



# The Up to Date Status of Three-Dimensional Ultrasonography in Postmenopausal Bleeding

Canverenler E<sup>1\*</sup>, Buke B<sup>2</sup> and Canverenler S<sup>3</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Medical Park Usak Hospital, Usak, Turkey

<sup>2</sup>Department of Perinatology, Irenbe Women's Hospital, Izmir, Turkey

<sup>3</sup>Department of Radiology, Medical Park Usak Hospital, Usak, Turkey

\*Corresponding Author: Emre Canverenler, Department of Obstetrics and Gynecology, Medical Park Usak Hospital, Usak, Turkey, E-mail: canverenleremre@gmail.com

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## Abstract

Postmenopausal bleeding is a frequent clinical problem. Accurate diagnosis is necessary for an adequate clinical management. Currently, 2D ultrasound is considered as a first line imaging technique for discriminating benign situations from malignant lesions. However, some limitations of this technique exist. Three-dimensional ultrasound is a relatively new technique that allows some unique ways for assessing postmenopausal bleeding by ultrasound. In this article, we shall review current evidence about the use of three-dimensional ultrasound for assessing postmenopausal bleeding.

**Keywords:** Three-dimensional ultrasound; Postmenopausal bleeding; Menopause; Endometrium

## Introduction

Ultrasound is the most recent cross-sectional imaging technique to obtain three-dimensional (3D) capabilities. As against computed tomography (CT) and magnetic resonance imaging (MRI), the ability to stage multiplanar reconstruction from volumetric ultrasound data was progressed significantly more slowly. Current equipment, however, is able to produce high-resolution diagnostic images in three dimensions, comprising real-time surface-rendered images, whereas CT and MRI still have meager real-time imaging capabilities. The application of 3D ultrasonography in gynaecology was expedited with the evolution of the endovaginal volume transducer. Although primarily designed as an auxiliary to two-dimensional (2D) transvaginal ultrasonography, 3D ultrasonography is now the imaging choice for the many gynecological disorders such as assessment of Müllerian duct anomalies and the location of intrauterine devices (IUDs). Its practices in clinical scope continue to expand as new volumetric data manipulation capabilities are added.

Bleeding after menopause is a common problem, with 10%-15% of cases later suffering from cancer of the endometrium. It differs from other malignancies, in that early symptomization is common, allowing early cure. Survival reduces with late stages and so studies should struggle to increase the precision of various diagnostic practices [1]. The ideal diagnostic way is still arguable. A thin endometrium measuring less than 5 mm by vaginal scanning in postmenopausal bleeding rules out about 99% of endometrial cancers. Endometrial sampling is the method of choice in those patients with an endometrium  $\geq 5$  mm. However, many "normal" women with postmenopausal bleeding and thickened endometrium will undergo unnecessary diagnostic operations [2]. Three-dimensional (3D) ultrasonography and PD (power doppler) is a novel sonographic diagnostic modality. This technology allows obtaining of the volume of the endometrium and evaluation of its vasculature using 3D PD mapping. Using Virtual Organ Computer-aided Analysis (VOCAL™) software, three vascularity indices can be acquired automatically: the vascularization index (VI), the flow index (FI), and the vascularization flow index (VFI). This technique has been proven to be immensely reproducible and consistent for analyzing the volume of the endometrium and 3D PD indices of patients with malignancy of the endometrium [3].

## Background and Transducer Technology

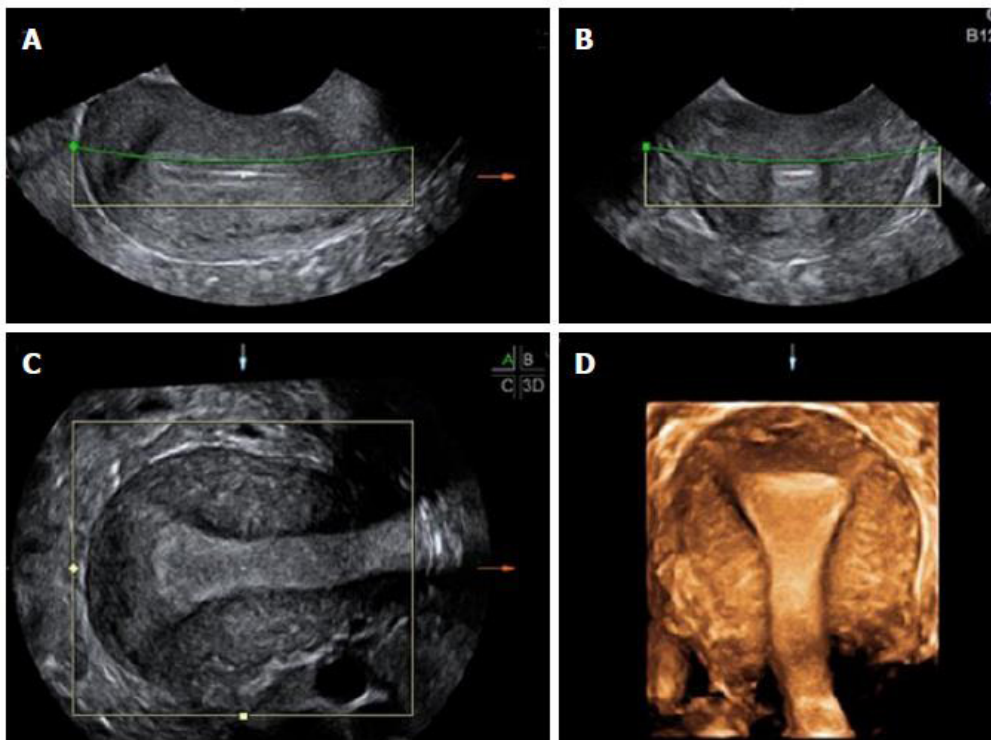
Scientific investigations and studies on the 3D display of ultrasound images have been performed by researchers since the 1970s. However, 3D ultrasound merely became commercially obtainable in 1989 when Kretztechnik launched a machine using a particularly built volumetric transducer [4]. The volumetric transducer included a built-in motorised contraction to move the covered transducer over the area to be examined, obtaining the images in a single sweep. The same transducer is also used for classic 2D scanning. Following progress led to other ultrasound machines that use conventional transducers for manual accession of volumetric data. These resulted in less optimal image quality compared to the automated or volumetric transducers and are being phased out. Not long ago, fully electronic matrix array transducers which can produce 3D images without the use of any moving parts have been launched.

Volumetric scanning capabilities firstly improved for the convex transducer have been gradually introduced to linear and endocavity transducers, which will expand the use of 3D ultrasound in other areas. These transducers can obtain volumetric data just in a few seconds for each plane.

## Image display technique

Although much of the inceptive interest in 3D ultrasonography, especially in obstetrics, was paid particular attention to the display of surface rendered images, the applications of 3D ultrasonography gradually expanded to fields such as multiplanar reconstructions, tomographic slicing, volume calculations, and other forms of image rendering.

The initial images from 3D ultrasonography are generally displayed in three planes, depending on the equipment and the selected display mode, : the plane of volume acquisition and two orthogonal planes. Depending on the type of acquisition, the rendered image may be shown as well. The ideal display of the coronal plane of the uterus usually in need of some manipulation of the data set. One technique was described by Abuhamad., *et al.* [5]. The coronal plane, or C-plane, is the best anatomical view of the uterus, because it gives information of the endometrial cavity, which is essential for the assessment of postmenopausal bleeding (Figure 1).



**Figure 1:** Multiplanar and rendering modes of the uterus. Multiplanar reconstructions from 3D ultrasound show a normal uterus in sagittal (A), transverse (B) and true coronal (C) planes. Surface rendering reconstructed image in a coronal plane of the uterus demonstrating a normal uterine fundal contour (D)

Developments in data acquisition and processing provides nearly isometric reconstruction of the data to useful images in planes other than the one originally obtained. There are a few of specific software programs have been developed for the manipulation of volumetric data. Depending on the producer, the volumetric data may be reprocessed into slices as above CT and MRI. Such capabilities allow for a more adequate workflow, as volumetric data can be obtained through standard acquisition methods, and image analysis may be performed off-line. Data may also be processed for

information like volume and vascular density. Progress in the field of software combined with faster processors have allowed faster reconstructions and reinterpretation of data.

Examples of image manipulation incorporate the inversion mode, in which fluid-containing structures are made echogenic and solid structures are removed allowing simultaneous display of the cystic structures [6]. Other examples of image manipulation using the volume data include volume contrast imaging, in which data acquired from a thick slice is reconstructed over a 2D display to enhance the contrast between tissues, enabling better difference between the different tissue types. The surface rendering mode is less often used in gynaecology than in obstetrics, because the areas surveyed are normally not covered by fluid. Advanced developments in transducer technology have allowed realtime 3D displays. More recently, special effects such as a virtual "light source" have been associated to produce photorealistic effects in images. However this is mostly used in obstetric ultrasounds, its use has also been announced in gynaecological ultrasonography [7].

Ultrasonography is the imaging method for the evaluation of many gynaecological disorders. The role of 3D ultrasonography in gynaecology includes the assessment of Müllerian abnormalities, IUDs, the endometrium, polyps, the location of a pregnancy, and the mapping of uterine leiomyomata, ovarian follicles and adnexal lesions.

Although 3D ultrasonography is considered a problem-solving tool in many conditions, it has become the modality of choice for the evaluation of Müllerian abnormalities and IUDs. An additional utility of using 3D ultrasonography is finding anomalies not detected on 2D studies. In a study by Benacerraf, *et al.* [17] on 66 patients, the reconstructed coronal view of the uterus ensured extra information not seen on 2D ultrasonography, and ameliorated the reliance of the diagnosis of suspected anomalies in 24% of patients. Using a technique described by Abuhamad, *et al.* the additional findings detected on 3D ultrasonography were a polyp or submucous fibroid, three arcuate uteri, and a subseptate uterus that were not detected using 2D ultrasonography [5].

In postmenopausal bleeding cases, problems mostly concern with the endometrium. Submucosal myomas, polyps, endometrial hyperplasia and endometrial cancer, that causes irregularity in the endometrium, can be examined in more detailed by 3D ultrasonography.

### **Postmenopausal bleeding**

Postmenopausal bleeding is a common symptom in general gynecological practice. The incidence of vaginal bleeding in postmenopausal women is almost 10% immediately after menopause and 5% of all cases of menopause [8,9]. Various benign genital causes of postmenopausal vaginal bleeding include atrophic vaginitis, endometrial and cervical polyps, endometrial hyperplasia, and submucosal fibroids. However, 10% of all women presenting with postmenopausal bleeding may have endometrial malignancy. Clinical researches for those patients are mainly focused on to exclude malignant and premalignant lesions [10,11].

In the United States, endometrial cancer is the most common type of gynecological cancer, and fourth among all types of cancer and seventh among all causes of death by cancer [12]. Cancers in the female reproductive organs constitute 15.2% of all types of cancer; however, endometrial cancer comprises only 1.9% of all types of cancer, but the incidence is increasing with the increased average lifespan and popularity of hormone replacement therapy [13]. Endometrial cancer comes about in both the pre- and postmenopausal periods, peaking when patients are in 50s, and postmenopausal uterine bleeding is the most common manifestation of endometrial cancer.

According to the literature, endometrial biopsy and histopathologic analysis can provide a temporary diagnosis [14]. Transvaginal ultrasound is the most frequently used first-line investigation for women with postmenopausal endometrial bleeding before endometrial biopsy. Generally, a thick endometrium is determinative further invasive procedures such as endometrial biopsy and/or hysteroscopy [15,16]. However, conventional two-dimensional (2D) ultrasound cannot assess all possible endometrial pathologies. The recent developments with ultrasound equipment enable new imaging techniques for volume scanning. Unlike 2D ultrasound, three-dimensional ultrasound visualizes the whole endometrium on a coronal plane and can integrate Doppler imaging to display the vascularity in the interested areas.

### **Endometrial cancer / hyperplasia**

Few studies have showed the role of 3D ultrasound in the diagnosis and assessment of endometrial cancer. Three-dimensional ultrasound allows the assessment of endometrial volume. According to the literature, this measurement is highly reproducible [18].

In the study of Gruboeck *et al*, the diagnostic performance of endometrial thickness and endometrial volume in a series of 103 women with postmenopausal bleeding were compared. Mean endometrial thickness (29.5 vs 15.6 mm) and endometrial volume (39.0 vs 5.5 ml) values were significantly higher in women with endometrial cancer as compared with those with benign conditions [19]. This parameter was more sensitive (100 vs 83%) and had a higher positive predictive value (91.7 vs 54.5%) with a cutoff of 15 mm for endometrial thickness and 13 ml for endometrial volume.

41 women with suspected endometrial pathology were analyzed by Kurjak, *et al*. In that study, obtained results were similar. They reported that endometrial volume as well as endometrial thickness was significantly higher in women with endometrial cancer as compared with those patients with benign conditions such as polyps, endometrial hyperplasia or cystic atrophy [20].

Mansour, *et al* compared endometrial volume and thickness in a series of 170 women with postmenopausal bleeding and reached the same outcomes as Gruboeck, *et al*. [21]. However, these authors reported the cutoff for endometrial volume was 1.35 ml with a sensitivity of 100% and a false-positive rate of 29%, which is much higher than Gruboeck. A clarification for that is that Mansour's study included patients with 'endometrial atypia' in the cancer group.

However, in a study by Yaman, *et al*. it is found that endometrial volume was more specific than endometrial thickness in a series of 213 women, 42 with endometrial cancer. With a cutoff of 2.7 ml, sensitivity was 100% and specificity was 69%. Odeh, *et al*. and Merce, *et al*. have reported similar findings [22,23,3].

Opolskiene, *et al*. did not find significant divergence between endometrial volume and thickness in the terms of sensitivity and specificity for diagnosing endometrial cancer [24].

The utilization of 3D ultrasound has been also found to be beneficial to specify myometrial invasion in endometrial cancer by analyzing the myometrial-endometrial interface and to predict the maximum penetration of the tumor within the myometrium [25].

This new technique was based upon a 3D virtual navigation through the uterus for defining the deepest point of myometrial infiltration in a series of 96 women with endometrial cancer. Sixty-nine women had <50% myometrial infiltration on histopathologic examination and 27 had >50% myometrial infiltration. The most interesting outcomes from this study was the negative predictive value notified (100%) with this technique. The false-positive rate notified was 39%. The reproducibility of the technique was good.

Another facility for 3D ultrasound is the evaluation of tumor vascularity by 3D PD [26]. This technique allows the illustration of vascular network in endometrial lesions as well as the prediction of three vascular indexes (VI, FI and VFI) by the VOCAL™ (VIRTUAL ORGAN COMPUTER-AIDED ANALYSIS) rotational method. (Figure 2) Vascular network in malignant tumor used to be nonuniform with disordered branching, changes in vessels diameter, pseudoaneurysms. Moreover, these features used to be absent in benign conditions such as polyp or hyperplasia.

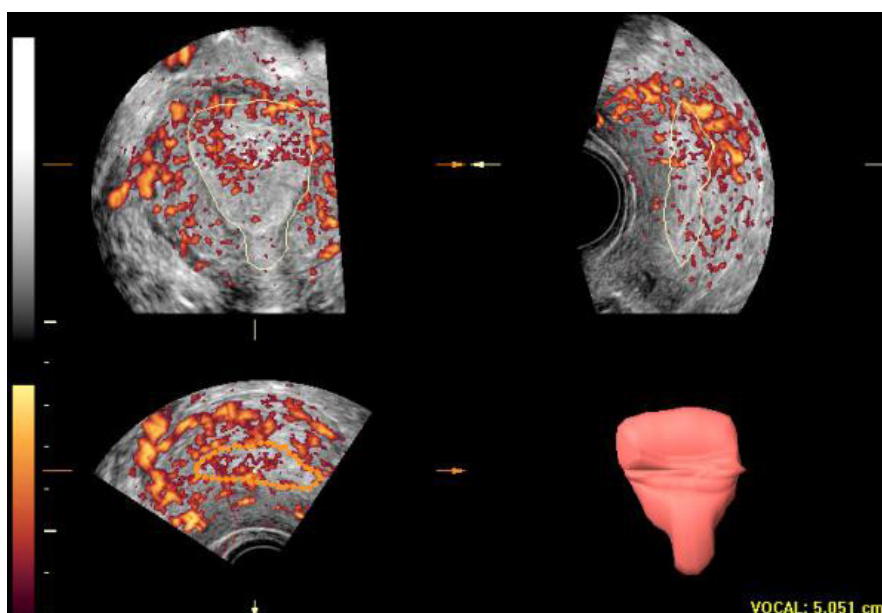


Figure 2: Virtual organ computer-aided analysis of the endometrium

Kupesic., *et al.* stated that evaluating the vascular network by 3D PD they were able to define accurately the depth of myometrial invasion in 21 out of 22 women with endometrial cancer [27]. They assessed the presence of disordered vessels in the endometrial-myometrial interface. Depending on whether more than half or less than half of the myometrium was invaded by these disordered vessel, patients were noted as having deep or superficial myometrial invasion.

The utilization of vascular indexes has not been broadly assessed. Odeh., *et al.* reported that all three 3D PD indexes were significantly higher in women with endometrial cancer than those with benign pathology [23]. However, they did not compare with conventional 2D PD and the specificity reported was low. In a study by Mercé., *et al.* it is found that 3D PD indexes were significantly higher in women with endometrial cancer as compared with those with endometrial hyperplasia [28]. Alcázar., *et al.* also found that 3D PD indexes were significantly higher in women with endometrial cancer as compared with those with benign pathology but this study included only women with endometrial thickness over 5 mm and did not compare 3D results with conventional 2D color Doppler [29]. Opolskiene., *et al.* reported data in a series of women with postmenopausal bleeding and endometrial thickness > 4.5 mm [24]. They reported that in spite of the fact that 3D PD indexes were significantly higher in women with endometrial cancer as compared with those with benign pathology, this method adds little details to endometrial thickness or volume. Lieng., *et al.* analyzed a small group of women with endometrial polyps and endometrial cancer comparing 3D PD indexes within the lesions before and after contrast boosted examination [30]. They did not find any significant differences between groups in 3D PD indexes.

Galvan., *et al.* assessed the relationship between intratumoral 3D PD indexes and particular histological tumor features in a series of 99 women with endometrial cancer [31]. According to their study, endometrial volume and vascularization index were separately correlated with myometrial infiltration and tumor stage, vascularization index was separately correlated with tumor grade and endometrial volume correlated with lymph node metastases.

In general, endometrial volume seems to be a better marker for endometrial cancer than endometrial thickness in women with postmenopausal bleeding. The 3D PD assessment of endometrial vascularity is reproducible and looks like useful for discriminating endometrial cancer than benign endometrial conditions. Its efficiency seems to be better than endometrial volume. This technique also seems to be useful to predict some histological features of endometrial cancers, especially myometrial invasion.

### **Submucosal masses (Uterine leiomyomas / Endometrial polyps)**

Uterine fibroids are the most common pelvic tumors of women. Especially, submucosal myomas may be associated with postmenopausal bleeding. Endometrial polyps due to similar sonographic and clinical findings were also evaluated in this category.

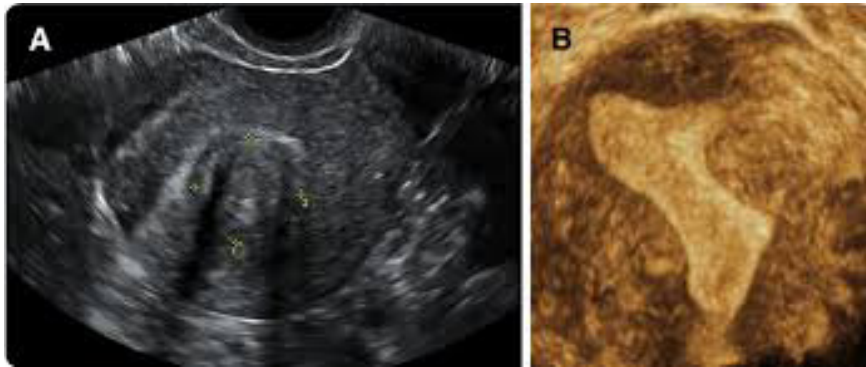
Minimally invasive surgery for the treatment of submucosal masses requires an proper evaluation of their location. Vaginal resection of submucosal uterine fibroids or endometrial polyps, a hysteroscopic procedure, makes possible the removal without open surgery. The attentive selection of patients is necessary, as not all submucosal masses can be extirpated with this technique. Assessing conformity for hysteroscopic resection requires evaluating the size of the mass, the size of the intramural component, and the degree of protrusion into the endometrial cavity [32]. Submucosal fibroids may be categorized depending on their bulging into the endometrial cavity [33]. They are classified into three groups: type 0 (fibroid polyps), type I (<50% contained within the myometrium), and type II (>50% contained within the myometrium). 3D saline sonohysterography shows good overall agreement with diagnostic hysteroscopy in assessing the type of submucosal fibroids (Figure 3) [34].

The sonographic view of uterine leiomyomas use to be a hypoechoic well-defined lesion arising from the myometrium. The use of 3D ultrasound in the assessment of uterine fibroids has been evaluated in few studies.

Salim., *et al.* found that 3D sonohysterography is very beneficial to categorize submucous myomas and the agreement with the hysteroscopic classification is high [34].

This evaluation plainly shows that typical vascular network of uterine fibroids has a 'nest' appearance. Their findings are in agreement with those studies based on corrosion analysis of vascular network [35].

One possible clinical implementation of this method is its use for anticipating outcome of medical treatment. Muñiz., *et al.* assessed 15 women with uterine fibroids prior to uterine artery embolization by 3D PD and determined that this technique can reveal collateral blood flow not detected by uterine artery arteriography and could anticipate response to treatment [36].



**Figure 3:** (A) Two-dimensional longitudinal view of the uterus that contains a central fibroid tumor (calipers). (B) The 3-dimensional coronal view shows that the fibroid tumor is partly submucosal in the leftcornual region, hence mapping the location of the fibroid tumor precisely

Exacoustos., *et al.* compared the role of 2D and 3D ultrasound in 10 women with uterine fibroid who undergone laparoscopic cryomyolysis [37]. The authors used a semi-quantitative evaluation of blood flow at the level of the fibroid capsule and inside the tumor. This study showed that both, 2D and 3D PD ultrasound was beneficial to assess fibroid vascularization but 3D PD were best to evaluate such an evaluation.

In conclusion, 3D PD USG seems to be a prospective instrument for diagnosing, predicting response to medical therapy of uterine fibroids and to assess their growth possibility.

### Benefits and Limitations

With 3D volume acquisition of ultrasound data, the workflow maybe redesigned to improve efficiency. Benacerraf., *et al.* showed that the examination time may be reduced by using standardised volume acquisition protocols that were subsequently evaluated offline [38].

As well as the benefits and capabilities of 3D ultrasonography, the sonologist should also be aware of the presence of artefacts and its physical limitations. These limitations reflect the inherent physics of ultrasound. However, artefacts can sometimes be useful, as in the use of the acoustic shadow for the evaluation of IUDs.

### Standardisation of Practice

Practitioners of 3D ultrasonography need to learn not only acquisition techniques, but each software module used. Even sonographers and sonologists who are experienced in 2D imaging undergo a learning curve with 3D methodology [39]. With large volumes of ultrasound data and latitude in demonstrating multiplanar images, spatial orientation can be challenging for less experienced practitioners. The orientation of structures (i.e., ventral, posterior, right, and left sides) no longer corresponds to the edges of the display screen, but to the object itself. With current equipment, the orientation of the display is still dependant on the operator. Proposed guidelines for the standardised display of 3D images have been published by the International Society of Ultrasound in Obstetrics and Gynecology 3D Focus Group with the aim of providing some degree of standardisation of image display [40].

### Conclusion

The proven efficacy of 3D ultrasonography for the diagnosis of postmenopausal bleeding as well as adjunctive roles in ultrasound studies for the assessment of müllerian duct anomalies, locating IUDs, infertility and the preoperative evaluation of submucosal uterine leiomyomata, has made it a cost-effective first-line imaging technique. As 3D ultrasonography capability is becoming a standard feature of many mid-range to high-end ultrasound machines, ultrasound practitioners should develop the necessary proficiency and skills to take advantage of its applications.

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