

Role of Transvaginal Sonography and Serum CA-125 Values in Determining the Nature of the Postmenopausal Ovarian Cysts

Oktay KAYMAK, Emin ÜSTÜNYURT, R. Emre OKYAY, Şenol KALYONCU, Leyla MOLLAMAHMUTOĞLU

Zekai Tahir Burak Women's Health Education and Research Hospital, Cebeçi, Ankara, Turkey

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Abstract

Objective: To determine the diagnostic accuracy of ultrasound and serum CA-125 values in asymptomatic postmenopausal women undergoing laparotomy for a clinical diagnosis of an ovarian cyst.

Materials and Methods: Data were obtained retrospectively from 114 asymptomatic postmenopausal women who underwent laparotomy for adnexal cysts. Transvaginal sonography (TVS) and serum CA-125 measurement were performed in all patients. Each ovarian cyst was classified based on two-dimensional sonographic criteria such as maximum cyst diameter, echogenicity, uni- or multilocular appearance, structure of the cyst wall and solid areas. All of the tissues removed were pathologically examined, and sonographic findings were compared with the histopathologic diagnosis.

Results: In histopathological examination of 114 cysts; 89 (78.1%) non neoplastic cysts were found among which simple cysts being the most common (53.5%). Benign neoplastic cysts were found in 18.4% (21/114) among which serous cyadenomas being the most common (8.8%). Four (3.5%) patients were found to have ovarian cancer. While the frequency of malignancy in patients with complex ovarian cysts (n=26) (unilocular echogenicity) was 11.3%, only 1.66% of the patients with simple cysts (n=60) (anechogenic, smooth and unilocular) were found to have malignant lesion. The serum CA-125 values differed significantly between the benign and malignant patient groups ($p<0.001$).

Conclusion: Both serum CA-125 values and TVS are useful diagnostic tools for predicting the nature of postmenopausal ovarian cysts. The risk of malignancy in simple unilocular cysts with normal serum CA-125 levels is extremely low. Conservative management of these cysts is a more reasonable alternative to surgical removal.

Keywords: postmenopause, ovarian cysts, CA-125 antigen, ultrasonography

Özet

Postmenopozal Over Kistlerinin Değerlendirilmesinde Transvajinal Sonografi ile Serum CA-125 Değerlerinin Rolü

Amaç: Over kisti klinik tanısı ile laparotomi yapılan asemptomatik postmenopozal hastalarda ultrasonografi ile serum Ca-125 değerlerinin tanıdaki etkinliğini belirlemek.

Materyal ve Metot: Veriler, adneksiyal kist nedeniyle laparotomi yapılan 114 asemptomatik postmenopozal hastadan retrospektif olarak elde edildi. Transvajinal ultrasonografi (TVS) ve serum Ca-125 ölçümü tüm hastalara uygulandı. Her bir over kisti maksimal çap, ekojenite, uniloküler ya da multiloküler görünüm, kistin duvar yapısı, solid alan içeriği gibi iki boyutlu ultrasonografik kriterlerle sınıflandırıldı. Çıkarılan tüm dokular patolojik olarak incelendi ve ultrasonografik bulgular ile histopatolojik tanıları karşılaştırıldı.

Sonuçlar: 114 kistin histopatolojik incelemesinde; en sık basit kist (%53.5) olmak üzere 89 (%78.1) non-neoplastik kist saptandı. En sık seröz kistadenom (%8.8) olmak üzere %18.4 (21/114) hastada benign neoplastik kist saptandı. Dört (%3.5) hastada over kanseri saptandı. Kompleks over kisti (uniloküler ekojenite) olan hastalarda (n=26) malign lezyon sıklığı %11.3 olarak saptanırken, basit kisti (anekoik, düzgün yüzeyle, uniloküler) olan (n=60) hastaların %1.66'sında

Corresponding Author: Dr. Oktay Kaymak
Beşikkaya Mah. 460. Sok. No: 3/2, Siteler, Ankara, Türkiye
Phone : +90 532 645 19 03
Fax : +90 312 468 12 19
E-mail : drkaymak@hotmail.com

malign lezyon bulundu. Serum Ca-125 değerleri, malign ve benign hasta grupları arasında anlamlı olarak farklıydı ($P<0.001$).

Tartışma: Gerek serum Ca-125 değerleri, gerekse TVS postmenopozal over kistlerinin histolojilerinin tahmin edilmesinde faydalı tanısal yöntemlerdir. Serum Ca-125 değerleri normal olan basit uniloküler kistlerde malignite riski belirgin olarak düşüktür. Bu kistlerde konservatif yaklaşım cerrahiye göre daha mantıklı bir alternatiftir.

Anahtar sözcükler: postmenopoz, over kisti, CA-125, ultrasonografi

Introduction

Asymptomatic ovarian cysts are not uncommon in postmenopausal women as was thought in the past. The available studies give prevalence rates between 3.3 and 14.8% (1-3). As a result of increasing use of transvaginal sonography in clinical practice, it has become evident that cysts occur quite frequently in the adnexa of asymptomatic postmenopausal women. (4). The clinical dilemma is the conflict between identification of ovarian malignancy as early as possible and avoiding unnecessary operations. Therefore knowledge of the nature of an ovarian cyst is extremely important to establish the correct management. Transvaginal ultrasonography (TVS) is a quick and inexpensive imaging technique for detection and characterization of ovarian cysts. It has been shown to be an effective screening method for ovarian cancer (5). However its positive predictive value (PPV) is low, approaching only 0.1 in postmenopausal women. The use of morphologic indexing of sonographic findings has been proposed as means to increase the PPV of TVS (6,7). Simple, thin-walled, unilocular and smaller cysts are more likely to be benign. In contrast, the presence of solid components, papillary projections, thick walls, and ascites strongly suggest malignancy (3). Other features suspicious for malignancy include size greater than 10 cm and bilaterality (8).

The serum CA-125 is a powerful marker for prediction of histology in postmenopausal ovarian cyst (9). Although serum CA-125 levels can be raised in a number of other benign and malignant conditions (5,10) and additionally mucinous tumors are less frequently associated with elevated levels of CA-125 (5); a large body of evidence confirms that combining serum CA-125 values with sonographic findings improves the sensitivity and specificity in predicting malignancy in postmenopausal ovarian cysts (11-14).

The purposes of this retrospective study were:

1. To investigate the risk of malignancy in ovarian cysts, detected by transvaginal sonography in a population of asymptomatic, postmenopausal women;
2. To determine the diagnostic accuracy of ultrasound and serum CA-125 values in postmenopausal women undergoing laparotomy for a clinical diagnosis of an ovarian cyst.

Materials and Methods

We retrospectively evaluated the hospital records of asymptomatic postmenopausal patients who underwent laparotomy

for adnexal cysts in our department from January 1999 to December 2003. Medical, reproductive and family histories and demographic features were thoroughly taken for all patients. The exclusion criteria was either a personal or family history of breast, endometrial or ovarian cancer or the use of hormone replacement therapy. Preoperative evaluation comprised physical, as well as pelvic examination, endovaginal sonography, CA-125 level and presurgery assessment by anesthesiologist. As a part of gynecologic examination, real-time transvaginal ultrasound scanning was performed. Each ovarian cyst was initially classified based on two-dimensional sonographic criteria such as maximum diameter, echogenicity, uni- or multilocular appearance, cyst wall structure and solid areas. An ultrasound machine with high-frequency transducers of 5.0 MHz was used (Prolog 200, GE, USA).

The indications for surgery were: (1) Ovarian cysts that did not meet all the criteria of a simple cysts (unilocular, unilateral, with no papillation or septation and up to 5 cm) (2) Were larger than 5 cm; (3) Elevated CA-125 level; (4) Persistent ovarian cysts. Preoperative serum CA-125 levels were determined by enzyme immunoassay (Biodpc, Immulite 2000, USA). Levels below 35 IU/mL were considered normal. All patients underwent surgical exploration. Pathologists examined the tissue removed at operations, and ultrasonographic and macroscopic appearances were compared with the histopathologic diagnosis. On the basis of histopathologic study the removed tissue was characterized as benign, borderline, or malignant. All data were processed using the SPSS/PC 11.0 package (SPSS Inc: Chicago, IL). Statistical evaluation of the data was performed by chi-square test. The level of significance was set at $p<0.05$.

Results

Hundred and fourteen postmenopausal women who underwent laparotomy for adnexal cysts were included in this study. The mean \pm SD age of the women included was 50.7 ± 6.2 years, with a median of 49 years and a range of 45-72 years. 70.2% (80/114) of women were in menopause for less than 5 years and 29.9% (34/114) of them were in menopause for more than 5 years. 54 patients were suffered from chronic disease; of these 38 were hypertensive, 16 had diabetes mellitus. The demographic data of 114 patients is presented in Table 1.

At ultrasound exam, 19.3% (22/114) of women had simple cysts (anechoic, smooth-walled, unilocular) <5 cm,

Table 1. Demographic data of 114 postmenopausal patients

Demographic data	Histology		
	Non neoplastic* (n=89)	Benign (n=21)	Malignant (n=4)
Age (years)			
median	48	51	60
range	45-72	45-60	45-69
Nulligravida	4.49%	4.76%	50%
Menopause			
<5 years	75.29%	57.15%	25%
>5 years	24.71%	42.81%	75%

*Includes simple cysts, functional cysts, endometriomas, hydrosalpinx, tuba-ovarian abscess

42.1% (48/114) had simple cysts >5 cm, 7.0% (8/114) had unilocular cysts with some echoes <5 cm, 15.8% (18/114) had unilocular cysts with some echoes >5 cm, 3.5% (4/114) had multilocular cysts <5 cm, and 12.3% (14/114) had multilocular cysts >5 cm. The relationship between sonographic findings and histopathologic diagnoses is presented in Table 2.

In histopathological examination of 114 cysts; 89 (78.1%) were diagnosed as non neoplastic, most commonly simple cysts (53.5%). 18.4% (21/114) of patients had benign neoplastic cysts, most commonly serous cytadenomas (8.8%). Four (3.5%) patients had ovarian cancer. The histologic diagnoses of these lesions are presented in Table 3.

The frequency of malignancy in patients with complex ovarian cysts (n=26) (unilocular, some echoes) was 11.53% as opposed to 1.66% in patients with simple cysts (n=60) (anechoic, smooth-walled, unilocular). The sonographic findings and serum CA-125 levels of the malignant cases is presented in Table 4.

Two patient had serous cystadenocarcinoma, one had borderline serous tumor and one had borderline mucinous tumor. Two of the 4 ovarian cancer were >5 cm in diameter in sonography. One of them which was borderline mucinous tumor

had a simple morphology (anechoic, smooth-walled, unilocular) whereas the remainings had complex structure in sonographic examinations. Three of the malignant cases had elevated serum CA-125 levels however one of them which was a borderline mucinous tumor had a normal serum CA-125 value. 11.4% (13/114) of patients had raised serum CA-125 levels. The mean serum CA-125 values of simple, functional, benign and malignant groups were 13.40, 13.07, 12.07 and 143.07 IU/mL, respectively. The frequency of malignancy in patients whose serum CA-125 levels were greater than 35 IU/mL (n=12) was 16.66% as opposed to 1.96% in patients whose serum CA-125 levels were less than 35 IU/mL (n=102) (p=0.009). The relationship between histopathologic diagnoses and serum CA-125 levels is presented in Table 5.

In this study, with 35 IU/mL as cut-off value, the sensitivity of serum CA-125 assay for the differentiation of non malignant and malignant ovarian cysts was 75%, the specificity 90.9%.

Discussion

Predicting whether an ovarian cyst is benign or malign is extremely important to establish the correct management, especially in postmenopause. Although there is a known significant decrease of the diagnostic accuracy of sonography in postmenopause compared with premenopause, TVS is still an important diagnostic tool for detection and characterization of postmenopausal ovarian cysts (15). Several studies have concluded that the only cystic ovarian lesion that is associated with a very low risk of malignancy is one that is simple, unilocular, echo-free and <50 mm in diameter (7,15,16). Osmers et al. (7,18) reported the risk of malignancy associated with unilocular cysts to be as high as 9.6% among postmenopausal women. Recently in a prospective analysis Ekerhovd et al. (19) reported that the risk of malignancy associated with unilocular cysts associated with unilocular echo-free cysts was not higher than 1.6%. Additionally, Bailey et al. (3) reported that approximately one half of the cysts with the same properties resolved spontaneously within 60 days and this finding is consistent with those of Levine and Gosink (4), who reported that 38 of 72 unilocular ovarian cysts in postmenopausal women disappeared spontaneously

Table 2. Sonographic findings of 114 ovarian cysts in postmenopausal women /• Includes simple cysts, functional cysts, endometriomas, hydrosalpinx, tuba-ovarian abscess ** Anechoic, smooth walled, unilocular

Criteria	Non-neoplastic*		Benign		Malignant		Total	
	N	%	N	%	N	%	N	%
Simple cyst**, <5 cm	20	17.5	2	1.8	0	0	22	19.3
Simple cyst**, >5 cm	39	34.2	8	7.0	1	0.9	48	42.1
Unilocular, some echoes, <5 cm	4	3.5	2	1.8	2	1.8	8	7.0
Unilocular, some echoes, >5 cm	11	9.6	6	5.3	1	0.9	18	15.8
Multilocular, <5 cm	4	3.5	0	0	0	0	4	3.5
Multilocular, >5 cm	11	9.6	3	2.6	0	0	14	12.3
Total	89	78.1	21	18.4	4	3.5	114	100

Table 3. Histopathologic diagnoses of the cysts
 * Includes corpus luteum, paraovarian, paratubal, ruptured cysts
 ** Includes endometrioma, hydrosalpinx, tuba-ovarian abscess

Histologic Type	N	%
Simple cyst	61	53.5
Functional cyst*	18	15.8
Others**	10	8.8
Benign neoplastic cyst	21	18.4
Serous cystadenoma	10	8.8
Mucinous cystadenoma	4	3.5
Teratoma	4	3.5
Fibrothecoma	3	2.6
Malign neoplastic cyst	4	3.5
Serous cystadenocarcinoma	2	1.7
Borderline serous tumor	1	0.9
Borderline mucinous tumor	1	0.9

within 24 months. Seven published studies in which a total of 333 postmenopausal women with 382 adnexal cysts with benign ultrasound morphology incidentally detected at ultrasound examination were followed for up to 9 years without any signs of the cysts being malignant at detection or becoming malignant during the follow-up (1,2,4,14,20-22). In our study we found the frequency of malignancy in postmenopausal cysts 3.5% (4/114). No malignancy was diagnosed in histopathological examination when the cyst was simple and smaller than 5 cm in diameter in sonography. However the frequency of malignancy in complex cysts (unilocular, some echoes) was 20% (3/15). According to these findings, conservative management is a reasonable choice for the cysts which have simple appearance in sonography. In contrast ovarian tumors with complex sonographic patterns including solid or papillary areas are associated with a significant risk for malignancy and should be removed surgically. CA-125 is a useful tumor-associated antigen in distinguishing benign from malignant conditions. Although serum CA-125 levels are also elevated in a variety of benign conditions including endometriosis, fibroids, adenomyosis, pelvic inflammatory disease, tuberculosis; this marker is more helpful in postmenopause than in reproductive period. Vasilev et al. (23) reported that 80% of women older than 50 years of age with pel-

Table 5. The relationship between serum CA 125 level and histology *Includes simple cysts, functional cysts, endometriomas, hydrosalpinx, tuba-ovarian abscess, benign neoplastic cysts

Serum CA-125 level	Histology		Total
	Non malignant* (n)	Malignant (n)	
< 35	100	1	101
> 35	10	3	13
Total	110	4	114

vic masses and CA-125 levels greater than 35 IU/mL had malignancies, compared with only 15% of patients less than 50 years of age. Einhorn et al. (12) measured CA-125 levels in 100 women undergoing diagnostic laparoscopy for palpable adnexal masses and found elevated CA-125 levels in all 11 patients with non-mucinous ovarian carcinoma. Similarly Schwartz (13) found CA-125 levels useful in distinguishing benign from malignant masses in postmenopausal women. In the study reported by Reimer et al. (11), serum CA-125 with a cut-off of 35 IU/mL had a sensitivity of 75%, a specificity of 95.6%. Botsis et al. (24) found the sensitivity and the specificity of CA-125 75.2% and 91.1%, respectively. Nardo et al. (25) reported that 33.3% of low risk postmenopausal women with increased CA-125 levels had well-differentiated serous cystadenocarcinoma. In this present study 16.66% of patients with increased CA-125 levels had malignancy. With 35 IU/mL as cut-off value, we found the sensitivity of serum CA-125 assay 75%, and the specificity 90.9%. Mucinous tumors are less frequently associated with elevated levels of CA-125 (5). Likewise in our four malignant cases, one of them had a serum CA-125 level (7.2 IU/mL) which was a borderline mucinous tumor.

Evidence suggest that there is a role for conservative management of low-risk postmenopausal women with unilocular ovarian cysts and normal serum CA-125 levels (4,19,22). In our study a total of 114 patients underwent laparotomy but only four had a histological diagnosis of ovarian malignancy. Additionally the percentage of patients with simple or functional cysts was 69.3% (n=79). According to these findings it can not be wrong to conclude that many of these operations were unnecessary.

Table 4. Malignant cases

Histology	Age (years)	Menopause (years)	Sonographic morphology	Serum CA-125 level (IU/mL)
Serous cystadenocarcinoma	61	>5	Unilocular, some echo <5 cm in diameter	59
Serous cystadenocarcinoma	60	>5	Unilocular, some echo <5 cm in diameter	500
Borderline mucinous tumor	45	<5	Simple cyst >5 cm in diameter	7.4
Borderline serous tumor	69	>5	Unilocular, some echo >5 cm in diameter	53.1

The advent of high-resolution ultrasound has led to the discovery of small ovarian cysts in asymptomatic postmenopausal women that otherwise would have not been detected. Although the risk of malignancy in simple unilocular cysts with normal serum CA-125 levels is extremely low and most of these cysts regress spontaneously; they are often managed too aggressively. Conservative management of these cysts is a reasonable alternative to surgical removal especially when serum CA-125 level is normal. Patients compliance with sonographic and CA-125 follow-up is essential. However should the cyst persist, increase in size, develop solid components, or be associated with elevated serum CA-125 levels, prompt surgical removal is indicated.

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