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Raised CA-125 Levels in Patients with Suspected Cases of Ovarian Malignancy

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ABSTRACT
Objective:- To determine frequency of raised CA-125 levels in patients with suspected cases of ovarian malignancy. **Material and methods:-** This Descriptive cross sectional study was conducted in the Department of Obstetrics and Gynecology, Nishtar hospital Multan from February 2016 to April 2017. One hundred and eleven cases of adnexal mass were admitted in Wards of Department of Obstetrics & Gynecology, Nishtar Hospital Multan with suspicion of ovarian malignancy. **Results:-** Mean age of the patients was 47.84±10.7 years. 70(63.1%) women were para 1–4 and 16(14.4%) para 5 or above. Family history of ovarian cancer was present in 60 patients (54.1%). In our study, frequency of raised CA-125 levels was 82.0%; (91/111) among patients with adnexal mass. Mean CA-125 levels were 938.66±697.7 µ/ml. Raised levels of CA-125 were associated with advance age, low parity and family history of ovarian cancer. **Conclusion:-** In our study, frequency of raised CA-125 levels was 82.0% among patients with suspicion of ovarian cancer. Raised CA-125 levels were associated with advance age, low parity and family history of ovarian cancer.
Key Words:- Ovarian carcinoma, raised CA-125 levels, adnexal mass

INTRODUCTION

Ovarian cancer is the 5th most common cancer in women in USA, and comprises 4% of all female cancers and 31% of all cancers of female genital tract.[1] Post menopausal women are at greatest risk of ovarian cancer.[2] 1 in 70 women will develop ovarian cancer in their life time.[1] It is a very deadly disease as it is rarely diagnosed at early stage.[3] Overall mortality rate is high, i.e. 5-year survival rates of approximately 35%.[4] In stage I or II, survival is 80–90% and 25% in stage III and IV.[5] Malignant lesions of the ovaries include primary lesions arising from normal structures within the ovary and secondary lesions from cancers arising elsewhere in the body. Primary lesions include epithelial ovarian carcinoma (70% of all ovarian malignancies), germ-cell tumors, sex-cord stromal tumors, and other more rare types. Metastases to the ovaries are relatively frequent, with the most common being from the endometrium, breast, colon, stomach, and cervix. Although many histologic types of ovarian tumors have been described, more than 90% of ovarian malignancies are epithelial tumors.[6]

The precise cause of ovarian cancer is unknown, but several risk and contributing factors (including both reproductive and genetic factors) have been identified. Symptoms are often non specific[7] like abdominal/pelvic pain, distension, urinary frequency, diarrhea or constipation, or there may be abnormal vaginal bleeding, weight loss, abdominal bloating and fatigue.[8] The overall mortality of ovarian cancer has remained unchanged[9] mainly because of a lack of success in diagnosing ovarian cancer at an early stage (nearly all patients with advanced stage of ovarian carcinoma die of the disease). On the other hand, 90% of those with the disease confined to the ovary survive.

Despite considerable efforts directed at early detection, no cost-effective screening tests have been developed.[10] Although pelvic and, more recently, vaginal sonography have been used to screen high-risk patients, both techniques lack sufficient sensitivity and specificity as screening tools for the general population. Thus, the search for tumor markers capable of early detection of ovarian carcinoma is of profound importance and represents one of the most urgent subjects in the study of ovarian cancer. Primary investigations for diagnosis of ovarian cancer have been ultrasonography and CA-125[11] which is a tumour marker and is considered gold standard.[12] This tumour marker was first identified by Bast, Knapp and colleagues in 1981. It is expressed by tissues derived from coelomic and Mullerian epithelia.[13] CA-125, a glycoprotein of 220 kDA molecular weight expressed on the surface of coelomic epithelium is elevated in about 80 per cent of women with carcinoma of ovary.[14] It has been used to differentiate malignant from benign pelvic masses[15] and is widely used for monitoring patients with ovarian cancers[16] and to define progression of ovarian cancer.[17]

CA-125 level of > 30 μ/ml is considered abnormal while > 250 μ/ml are almost always associated with malignant ovarian disease.[18] CA-125 is found to be raised in approximately 83% of women with advanced stage ovarian cancer and 50% of patients with stage I diease.[19] It is raised in approximately 90% of epithelial tumour.[13] Most of them are serous rather than mucinous.[20]

MATERIAL AND METHODS

This Descriptive cross sectional study was conducted in the Department of Obstetrics and Gynecology, Nishtar hospital Multan from February 2016 to April 2017. One hundred and eleven cases of adnexal mass were admitted in Ward of Department of Obstetrics & Gynecology, Nishtar Hospital Multan with suspicion of ovarian malignancy. Informed consent was taken from each patient. Blood samples of patients were sent to laboratory for CA-125 levels by the researcher and followed. Patients underwent surgery and biopsy was taken and sent for histopathology. Outcome variable i.e. raised level of CA-125 (> 250 μ/ml were considered as raised CA-125) were recorded on the performa by the researcher of this study

RESULTS

Family history of ovarian cancer was present in 60 patients (54.1%) while 51 patients (45.9%) had no family history of ovarian cancer. In our study, frequency of raised CA-125 levels was 82.0%; (91/111) among patients with adnexal mass. Mean CA-125 levels were 938.66±697.7 μ/ml. There were 12 patients (10.8%) of the age of 26–35 years. There were 34 patients (30.6%) each in the age group 36–45 years and 46–55 years. (Table-1). There were two unmarried patients (1.8%), 23(20.7%) nullipara, 70(63.1%) women were para 1–4 and 16(14.4%) para 5 or above (Table-2).

Out of 12 patients between 26–35 years, there were 3(25.0%) patients having raised CA-125 levels while 25(73.5%) patients out of total 34 patients between 36–45 years had raised CA-125 levels. Out of total 34 patients between 46–55 years, 33(97.1%) patients had raised levels of CA-125. Out of total 24 patients between 56–65 years, 23(95.8%) women had raised CA-125 levels and out of the total 7 patients between 66–75 years, all 7 (100%) had raised CA-125 levels as mentioned in Table-3. Significantly higher number of patients had raised CA-125 levels in advance age (p=0.003).

Out of total 2 unmarried patients, both of the 2(100%) were having raised CA-125 levels. Out of total 23 nulliparae, all 23(100%) had raised CA-125 levels. Out of the total 70 para 1–4, 55(78.6%) were having raised levels of CA-125. Out of the total 16 para ≥ 5, 11 patients (68.8%) had raised levels of CA-125 (Table-4). Low parity had significant effect on raised levels of CA-125 (p=0.003). Out of the total 60 patients having family history of ovarian cancer, 59 (98.3%) had raised levels of CA-125. Out of 51 patients with no family history of ovarian cancer, 32 patients (62.8%) had raised CA-125 levels as shown in Table-5. Significantly more number of patients with family history of ovarian cancer had raised CA-125 levels (p<0.0001).

Table-1 Age Distribution (n=111)

Age (years)	No. of Patients	Percentage
26 — 35	12	10.8
36 — 45	34	30.6
46 — 55	34	30.6
56 — 65	24	21.7
66-75	07	06.7

Table -2 Parity Distribution (n=111)

Parity	No. of Patients	Percentage
Unmarried	02	01.8
Nullipara	23	20.7
Para 1 — 4	70	63.1
Para ≥ 5	16	14.4

Table-3 Age Distribution of Suspected Cases of Ovarian Malignancy in Relation to Outcome

Age (years)	Total patients	Patients with raised CA-125	%age
26 – 35	12	03	25.0
36 – 45	34	25	73.5
46 – 55	34	33	97.1
56 – 65	24	23	95.8
66-75	07	07	100.0

P-value = 0.003

Table-4 Parity Distribution of Suspected Cases of Ovarian Malignancy in Relation to Outcome

Parity	Total patients	Patients with raised CA-125	%age
Unmarried	02	02	100.0
Nullipara	23	23	100.0
Para 1 —4	70	55	78.6
Para ≥ 5	16	11	68.8

P-value =0.001

Table-5 Family History of Suspected Cases of Ovarian Malignancy in Relation to Outcome

Family history	Total patients	Patients with raised CA-125	%age
Yes	60	59	93.3
No	51	32	62.8

P-value = <0.00001

DISCUSSION

Ovarian malignancies represent the greatest challenge. It is the second most commonly diagnosed malignancy of the female reproductive system and fifth leading cause of the death. Among gynecological malignancies it is unfortunately being increasingly encountered in Pakistan. According to multicenter study on the frequency of malignant ovarian tumour supported by Pakistan Medical Research Council (PMRC) incidence of ovarian malignancy was found to be 3.37% in 1973. Ovarian tumours are one of the major health problems confronting the general practitioners in general and gynaecologists in particular. Ovarian tumours may either be asymptomatic, found on the routine ultrasound examination or symptoms may be vague till the patient has an acute emergency like torsion or rupture of a benign cyst. The worst is late presentation of a malignant ovarian tumour. Ovarian tumors always present with wide spectrum of clinical, morphological and histological features. The majority of them are diagnosed at advance stage the survival rates have hardly improved since the three decades.[21] Variety of tumor markers with varying sensitivity and specificity are used for diagnosis of different malignancies.

Present study was conducted to determine frequency of raised CA-125 levels in patients with suspected cases of ovarian malignancy. Mean age of the patients was 47.84±10.7 years. 70(63.1%) women were para 1–4 and 16(14.4%) para 5 or above. Family history of ovarian cancer was present in 60 patients (54.1%). In our study, frequency of raised CA-125 levels was 82.0%. Our results are comparable with local and international literature. Modarres et al[22] evaluated simultaneous measurement of two serum markers (ca-125 and he-4) while diagnosing malignant ovarian epithelial tumors. The average serum level of CA-125 and HE-4 serum was notably higher in women with ovarian malignancy than in those with benignancy (CA-125: 502 vs. 19.3 v/ml, P < 0.001- HE4: 195 vs. 15.8 P mol/L, P < 0.001). As the disease stage rises, the level of these markers increases significantly. The sensitivity and specificity of simultaneous measurement of CA125 and HE4 for diagnosing epithelial ovarian cancer were calculated to be 99.5% and 100%, respectively. They concluded that simultaneous measurement of CA-125 and HE-4 increases the sensitivity and keep the specificity still high in diagnosing malignant epithelial tumors in ovary, compared with one-by-one measurement system.

Mehboob Associates[23] found that at a cut off value of 35 IU/ml, the CA-125 levels were sensitive in 34(68%) of the cases and specific in 45(90%). The levels increased were also found progressing with age and duration of disease among cases. No false positivity was found to correlate with advancing age in controls. The diagnostic accuracy was 79% and a positive predictive value of 87%. They concluded that CA-125 is a non invasive tumor marker for diagnosing ovarian tumor mode of assessing ovarian state. Yasmin et al[24] evaluated frequency of

benign and malignant ovarian tumours in a tertiary care hospital. Out of 71 cases, 61(89.71%) were benign ovarian tumors and 7(10.29%) were malignant ovarian tumors. Clinical diagnosis was confirmed with USG and CA-125 serum levels. Junejo et al[25] have found raised level of CA-125 in 11(73.3%) patients with malignancy using CA-125 serum levels. Khan et al[26] done a prospective study of ovarian tumors clinical pattern and their management. In most of malignant tumors CA 125 was raised above the cut of value 64%. Asif et al[27] have found the sensitivity and specificity of CA 125 alone for the diagnosis of ovarian cancer, at cutoff level of 35 U/ml, were 83% and 82% respectively. Using RMI, at cutoff level of 125, the sensitivity was 87%, and specificity was 88%. Parvez et al[28] in an analysis of the results revealed that different tumor markers had sensitivity varying from 76.9 - 95.8% and specificity varying from 75 - 90.9%. CA-125 was observed to be the most specific and sensitive tumor marker for ovarian tumors. J. Helzlsouer et al[29] have found that levels of serum CA-125 among cases were higher than among controls for each 3-year interval up to 12 years prior to the time of the cases' diagnoses. The median level for cases diagnosed within the first 3 years of follow-up was 35.4 U/mL compared with 9.0 U/mL for controls (*P*=.002). Measurement of serum CA-125 levels, particularly at a reference value of 35 U/mL, is not sufficiently sensitive to be used alone as a screening test for the detection of ovarian cancer. Lower CA-125 reference values could identify women at higher risk of developing ovarian cancer. Jacobs et al[30] found that the overall cumulative risk of developing an index cancer was 0.0022 for the entire study population and was lower for women with a serum CA 125 concentration < 30 U/ml (cumulative risk 0.0012) but was appreciably increased for women with a concentration > or = 30 U/ml (0.030) and > 100 U/ml (0.149). Compared with the entire study population the relative risk of developing an index cancer within one year and five years was increased 35.9-fold (95% confidence interval 18.3 to 70.4) and 14.3-fold (8.5 to 24.3) respectively after a serum CA 125 concentration > or = 30 U/ml and 204.8-fold (79.0 to 530.7) and 74.5-fold (31.1 to 178.3) respectively after a concentration > or = 100 U/ml. In one study[31] evaluating marker levels in the preoperative differentiation of borderline ovarian tumors and ovarian cancers, average preoperative serum CA-125 level in patients with ovarian cancer (600 U/mL) was higher compared to patients with a borderline ovarian tumor (115 U/mL; P = 0.004). Zou et al[32] evaluated efficacy of YKL-40 and CA125 as biomarkers for epithelial ovarian cancer. They found CA125 (524.9±972.5 vs 13.4±7.6 and 28.5±29.6 U/mL) levels were significantly higher ($P < 0.05$) in patients with ovarian cancer compared to the healthy and non-malignant groups. Our study is a hospital based with a small sample size and no controls and cannot represent the accuracy of CA-125 as marker for detection of ovarian carcinoma, further multicentre studies comparing other markers are needed.

CONCLUSION

In our study, frequency of raised CA-125 levels was 82.0% among patients with suspicion of ovarian cancer. Raised CA-125 levels were associated with advance age, low parity and family history of ovarian cancer.

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