ORIGINAL ARTICLE

Diagnostic Accuracy of Cancer Antigen 125 and Ultrasonography in Differenciation Between Benign & Malignant Ovarian Masses

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ABSTRACT

Objective
Objective of this study is to compare the diagnostic accuracy of cancer antigen 125 and ultrasonography in differentiation between benign and malignant ovarian masses by taking histopathology as gold standard..

Study Design
Comparative cross-sectional study

Sample Size
One hundred patients who were proven histologically to have ovarian masses were taken.

Setting
Department of Gynaecology & Obtetrics Unit-1, Sir .Ganga Ram Hospital, Lahore

Duration with Dates
One year from 03-03-2008 to 02-03-2009.

Sampling Technique
Convenient non-probability sampling

Inclusion Criteria
Above the age of fifteen years with histopathologically proven ovarian masses
1. Suitable for surgery.

Exclusion Criteria
1. Pregnancy with ovarian mass.
2. Hydatid cyst of ovary.

Data Collection
One hundred patients with ovarian masses were selected for this study. Blood samples were collected preoperatively for measurement of serum CA125 from these patients. Various cutoff levels of CA125 were used to classify masses into benign or malignant ones. All these patients also had preoperative ultrasound examination. Ultrasound echo pattern recognition was used to a mass as benign or malignant. Results from both assays were then compared with histological findings after surgery.

Statistical Analysis
The collected data was transferred into SPSS version 12 and analysed through this statistical programme. Descriptive statistics had been calculated. Age, duration of menstrual cycle, age of menarche and menopause (where applicable) and level of cancer antigen 125 had been calculated as mean and standard deviation. While education, marital status, occupation had been presented as percentages. Sensitivity, Specificity, Positive predictive value, Negative predictive value had been calculated by using histopathology as gold standard. Specific variable (type of tumour) had been associated with demographic variable, association that had been tested for significance by applying Chi Square test as this variable was qualitative in nature. P value equal to or less than 0.05 was considered significant.

Results
One hundred patients of ovarian masses were selected. Benign masses were 78% and 22% were malignant. The most common clinical presentation was abdominal pain followed by abdominal mass. The sensitivity and specificity of CA125, at cutoff level of 35U/ml were 82% and 83% respectively to classify masses into benign or malignant ones. Ultrasonographic differentiation of benign and malignant ovarian tumours showed results with a sensitivity of 86% and specificity of 87%.

Conclusion
It is concluded that there is a 22% risk of malignancy in patients presenting with an ovarian mass. Women especially in the reproductive age presenting with abdominal pain should be carefully evaluated for a

ovarian mass. Anechoic masses have high probability of being benign and possibility of malignancy increases with the presence of solid component. CA125 has lower sensitivity and specificity than that of ultrasonography for discrimination between benign and malignant ovarian masses.

Key Words: Ovarian tumour, Ovarian masses, Cancer Antigen 125, and Ultrasonography of ovarian masses.

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer related deaths in female population. The frequency is variable in different parts of the world.[8]

Due to the complex embryological and histogenetic development, the ovaries are the source of great variety of tumours.[1] Ovarian tumours may be physiological or pathological and may arise from any tissue of the ovary.[2] Pathological tumours are further classified into benign and malignant. Most benign ovarian tumours are cystic and finding solid elements makes malignancy more likely.[3] Ovarian neoplasms present asymptomatically or with pain, abdominal swelling, pressure effects, menstrual disturbances, hormonal effects or an abnormal cervical smear.[4] Ninety percent of all ovarian tumours are benign, mostly cystic and often resolve spontaneously.[5] Benign ovarian neoplasms have the capacity to undergo malignant change and difficult to diagnose in early stages. The relative frequency of malignant ovarian tumours of all gynaecological malignancies is found to be 24.01%.[6]

In Pakistan ovarian cancer is the second common cancer in females and most frequent cause of death due to gynaecological cancers.[8] Despite the increases in our understanding of the molecular events underlying malignancy, improved surgical techniques and novel chemotherapeutic agents, ovarian cancer remains a challenging condition to manage and survival rates have hardly improved over the last three decades when it is at advanced stage at the time of diagnosis. Most ovarian tumours are epithelial in origin. Due to their painless nature and non-disturbance of menstrual function, these tumours remain occult for a prolonged period. Ovarian cancers are mostly detected at late stages so overall five year survival rate is poor.[10] Eventually 75-80% of women with ovarian cancer will die from their disease.[11] Epithelial tumours are most frequently associated with nulliparity, early menarche, late age at menopause and a long estimated number of years of ovulation ,use of fertility drugs, certain environmental factors like exposure to asbestos, cigarette smoking, talc and high fat intake.[9] Surgery must be considered for ovarian neoplasms.[12] Mortality may be reduced if disease can be diagnosed at earlier stage with smaller tumour burden.[13] Over the last two decades, advances in epidemiology, diagnostic techniques, screening and treatment have led to earlier diagnosis and improved prognosis.[14] Current modalities like bimanual pelvic examination, cancer antigen 125 and ultrasonography are being used in early detection and in differentiation between benign and malignant ovarian tumours.

Sonographic evaluation with predefined specific criteria for the detection of a solid tumour component is an accurate method of preoperative discrimination between benign and malignant ovarian tumours. But it is labour intensive and operator dependent and gives false positive results. Serum cancer antigen 125 assay may assist in eliminating false positive results.[15] However, CA125 has some limitations in the early detection of ovarian cancer due to non-specificity.

Optimal treatment can only be planned if benign or malignant nature of ovarian mass is known before operation. We designed this study to find out the best test which will be used in our women for the early detection and in differentiation between the benign and malignant ovarian tumours. So by using the best test, the better management of ovarian masses will be planned. In this way, we can improve five year survival rate, reduce undue morbidity and can avoid impairing future fertility of younger female patients.

RESULTS

One hundred patients who fulfilled the inclusion criteria were included in this study. Their levels of CA125 in blood were determined preoperatively. All patients underwent ultrasonographic examination before operation. They were operated and histopathology of the resected masses were done to confirm the diagnosis. The mean age was 50.4% for benign tumours and mean age of patients with malignant tumours was 59.2%. The most common clinical presentation was abdominal pain (38.46+36.36=74.82) followed by abdominal

mass(25.64+22.72=48.36). Menstrual irregularity, infertility, gastrointestinal complaints and frequency of urination. In our study, 78% of the patients had benign ovarian masses and 22% had malignant ovarian tumours. The different types of ovarian masses histologically were Epithelial tumours 66(66%), physiological cysts 16(16%), Germ cell tumours 13(13%), Endometriotic cysts 3(3%), Sex cord tumours 1(1%) Metastatic tumours 1(1%).

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value(NPV) at different levels of serum CA125 were determined. 82% of patients with histologically confirmed ovarian carcinoma had raised serum CA125 (> 35 U/ml), whereas only 13% patients with benign ovarian tumour showed elevated serum CA125. Evaluation of echogenic characteristics and histology of each tumour was done. Ultrasound diagnosed 86% of malignant findings in patients having histologically proven malignancy, whereas ultrasound showed findings of malignancy in 10% patients with benign ovarian masses. Thus sensitivity and specificity of ultrasound were 86% and 87%.In this series, majority of the tumours were serous cystadenomas(34%) and most of these were clear cysts(55.56%) and 22.22% had solid component and 22.22% had septations.

Table 1: Distribution of patients by age

Age (Years)	Benign (n=78)		Malignant (n=22)	
	No.	Percentage	No.	Percentage
20-29	16	20.5		
30-39	11	14.3		
40-49	10	12.8	2	9.1
50-59	9	11.5	8	36.36
60-69	12	15.3	10	45.45
70-79	20	25.6	2	9.09
Total	78	100	22	100
Mean±SD	50.4±18.9		59.2±9.09	

Key: SD Standard deviation

Table 2: Distribution of patients by presenting complaints

	No.	Percentage	No.	Percentage
Abdominal Pain	30	38.46	8	36.36
Abdominal Mass	20	Presenting Complaints	Benign (n=78)	Malignant (n=22)
Menstrual Irregularity	12	15.39	4	18.18
Infertility	8	10.25	3	13.64
Gastrointestinal Complaints	6	7.70	1	4.55
Frequency of Micturation	2	2.56	1	4.55
Total	78	100	22	100

Table 3: Distribution of patients by histopathological characteristic of Benign ovarian masses

Histopathological Diagnosis	Frequency	Percentage
Endometriotic cyst	3	3.85
Mucinous cystadenoma	14	17.95
Serous cystadenoma	34	43.58
Mature Cystic teratoma	8	10.25
Struma Ovarii	3	3.85
Follicular Cyst	3	3.85
Luteal Cyst	13	16.67
Total	78	100

Serous cystadenocarcinomas was the commonest malignant tumour (8%). 40% were predominantly solid and 60% were cystic with solid component.

All teratomas were diagnosed on ultrasound were benign. These showed typical features of teratomas i.e echogenic material, calcification and solid component. Granulosa cell tumours were solid in appearance. Dysgerminomas and Metastatic tumours were complex predominantly solid in appearance. Endometrioid carcinoma were 3% of the tumours and most of these were cystic with internal echoes. Most of the follicular cysts (50%) were anechoic in appearance while 33.34% were with septations and 16.66% had internal echoes. Solid component was present in 80% cases of malignant tumours and 20% of malignant tumours were cystic with septations. Solid

component was also seen in more than 20% of benign tumours. Unilocular clear cysts were all benign.

Table 4: Distribution of patients by histopathological characteristic of malignant ovarian masses

Histopathological Diagnosis	Frequency	Percentage
Serous cystadenocarcinoma	8	36.36
Mucinous cystadenocarcinoma	5	22.72
Endometrioidcarcinoma	3	13.62
Undifferentiated carcinoma	1	4.55
Clear cell carcinoma	1	4.55
Metastatic tumour	1	4.55
Dysgerminoma	1	4.55
Endodermal sinus tumour	1	4.55
Granulosa cell tumour	1	4.55
Total	22	100

Table 5: Distribution of patients by serum level of CA 125 for benign and malignant ovarian masses

CA 125(U/ml)	Benign(n=78)	Malignant (n=22)
Mean	26.5	1107
Minimum	2	15
Maximum	210	9540

Table 6: Sensitivity and Specificity of Serum CA125

True Malignant	False Positive
18	13
False Negative	True Benign
4	65

Sensitivity = 18x100 =82% 18+4 Specificity =65x100 = 83% 65+13

Table 7: Sensitivity and Specificity of Ultrasonography of Ovarian Masses

True Malignant	False Positive
19	10
False Negative	True Benign
3	68

Sensitivity = 19x100 =86% 19+3 Specificity =68x100 = 87% 68+10

DISCUSSION

The accurate diagnosis of an ovarian mass is a challenge to medical professionals before exploration by laparotomy or laparoscopy, because of its bizarre and atypical behaviour. Optimal treatment can only be planned, if its benign or malignant nature is known before exploration. Moreover, aggressive cytoreductive surgery demands timely diagnostic evaluation of extent of tumour spread, besides specific skill and experience of general gynaecologist.[16]

In different international studies, percentage of malignant ovarian tumours ranges from 28% to 33%.[17,18]. In some studies carried out in Pakistan, it ranged from 30% to 40%.[19, 20, 21] our percentage of malignant ovarian tumours was less at 22% and it compared with a study carried out at Karachi which was 21%. Maximum number of patients with ovarian masses in our study were from 35 to 55 years of age similar to other studies.[22]

In our study epithelial tumours were 66(66%) physiological cysts(16%), germ cell tumours13(13%), endometriotic cysts 3(3%), sex cord stromal tumours 1(1%), metastatic tumours 1(1%) of all the ovarian masses. In national and international studies epithelial tumours have ranged from 57% to 75%.[23, 24]

Nulliparity is considered to be a risk factor for the development of ovarian carcinoma. Most of western studies have shown that nulliparous women have higher incidence of ovarian cancer and the risk of ovarian cancer is inversely related to the number of full term pregnancies and each sibling is associated with a risk reduction.[25,26,27,28,29,30] However,37% of our patients were nullipara and 63% multipara. These findings in our study are similar to earlier observations from Rawalpindi, Karachi, Lahore and Nigeria.[31,32]

Among various tumour markers, CA125 along with ultrasound techniques, has been proposed to be more capable of differential diagnosis of benign and malignant ovarian masses.[33.] CA125 has been more precisely correlated with ovarian cancer. In our study, 82% of patients with histologically confirmed ovarian carcinoma had raised serim CA125 (>35 u/ml), where as only 13% patients with benign ovarian tumour showed elevated serum CA125. Thus sensitivity and specificity of CA125 for ovarian cancer at cut-off value of 35 u/ml was 82% and 83% respectively. These results are consistent with the study done by Manjunath et al.[34] who showed similar findings(sensitivity of 83% and specificity of 82%).A local study carried out on local population has revealed a lower sensitivity (76.7%) with relatively high specificity (90.9%) of

CA125 in differentiating between benign and malignant ovarian masses. However, Jacob et al.[71] have shown a lower specificity (75.2%) but similar sensitivity (81%) at same cut-off level of CA125.

In earlier studies by Moyle et al.[35], and Trinidad et al.[36], it has been reported that anechoic masses are benign. Our findings are consistent with this as all clear cysts were benign in this study. Masses showing solid component and thick septations are considered as malignant on ultrasound, histopathology showed that 27.58% of tumours with solid component on ultrasound were benign. It was found that this appearance was due to the presence of thick mucinous material adherent to the cyst wall and to the septa. In haemorrhagic cysts, complex appearance is due to the presence of organised blood. Eighty percent of the malignant tumours have solid component and 20% are cystic with septation. Incidence of serous cystadenocarcinoma is 3-4 times more than that of mucinous cystadenocarcinoma but in the present study, mucinous cystadenocarcinoma was more prevalent. Muzzaffar et al 4.[37] also reported similar incidence in Pakistani women. This may be related to genetic, environmental, or racial factors. Specific pathological diagnosis of teratomas can be made by ultrasound when highly echogenic focus, calcification and solid component are seen. This appearance is due to the presence of hairs, sebaceous material and teeth in them. The ultrasound findings showed 19 true malignant cases and 68 true benign cases when compared with histopathological diagnosis of ovarian masses.

This study shows that anechoic cystic masses have high probability of being benign. Possibility of malignancy increases with the presence of solid component, predominately solid tumours are more likely to be malignant. The earlier diagnosis of ovarian mass gives better result of treatment, so preoperative evaluation is basic to the successful management of ovarian mass.

CONCLUSION

It is concluded that there is a 22% risk of malignancy in patients presenting with an ovarian mass. Women especially in the reproductive age presenting with abdominal pain should be carefully evaluated for a ovarian mass. Anechoic masses have high probability of being benign and possibility of malignancy increases with the presence of solid component. CA125 has lower sensitivity and specificity than that of ultrasonography for discrimination between benign and malignant ovarian masses. It is concluded that ultrasound echo pattern is superior to serum CA 125 for discrimination between benign and malignant ovarian masses.

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