Evaluation of the 'Ovarian Crescent Sign' in the Preoperative Determination of the Nature of Adnexal Masses

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ABSTRACT:

BACKGROUND:

There are no universally accepted criteria for distinguishing between benign and malignant ovarian masses on the basis of ultrasound findings. Risk of malignancy indices have been proposed, but these methods use complex calculations and study multiple parameters to develop a score. The detection of normal ovarian tissue in the adnexal masses, the ovarian crescent sign, is highlighted as a single ultrasound parameter prejudging the nature of adnexal mass as benign or malignant. It has been reported that absence of the "ovarian crescent sign" is a more sensitive indicator of malignant nature than the risk of malignancy indices.

OBJECTIVE:

To evaluate whether the presence of normal ovarian tissue adjacent to adnexal masses (the 'ovarian crescent sign') could assist in the preoperative differential diagnosis of these masses, and to compare its accuracy with standard biochemical and sonographic indices.

METHODS:

Sixty four women with adnexal masses were included in this prospective observational study. Serum cancer antigen 125 levels were measured and transvaginal and/or transabdominal ultrasound scans of the adnexae were performed and the tissue adjacent to the mass was examined for the presence of the 'ovarian crescent sign'. The risk of malignancy index was calculated and all the findings were compared with the final histopathological diagnosis and the accuracy of each test was compared to the others in the form of sensitivity, specificity, positive and negative predictive values.

RESULTS:

Fifty five out of sixty four women were found to have benign masses, one had a borderline tumor and eight had invasive malignant lesions. Normal ovarian tissue 'ovarian crescent sign' was seen in fifty three out of fifty five women with benign lesions but it was not seen in any one of the nine women with malignant lesions.

In the absence of the "ovarian crescent sign", ovarian cancer was diagnosed with a sensitivity of 100% and a specificity of 96.4%. For the cancer antigen 125 test, the sensitivity was found to be 77.7%, specificity 92.7%; for the Risk of Malignancy Index, sensitivity was 55.6% and specificity was 89.1%.

CONCLUSION:

The "ovarian crescent" sign is a reliable sonomorphological feature that can help to exclude ovarian cancer in patients with adnexal masses, while its absence highly indicates malignancy.

KEY WORDS: adnexal masses, ovarian crescent sign, cancer antigen 125.

INTRODUCTION:

Adnexal abnormalities may be discovered by screening or by investigations performed specifically for a suspected pelvic mass [(1)]. The only definitive way of determining whether a mass is benign or malignant is histopathological examination after surgery [(1)]. However, the majority of women with adnexal masses will not have malignant disease and many do not require surgery [(2)]. International guidelines support the early involvement of a gynaecologic oncologist in the care of women who are likely to have ovarian cancer to perform optimal surgical staging and cytoreduction [(3,4)].

The preoperative evaluation of patients with an adnexal mass highly suspicious for ovarian cancer can be aided by ultrasound scan (transabdominal or transvaginal) and Doppler study [(5)]. Tumor markers are also used but only few of them can be utilized effectively for the early detection of ovarian cancer

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such as CA125, CEA (Carcinoembryonic antigen), hCG (human chorionic gonadotropin), LDH (Lactate dehydrogenase), AFP (alpha-fetoprotein), OVX1(a Lewis X determinant on mucin), prostatin and CA15-3 [5]. Some of the most promising include: HE4 (human epididymis protein 4), mesothelin, M-CSF (Macrophage colony-stimulating factor), osteopontin, kallikrein(s), and soluble EGFR (endothelial growth factor receptor) [6]. The most extensive experience has been with CA125 [6]. CA125 could be elevated in several benign conditions such as menstruation, endometriosis, pregnancy, and pelvic inflammatory diseases [6]. The cutoff for most of automated immunoassays for CA125 is 35 U/ml, established from the distribution of CA125 results in healthy women [6,7]. Despite the same cutoffs, these immunoassays can give different results on the same specimen; therefore their results are not interchangeable [7].

There are three models of the risk of malignancy index: RMI 1, RMI 2, and RMI 3[8,9,10]. Munjunath et al. (2001) found that RMI 2 performed better than the other 2 indices at cutoff level of 200, but also found that the RMI was not sensitive in nonepithelial ovarian cancer [11].The Northern Cancer Network (United Kingdom) guidelines recommend calculation of the RMI using the RMI 2 model with a cutoff level of 200 as being indicative of malignancy [12].

The "ovarian crescent sign" is the sonographic finding of normal ovarian tissue with a regular surface adjacent to an adnexal mass within the ovarian capsule [13]. This was first described in a prospective study by Hillaby et.al in 2004 who reported that this sign was a useful morphological feature in the pre-operative differential diagnosis of adnexal lesions [13]. It was highlighted as a single, simple and reproducible ultrasound parameter in prejudging the nature of adnexal masses as benign or malignant [14,15,16].

PATIENTS AND METHOD:

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at Al- Yarmouk Teaching Hospital, in cooperation with the Department of Ultrasound and Radiology, for the period between May 2010 and June 2011.

A total of 70 consecutive women were included in this study. The patients attended the gynaecology unit with ultrasonographic finding of adnexal masses that required surgical removal. Prior to operations all women underwent an additional detailed transvaginal (5-MHz frequency) and/or transabdominal (3.5-MHz) grey-scale ultrasound examinations by specialist radiologists, looking for the following details, using the available machines (Philips HD 11 XE and Philips Envisor C): the mass size (three diameters), presence of papillary proliferations (i.e. solid projections into the cyst cavity > 3mm in height), presence of septations and solid areas within the cyst, presence of ascites, and in the cases of bilateral masses, the mass with the most complex ultrasound morphology was included. The ovarian crescent sign was looked for by sweeping through the whole mass in different planes searching for normal ovarian tissue adjacent to the tumor. Normal ovarian tissue was identified as hypoechogenic tissue with or without ovarian follicles located adjacent to the cyst wall which could not be separated from the cyst by applying moderate amount of pressure (Figure 1).

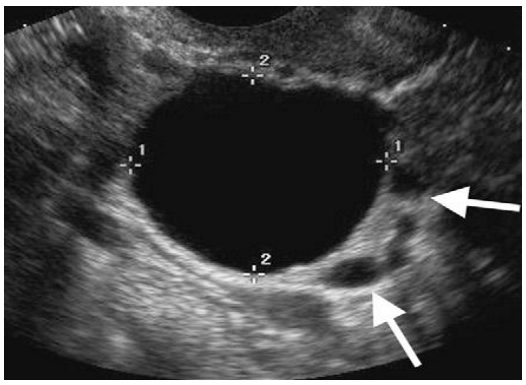

Figure 1: A transvaginal pelvic ultrasound showing normal ovarian tissue (OCS) clearly visible adjacent to a benign ovarian cyst.

Serum samples were collected preoperatively and serum CA125 levels were measured using Enzyme Linked ImmunoSorbant Assay (ELISA) by Roch Cobace e411 a product of Roch Company (FDA approved) in accordance with the manufacturer instructions. A serum CA125 level of 35 U/ml was considered as the upper limit of normal, a level > 35 U/ml was considered abnormal, and a level of 200 U/ml or more was considered to be highly indicative of a malignant lesion. The risk of malignancy index for each patient was calculated using the model known as (RMI 2) created by Tingulstad *et al.* in 1996 [9].

RMI 2= U x M x CA125 level
U= Ultrasound score
M= Menopausal status

Ultrasound score was assigned for the following morphological features in an adnexal mass: Multilocular cyst, solid areas, bilateral lesions, ascites, and intrabdominal metastases. Each one of these morphological features was given one point when present. The sum of all points is named "Ultrasound score". When the ultrasound score of a mass is 0 or 1, U in the equation above is given a value of 1; and when the ultrasound score is ≥ 2, U is given a value of 4 [9,10,11]. In premenopausal status, M= 1 and in postmenopausal status, M= 4 [9,10,11]. CA125 level was applied directly to the calculation. Histopathological examinations of the tumors were done in the teaching laboratories at Al-Yarmouk Hospital by specialist histopathologists and were considered as the gold standard reference to which the ultrasound results were compared. Women with the following criteria were excluded: masses due to ectopic pregnancy, pelvic inflammatory diseases, masses requiring no surgical intervention e.g. small simple cysts <5cm, and cases reported with a previous proven diagnosis of malignancy.

Statistical analysis:

Analysis of data was carried out using the available statistical package of SPSS-18 (Statistical Packages for Social Sciences- version 18 "PASW" Statistics). Differences between variables were measured by using T-test to study relation between continuous variables. Chi-square test was used to measure the association between discrete variables. A value of $P < 0.05$ was considered to be significant. The diagnostic accuracy of the tests was assessed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

RESULTS:

Data set were incomplete in 6 women who were excluded from the final data analysis. The demographic characteristics of the remaining 64 patients included are shown in table 1.

Table 1: Distribution of age, menopausal status and parity between benign and malignant pathologies.

Variable	Benign		Malignant		X^2	P-value
	n = 55	%=85.9	n = 9	% =14.1		
Age (years) mean± SD = 37.5 ± 14.6 range = 15-64 ≤20 21-30 31-40 41-50 >50	 5 18 14 9 9	 9 32.7 25.5 16 16	 0 1 2 3 3	 0 11 22 33 33	0.435	0.226
Menopausal status Premenopausal postmenopausal	 47 8	 85.5 14.5	 7 2	 77.8 22.2	0.35	0.557
Parity Mean ± SD = 2.75 ± 2.9 Range = 0-12 0 1 – 4 ≥ 5	 19 24 12	 34.5 43.6 21.8	 2 3 4	 22.2 33.3 44.5	2.14	0.344

According to the final histopathological reports of the cases studied, fifty five (85.9%) women had benign ovarian tumors and 9 (14.1%) were reported to have malignant tumors. The ovarian crescent sign was detected in 53 masses, all of them were benign in nature, while it was not detected in 11 masses two of which were benign, 8 were invasive malignant tumors, and 1 was a borderline tumor, giving a sensitivity of 100%, specificity of 96.32%, positive predictive value of 81.81%, and a negative predictive value of 100% (table 6). There were two false - positive diagnoses of ovarian cancer, one was for a huge benign mucinous cystadenoma, and the other one was for a dermoid cyst.

The mean CA125 level of the whole cases was 47.82 ± 137.59 U/ml with the lowest level being of 5.26 U/ml for a patient with a benign paraovarian mass and the highest level was of 1071 U/ml for a patient with a serous cystadenocarcinoma – stage III. The mean CA125 level for benign lesions was 24.09±19.41 U/ml, while that of the malignant lesions was 192.75±345 U/ml, which revealed a significant difference (p= 0.0001) (table 2). The sensitivity of CA125 alone at cutoff level of 35 U/ml was calculated to be 77.7% and the specificity was 92.7%, positive predictive value was 63.6% and negative predictive value was 96.2%. We compared the rates of correct preoperative diagnoses of masses as benign or malignant using CA125 and OCS, and distributed them according to the final histological types of the masses (table 3). OCS correctly classified 96.87% of all masses as benign or malignant. Serum CA125 level classified 89% of all tumors correctly at cutoff value of 35 U/ml, 82.8 % at cutoff value of 65 U/ml, 85.9% at 100 U/ml, and 89 % at cutoff value of 200 U/ml (table 3).

Table 2 : Serum CA125 levels in benign and malignant masses.

CA125 level (U/ml) Range (5.6-1071)	Benign masses (n= 55)	Malignant masses (n= 9)	Total (n= 64)
≤ 35	50	2	52
36-100	3	5	8
101-199	2	0	2
≥ 200	0	2	2
Mean ± SD	24.09 ± 19.41	192.75 ± 345.01	47.82 ± 137.59

χ^2=27.98, d.f.=2, P=0.0001

Table 3: Rate of correct diagnosis in benign and malignant masses using OCS versus using CA125.

Histopathological results	n = 64	Correct diagnosis by OCS, n (%)	Correctly diagnosed as benign or malignant according to CA125, n (%)			
			CA125 cutoff			
			35 U/ml	65 U/ml	100 U/ml	200 U/ml
benign masses	55	53(96.36)	50(90.9)	50(90.9)	53(96.4)	55(100)
malignant masses	9	9 (100)	7 (77.7)	3 (33.3)	2 (22.2)	2 (22.2)
Invasive epithelial tumors	4	4 (100)	4 (100)	3 (75)	2 (50)	2 (50)
Invasive non-epithelial tumors	4	4 (100)	3 (75)	2 (50)	1 (25)	1 (25)
Borderline tumor	1	1 (100)	0	0	0	0
Total	64	62(96.87)	57 (89)	53(82.8)	55(85.9)	57(89)

The mean Risk of Malignancy Index 2 (RMI 2) for the whole cases was 183.8 with the lowest value of 5 for a patient with a benign paraovarian cyst and the highest value was 4284 for a patient with serous cystadenocarcinoma stage III. The mean RMI 2 for benign masses was 88.04±169.1, while that for malignant masses was 768.8±576, giving a significant difference (p=0.0001) (table 4).

Table 4: Results of evaluation by RMI 2.

RMI 2	Benign masses		Malignant masses		total	
	n=55	%	n=9	%	n=64	%
< 200	49	89.1	4	44.4	53	82.8
≥ 200	6	10.9	5	55.6	11	17.2
Mean ± SD	88.04 ± 169.1		768.8 ± 138.2		183.8 ± 576	

χ^2=10.83, d.f.=1, P=0.0001

The sensitivity of RMI 2 was 55.6%, specificity was 89.1%, positive predictive value was 45.5% and negative predictive value was 92.5%.

Seven out of the sixty four masses were found to have papillary proliferations, six of which were benign lesions (five were cystadenofibromas and one papillary serous cystadenoma), while only one was malignant (papillary cystadenocarcinoma). This gives a sensitivity of 11.1%, a specificity of 89.1%, PPV of 14.3 % and a NPV of 85.96%.

The ovarian crescent sign diagnosed malignant ovarian lesions with sensitivity and specificity which were better than serum CA125 measurement alone, presence of papillary proliferations on ultrasound, and the Risk of Malignancy Index 2 (table 5 and 6). A comparison of the sensitivity, specificity, positive predictive value and negative predictive value of the diagnostic methods used in the present study is shown in table 6.

Table 5: Ultrasound and biochemical characteristics of women with benign and malignant adnexal masses.

Variable	Benign lesions (n=55)	Malignant lesions (n=9)	t-test	P
Tumor size (mean largest diameter ± SD) (cm)	83.07±41.67	98.44±35.88cm	1.19	0.301
CA125 (mean ± SD)	24.09 ± 19.41	192.75 ± 345.01	2.16	0.0001
RMI 2 (mean ± SD)	88.04 ± 169.1	768.8 ± 138.2	17151	<0.0001
Papillary proliferations (n (%))	6 (10.9)	1 (11.1)	0.01	0.971
Negative OCS (n (%))	2 (3.6)	9 (100)	-	-

Table 6: The sensitivity, specificity, positive and negative predictive values of OCS compared to CA125, RMI 2 and sonographic morphological features.

Indices	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CA125 U/ml (>35)	77.7	92.7	63.6	96.2
RMI 2 (≥200)	55.6	89.1	45.5	92.5
Papillary proliferations	11.1	89.1	14.3	85.96
Negative OCS	100	96.36	81.81	100

DISCUSSION:

This study was based on the hypothesis that the presence of normal ovarian tissue adjacent to an adnexal mass (the ovarian crescent sign) excluded the likelihood of a malignant lesion. In the current

study the absence of healthy ovarian tissue adjacent to an ovarian mass was strongly associated with the histological diagnosis of ovarian cancer.

Malignant ovarian lesions could be diagnosed by this method with a sensitivity of 100%, and specificity of 96.36% which is similar to other more complex tests to identify ovarian malignancy. The proportion of borderline ovarian tumors in the present study was low (only one case out of nine malignant tumors) with a negative ovarian crescent sign compared to the study by Hillaby *et al*. [13] in which there was an unusually high proportion of borderline tumors (9 out of 33 malignant tumors; 27%) two of which gave a positive ovarian crescent sign (22%).

The ovarian crescent sign in the study by Hillaby *et al.* [13] gave a sensitivity of 96% and a specificity of 76% and a PPV of 56%. The study also proved that OCS had a better sensitivity and specificity than other sonographic features as papillary proliferations (41% and 87% respectively), tumor volume (79% and 54% respectively), and pulsatility index by Doppler study (58% and 89% respectively). In a similar study, Kushtagi (2008) [16] studied the validity of the ovarian crescent sign in a group of 60 women with adnexal masses and got a sensitivity of 90.0% specificity of 77.6%, PPV of 47.6% and NPV of 97.4%. [16]

In our study, RMI 2 appeared less sensitive (55.6%) and less specific (89.1%) than both CA125 and OCS and also less than those found by previous studies as that of Yazbek et al. [14] and Hillaby et al. [13]. The RMI 2 gave high false positive rates (9%) in the present study. False positive rates are particularly important when the tests are applied to low-risk populations diagnosed with ovarian tumors during opportunistic screening for ovarian abnormalities. The RMI 2 was sensitive to elevation of CA 125 levels, but more affected by the menopausal status which was the main reason for higher scores in benign pathology, as 8 out of 10 postmenopausal patients in our study had had RMI 2 > 200 but were diagnosed with benign masses according to the final histopathological reports.

Discrimination between benign and malignant tumors by using the OCS is more accurate in comparison with previously published methods for ultrasound diagnosis of ovarian cancer. Asalm et al. [17] prospectively evaluated the value of RMI 1 and the RMI 2 in a group of 61 women. Both models missed 3/23 (13%) cases of invasive cancers with false – positive rates of 15% and 20% respectively.

Prospective studies of logistic regression models such as those by Aslam et al. (2000) [18], Valentin et al. (2001) [19] and Szpurek et al. (2005) [20] showed relatively poor diagnostic performance with the models achieving sensitivities of 9-73 % [18,19,20].

The difference between the results obtained in the present study and those in other studies can be explained by differences in study populations, inconsistencies in definitions of various morphological features, such as papillary proliferations, and the great varieties of morphological appearance within tumors of the same histological type, while the ovarian crescent sign depends on presence of normal ovarian tissue which has almost a constant appearance on ultrasound scan regardless the pathology present and does not require high experience in ultrasound to recognize it even by the gynaecologists.

The main drawback of the morphological analysis of adnexal tumors using the ovarian crescent sign is the inability to differentiate between borderline tumors and benign tumors. As a result, some women with borderline tumors may be initially managed expectantly.

Although the only borderline tumor in our study gave a negative OCS, other published studies which involved more percentages of borderline tumors gave different results alternating between positive and negative OCS. However, the importance of accurate preoperative distinction between benign and borderline tumors may be less relevant for optimal clinical management than distinction between invasive and non-invasive lesions. The prognosis of invasive epithelial cancer is poor; therefore a staging laparotomy including total abdominal hysterectomy and bilateral oophorectomy remains the mainstay of the initial clinical management. In contrast, the prognosis of borderline ovarian tumors is very good with a 10-year survival rate of 95% [21].

The main benefit of the OCS is likely to be in women with incidental finding of an ovarian mass on routine pelvic scan. Although the risk of malignancy in this situation is low, women are often counseled that ovarian malignancy is a possibility and further follow-up scans and additional biochemical and surgical diagnostic tests are often used to clarify the diagnosis. This diagnostic uncertainty causes considerable anxiety in otherwise healthy women, generates significant morbidity caused by avoidable interventions, and increases costs to health providers.

CONCLUSION:

The ovarian crescent sign is a highly sensitive and specific diagnostic sign for differentiation between benign and malignant ovarian tumors, which is not affected by the histological types of these tumors. It can be recognized easily and does not require highly expertise operators. Its accuracy is highly comparable to other diagnostic modalities such as CA125 and sonographic indices (RMI 2).

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