was divided in 3 categories out of which most presented in reproductive age i.e., 20-40 years which was 63.5% while 5(5.9%) patients were below 20 years and 25(29.4%) presented at age more than 40years.

In this study married women were 67 (78.8%) and unmarried were 18 (21.2%). In married women, there were 50 (58.8%) cases which were benign and 17 (20%) cases were malignant. While in unmarried women 8 cases

Table 1: CA 125 * Histopathalogy Result Crosstabulation

		Histopathalogy Result		Total
		Benign Mass	Malignant Tumor	
CA 125	Normall	43 50.6%	2 2.4%	45 52.9%
	Abnormal	15 17.6%	25 29.4%	40 47.1%
Total		58 68.2%	27 31.8%	85 100.0%

Table 2: Diagnostic or Screening Test Evaluation

Parameter	Estimate	Lower - Upper 95% CIs	Method
Sensitivity	74.14%	(83.65 ,61.62)	Wilson Score
Specificity	92.59%	(97.94 ,76.63)	Wilson Score
Positive Predictive Value	95.56%	(98.77 ,85.17)	Wilson Score
Negative Predictive Value	62.5%	(75.78 ,47.03)	Wilson Score
Diagnostic Accuracy	80%	(87.12 ,70.28)	Wilson Score

Table 3: Histopathalogy Result wise distribution of Postmenopausal

		Postmenopausal		Total
		Yes	No	
Histopathalogy Result	Benign Mass	5	53	58
		5.9%	62.4%	68.2%
	Malignant Tumor	9	18	27
		10.6%	21.2%	31.8%
Total		14	71	85
		16.5%	83.5%	100.0%

(9.4%) were benign and 10 cases (11.8%) (the total cases of benign and malignant should by 85 while these are 75) were malignant.

In those who were married were mostly nulliparous with 30.6% while about 16.5% were belonging to group who were parity 2 while 15.3% were parity 3. Thus women with ascending order parity had decrease incidence of ovarian mass.

Most of the ovarian mass was unilateral (67 patients) with 47% on left while on right side it was 31.8%. Sizes of tumor presentation were mostly between 5-10cm and constituted 48.2% while size less than 5cm included 3.5%.

Postmenopausal cases presenting with ovarian mass were 14 (16.5%) out of which 5 cases (5.9%) were benign and 9 (10.6%) cases were malignant tumors (Table 3).

DISCUSSION

Serum CA125 is significantly elevated in over 90% of patients with advanced epithelial ovarian cancer and 40% of overall cases with advanced intra-abdominal malignancies.[5] A recent published study has shown that elevated serum CA125 (>35IU/ml) could be found in many benign condition such as menstruation, pregnancy[6], functional cyst, pelvic infection, and endometriosis[7,8]. Since these condition are more likely to occur in a women in reproductive age, so determination of serum CA125 is more specific in predicting ovarian cancer when it is used in postmenopausal women with pelvic mass[9].

The sensitivity and specificity and accuracy of serum CA125 at the cutoff levels of 35u/ml for prediction of ovarian cancer is 83.1%, 39.3%, and 60.8% respectively, with 57.0%positive predictive value, 70.6% negative predictive value, 60.8% false positive rate and 16.9% false negative rate[10].

In another study effectively combining information on CA125, CA72-4 and M-CSF significantly increased preoperative early stage sensitivity from 45% with CA125 alone to 70%, while maintaining 98% first line specificity[11].

The main limit of serum CA125 is that it may be high (100-200 U/ml) in benign diseases, especially in the reproductive age. To increase the discriminative power many studies have stressed the usefulness of the combination of serum CA125 levels with menopausal status and pelvic ultrasonography. Study from the National Cancer Institute (NCI) shows that combined transvaginal ultrasound (TVU) and CA-125 levels abnormality can detect ovarian cancer with high predictive value[12, 13].

In our study the false positive results were seen in tumor-like conditions like a case with endometriotic cyst (1 case), adenofibroma (1case), 1 case of low malignant potential serous tumor and rest in benign epithelial ovarian tumor. A recent published study has shown that elevated serum CA125 (> 35 U/mL) could be found in many benign conditions such as menstruation, pregnancy, functional cyst, pelvic infection, and endometriosis[14-16]. Although serum CA125 levels is more sensitive in predicting malignant ovarian massin postmenopausal women compared to premenopausal women, the present findings in our study are not consistent with those mentioned in the literature as sensitivity and specificity in postmenopausal is reduced as compared to premenopausal women.

In our study most of the tumor were unilateral 78.8%, more on left side(47.1%) and only 21.1% were bilateral. This is consistent with the findings reported by Tuncer ZS et al[17].

Among the benign ovarian tumors, fifteen cases were interpreted as malignancy due to serum CA125 level of higher than 35 U/mL. Thirteen out of these had slightly raised CA125, while two of these cases had highly raised ca125 (350 and 890 iu/ml) shown in table 2, especially in case of adenofibroma with massive ascites and has been reported elsewhere in literature to cause highly elevated serum Ca125[19, 20].

In girls with age group of <20 years, 5 cases were admitted with ovarian masses. Out of which 2 were malignant with raised CA125. These tumors were mucinous cystadenocarcinoma and mixed germ cell tumor. Rest of tumors were benign with normal ca125 and included mature cystic teratoma and mucinous cystadenoma. Although age 20 was in another group, it was seen that girls at 20 age two had germ cell tumors i.e., yolk sac tumor with raised ca125 levels. These findings are consistent with the literature. Germ cell tumor are more common in age group up to 20 years[20,21]. Our finding of germ cell tumor with raised ca125 was consistent with local study by Shahla Balouch[22].

Despite a number of trials examining CA-125, with or without the use of sonography, in women with a pelvic mass, it has become increasingly clear that no one modality will be sufficient to predict accurately the presence of an ovarian malignancy. Many different tumor markers have been analyzed, but none has achieved the sensitivity or specificity to be clinically useful as an individual test[23].

In this study ultrasound was done by radiologist in radiology department of Hayatabad Medical Complex. Pattern recognition by ultrasound correctly classified 69.64% of the tumors as benign or malignant. Serum CA-125 correctly classified at best 74.14% of the masses. Combining parameters OF CA125 levels and ultrasound, the diagnostic accuracy increased to 86.75% with sensitivity of 80.36%, specificity 100%, positive predictive value 100% and negative predictive value of 71.05%.

Recently, the addition of HE-4 to CA-125, without the use of ultrasound, has increased the sensitivity of CA-125 by 22% at a specificity of 90%[24].

A risk of malignancy index (RMI), having combination of ultrasound, CA125, and menopausal status, achieves a sensitivity of 85% with a specificity of 97% for predicting the presence of ovarian cancers in women with pelvic masses[25].

The architectural features of ovarian neoplasm's on pelvic ultrasound was used to predict a probability of malignancy without the use of CA-125 in study by De Priest[26]. The morphology index achieved a positive predictive value of up to 0.45. Although many of the morphologic features and measurements that comprise the morphology index are routinely performed and reported in standard pelvic ultrasounds, many of the variables are often not reported or measured, therefore limiting its clinical utility in community practice.

Timmerman et al reported data collected by the International Ovarian Tumor Analysis Group (IOTAG). More than 50 defined variables were recorded and analyzed which included age, personal history of ovarian cancer, maximum diameter of the lesion, and maximum diameter of the solid component, presence of ascites, Doppler blood flow, a purely solid lesion, irregular internal cyst wall, increase color score, hormone therapy, and pain with ultrasound. A logistic regression model was created using each of these variables, called the M1 model. The M1 model, with a probability value of .01, achieved a sensitivity of 93% and specificity of 77% in the IOTAG cohort[27].

Timmerman et al added CA-125 levels as a variable to the M1 model. Analysis of the premenopausal group revealed no statistical difference in the AUC of the ROC curves when CA-125 was added to M1. This finding is not surprising because CA-125 tends to be elevated by many of the benign gynecologic conditions that present in this age group and is less frequently elevated in mucinous cancers and in borderline tumors that occur in younger women. Also, the prevalence of ovarian malignancy in the younger population is much lower than that in the postmenopausal group, making it more difficult to detect a significant difference with a limited number of premenopausal cases[24].

While a single value of CA-125 lacks the specificity and sensitivity required for early detection, greater specificity and screening performance has been attained in preclinical detection of ovarian cancer, using serial CA-125 levels interpreted with the risk calculation[28].

CONCLUSION

Pattern recognition of ovarian masses by ultrasound alone was inferior to serum CA-125. As stand-alone modality, serum CA125 of more than 35 U/mL in predicting ovarian cancer revealed modest diagnostic accuracy. There is a need to be careful for false positive in women at reproductive age group and false negative results in early-stage disease or ovarian cancer with low level of serum Ca125.

Combining both parameters of ultrasound and serum CA125 levels for discrimination between benign and malignant ovarian masses further increases the diagnostic accuracy.

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None Declared

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Globel cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Pervaiz T. Cancer ovary, present and future of management. J Ayub Medical Coll Abbottabad 2003;15:65-8.
3. Cannistra S. Cancer of the ovary. N Engl J Med 2004;351:2519.
4. Rasool R, Shah ZA, Salahuddin M, Bashir M. J K Practitioner 2003;1093:224-5.
5. Tuxen MK, Soletormos G, Dombernowsky P. Tumor markers in the management of patients with ovarian cancer. Cancer Treat Rev 1995;21:215-45.
6. Pauler DK, Menon U, McIntosh M. Factors influencing serum CA125II levels in healthy postmenopausal women. Cancer Epidemiol Biomarkers Prev 2001;10:489-93.
7. Gaducci A, Cosio S, Carpi A, Nicolini A, Genazzani AR. Serum tumor markers in tha management of ovarian, endometrial and cervical cancer. Biomed Pharmacother 2004;58:24-38.
8. Asher V, Hammond R, Duncan TJ. Pelvic mass associated with raised CA 125 for benign condition: a case report. World J Surg Oncol 2010;8-28.
9. Maggino T, Gadducci A, D'Addario V, Pecorolli S, Lissoni A, Stella M, et al. Prospective multicenter study on CA125 in postmenapausal pelvic masses. Gynecol Oncol 1994;54:117-23.
10. Benjapibal M, Neungton C. Pre-operative prediction of serum CA125 levels in women with ovarian masses. J Med Assoc Thai 2007;90:1986-9.
11. Skayes SJ, Horicks N, Yu Y, Xu FJ, Berchuck A, Havrilesky LJ, et al. Preoperative sensitivity and specificity for early stage ovarian cancer when combining CA125, CA15-3, CA72-4 and macrophage colony stimulating factor using mixture of multivariate normal distributions. J Clin Onco 2004;22:4059-66.
12. Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 2008;18:414-20.
13. Buys SS, Partridge E. Ovarian cancer screening in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial Am J Obstet Gynecol 2005;193:1630-9.
14. Jacobs IJ, Skates S, Davies AP, Woolas RP, Jeyerajah A, Weidemann P, et al. Risk of diagnosis of ovarian cancer after raised serum CA 125 concentration: a prospective cohort study. BMJ 1996;313:1355-8.
15. Kudlacek S, Schieder K, Kolbl H, Neunteufel W, Nowotny C, Breitenecker G, et al. Use of CA 125 monoclonal antibody to monitor patients with ovarian cancer. Gynecol Oncol 1989;35:323-9.
16. Maggino T, Sopracordevole F, Matarese M, Di Pasquale C, Tambuscio G. CA-125 serum level in the diagnosis of pelvic masses: comparison with other methods. Eur J Gynaecol Oncol 1987;8:590-5.
17. Abad A, Cazorla E, Ruiz F, Aznar I, Asins E, Llixiona J. Meigs'syndrome with elevated CA125: case report and review of the literature. Eur J Obstet Gynecol Reprod Biol 1999;82:97-9.
18. Querleu D, Mery E, Ferron G, Benito V, Afii A, Gladieff L. Pitfalls of CA-125 levels in the preoperative work-up of ovarian masses. J Clin Oncol 2008;26:512-3.
19. Breen J, Maxon WS. Ovarian tumours in childhood and adolescence. Clin Obstet Gynecol 1977;20:607-23.
20. Morowitz M, Huff D, Von Allmen D. Epithelial ovarian tumours in children: a retrospective analysis. J Pediatr Surg 2003;38:331-5.
21. Baloch S, Khaskheli M, Malik AM, Sheeba A, Imdad A. Khushk .Clinical spectrum and management of ovarian tumors in young girls upto 20 years of age. J Ayub Med Coll Abbottabad 2008;20:14-7.
22. Bast RC Jr, Urban N, Shridhar V. Early detection of ovarian cancer: promise and reality. Cancer Treat Res 2002:107:61-97.
23. Moore RG, Brown AK, Miller CM. A novel multiple biomarker assay for the detection of ovarian carcinoma. J Clin Oncol 2006;24:261.
24. Jacobs I, Oram D, Fairbanks J. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97:922-9.
25. DePriest PD, Shenson D, Fried A. A morphology index based on sonographic

findings in ovarian cancer. Gynecol Oncol 1993;51:7-11.

26. Timmerman D, Testa AC, Bourne T. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. J Clin Oncol 2005;23:8794-801.
27. Timmerman D, Van Claster B, Jurkovic D, Valentin L, Testa AC, Bernard JP, et al. Inclusion of CA-125 does not improve mathematical models developed to distinguish between benign and malignant adnexal tumors. J Clin Oncol 2007;25:4194-200.
28. Rosenthal A, Jacobs I. Ovarian cancer screening. Semin Oncol 1998;25:315-25.

CONTRIBUTORS

F conceived the idea and planned the study. SW helped in data collection. LH supervised the study and helped in the writing of manuscript. All authors contributed signiflcantly to the research.