

Conservative management of unilateral and unilocular ovarian cysts ≥ 10 cm in diameter in postmenopausal women

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Objective: To evaluate and follow up the native behaviour of large ovarian cysts in postmenopausal women and establish the best approach based on advanced imaging technology. **Study Design:** The number of patients that were evaluated from January 2015 to September 2019 were 417. At the end of this study period, 375 patients were considered for this prospective evaluation. The patients with an ultrasound diagnosis of unilateral and unilocular ovarian cysts with regular septa ≥ 10 cm in diameter at menopause were enrolled in this study. During the follow-ups, the patients who developed irregular or thick septa, papillary formation or solid areas, exhibited any suspicious sign of malignancy in magnetic resonance imaging (MRI) results or displayed an augmentation in CA-125 levels were excluded from the study. In this study cancer antigen-125 (CA-125) values > 65 IU/mL were considered abnormal. The patients who met these criteria were followed with periodical ultrasounds and yearly MRI. **Results:** The 42 patients who were excluded from the study had significant morphological changes. These patients were showing an increase in CA-125 levels along with abnormal MRI findings during the follow-ups and in addition, they had surgical removal of cysts. All the significant morphological changes were detected by transvaginal ultrasounds. Postoperative histopathological diagnosis of these ovarian cysts revealed no abnormality. From 375 patient's cysts samples one hundred and twenty-five (33.3%) cysts had significantly decrease in size, one hundred and eleven (29.6%) of the cysts had spontaneous resolution and one hundred thirty-nine (37%) cysts persistently remained unchanged during the follow up period. The diameter of the cysts ranged from 10.4 to 18.4 cm. The cysts were categorized into three groups corresponding to a range of diameters i.e., 10–12.9 cm (62%), 13–15.9 cm (24.1%) and ≥ 16 cm (13.8%) respectively. The patients who showed spontaneous resolution were discontinued with the follow-ups while the rest of the patients were continued with their regular follow up examinations. **Conclusion:** The cysts should be monitored conservatively as long as possible before proceeding to a surgical treatment regardless of the size of the unilateral and unilocular ovarian cysts at postmenopausal period with limited oncogenic potential and without significant morphological changes.

Keywords

Cyst morphology and size; Ovarian cysts; Postmenopausal period

1. Introduction

We know that 85% of the ovarian malignancies are diagnosed at postmenopausal period [1]. Thus, postmenopausal ovarian cysts are particularly associated with the risk of unnecessary surgery due to malignancy concerns. The majority of ovarian cysts, without absolute malignancy characteristics, such as solid areas, papillary structures or thick irregular septation, in postmenopausal women are benign. Ultimate improvement in imaging system and based on use of highly resolution transvaginal ultrasonography in gynaecological examination have raised the sensitivity and specificity of adnexal cysts in asymptomatic postmenopausal women [2].

Worldwide prevalence of simple ovarian cysts in postmenopausal women may range from 3% to 15% [1]. About 7% of women have ovarian cysts at some age during their lives [2]. Actually, the probability of unilocular ovarian cysts being malignant is regarded very low and it has been recommended that unilocular cysts < 5 cm in diameter in postmenopausal women require possibly follow-up scans rather than surgical approach [3–6]. However, management of cysts > 5 cm in diameter remains under discussion. While some guidelines [7] emphasized surgery for the cysts > 5 cm in postmenopausal women, on the other hand some groups [8, 9] have announced that simple cysts of up to 7 or 10 cm in diameter could be safely followed without intervention. Since 1989 numerous studies have been published in the literature emphasizing conservative approach regarding postmenopausal ovarian simple cysts, unfortunately most of them are still being removed by laparoscopic surgery because of the fear of progression to malignancy.

It is very clear that particular ultrasound images of ovarian cysts, such as papillary projections, solid areas or thick irregular septation are more evident clues for surgical approach. The aim of this study was to evaluate the value of long-term follow-ups; in the management of unilateral and unilocular large ovarian cysts without absolute malignancy or morphological change and observe the natural progress of these cysts in postmenopausal women.

2. Materials and methods

This research was undertaken in the Department of Obstetrics and Gynaecology of Medicana-Atılım University Hospital, Ankara, Turkey.

All participants provided informed consent and the study was approved by ethical committee of the hospital. The women who had a cessation of menstruation of 12 sequential months or more in women ≥ 45 years of age before the first examination, accepted as postmenopausal. Between January 2015 to September 2019, 417 patients were enrolled in the study but towards the end of the study, 375 patients were left eligible for this study because of emerging unfavourable features of the cysts during the follow-ups.

All sonographic examinations were performed by two obstetrics and gynaecology specialists on GE Volusion 730 Pro and Volusion E 8 ultrasound machines were equipped with an IC5-9, RIC5-9 and 4-9 MHz endovaginal probes respectively along with colour and spectral Doppler capabilities. The scoring system of unilocular simple cysts were defined by following ultrasonographic morphologic criteria of International Ovarian Tumour Analysis (IOTA) group [10].

To evaluate each ovarian cyst atransvaginal ultrasound was performed for dimension and ovarian morphology. After collecting all the dates regarding the distribution of the diameter of the cysts, we proceeded to categorize the cysts randomly into three groups; 10–12.9 cm, 13–15.9 cm and ≥ 16 cm. Symptomatic or asymptomatic postmenopausal patients with a diagnosis of unilateral and unilocular ovarian cyst ≥ 10 cm in diameter were considered eligible for the study. Simple cyst of ovary was accepted as an echo-free cyst with a smooth-walled with regular septate or without solid areas or papillary projections within the cyst cavity.

The patients who had ovarian cysts diagnosed by ultrasonography, CA-125 levels were measured while CA-125 levels > 65 IU/mL were considered abnormal.

The cysts, which did not develop significant morphological changes, underwent conservative monitoring by ultrasonography. During the follow-up examinations, dimensions and morphology of the ovarian cysts were scored and saved. During the follow-ups, some of the patients with > 16 cm cysts complained of having a dull pain and pressure on the side of the cyst. As all the women were at menopause, dyspareunia was one of the main complaint in the patients. In addition to that, during gynecological examinations, swelling and pain were the other frequent complaints but none of them required surgery and conservative approach was enough for the patients. In the first year, all the patients initially examined in every 3 months, in the second year in every 6 months and yearly for remaining consecutive years. Annual pelvic MRI was also performed with 1.5 Tesla Philips Achieva. Additionally, CA-125 levels were also measured during every examination. Patients with abnormal finding of MRI and a significant change in cyst morphology, such as irregular septa, papillary projection or solid area in transvaginal ultrasound or elevated CA-125 levels at any

time of the follow-ups were referred for surgery. More exclusively an increase in size of the cyst without any morphological change was not accepted a candidate for surgery. The patients who coincide with the above-mentioned features for surgery either initially or in the follow-up period and who rejected to enroll in the study and asked for surgery were fully informed and underwent surgery after providing informed consent. To present results descriptive statistics were used.

3. Results

Four hundred and seventeen (417) cases simple ovarian cyst cases were diagnosed with transvaginal ultrasound and enrolled in this study. During the follow-ups 42 patients who presented significant change in cyst morphology, abnormal MRI findings or elevated CA-125, levels were referred for surgery.

During the follow up exams, forty-two patients underwent surgery but no malignancy was observed in this group. In the surgery group the mean age of the patients was 68 years ranging from 63 to 79 years. The reason for patients who underwent surgery included solid areas or papillary projections in the cysts in twenty-nine patients (69%), irregular septal formation or progressing from simple cyst to complex cyst in six patients (14.2%), raising in CA-125 in four patients (9.5%) and abnormal MRI findings in three patients (7.1%). In the surgery group, serous cystadenoma was the most common pathology, which were 30 out of 42 cysts (71.4%). The other cases were reported as mucinous cystadenoma, endometrioma, follicular cyst, dermoid cyst, inclusion cyst and cyst adenofibroma respectively. In both endometrioma and dermoid cyst cases, most of the component of these cysts were serous cystadenoma but in addition to that, a small dermoid and endometrioma component were also detected in these cysts (Table 1).

Table 1. Clinical characteristics and histologic diagnosis of 42 patients in surgery group N (%).

Demographic parameters	
-Age	Mean: 68 range: 63–79
-Parity	Mean: 3 range: 3–7
Indication for surgery	
-Morphological change	29 (69)
-Irregular septal formation or progressing to complex cyst	6 (14.2)
-Increase CA-125 level	4 (9.5)
-Abnormal MR findings	3 (7.1)
Histologic diagnosis	
-Serous cystadenoma	30 (71.4)
-Mucinous cystadenoma	5 (11.9)
-Follicular cyst	2 (4.7)
-Endometrioma	2 (4.7)
-Dermoid cyst	1 (2.3)
-Cystadenofibroma	1 (2.3)
-Inclusion cyst	1 (2.3)

375 patients underwent follow-up study. In the follow-up study group, the mean age was 62 years with range of 45–74. Out of 375 cysts one hundred eleven (29.6%) of the cysts had spontaneous resolution. Within the spontaneous resolution group in 34 patients, we detected a small amount of free fluid in the Douglas that could be the sign of cyst rupture before resolution of the cysts. None of these patients was hospitalized during their follow-ups. One hundred twenty-five (33.3%) cysts significantly decreased in size and one hundred thirty-nine (37%) cysts were persistently unchanged over the follow up period. The mean cyst diameter was 15.4 cm (range 10.4 and 18.4 cm). The cysts were categorized into three groups according to their diameters; 10–12.9 cm in 233 patients (62%), 13–15.9 cm in 90 patients (24.1%) and ≥ 16 cm in 52 patients (13.8%), respectively Table 2. The patients who had exclusive increase in size of the cyst without any morphological change were not referred for surgery. The patients who had spontaneous resolution were terminated from the follow-ups while the others were continued with their regular follow up examinations. It was observed that the resolution and regression rate of the cysts were increasing as the monitoring proceeded further. During the follow-ups, there had been no complication, which lead to an urgent surgery such as twisting of the ovary.

Table 2. Demographic and clinical representation of the patients N (%).

-Total number of the patients	417
-Number of patients excluded from the study and underwent for surgery	42
-Number of patients underwent follow-up study	375
-Age (years)	Mean: 62 range: 45–74
-Parity	Mean: 4 range: 2–8
-Cyst diameters	
10–12.9 cm	233 (62.1)
13–15.9 cm	90 (24.1)
≥ 16 cm	52 (13.8)
-Cyst evaluation	
Spontaneous resolution	111 (29.6)
Decrease in size	125 (33.3)
Persistence	139 (37)

Spontaneous resolution rate was high in cysts with diameter 10–12.9 cm where as significant decrease in size was observed in ≥ 16 cm group and high persistence rate was observed in 13–15.9 cm group. During the follow-ups the behaviour of the cysts according to their diameters were presented in Table 3.

4. Comments

Unilocular-simple cysts of the ovary at postmenopausal period is common finding. The information about of the natural behaviour of a postmenopausal ovarian cyst is very crucial for distinguishing the surgical cases from the conservative approach cases. We know that majority of these cysts are

Table 3. Natural progress of the cysts N (%).

Cyst behaviour	Cyst diameter		
	10–12.9 cm	13–15.9 cm	≥ 16 cm
-Spontaneous resolution	75 (67.5)	25 (22.5)	11 (9.9)
-Decrease in size	13 (10.4)	43 (34.4)	69 (55.2)
-Persistence	44 (31.6)	66 (47.4)	29 (20.8)

benign, all these cases require careful evaluation before addressing for surgery or long meticulous follow-ups. The use of ultrasound to differentiate malignant and benign ovarian cysts originated by the papers in 1989. Since than extensive papers have been published on this subject [10]. We know that Doppler flow study or measurement of CA-125 level increases specificity but does not increase sensitivity. However, it still seems like the best strategy is the transvaginal ultrasound with the use of a morphological index which was defined by IOTA group. In our opinion, this is a unique investigation with respect to its study design and with selected patient group when we compare it with the similar studies in the literature. In our current investigation, we aimed to use all the conservative approaches as long as we can while carefully evaluating the selected ≥ 10 cm postmenopausal cysts before surgery.

In a meta-analysis study by Fabio P. *et al.*, it was pointed out that, in unilocular adnexal cysts including borderline conditions the oncogenic risk was about 1% [11]. In this systematic review, the papers for the last 30 years comprehended in the study. There was a potential limitation of this analysis because of the heterogeneity of the results. Another remarkable point was the classification of unilocular cysts in different ways, which once again limits the analysis. Another issue that emerged in this meta-analysis was pertaining to quality of ultrasound images, especially when including older data. The tumours other than simple unilocular tumours were enrolled in the studies. In our opinion when considering the factors mentioned above, the older technical quality of the ultrasounds in the past, most probably would have influenced them to take oncogenic risk of ovarian cysts to a higher level in this meta-analysis. It is evident that systematic reviews with meta-analyses provide a specific method for synthesizing evidence and overcomes the low power of the single study, but on the other hand as a single large observational study could be more worthy.

At present, it is still not clearly established how to manage the ovarian cysts larger than 5 cm. Some guidelines [7] recommend surgical approach for the cysts in postmenopausal women, others [8, 9] have insist that the simple cysts up to 7 or 10 cm in could be managed conservatively. Unfortunately, when we review the literature, there was no specific study that evaluates ≥ 10 cm postmenopausal unilocular cyst as a patient group within the study. Therefore, we were obligated to compare our results under the scope of these published studies.

In our study, 73.8% of the histopathological diagnosis of cyst in the surgery group was serous cystadenoma while only two molecular studies' results encouraged that serous cystadenomas does not have the risk of high-grade serous carcinomas [12, 13].

When there is an uncertainty or inadequate imaging for ovarian cysts by transvaginal ultrasound, a valuable tool Magnetic resonance imaging (MRI) should be considered. In suspicious adnexal masses, transvaginal ultrasound followed by MRI decreases the risk of misdiagnosing a benign mass as malignant and increases the specificity of a benign diagnosis [14]. MRI is also highly sensitive (96.6%) and specific (83.7%–94.0%) in differentiating the malign cases from the benign ones [15, 16]. In a meta-analyze, which was conducted by Anthoulakis and Nikoloudis it was pointed out that MRI with contrast enhancement provides higher post test probability of ovarian cancer confirmation than sonography with Doppler imaging, computed tomography or positron emission tomography in the subsequent evaluation of ultrasound indeterminate adnexal masses [17]. In our study, three patients were referred to MRI because of unsatisfactory information about the morphological changes of the cysts. After MRI exams, none of the patients went for surgery and they were all kept in the follow-up group.

Modesitt *et al.* reported with the study group of 15,106 women > 55 years of age in an ovarian screening program studied the natural behaviour of unilocular cysts smaller 10 cm managed conservatively [3]. They concluded that after a mean 6.3-year follow-up period the persisting rate of unilocular cyst was 18% while most of the cysts disappeared spontaneously and no unilocular cyst transformed to malignancy. The study also pointed out that out of 117 persistent ovarian cysts the ones, which surgically removed, were serous cystadenomas with 52%, and none was malignant or border line. In another study by Greenlee *et al.*, following the postmenopausal women more than 4 years for Ovarian Cancer Screening, they detected unilocular simple cysts in 14% of the patients [18]. Correspondingly, at the end of 1 year, most of the cysts had regressed spontaneously and 8 years later, they concluded that between women with and without unilocular-simple cysts, the risk of ovarian cancer did not change at all. Taking into account, the results of these two similar long studies we can say that unilocular cysts in postmenopausal women almost do not have the chance of ovarian cancer. It seems wiser to perform exclusive follow up instead of removing the simple cysts, which could induce potential morbidity risks. We had significant limitations of the current study: first, our patient pool was small when we compare with the numbers of patients in the other studies, second, the follow-up period was not long enough and lastly there was very limited published papers in the literature evaluating cysts ≥ 10 cm in postmenopausal women. In the current study, the number of the patients were very limited and the cysts diameters were ≥ 10 cm. While in other two large studies the cysts were < 10 cm [3, 18]. It was also observed

in the present study that 87 cases monitored for a mean period of 13 months and there was no significant morphological change in the follow-up group and in 30 patients who were referred for surgery because of morphological abnormalities of the cyst, no malignant or borderline histology was observed. Twenty-three (26.4%) of the cysts had spontaneous resolution and thirty-eight (43.6%) cysts had significantly decrease in size and twenty-six (29.8%) cysts persisted. Almost 70% of the cysts had disappeared or significantly decreased in size. The resolution and regression rate of the cysts were increasing as the monitoring time was increasing. Taking into consideration the results of these two extensive comprehensive trials [3, 18] along many parallel studies [19, 20] we conclude that in postmenopausal women with unilocular simple cysts the risk of ovarian cancer is very low. Most of the studies and our current study strongly emphasizes exclusive close follow up before making a decision to perform surgery. Ekerhowd *et al.* declared that out of 247 unilocular cysts in postmenopausal women, borderline or malignancy was reported only in all four (1.6%) cysts > 7.5 cm [21]. However, the study also reported that those unilocular cysts in which cancer detected might be overlooked for features of malignancy and undefined complicated cysts. In another retrospective study, which was conducted by Hakan G *et al.*, 176 and 89 cysts were ≥ 5 and ≥ 7 cm respectively and there was no borderline or cancer cases [22]. McDonald *et al.* elevated 395 cysts in postmenopausal women and out of 395 cysts, there were 27 cysts > 10 cm. In these 27 patients, no malignancies were detected [23]. These two studies also present that in postmenopausal women with unilocular cysts the cyst diameter do not play any important role in the development of ovarian cancer.

Sharma *et al.* [24] and Jacobs *et al.* [25] enrolled 48,053 postmenopausal women in their study, from these patients 2,531 had unilocular cysts. In the first three years of this follow up, in 5 patients a borderline tumour, and in 4 patients 2 epithelial ovarian serous cyst adenocarcinoma was detected, pointing out the risk of associated ovarian cancer for simple large cysts was 0.35% (9 out of 2,531). The study addressed that in the evolution of ovarian malignancy we are expecting a prominent structural change in the large simple cysts. Regardless of the above observations, there is two-highlighted issue: (a) simple or unilocular cyst should not be referred immediately for surgery; (b) transvaginal ultrasounds, which were performed meticulously during the follow-ups, are indigenous to diagnose very small cysts (< 0.4%) that is difficult to evaluate in the first scan or might develop morphologic changes. Our results console dates the argument that unilocular-simple cysts ≥ 10 cm most probably are not cancer precursors, and they do not create a risk for ovarian malignancy and can be managed conservatively.

In conclusion, in the light of the literature and our study we can strongly state that the most appropriate diagnostic approach for evaluating postmenopausal large simple cyst is transvaginal ultrasound. In assessing difficult cases, MRI plays a much better role in sophisticated investigation of

unilocular cysts with small solid areas and it should be used to increase the accuracy of diagnosis before referring the patient for surgery. TVU data from large cancer screening trial confirms that simple ovarian cysts are common incidental findings among women over age 55 upon transvaginal ultrasonography, and it remains common after several screening rounds as women age. Most probably unilateral and unilocular cysts regardless of the size, in fact never harbor malignant component, and this concept needs to be assimilate by both patients and doctors. However, it is very important to perform a high-quality transvaginal ultrasound to confirm the absence of any solid/papillary structures before deciding a cyst as a simple innocent cyst. In order to prevent over diagnosis and over treatment, performing serial meticulous transvaginal ultrasound is an ideal modality however, hitherto there are limited prospective data to point out an exact interval and duration for these unilocular and unilateral cysts. The risk of transforming to cancer is extremely low and frequently these cysts resolves by time or persists without any progression; therefore, initially, at least a certain period of follow-up should be sine qua non.

We believe that in the very near future; clinical practice will eventually be integrating the artificial intelligence in the imaging systems and will encourage most of the physicians to agree on long-term follow-ups of unilocular ovarian cysts in postmenopausal women regardless of the size of the cysts.

Author contributions

MSO designed the study, drafted the manuscript, performed the sonographic examinations, carried out the statistical analysis and the follow-ups. TE participated in the sonographic examinations and helped to carry out the follow-ups. GTS helped to draft the manuscript and collected the medical documentations.

Ethics approval and consent to participate

All participants provided informed consent and the study was approved by ethical committee of the hospital.

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Conflict of interest

The authors declare no conflict of interest.

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