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RESEARCH ARTICLE
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DIAGNOSTIC ACCURACY OF RISK OF MALLIGNANCY INDEX (RMI) BASED ON SERUM CA 125, ULTRASOUND SCORE AND MENOPAUSAL STATUS IN DETERMINING THE MALIGNANCY RISK IN ADNEXAL MASS

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ABSTRACT

Introduction: The presence of an adnexal mass is a frequent reason for a woman to be referred to a gynecologist. An adnexal mass may be benign or malignant. It is the risk of malignancy that propels us for early, accurate and prompt diagnosis to lessen mortality and morbidity.

Objective: To determine diagnostic accuracy of risk of mallignancy index (RMI) based on serum ca 125, ultrasound score and menopausal status in determining the malignancy risk in adnexal mass

Methodology: This cross-sectional study was conducted in the Department of Obstetrics & Gynecology, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, from May 10th, 2023, to November 10th, 2023. The sample size of 100 women was determined using WHO software for sample size calculation. Patients between the ages 25-75 years, presenting with any symptom and diagnosed to have adnexal mass diagnosed on ultrasound were enrolled. Detailed history of patient, clinical examination, preoperative serum CA 125 levels and Trans-abdominal abdominopelvic ultrasound was performed. Characteristics of mass were determined on ultrasonography by a senior radiologist. Data was analyzed on SPSS version 23.

Results: The average age of study patients was 29.4 $\pm$ 5.5 years. Primary infertility was experienced by 30.0% women whereas secondary infertility was found in 45.0% women in this study. It was witnessed that 96.0% of the study women had disturbed menstrual cycles and 19.0% had passage of clot. The pre-operative mean CA 125 level was 60.5 $\pm$ 46.4 IU/ml while post operatively after 6 weeks it was found at 27.5 $\pm$ 17.5 IU/ml and this difference between pre operative and post operative CA 125 levels was highly statistically significant (p-value = <0.001). The percentage decrease was 45.1% from preoperative readings to post operative levels of CA 125 in this study.

Conclusion: The risk of malignancy index to be a valuable, reliable, and applicable method in the primary evaluation of patients with ovarian masses and a usable method in referral of relevant patients for centralized surgical treatment.

Keywords: Diagnostic accuracy; Risk of mallignancy index; Serum ca 125, ultrasound score; Menopausal status

INTRODUCTION

The presence of an adnexal mass is a frequent reason for a woman to be referred to a gynecologist. An adnexal mass may be benign or malignant. It is the risk of malignancy that propels us for early, accurate and prompt diagnosis to lessen mortality and morbidity. In India, ovarian cancer has emerged as the fourth most common malignancy among females with incidence varying between 5.4 and 8 per 100,000populations in different parts of the country.[1]As the symptoms of the ovarian cancer are very vague like bloating, pelvic or abdominal pain, poor appetite, feeling full quickly, and urinary urgency it is also known as "silent killer".

Thus, silent occurrence and slow progression, added to the fact that few effective methods for early diagnosis and no universal screening method for diagnosis of malignant ovarian tumor exists, made its mortality rate highest among gynecologic malignancies.[2] The main challenge is to identify patients with high-risk adnexal masses preoperatively and this is compounded by the lack of definitive noninvasive diagnostic test. The discrimination between benign and malignant adnexal mass is central to decision regarding clinical management and surgical planning in such patients. The standardize method for preoperative identification of probable malignant masses would allow optimization of first line treatment for women with ovarian cancer. Early identification of ovarian carcinomas and referral to a gyneco-oncologist can facilitate accurate staging of the disease and optimal cytoreductive treatment, enhancing patientsurvival.[3, 4] Currently clinical examination, ultrasound assessment, assay of tumor markers are part of standard work up for adnexal mass but none of these indicators alone is very sensitive or specific for detecting malignancy in ovarian masses.

To reduce the diagnostic dilemma between benign and malignant ovarian masses, a formula-based scoring system known as risk of malignancy index (RMI) was introduced by Jacobs et al. [5]. in 1990, which was term as RMI 1. It is a product of ultrasound findings (U), the menopausal status (M), and serum CA-125 levels (RMI = U X M X CA-125). The original RMI (RMI-1) has been modified in 1996 by Tingulstadet al. [6]. Known as (RMI2) and again in 1999 known as (RMI3).[7,8] The difference between the new indices lies in the different scoring of ultrasound characteristics and menopausal status.

MATERIAL AND METHODS

This cross-sectional study was conducted in the Department of Obstetrics & Gynecology at Allama Iqbal Teaching Hospital, Dera Ghazi Khan, from May 10th, 2023, to November 10th, 2023. The sample size of 100 women was determined using WHO software for sample size calculation, assuming a 95% confidence interval, a 50% anticipated proportion of women with multiple pregnancies, and an absolute precision of 7%. A non-probability consecutive sampling technique was employed. Patients between the ages 25-75 years, presenting with any symptom and diagnosed to have adnexal mass diagnosed on ultrasound were enrolled. Detailed history of patient, clinical examination, preoperative serum CA 125 levels and Trans-abdominal abdominopelvic ultrasound was performed. Characteristics of mass were determined on ultrasonography by senior radiologist. Patients were managed as per protocol pre-operatively and during surgery. Their tumor masses were sent to hospital lab for histopathology along with all other tissues removed during staging laparotomy. Patients were followed up with their histopathology reports. Those patients whose reports could not be traced were excluded from study. All pre-operative information including RMI and histopathology reports were entered in a structured proforma. Data was analyzed on SPSS version 23. RMI score was calculated as follows: A cutoff of >200 is used to designate as malignant and <200 is considered as benign. Patients in which the histopathology could not be obtained were excluded.

RESULTS

In this study a total of 100 women were enrolled. Almost 80.0% of the women were between 25 and 40 years of age. Four percent of the study cases were found to have age up to 20 years whereas 3% were found having 41 years or above age. The average age was 29.4 ± 5.5 years. Of the total 100 study cases, 53.0% were nulliparous, 10.0% were primiparous while 37.% of the women were found to be multiparous. The details regarding infertility were analysed in the study patients. Primary infertility was experienced by 30.0% women whereas secondary infertility was found in 45.0% women in this study.

It was witnessed that 96.0% of the study women had disturbed menstrual cycles. And 19.0% of the cases were having passage of clot. In our study population, 53.0% cases had history of failed medical treatment for endometriosis whereas 34.0% women had history of recurrent endometriosis. (Table 1)

As per study objective level of CA 125 was compared among study patients before and after operation for endometriosis. The pre operative mean CA 125 level was 60.5 ± 46.4 IU/ml while post operatively after 6 weeks it was found at 27.5 ± 17.5 IU/ml and this difference between pre operative and post operative CA 125 levels was highly statistically significant (p-value = <0.001).

The mean decrease observed in CA 125 level was 33.0 IU/ml. According to average CA 125 levels in percentages a decrease of 45.1% was seen from preoperative to post operative levels of CA 125 in this study. (Table 2)

Table 1: Age, parity of study patients (n=100)

Variables		**Number of cases**	**%age**
Age (years)	Up to 20	4	4.0%
	21 to 25	13	13.0%
	26 to 30	45	45.0%
	31 to 40	33	33.0%
	41 or above	3	3.0%
	Mean + SD	29.4 ± 5.5 years	
Parity	Nulliparous	53	53.0%
	Primaparous	10	10.0%
	Multiparous	37	37.0%
Infertility	Primary	30	30.0%
	Secondary	45	45.0%
Menstrual history	Disturbed cycle	96	96.0%
	Passage of clot	19	19.0%
History of failed treatment and recurrent endometriosis	H/O failed medical treatment	53	53.0%
	H/O recurrent endometriosis	34	34.0%
Mean + SD		29.4 ± 5.5	

Table 2: Comparison of pre and post-operative CA 125 level in the study

	Pre-operative	**Post operative**	**p-value**
CA 125 (IU/ml)			
Mean ± SD	60.5 ± 46.4	27.5 ± 17.5	<0.001

Mean decrease in CA 125 = 33.0 IU/ml

Percentual decrease between pre and post operative CA 125 levels = 54.5%

DISCUSSION

About 10% of women undergo exploratory surgery for evaluation of ovarian masses during their lifetime.[8] Prompt identifications of ovarian malignancies and referral to a gyneco-oncologist can enhance the patient survival rates.[9] but a single method which can accurately predict ovarian malignancy is still unavailable. In the pre-operative assessment of adnexal mass, the major diagnostic tools are still clinical impression and ultrasound examination. However, due to limitation of clinical impression and sonographic findings to predict ovarian malignancy, it is not surprising that gynecologists may detect an unexpected ovarian malignancy intra-operatively. Often an improper incision is made, the bowel is not adequately prepared or the surgeon is confronted with need to

perform an unplanned cytoreductive surgery. A scoring system that predict ovarian malignancy can improve the chance of better preoperative counseling, better preoperative preparation and where appropriate referring the patients to a specialized center. Herein we report that the multiparametric RMI score can be a useful tool in prediction of malignant ovarian disease, in low-resource settings. Subsequent to introduction to RMI the same research group had reevaluated their diagnostic method in a new group of patients admitted for pelvic masses and confirmed the sensitivity and specificity of RMI and its priority compared to individual criteria.[10] Serological testing of CA125 is used for initial detection and monitoring of progression of disease. CA 125, a cell surface glycoprotein is also raised in other conditions such as menstruation, pregnancy, pelvic inflammatory disease, fibromas, genital neoplasm. In a prospective pilot study it was proved that during combined treatment with aromatase inhibitor and GnRH-agonist endometriomal volume and serum CA 125 level decreased by 29% and 61% respectively[5].

Maiorana and colleague conducted a study to investigate clinical value of CA 125 for the diagnosis and determining the severity of pelvic pain associated with endometriosis[6]. They found elevated CA 125 levels in severe dysmenrrhea and dyspareunia.

Another study by Marana R et al found that with medical treatment (GnRH agonists) CA 125 level decreased about 40% in 6 month therapy[9].

Many studies have been conducted previously which shows a decrease in CA 125 level after surgery but no percentage fall in CA 125 after the surgery has been reported.

We planned a prospective study on women with endometriosis undergoing surgical procedure and observed the pre and post-operative CA 125 levels in these patients. The study outcome was to determine the total percentage fall in CA 125 levels.

The current study was a descriptive case series conducted at the outpatient and Gynecological Ward in the Mother and Child health Center, Pakistan Institute of Medical Sciences, Islamabad. A total of 100 patients with endometriosis were enrolled during the study period of 6 months. All women of reproductive age presenting with endometriosis, infertility, preoperative CA level of > 35 IU/ml were included. Patients who had previous surgery for endometriosis, who had failed medical treatment and had recurrence of endometriosis were also included in the study. Patients who had menstruation, had fibromas, pelvic inflammatory disease or genital neoplasm were all excluded from the study.

The original study sample was estimated to enroll 93 cases, however, we rounded it off and enrolled 100 women in this study. The average age of patients was 29.4 $\pm$ 5.5 years in this study. Majority of the cases were from 25 to 40 years. A previous study on a similar topic by Somigliana E and colleagues reported mean age of 32.0 $\pm$ 4.2 years of their study population with endometriosis[10].

Another study by Moore RG and colleagues to assess whether serum HE4 levels are less frequently elevated than CA 125 IU/ml in women with benign gynecologic disorders, they reported mean age of women in premenopausal group 40 years ranging from 18 to 56 years while in the postmenopausal group it was 62 years ranging from 39 to 89 years[11].

In the current study primary infertility was witnessed in 30.0% of the cases while secondary infertility was found in 45% of the cases. Almost all the study cases were experiencing disturbed menstrual cycles, and 19% of the women were experiencing passage of clot. In our group of patients 53% had history of failed medical treatment and 34% had history of recurrent endometriosis.

In our study the mean level of CA 125 was found very high pre operatively 60.5 $\pm$ 46.4 whereas post operatively after 6 weeks it was found at 27.5 $\pm$ 17.5 IU/ml and this decrease in means was found statistically significant (<0.001). A perceptual decrease of 54.5% was witnessed in CA 125 levels post operatively.

A previous study by Garzetti GG et al reported that serum levels of CA 125 significant increase in patients of endometriosis compared to the controls. They concluded that post operatively CA 125 level was related to clinical evolution of the disease, being higher in patients whose disease recurred in comparison to those with negative follow-up. In their study serum CA 125 level was directly related to adhesion score and peritoneal involvement suggesting a central role of pelvic and peritoneal irritation in the increase in level of serum marker[12].

In a recent study Maiorana A et al investigated the clinical value of serum CA 125 level for the diagnosis and determination of severity of endometriosis and pelvic pain associated with endometriosis. They found out that mean CA 125 levels were higher in patients with endometriosis than those of the control group[6].

Marana R et al reported that mean CA 125 level decreased from 38.4 U/ml to 15.5 after 6 months of therapy with gonadotrophin releasing hormone agonist given for the treatment of endometriosis[9].

Similarly, Chen FP et al witnessed that CA 125 level is not an effective tool for patients with dysmenorrheal and monitoring therapy for endometriosis, however, it is a valuable adjuvant in the follow-up of recurrence in patients with advanced endometriosis and initially elevated CA 125 levels[13].

It is well known that CA-125 has been the most extensively evaluated biomarker in epithelial ovarian cancer. It is used in the settings not only of distinguishing benign from malignant ovarian masses but also ovarian cancer screening, diagnosing ovarian cancer recurrence, and monitoring response to therapy. Unfortunately, CA-125 levels do not always correlate with the presence or absence of ovarian cancer. Jacob I and colleagues witnessed that elevated CA-125 level is found in only 50% of patients with stage I ovarian cancer, whereas more than 90% of patients with advanced-stage disease have an elevated CA-125 level[14].

In premenopausal patients, interpretation of an elevated CA-125 level can be problematic. The most common reason is endometriosis for an elevated CA-125 level in a premenopausal patient. Many investigators have witnessed that cases of CA-125 levels higher than 1,000 U/mL have been described in patients with endometriosis and fibroids[15].

ACOG and the Society of Gynecologic Oncologists (SGO) recommend that premenopausal patients with an adnexal mass and elevated CA-125 level (> 200 U/mL) be referred to a gynecologic oncologist for surgical evaluation[16].

There is abundance of literature on CA 125 level investigated as a diagnostic tool and monitoring medical treatment, however, data on pre and post-operative condition of these levels is not available. The current study is one of the first attempts to determine the decrease in CA 125 levels after surgery. Our results have important implications for programmes and protocols related to gynecology and obstetrics. We saw a significant decrease in the CA 125 levels in the current study with more than 45% decrease in the pre-operative readings to after 6 weeks post operatively.

There are some limitations of the current study as well, the detailed data regarding histopathological confirmation and type is missing which could have given a much greater information regarding endometriosis presenting to our local setting. The data regarding clinical presentation is also missing which could have lead to screen out signs and conditions needing urgent attention.

For future research on this topic we suggest that detailed information regarding patients with endometriosis should also be collected in terms of clinical, radiological and pathological along with validating our results which have significant implications of difference in pre and post-operative levels.

CONCLUSION

The present study has demonstrated the risk of malignancy index to be a valuable, reliable, and applicable method in the primary evaluation of patients with ovarian masses and a usable method in referral of relevant patients for centralized surgical treatment. Other models of preoperative evaluation should be developed to improve the detection of non-epithelial ovarian cancers, borderline ovarian tumours, and early stage invasive disease. Use of the methods in routine practice should be an important element of these methods.

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