

# Asymptomatic adnexal mass in postmenopausal women

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## Summary

The widespread use of vaginal ultrasound as an integral part of the gynecologic clinical examination in many countries has led to the unexpected finding of adnexal mass. The implications of the finding of an adnexal mass in an asymptomatic postmenopausal woman can be serious if it is malignant and is not excised, because ovarian cancer has an indolent course and when it becomes symptomatic it is often fatal. The aim of the present review is to discuss the evaluation and management of incidental adnexal masses in postmenopausal women. Despite careful evaluation with ultrasound and biomarkers, a small number of patients will remain without a conclusive diagnosis. It is our opinion, based on empirical evidence discussed here, that conservative therapy with observation can be safely applied in the majority of these patients.

**Key words:** Adnexal mass; CA 125; Malignancy; Ultrasound.

## Introduction

The widespread use of vaginal ultrasound as an integral part of the gynecologic clinical examination in many countries has led to the unexpected finding of adnexal lesions that are considered deviations from normal anatomy. Evidence gathered from large trials for the screening of ovarian cancer by transvaginal ultrasound (TVS) [1], or by the tumor marker CA 125 in combination with TVS [2], revealed that ovarian masses of variable morphology are not uncommon. Indeed, autopsy studies have revealed an incidence of ovarian cysts among postmenopausal women up to 50% [3], whereas in studies of TVS in postmenopausal women the incidence was about 2.5% [4].

The implications of the finding of an adnexal mass in an asymptomatic postmenopausal woman can be serious if it is cancerous and it is not excised, because ovarian cancer has an indolent course and when it becomes symptomatic it is often fatal. The recent update on screening for ovarian cancer by the US Preventive Services Task Force Task has concluded that screening is not recommended as it does not provide a timely diagnosis and survival advantage [5]. Intervention can result in substantial morbidity since the appropriate action will be an invasive procedure by laparoscopy or even laparotomy. This is seen as undue risk of harm, as most simple or complex adnexal structures are benign. The aim of the present review is to discuss various options available for the evaluation and management of incidental adnexal masses in postmenopausal women.

## Case Presentation

### *Investigation of adnexal mass*

Several morphologic criteria, with ultrasound alone or combined with biochemical markers, have been reported for evaluation of possible malignancy in adnexal masses [6]. In our opinion, morphologic evaluation by ultrasound with the IOTA LR2 system, even in the hands of non-expert sonographers, has been the simplest and comprehensive approach that has been validated by independent groups [7, 8]. An application for smartphones has further simplified its use. According to this system, the presence of one or more of malignant features (irregular solid tumor, ascites, at least 4 papillary structures, multilocular > 100 mm and increased blood flow) is diagnostic of malignancy. However, about 25% of the tumors scored by this system fall in the category of undetermined risk for malignancy, in which case, expert opinion has been consistently found to be more accurate than the IOTA LR2 system alone [9]. Doppler ultrasound for the evaluation of tumor vascularity or measuring the pulsatility index in Doppler waveforms was found to be sensitive, [10] but is not consistently reproducible in non-expert hands. Various computing methods of vascularity, such as 3D ultrasound, are expected to improve accuracy in the future but they have not replaced 2D ultrasound yet [11].

Biological markers used alone or in combination with ultrasound morphology have been investigated extensively. New markers are studied when they are isolated from proteomic profiles of ovarian cancer patients or blood banks of patients serially screened and eventually developing ovarian cancer [12]. CA 125 has been widely used and appears to be performing very well (sensitivity 77%, speci-

ficity 73%, negative predictive value (NPV) 88%, positive predictive value (PPV) 88%) in a mixed population of pre- and postmenopausal women, at a threshold of 75 u/mL. In the UKTOS trial, serial measurements were computed to reveal a significant trend [2]. However, about 50% of patients with localized ovarian cancer did not have elevated CA 125 levels [13]. Diagnosis of ovarian lesions in premenopausal patients are particularly challenging since they can be caused by diverse diseases, and CA 125 levels can be high in many benign conditions before menopause [14]. Another protein, the human epididymis 4 (HE4), has been shown to be useful in triaging adnexal lesions, especially in premenopausal patients with raised CA 125 levels [15]. Combinations of markers, including CA125, HE4, carcinoembryonic antigen and vascular cell adhesion molecule 1 [16], (these can be incorporated in assays such as OVA1) also appear to be useful [17, 18].

A combination of clinical parameters, ultrasound morphological criteria and CA 125, referred to as the Risk of Malignancy Index (RMI) [19], has shown a promising performance at a threshold of > 200 (sensitivity 87.4%, PPV 86.8%) [20]. The RMI has been successfully used as a criterion for referral of ovarian cancer patients to oncologic units. The American College of Obstetricians and Gynecologists has suggested adapted criteria of the RMI for the diagnosis of ovarian cancer [21] but they appear to perform poorly, especially in premenopausal women without extensive disease [22].

The ROMA index value is an algorithm that combines the levels of CA 125 and HE4 together for women with menopausal status, using quantitative and objective parameters [23], but despite its excellent performance (sensitivity 91.89%, specificity 96.97%, PPV 97.14% and NPV 91.43%), the ROMA index has not gained wider use [24]. Many other scoring systems and algorithms exist for the assessment of adnexal masses, and have shown good performance on a limited basis, but have not been adequately validated [25, 26]. It appears that the opinion of an experienced physician has comparable accuracy with these algorithms. Of note, sensitivity never reaches 100%, and when it is high it is at the cost of specificity, which results in misdiagnosis in at least 20% of postmenopausal patients. Magnetic resonance imaging (MRI) appears to be helpful, particularly for identifying the presence of fat or hemorrhagic fluid [27, 28]. In one study, the combination of IOTA LR2 with MRI had 100% accuracy [29].

#### *Management decisions*

Significant experience has accumulated over the years for the natural history of simple cysts < 7 cm or even < 10 cm in size, suggesting that malignancy is extremely rare [30, 31]. When malignancy is present, it is usually associated with small solid parts or papillae that remain undetected in imaging [26]. Therefore, it appears safe to observe patients with simple cysts after an initial careful scan and measurement of CA 125 levels, since many will regress and no malignancy will develop [32-34]. Elevated CA 125, at

baseline or during follow-up, should prompt further evaluation. Consensus statements of ultrasound radiologists suggest that cysts > 7 cm should be imaged with MRI and cysts > 3 cm should be followed up at least annually in the first years and then at the discretion of the physician [33]. Hemorrhagic cysts after menopause years might require surgical removal. It has been suggested that if an adnexal mass is not changing in two years, further testing increases anxiety and often results in unnecessary operations [35].

A study of 2,870 septated cysts [36] showed that the likelihood of malignancy in these lesions is small (one case of borderline tumor in 1,114 masses) if they remain stable during a 4-6 months' follow-up. Moreover, 38.8% of these cysts regressed spontaneously during follow-up. Importantly, the thickness of septae was not associated with regression or the presence of malignancy. It appears that septated cysts can be treated conservatively even though consensus statements of ultrasound radiologists suggest that they should be removed if the septations are multiple [33].

A study including 1,363 patients with complex masses (i.e. cystic with solid components) < 6 cm with no vascularity on Doppler showed that observation is safe provided that they do not increase in size at reevaluation after 6-8 weeks and 6 months [37]. During this follow-up, malignancy or borderline tumor was identified in 1.3% of cases, all progressed during the first 7 months and only 2/12 were advanced stage cancers.

There is no debate regarding the management when malignant features, ascites or other features of spread (malignant features according to the IOTA LR2 system) are present. In these cases, the patient should be referred to a gynecologic oncology unit [38] and further decisions should be taken regarding primary surgical intervention or surgery after initial chemotherapy to improve the possibility of an R0 resection [39]. The patient's age, health status and a computed tomography scan or laparoscopic assessment are considered for guiding further therapy [40]. Although all these methods have some limitations, the goal is to achieve complete resection without jeopardizing patient's treatment options without increasing the risk of complications.

## **Conclusions**

Adnexal masses in postmenopausal women are not an uncommon problem. Despite careful evaluation with ultrasound and biomarkers, a small number of patients will remain without a conclusive diagnosis. Conservative therapy with observation can be safely applied in the majority of these patients.

## **Conflict of Interest**

The authors declare no conflict of interest.

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