Postmenopausal Dilemmas: The Role of Ultrasound

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Abstract: The postmenopausal patient presents unique challenges in ultrasound. With age being a major risk factor for most malignancies, the results of the examination can result in a clinician being more apt to conduct more invasive tests or elect for a surgical cure. This article is aimed to review the common gynecological pathology in post-menopausal patients and how ultrasound can aid the clinician in diagnosis and management. As noninvasive and nonradiation imaging modality, pelvic ultrasound allows valuable approach to assessment of anatomy and pathology of the uterus and adnexa in postmenopausal patients. Validity for the delineation of morphological characteristics of pelvic abnormalities is widely tested and already applied to routine clinical care. The early detection of pelvic carcinoma is still the most attractive for further studies.

Key words: Postmenopause, ultrasound, uterine mass, ovarian mass

Learning objectives

- To discuss how ultrasound can help in management of postmenopausal bleeding
- To present the role of ultrasound in diagnosing pelvic masses
- To understand ultrasound contribution in screening for pelvic malignancies.

INTRODUCTION

The postmenopausal patient presents unique challenges in ultrasound. The deficient hormonal milieu results in the potential for a more uncomfortable examination, atrophied ovaries and a thin endometrial stripe. With age being a major risk factor for most malignancies, the results of the examination can result in a clinician being more apt to conduct more invasive tests or elect for a surgical cure. This article is aimed to review the common gynecological pathology in postmenopause and how ultrasound can aid clinician in diagnosing the patient.

ANATOMY

Technique for measurement of the uterus and cervix in the postmenopausal patient is the same as in other patients. The length and height are obtained in the sagittal plane at its midline and the width is taken in the coronal plane (Fig. 1). The uterine length should not include the cervix. The endometrial stripe is the total of the anterior and posterior layers at the maximal thickness in the sagittal plane (Fig. 2). The hypoechoic area representing the basalis layer, that is common in premenopausal patients, is typically absent but if present should not be included in the measurement of endometrial stripe thickness. Ovarian length is measured in an oblique to sagittal plane. The width and height are measured in the coronal plane (Fig. 3).

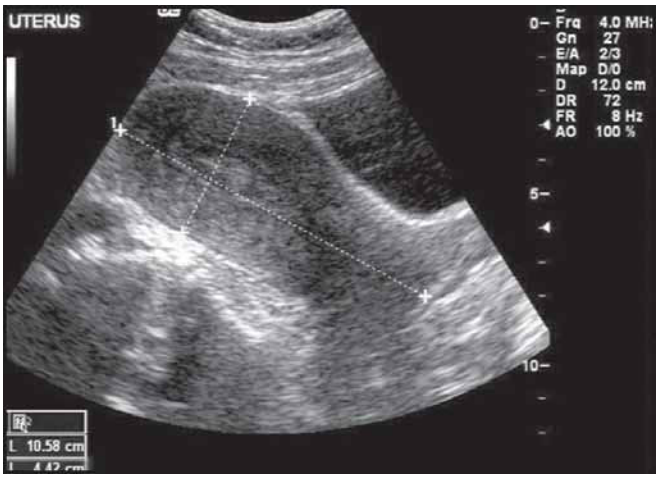

Fig. 1: Anteverted and enlarged postmenopausal uterus

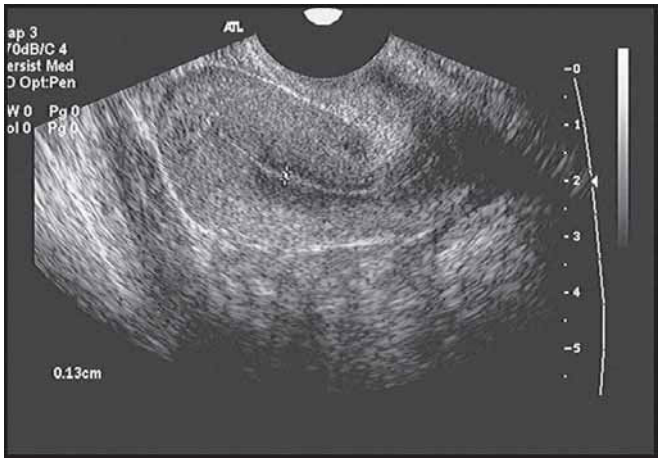

Fig. 2: Normal postmenopausal endometrium

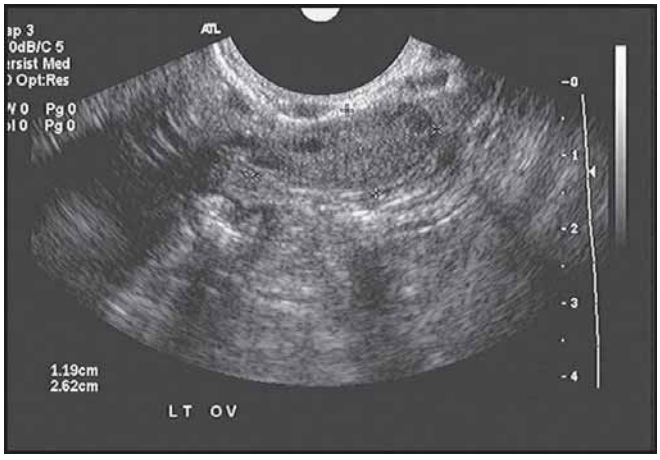

Fig. 3: Normal postmenopausal ovary

The size of the uterus and ovaries varies based on how long the woman is postmenopause. Merz *et al* compiled anatomical measurements of 108 postmenopausal women.[1] Based on their study, the mean uterine corpus measurements were 6.7 × 3.8 × 3.6 cm and 5.6 × 3.3 × 3.1 cm in a normal postmenopausal patient < 5 years and > 5 years, respectively. The endometrial stripe ranges from 0.5 to 1.7 mm. The cervix in the patient < 5 years postmenopause was 2.9 × 2.7 × 2.4 cm. In a patient 5 years or more the cervix was 2.4 × 2.3 × 2.1 cm. The ovaries are approximately 3.5 cm^3 in a patient < 5 years postmenopausal and 2.5 cm^3 in a patient who is > 5 years postmenopausal.[1,2]

CLINICAL INDICATIONS FOR ULTRASOUND

Any patient with postmenopausal bleeding,[3] enlarged uterus or uterus increasing in size on bimanual examination or any patient with an adnexal mass on examination should have an ultrasound. Although MRI and CT may be considered, pelvic ultrasound is the least expensive of the 3 imaging techniques, is not hindered by the bony pelvis and allows for dynamic viewing of the anatomical structures. For these reasons, the pelvic ultrasound is the recommended first test.

Postmenopausal bleeding (PMB) encompasses any vaginal bleeding in a women not taking sequential hormone replacement therapy (HRT) with a documented 12-month period of amenorrhea secondary to complete or near complete ovarian follicle depletion. If they are on HRT, PMB would be any unscheduled bleeding. This is one of the most common symptoms in this patient population and is found in the majority of pathology affecting the uterus. The incidence and etiology is related to the time a woman has been in the postmenopausal state. In the first few years after menopause, the most likely causes include endometrial hyperplasia, polyps and submucosal fibroids. As a patient progresses well into her postmenopausal period, the most likely cause is atrophy of the endometrium and/or vaginal mucosa. Endometrial cancer has to be considered in any postmenopausal patient with vaginal bleeding as it is considered to be present approximately 10% of the time.

An enlarging uterus or a uterus that is increasing in size is worrisome in a postmenopausal woman. The two most common benign conditions that cause uterine enlargement, i.e. adenomyosis and leiomyoma, require estrogen. When estrogen is low, these conditions atrophy resulting in a decrease in size. When a postmenopausal women has an enlarging uterus one needs to consider the rare chance that she has developed leiomyosarcoma or another malignant condition that has caused estrogen levels to increase.

Similar to the uterus, the ovaries atrophy over time as mentioned above. Because the ovaries are a little more than 1 cm in either dimension they often are not palpated in the postmenopausal patient. A patient well into her postmenopausal period with an adnexal mass warrants further investigation. Suspicion should be high for an ovarian malignancy until ruled out.

Endometrial Cancer

Given the mortality of an undetected uterine malignancy, there is intention in the diagnostic work-up to rule out this pathology. Tissue biopsy for years was the only acceptable method in attaining this goal. Since the mid 1990s, this premise has been challenged. A meta-analysis by Smith-Bindman *et al* in 1998 looked at 35 prospective trials for a total of 5,892 patients where endovaginal ultrasound was used to evaluate women with postmenopausal bleeding (PMB).[4] The study showed that when an endometrial lining > 5 mm was interpreted as abnormal, there was a 96% sensitivity for endometrial cancer and 92% for any uterine pathology. This is comparable if not better than blind endometrial biopsy. It also established the negative likelihood ratio for a normal endometrial stripe (homogeneous, < 4 mm) in patients with PMB as 0.05 for non-HRT users and 0.12 when using HRT. These ratios indicate a < 1% chance of endometrial

cancer presuming a 10% prevalence. Studies since have supported the data from this analysis.[5,6] As a result, endovaginal ultrasound for many has become the acceptable first step in the clinical evaluation for PMB.

In making endovaginal ultrasound the first step, one has to be aware that some cancer cases will get missed. Buyuk *et al* showed that using < 5 mm as a cut-off for normal endometrial stripe will result in 1 in 250 endometrial cancers (mostly type II) going undetected.[7] Often times the endometrial stripe, though this is heterogeneous with cystic appearing structures within it. Also symptoms in these patients tend to persist. For these reasons, the following criteria warrant further diagnostic work-up: (i) endometrial stripe > 5 mm; (ii) stripe is heterogeneous independent of its thickness; and (iii) patient's symptoms persist (Fig. 4). Further diagnostic testing usually performed by hysteroscopy to allow direct visualization of the endometrial lining and take directed biopsies. It has been argued that ultrasound should be excluded all together and in office hysteroscopy should be the first diagnostic tool of choice.[8] The improvement in optics allows for a 2.5 mm hysteroscope through which biopsy can be obtained. All patients are not amenable to in office hysteroscopy, data are limited so far as to the effectiveness of this method and a cost analysis has not been performed. Until in office hysteroscopy becomes widespread and data show a greater sensitivity and specificity than transvaginal ultrasound, imaging will continue to be the first choice.

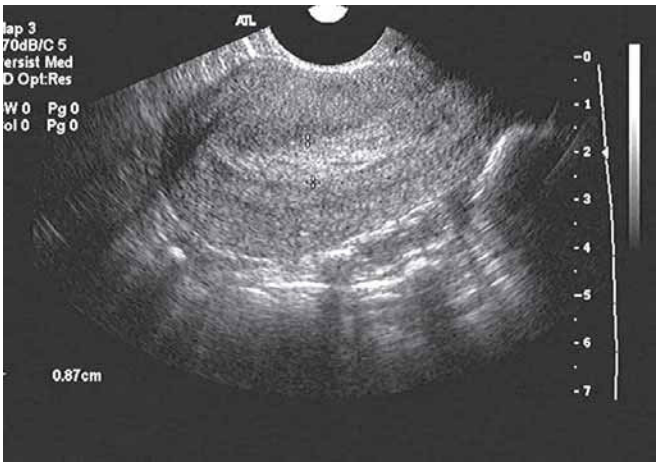

Fig. 4: The patient with postmenopausal bleed. Thick, inhomogeneous and irregularly shaped endometrium suspicious of intracavitary mass

Endometrial Polyps

Polyps are present in approximately half of patients with postmenopausal bleeding. Endometrial polyps are sessile masses that project into the uterine cavity. Most commonly, they are made from hyperplastic endometrium of a cystic variety, but can be functional endometrium. The clonal nature of the stroma cells in polyps suggest that genetic abnormalities can lead to their development. Rarely, adenocarcinomas can be detected within the polyp.

Polyps on endovaginal ultrasound can appear as a focal thickening of the endometrial stripe. They are commonly a hyperechoic area surrounded by hypoechoic endometrium. There may be cystic spaces within the hyperechoic areas. When a polyp is suspected, saline infusion sonogram (SIS) provides increased contrast that facilitates the diagnosis and characterization of a polyp. Most polyps are benign but because the rare adenocarcinoma is found within these structures, they should be removed hysteroscopically.

Saline Infusion Sonogram

Sonohysterography involves placing a 2 mm catheter intracervically into the uterine cavity and instilling 5 to 10 cc of normal saline while ultrasound is being performed. Some catheters have a 1 cc balloon at the end that can be inflated to tamponade the internal cervical os and prevent fluid from leaking out. The infusion of saline distends the uterine cavity and creates a background that provides good contrast for evaluating intracavitary pathology like polyps or submucous fibroids (Figs 5 and 6). The SIS has a 93% sensitivity and 94% specificity in diagnosing endometrial polyps.[9,10] It allows for assessment of size and location of the polyps base. Blood clots and air bubbles can often mimic polyps. The balloon at the end of the catheter can be used to break up blood clot and disrupt air bubbles, thus, allowing one to distinguish these artifacts from a polyp. The balloon on the end of the catheter can often mask pathology at the internal os. To avoid this, the balloon should be deflated and a stream of water injected as the catheter is slowly removed. This maneuver aids in assessing any pathology, especially polyps at the mouth of the uterus.

Endometrial Hyperplasia

Endometrial hyperplasia is defined by the presence of an increased endometrial gland to stroma ratio and abnormalities in epithelial growth compared to normal endometrium. It is associated with a chronic elevation of estrogen, a state that can occur in with menopausal annovulation, estrogen replacement or tamoxifen therapy. Because of its high association with endometrial cancer, biopsy is indicated when this is suspected.

Hyperplasia appears on ultrasound as a thickened endometrial stripe. The thickening is usually focal but can involve the entire endometrial cavity. The interface between the endometrium and the myometrium is generally not disrupted. As discussed previously, when the endometrial stripe is > 5 mm a biopsy should be performed. There is a debate as to whether this biopsy can be performed blind with a pipelle or required hysteroscopic direction. Given that pipelle sensitivity is equivalent or worse than transvaginal ultrasound, a more definitive diagnosis would be made using hysteroscopy.[11] If a

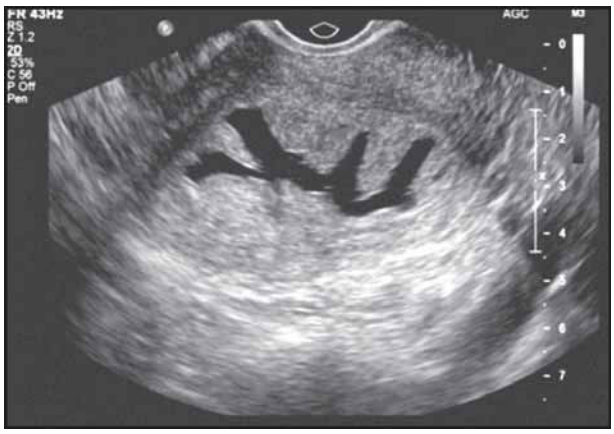

Fig. 5: Multiple endometrial polyps as seen on sonohysterogram

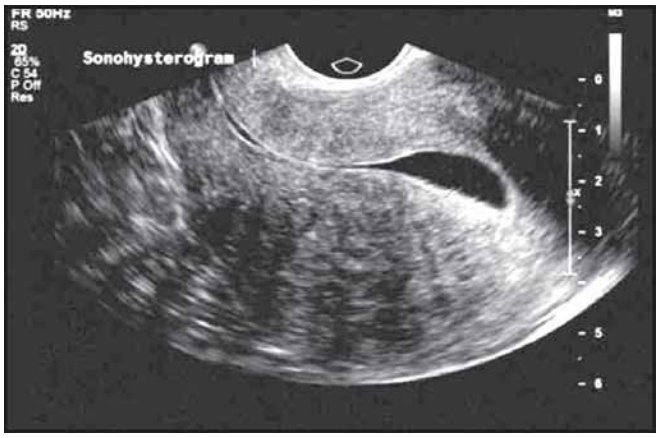

Fig. 7: Retroverted uterus. Thin atrophic endometrium seen on sonohysterogram

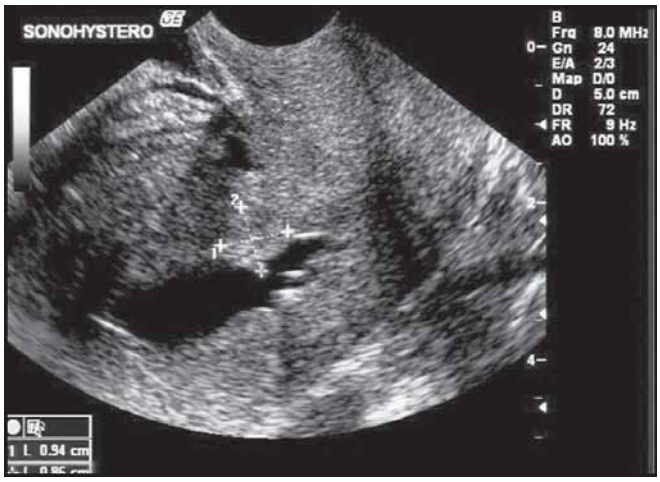

Fig. 6: A small submucous fibroid seen on sonohysterogram

pipelle biopsy is performed and comes back positive for pathology, however, the hysteroscopy could be avoided.

Atrophic Endometrium

When estrogen levels are low, the endometrium atrophies exposing blood vessels in the basalis layer that can lead to bleeding. Given the deficiency of estrogen and progesterone in the postmenopausal state, this is one of the more common causes of bleeding in a patient who is several years past her menopause. Ultrasound of an atrophic endometrium typically shows an endometrial stripe 1 to 2 mm (Fig. 7). When the stripe is homogeneous and < 4 mm, the patient can be followed. If the symptoms persist, however, hysteroscopy is warranted.

Uterine Leiomyomas (Fibroids)

Commonly called fibroids, these are benign smooth muscle tumors. Though present in other anatomical areas, fibroids are most commonly found on the uterus. They are classified as to their location: subserosal, intramural and submucosal. Submucosal fibroids are associated with uterine bleeding. Fibroids are hormonal dependent and regress in size in an estrogen deficient environment; so, they are going to be more common in the patient recently postmenopausal or receiving tamoxifen or estrogen replacement therapy. A postmenopausal uterus with increasing fibroid size warrants immediate evaluation and, though very rare, should be assumed to be leiomyosarcoma until proven otherwise.

On ultrasound, fibroids can vary in appearance based on location and state of degeneration (Figs 8 and 9). The core of fibroids can be filled with hemorrhagic cyst, fat and/or calcification. Submucousal fibroids are best evaluated using SIS. The contrast of the injected saline allows the fibroid to be distinguished from a polyp or blood clot. The location of the fibroid and the degree to which it distends into the uterine cavity can be determined. A fibroid with > 50% projecting into the cavity is amenable to hysteroscopic resection. If a fibroid cannot be removed hysteroscopically, the patient should consider hysterectomy for definitive cure.

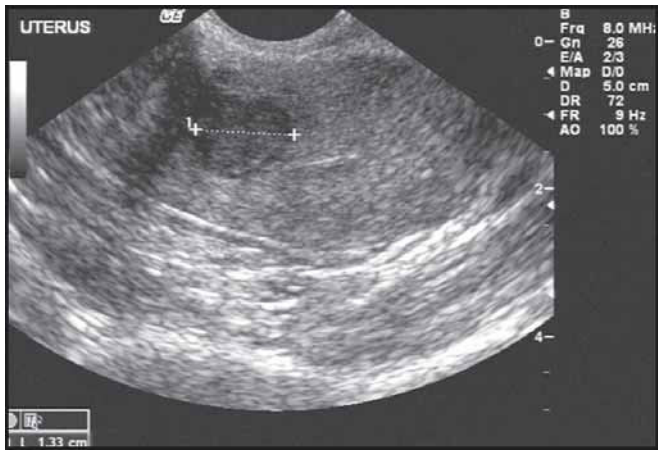

Fig. 8: A small intramural fibroid

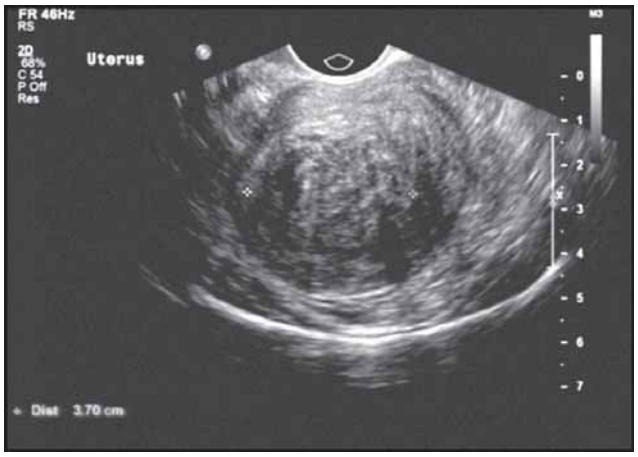

Fig. 9: Degenerating fibroid

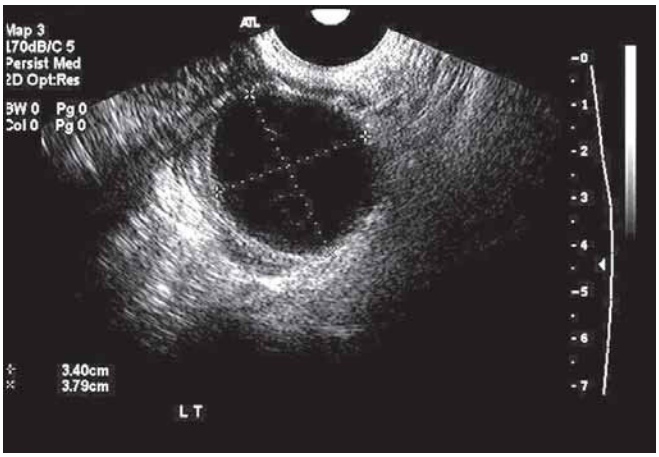

Fig. 10: Small ovarian cyst seen in asymptomatic patient

Ovarian Mass

Similar to postmenopausal bleeding, a palpable adnexa on bimanual examination in the postmenopausal patient raises concern for potential malignancy. This concern is rooted in the statistics that a patient in their 60s is at an approximate 10-fold increase in developing ovarian cancer and although rare is the most lethal of gynecological malignancies. In 1971, Barber and Graber made a strong argument for removing any adnexal mass found on examination.[12] In some, this notion is still held. The development of high resolution ultrasound, however, has challenged this idea.

Numerous studies have been performed determining the rate of ovarian cysts in postmenopausal women ranging from 3 to 15% prevalence (Fig. 10).[13-16] Out of these studies, the ones that were followed out for 2 to 3 years showed only 3 cancers develop from 898 cysts. When the cysts are surgically removed, the most common finding is serous cystadenomas (71 to 83%). Other findings include paratubal and paraovarian cysts, endometriotic cysts, hydrosalpinx, peritoneal cysts and mucinous cystadenoma.[14,16,17] These data overwhelmingly contradict Barber and Graber and make a strong argument for expectantly managing ovarian cysts. This, of course, raises the next question as to what are the criteria for conservative management.

When a cyst is discovered on ultrasound a morphologic characterization is performed to assess its likelihood for malignancy. Factors include the locularity and size of the cyst, the thickness of the cyst wall and any septations present, the presence of solid nodules or papillary projections, blood flow in any solid component of the cyst especially with low resistance and the presence of ascites (Figs 11 and 12). No one characteristic confirms malignancy but rather it is a subjective decision taking into account characteristics on ultrasound as well as the patient's age and other risk factors. Malignancy is more likely when the cyst is > 10 mm, the septations are > 2 to 3 mm thick,

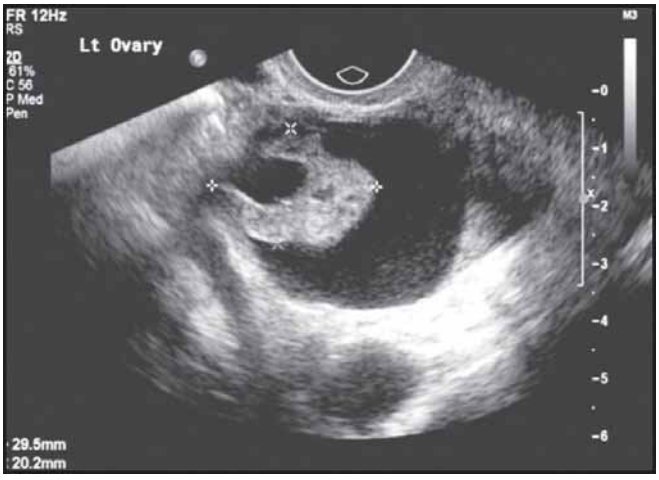

Fig. 11: Complex predominantly cystic ovarian mass with solid components and papillary projections

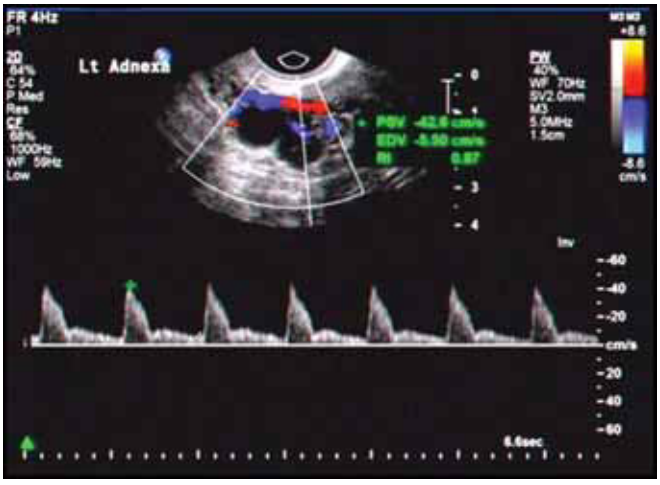

Fig. 12: Complex ovarian mass. Doppler ultrasound with high resistance blood flow not suggestive for neovascularization

there is the presence of solid components with blood flow, the blood flow on Doppler has a resistance index of < 0.4 or a pulsatility index < 1.0 and any ascites in the postmenopausal patient.[18-23]

Screening for Pelvic Cancer

For more than 20 years, there has been a search to identify a screening test for ovarian cancer. Research studies have assessed the pelvic examination, serum tumor markers, protein profiling and US. Studies investigating the use of ultrasound as a screening for ovarian cancer have looked at a high risk population (i.e. BRCA1 and 2, HNPCC mutations) and the general population.[24] Transvaginal ultrasound alone lacks the required specificity for it to be used as a screening test. One of the largest studies performed by van Nagell *et al* at the University of Kentucky conducted screening ultrasounds on 14,469 women who were either > 50 years old or > 25 years with a family history of ovarian cancer.[25] They reported a 81% sensitivity, 98.9% specificity and a PPV of 9.4%.[6] Notably in that study, 4 patients with negative screens developed stages II to III ovarian cancer with 12 months of their last screen, 2 of which had normal size ovaries. It has been determined by expert opinion that for a screening test be beneficial it has to have at least a PPV > 10% thus limiting the number of unnecessary surgeries.

All single variable screening tests have a PPV that ranges from 1 to 9%. In an attempt to improve the PPV, recent studies are testing multivariable algorithms to assess risk. The Prostate, Lung, Colorectal and Ovarian Cancer Screening trial is a multicenter study is looking at 25,000 women.[26] Reports from initial screening showed CA-125 screening and TVUS individually to have a PPV for invasive cancer of 3.7% and 1.0%, respectively. When these variables were combined the PPV increased to 23.5%. Unfortunately, if the screen required both tests to be abnormal before surgery was performed 2/3rd of the ovarian malignancies would not have been detected. Skates hypothesized that rather than using a single CA-125, risk would be more related to a change of CA-125 from a baseline.[27] With this as the primary screening he developed the Risk of Ovarian Cancer Algorithm (ROCA). This screening protocol determines a patient's risk based on serial log values of a CA-125, the patient's age and any change of the CA-125 level from baseline. Patients with changing CA-125 values undergo an ultrasound to assess the pelvis. Patients in high risk for ovarian cancer undergo surgery. Given the low incidence of ovarian cancer in the general population (13.1 per 100,000), a screening test for ovarian cancer must have an extremely high specificity to avoid unnecessary surgery.

The advent of 3D ultrasound and Doppler ultrasound is now been tested as a new armamentarium in early detection of pelvic carcinoma.[28-32] Cohen *et al* studied if 3D power Doppler ultrasound improves the specificity for ovarian cancer detection as compared with 2D ultrasound.[28] In this study, 71 women with a known complex pelvic mass were referred for a preoperative ultrasound evaluation with both 2D and 3D ultrasound. Two-dimensional ultrasound identified 40 masses as suspicious for cancer, including all 14 malignancies, yielding a sensitivity, specificity, and positive predictive value of 100, 54, and 35%, respectively. However, evaluation with 3D power Doppler identified only 28 cases as suspicious (including all 14 cancers), resulting in a sensitivity, specificity, and positive predictive value of 100, 75, and 50%, respectively. The authors concluded that 3D power Doppler imaging better defines the morphological and vascular characteristics of ovarian lesions. All malignancies were correctly identified by both 2D and 3D imaging; however, the specificity significantly improved with the addition of 3D power Doppler. This improved diagnostic accuracy may promote improved patient care by separating complex benign masses from ovarian cancer. Kurjak and coauthors wanted to determine the diagnostic accuracy of 3D ultrasound and 3D power Doppler imaging, used together with standard 2D transvaginal gray-scale and color/power Doppler modalities, for preoperative ultrasound assessment of suspected ovarian lesions.[29] They performed 5-year retrospective analysis on the reports from 43 patients with suspected stage I ovarian cancer. Preoperative sonographic assessment included examination of ovarian volume, morphology, and vascularity. Out of the 43 stage I ovarian cancers, 42 cases were successfully detected preoperatively. Morphological analysis obtained by 3D sonography alone detected 32 of 43 ovarian malignancies, reaching a diagnostic rate of 74.4%. Qualitative analysis of tumor vascularity architecture by 3D power Doppler significantly improved the sonographic management process and successfully detected 41 cases of stage I ovarian cancer (95.4%). When morphological features obtained by 3D sonography were added to 3D power Doppler findings, they achieved higher diagnostic accuracy of 97.7%. Most recently Alcazar published his study aimed to evaluate tumor vascularity by 3D power Doppler ultrasound in early and advanced stage primary ovarian cancers and in metastatic tumors to the ovary.[30] Vascularization index (VI), flow index (FI) and vascularization flow index (VFI) from solid portions or papillary projections in the tumors were calculated. Among the 49 women, 10 had stage I primary cancers, 26 had advanced stage primary ovarian cancers and 13 had metastatic tumors to the ovary. Mean VI and VFI were significantly higher in advanced stage tumors and metastatic tumors as compared with early stage tumors. No differences in 3D Doppler indices were found between advanced stage and metastatic cancers. He concluded that the vascular indices tend to be higher in advanced stage and metastatic ovarian cancers as compared with early stage ovarian tumors. The combination of more sensitive color Doppler sonography and 3D imaging provides both anatomic and physiologic assessment of the

vascularity and blood flow of the ovary and uterus.[31] Further studies are needed.

CONCLUSIONS

Pelvic ultrasound allows valuable and noninvasive approach to assessment of anatomy and pathology of the uterus and adnexa in postmenopausal patients. Validity for the delineation of morphological characteristics of pelvic abnormalities is widely tested and already applied to routine clinical care. The early detection of pelvic carcinoma is still the most attractive for further studies.

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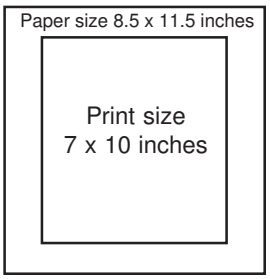

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