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REVIEW ARTICLE

Role of Imaging in Dilemma of Adnexal Masses in Postmenopausal Women

[1]Poonam Yadav, [2]Meeta Gupta, [3]Mohita Agarwal, [4]Ruchika Garg, [5]Urvashi Verma, [6]Shweta Gupta

ABSTRACT

Adnexal masses in postmenopausal women represent a spectrum of conditions from gynaecologic and non gynaecologic sources. Post-menopausal women are especially at high risk of gynaecologic malignancy however even in this population majority of adnexal masses are benign. Tumor markers and high frequency transvaginal ultrasonography with doppler studies project high quality images allowing for detailed macroscopic appearances of masses and remain the least expensive modalities available. Adnexal masses that are suspicious for cancer, women should be referred to gynaecologic oncologist for optimal care.

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INTRODUCTION

The adnexal mass in postpartum women poses an important diagnostic and management dilemma for health-care providers. Postmenopausal women are at higher risk of gynecological malignancy; yet, even in this age group, most of the adnexal masses are benign. Imaging and tumor markers can help in evaluation of adnexal masses in women. Transvaginal ultrasound (US) has long been considered the imaging modality of choice for the evaluation of adnexal masses and remains the least expensive of all imaging modalities currently available.

[1-5]Assistant Professor, [6]Senior Resident

[1,3-6]Department of Obstetrics and Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

[2]Department of Obstetrics and Gynecology, Acharaya Shri Chander College of Medical Sciences, Jammu, Jammu and Kashmir, India

Corresponding Author: Poonam Yadav, Assistant Professor Department of Obstetrics and Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, e-mail: dr.poonamneeraj@gmail.com

EPIDEMIOLOGY

Life-time risk of developing ovarian cancer is approximately 1 in 70. Although >90% of patients with cancer confined to the ovary will be alive 5 years after diagnosis, the majority of patients are diagnosed with disseminated disease, and hence only 27% likelihood of survival at 5 years.[1]

Age is the most significant risk factor for ovarian cancer, with steeply increasing incidence after menopause. Women older than 65 years are nearly six times more likely to be diagnosed with ovarian cancer than those under 65 years. Other risk factors for ovarian cancer include genetic predisposition including BRCA1 and BRCA2 mutations and hereditary nonpolyposis colorectal cancer, as well as infertility, nulliparity, and endometriosis.[2]

Adnexal masses are more common than ovarian malignancies. Among 33,260 asymptomatic postmenopausal women enrolled in the Kentucky Ovarian cancer screening program, 17% were found to have ovarian enlargement, ovarian cyst, or solid adnexal masses on first screening transvaginal US.[3]

The annual incidence of developing an adnexal lesion among postmenopausal women with normal baseline US was approximately 8% in both large screening studies, and lesions, even with significant complexity, often resolve spontaneously.[3,4]

It is difficult to find out the true frequency of benign and malignant causes of adnexal masses as histology is available only for patients who undergo surgery. Among postmenopausal women who undergo surgery for a suspicious adnexal mass, the reported frequency of malignancy ranges from 36 to 59%.[5,6]

CLINICAL PRESENTATIONS

Most of the adnexal masses are asymptomatic but they may also cause chronic pain or pressure symptoms. Acute pelvic pain may arise in case if adnexal torsion accompanied by nausea and vomiting. At an early stage, lots of patients experience nonspecific symptoms, such as increase in abdominal size, bloating, fatigue, abdominal

or pelvic pain, urinary symptoms, or changes in dietary or bowel habits. Rarely, Meigs syndrome- a benign condition which includes ovarian fibroma, ascites and pleural effusion presents with abdominal pain and distension with or without dyspnea. Tubo-ovarian abscesses are rare in postmenopausal women but may present with pain and fever. Cases of ovarian mass with postmenopausal bleeding may be because of estrogen-producing tumor-like granulosa cell tumor or thecoma or virilization, which suggests an androgen-producing tumor.

Utility of pelvic examination is quite low in identification and differentiation of adnexal masses. Patient obesity and examiner's inexperience increase the likelihood of failure to detect a mass. However, irregular, fixed, nodular masses and the presence of ascites are associated with the malignancy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for simple cystic adnexal masses includes gynecologic etiologies hydrosalpinx and cystadenomas (Table 1). Nongynecologic etiologies include bladder diverticulum, peritoneal inclusion cysts, paratubal cysts, and cysts of gastrointestinal origin. Although malignancy cannot be completely ruled out based on simple cystic nature, multiple studies have shown that the risk of malignancy in these lesions is extremely low (<1%).[7]

The prevalence of complex ovarian masses in postmenopausal women has been reported to be 3.2%. The differential diagnosis for complex adnexal masses are benign masses, causes, such as endometrioma, hemorrhagic cyst, cystic teratoma, tubo-ovarian abscesses, and lymphoceles. Malignant primary ovarian cancers (epithelial, germcell, stromal) and metastatic cancer [breast, gastrointestinal (GI), uterus/cervix, and fallopian tube] can also present as complex cystic adnexal masses.

Adnexal masses can also be characterized as solid or containing solid components. However, the majority of predominantly solid adnexal lesion encountered will represent benign tumors, such as fibroids, fibromas, thecomas, fibrothecomas, benign Brenner tumors, and mature teratomas. Primary ovarian malignancies, such as dysgerminomas, granulosa cell tumors, or malignant Brenner tumors, can appear predominantly solid in appearance. Cystic lesions with solid components, such as septae, papillary projections, and mural nodules, are more associated with primary ovarian epithelial neoplasm. Solid masses may also represent nongynecologic etiologies, such as lymphadenopathy, genitourinary or GI masses, and metastatic malignancies.

EVALUATION

Tumor Markers

Cancer Antigen 125

Cancer antigen 125 (CA-125) is the most extensively investigated tumor marker for ovarian cancer. It is a glycoprotein not expressed by normal ovarian epithelium, but can be synthesized by benign as well as malignant ovarian tumors. Elevated CA-125 levels have been reported in 80 to 85% of patients with ovarian cancer.[8]

Elevated CA-125 have also been seen in any condition which causes peritoneal or mesothelial changes.[8] Elevated levels of CA-125 may be associated with certain benign condition, such as endometriosis, adenomyosis, pelvic inflammatory disease, pregnancy, menstruation, pancreatitis, cirrhosis, and peritonitis.[9]

A meta-analysis by Myers et al[8] investigated the use of CA-125 as a serum marker for discrimination of adnexal masses with malignant potential. Using the data from 66 studies included in their meta-analysis, only 9 contained data that allowed for stratification of results

Table 1: Differential diagnosis of postmenopausal women with adnexal mass

Gynecological ovarian	*Gynecological extraovarian*	*Nongynecological*
Benign	*Benign*	*Benign*
• Mature teratoma	• Endometrioma	• Appendiceal abscess
• Ovarian torsion	• Hydrosalpinx	• Appendicitis
• Polycystic ovaries	• Tubo-ovarian abscess	• Bladder diverticulum
• Endometrioma	• Paraovarian cyst	• Nerve sheath tumor
• Simple cyst	• Peritoneal inclusion cyst	• Pelvic kidney
• Cystadenoma	• Pedunculated fibroid	• Peritoneal cyst
		• Ureteral diverticulum
Malignant	*Malignant*	*Malignant*
• Borderline tumor	• Endometrial carcinoma	• Metastasis (breast, lymphoma, etc.)
• Epithelial carcinoma	• Fallopian tube carcinoma	• Krukenberg tumor
• Ovarian germ cell tumor		• Retroperitoneal sarcoma
• Ovarian sarcoma		
• Sex cord or stromal tumor		

by menopausal status. Sensitivities within these studies ranged from 0.69 to 0.97 and specificities from 0.81 to 1. However, CA-125 by itself has not proven to be a sufficiently sensitive or specific test to use as a screening tool for the detection malignancy in adnexal masses, but multiple studies have shown consistently that it is more helpful in detecting malignant lesions in postmenopausal women when compared with premenopausal women.

Single threshold CA-125 level seems to be of less utility for both screening for ovarian cancer and for predicting malignant potential in adnexal masses. However, strategy of serial CA-125 testing remains an area for further research.

Human Epididymis 4

Human epididymis 4 (HE4) is a serum protein that was initially identified in epithelial cells of epididymis of human. Complete function of this protein remains unknown, but recent studies have shown that ovarian cancer cells commonly express it.[9] Human epididymis 4 was positive in 93% of serous tumors, 100% of endometrioid tumors, and 50% of clear cell tumors. Human epididymis 4 was not found to be positive in any mucinous tumors. Microarray profiling of genes in ovarian carcinoma found that HE4 overexpressed in malignant tissues and it importantly was not amplified in any of the 19 normal tissue samples from women with benign ovarian masses.[9] Hellstrom et al[9] found that HE4 had a sensitivity and specificity for detecting ovarian cancer similar to that of CA-125 but its main advantage over CA-125 was that it was less frequently positive in postmenopausal women with benign disease. A recent systematic review and meta-analysis using a total of 18 studies and 3,865 patients found a pooled sensitivity for HE4 of 74.5% and a pooled specificity of 85.8%.[10]

Various studies have shown that HE4 alone is comparable with CA-125 in terms of its sensitivity and specificity detecting malignant potential of adnexal masses. Abdel-Azeez et al[11] showed that CA-125 when combined with HE4 was a more sensitive predictor of early-stage ovarian malignancy at 84.6% than either CA-125 (61%) or HE4 (76.9%) alone.

Multivariate Index Assay

Multivariate index assay that is OVA1 is comprised of five serum proteins: CA-125, transthyretin (prealbumin), apolipoprotein, β_2-microglobulin, and transferrin. A prospective multi-institutional trial by Ueland et al[12] evaluated 516 woman preoperatively. They found out that multivariate assay has higher sensitivity but low specificity in detecting ovarian malignancy in comparison to CA-125 alone. A study by Longoria et al[13] showed that multivariate index was superior in sensitivity when combined with physician assessment (95.3%) than either physician assessment or CA-125 alone, and their findings were significant in postmenopausal women. However, the role of the OVA1 test in general practice is still evolving.

Imaging

Ultrasonography

Gray-scale US has long been considered the imaging modality of choice for the modality of choice for the evaluation of adnexal masses, especially in the settings of high-frequency transvaginal probes. However, diagnostic accuracy and interpretation reliability are based on the subjective assessment and experience of the ultrasonographer.

Several groups have proposed morphological scoring system to increase the accuracy of US discrimination between benign and malignant masses. The majority of scoring systems included morphology, wall structure/thickness, ovarian volume, and septations and in some studies also included echogenicity, vegetations, and shadowing. Results of various studies show that overall, the scoring systems had poor specificity and positive predictive value (PPV). However, PPV was slightly increased for postmenopausal women, which likely reflects the higher prevalence of ovarian malignancy in this population.

It is well known that in comparison with normal or benign tissue, malignant neoplastic have increased vascularity secondary to continued creation of new blood vessels to keep up with their increased metabolic demand. Along with increased vascularity, there tends to be decreased peripheral flow resistance and increased blood flow velocity within these vessels, when compared with benign tissue. However, there are significant similarities in Doppler flow indices between benign and malignant adnexal masses.

With the introduction of pulsed Doppler spectral analysis, evaluation of the presence or absence of flow, the distribution of flow, and the flow velocity waveforms has provided a whole new series of researches. Malignant tumors require neovascularization to grow beyond 1 to 2 mm in size. This is acquired from adjacent normal tissue vasculature under the influence of angiogenesis factors secreted by its relative structural disorder compared with normal vessels.

Resistive Index and Pulsatility Index

An enormous amount of research has been performed on resistive index (RI) and pulsatility index (PI). Both quantify the effects on the Doppler waveforms of the peripheral resistance to the flow by expressing the difference between the peak systolic velocity (PSV) and

end-diastolic velocity, normalized to the peak velocity in the case of the RI or to the time-averaged mean velocity in the case of PI. The RI generally ranges from 0 to 1.

Being ratios, both indexes are independent of the isonation angle, provided that the Doppler shift is sufficient to cross the sensitive threshold of the system, rendering them easy to obtain and reproducible.

Early work using RI and PI has produced encouraging results; a different range of values was demonstrated in benign *vs* malignant ovarian tumors. Most authors used a cut-off for malignancy of less than 0.4 for RI and 1.0 for PI.

Velocity Index

More recently, attention has turned to indices that measure the flow velocity in an attempt to find a more discriminating parameter. The routine detection of low-impedance waveform (PI < 1) in normal ovaries and benign tumors has eroded the ability of RI and PI to discriminate between malignant and benign ovarian lesions. Neovascularity in malignancy is characterized by low-impedance, high-velocity flow, resulting in increased blood flow compared with benign lesions.

By incorporating velocity index, these show low-impedance signals that can be recognized as benign and thus do not compromise the discriminating abilities of RI and PI. The PSV and TAMXV (time-averaged maximum velocity) are velocity parameters calculated electronically from a smooth curve fitted to the pulsed Doppler waveform. Some authors found TAMXV to be the most discriminating parameter in separating benign from malignant lesions using the cut-off values of greater than 12 cm per second to indicate malignancy. The sensitivity and specificity were 88.9 and 81% respectively. At the same time, the sensitivity level and TAMXV were more specific than PI, RI, and PSV. Discrimination was improved further by combining TAMXV and PI, producing an increase in specificity to 88.1%.

Most useful discriminating parameter was summation of all flow velocities, which, when used alone, achieved a sensitivity of 93% and specificity of 85% in postmenopausal patients and reduced values of 91 and 76% respectively. Premenopausal patients were included outperforming the RI and PI. Because of overlap of different flow data, tumor differentiation using a single parameter was limited.

Currently, however, despite extensive investigation, color flow Doppler analysis must still be considered a research tool in need of further study and standardization of quantifiable results.

Tumor Color, Vessel Location, and Diastolic Notch

Additional parameters have been suggested to improve tissue characterization with transvaginal color Doppler US, including vascular density, vessel location, and demonstration of diastolic notch.

Tumor color score in which each tumor is characterized by the color content of the Doppler scan and rated subjectively on a visual analog scale ranging from 0 to 100 arbitrary units. Tumor color is very good Doppler variable for distinguishing between malignant and benign tumor, outperforming both impedance and velocity parameters. However, problems do exist with the technique that it is subjective and vulnerable to observer bias.

Peripheral vascularization appears to be more common in benign tumors, whereas malignant tumors tend to have more centrally located vessels. Benign masses tend to have regularly spaced vessels, whereas malignant tumor demonstrates a more random distribution of vessels.

Absence of a diastolic notch has been associated with malignant tumor, most likely resulting from lack of normal arterial musculature and possibly the increased permeability of the neovasculature.

Several authors suggested that the data provided by Doppler sonography when added to sonographic morphologic assessment improve the sensitivity and specificity of distinguishing between benign and malignant ovarian tumors.

Computed Tomography

Even though US remains the most common imaging modality in the evaluation of adnexal masses in postmenopausal women, newer technologies, such as computed tomography (CT), are available. Given the small number of prospective studies, using CT to evaluate adnexal masses of postmenopausal women show limited data. However, despite the unclear role of CT in initial evaluation of adnexal masses, CT is the preferred modality for prospective imaging of patients with a high suspicion or known ovarian cancer to optimize surgical planning.

Magnetic Resonance Imaging

Various studies have shown magnetic resonance imaging (MRI) to be superior to US in the differentiation of benign from malignant adnexal masses. Studies have shown that MRI demonstrates sensitivity of 67 to 100% and specificity of 77 to 100% in the diagnosis of cancer.[14,15] These analysis also imply that MRI in some circumstance is recommended as second-line investigation for the characterization of complex adnexal masses that are indeterminate on US, although it is a more inexpensive investigation and is less readily available than US.

Positron Emission Tomography

Until recently, (^{18}F) flourodeoxy-glucose (FDG)-positron emission tomography (PET) and PET/CT have had only a limited role in the diagnosis and staging of disease in patients presenting with ovarian cancer. The strength of PET lies in the ability to identify abnormal biological processes associated with cancer, such as increased glucose metabolism using FDG. Ovarian cancer is typically characterized by increased glucose metabolism and presents with increased FDG uptake, whereas benign tumors are usually negative on PET. Although false-positive FDG-PET is seen in various conditions in normal ovaries during ovulation, physiological activity in bowel, endometrium, ureter, benign cystadenomas, teratomas, schwannomas, endometriomas, and inflammatory processes exhibit increased glucose metabolism. However, coregistration of CT images with the PET image has overcome many of the difficulties. Although the results of PET-CT reported in various studies are impressive, currently, this technology is not recommended in the management of postmenopausal women with adnexal masses, except in particular circumstances.

MANAGEMENT

Women with adnexal masses that are highly suspicious for cancer should be referred to gynecologic oncologist, as outcomes of staging and cytoreduction have been shown to be better than when the procedure is performed by the subspecialist.[16] In addition, women with ovarian cancer who are referred to high-volume expert cancer center have improved overall survival. High-volume physicians were more likely to perform proper surgery, cytoreduction, administration of correct chemotherapy, and provide appropriate treatment to ovarian cancer patients than low-volume physicians.

Table 2: The Society of Gynaecologic Oncologists and the American College of Obstetrics and Gynecology guidelines for patients with newly diagnosed pelvic masses

Premenopausal women (younger than 50 years)
• CA-125 antigen level >200 U/mL
• Ascites
• Evidence of abdominal or distant metastasis (by results or imaging study)
• Family history of breast or ovarian cancer (in first-degree relative)
Postmenopausal women (50 years or older)
• CA-125 antigen level >35 U/mL
• Ascites
• Nodular or fixed pelvic mass
• Evidence of abdominal or distant metastasis (by results of examination or imaging studies)
• Family history of breast or ovarian cancer (in first-degree relatives)

The American Congress of Obstetricians and Gynaecologists in conjunction with the Society of Gynaecologic Oncologists has developed guidelines for referral of patients with pelvic masses to gynecologic oncologists (Table 2).[17]

In women with an adnexal mass, surgical evaluation allows a definitive histologic diagnosis. Surgery could be performed laproscopically or laparotomy and the approach depends upon the degree of suspicion of cancer. Laparotomy with vertical midline incision is recommended for any patient with an obvious malignancy, and a complete staging should be done. If there is a low or moderate suspicion of malignancy, a laparoscopic approach is typically used. Frozen section for the intraoperative diagnosis of a suspicious adnexal mass is recommended in the setting in which availability and patient preference allow.

CONCLUSION

The adnexal mass in postmenopausal women always poses a diagnostic and management dilemma for the primary provider or gynecologists. Tumor markers and imaging can help in evaluation of adnexal mass. Transvaginal US particularly in the setting of high-frequency utilization of transvaginal probes, which projects high-quality images allowing for detailed description of macroscopic appearances of the mass, remains the least expensive of all imaging modalities, currently available. Computed tomography, MRI, and PET are not indicated routinely in the evaluation of an asymptomatic adnexal mass due to their inherent costs and little additional information they afford. Women with adnexal masses that are highly suspicious for cancer should be referred to a gynecologic oncologist and facility for optimal care.

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