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Original Article

Utility of three dimensional (3-D) ultrasound and power Doppler in identification of high risk endometrial cancer at a tertiary care hospital in southern India: A preliminary study

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ABSTRACT

Objective: The study was conducted to find the utility of three dimensional (3-D) ultrasound and Doppler sonography in differentiating benign and malignant endometrial lesions and to ascertain the association of sonology parameters with type, grade and stage of endometrial cancer.

Materials and methods: Women attending the gynaecology department of a tertiary care hospital, with a provisional diagnosis of carcinoma endometrium were subjected to three dimensional power Doppler ultrasound evaluation and assessment of vascular patterns. VOCAL (Virtual Organ Computer-aided Analysis) software was used to assess volume, Vascularisation Index (VI), Flow Index (FI) and Vascularisation Flow Index (VFI). Ultrasound parameters were compared with histologic diagnosis to evaluate the diagnostic performance using Receiver Operating Characteristic (ROC) Curve.

Results: Sixty-four women were included in the study, 33 with benign and 31 with malignant endometrial lesions. Larger endometrial volume and higher Doppler indices correlated with malignant lesions. The variables with good discriminatory potential between benign and malignant status were VI and VFI, having a sensitivity of 90.3% and specificity of around 80%. VFI (adjusted odds ratio of 40.4; (95% CI − 8.46–192.88), p value < 0.001) was the only significant variable identified by multivariate logistic regression, when adjusted for age and post-menopausal status. Multiple global and focal vessel pattern was seen predominantly in malignant cases (specificity 93.9%), although the sensitivity was low (61.2%). Higher stages and grades of tumour and non-endometrioid types had higher Doppler indices, and requires further evaluation.

Conclusions: 3-D ultrasound has good discrimination potential between benign and malignant endometrial lesions and could be useful as a screening tool. However, utility of 3-D tool for differentiation between tumour characteristics needs further validation.

Introduction

Women with endometrial cancer mostly present either with postmenopausal bleeding or peri-menopausal abnormal bleeding. A two dimensional (2D) trans-vaginal sonography has long been the first line modality in endometrial evaluation. Three dimensional (3-D) ultrasound is a relatively new advance, which can be used to assess several morphological and vascular parameters of endometrium.

Power Doppler measures endometrial volume and vascular indices such as Vascularisation index (VI), FI (Flow index) and VFI (Vascular flow index) using Virtual Organ Computer-aided Analysis (VOCAL) software. These indices point towards tumor neovascularisation thereby raising the suspicion of malignancy. Besides, studying the vessel patterns provide additional information on the nature of the tumor. Several researchers have reported power doppler to be useful in differentiating malignant endometrial lesions from benign ones, but there is only one report that comprehensively showed correlation between power Doppler indices and endometrial histological types, grade, myometrial and cervical invasion and lymph vascular space invasion [1–4].

In India, endometrial cancers are diagnosed and managed mostly by the general gynaecologists; due to limited availability of gynaeco-oncologists at most centres. In one of the few reports on

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Table 1
Comparison of baseline characteristics of benign and malignant cases.

Baseline characteristics	Benign (n = 33) n (%)	Malignant (n = 31) n (%)	Fisher's exact test p value
Age group (yrs)			0.05
35–44	5 (15.2)	3 (9.7)	
45–54	18 (54.5)	9 (29.0)	
>55	10 (30.3)	19 (61.3)	
BMI (kg/m^2)			0.12
<25	24 (72.7)	16 (51.6)	
>25	9 (27.3)	15 (48.4)	
Family history			0.23
Yes	0	2 (6.5)	
No	33 (100)	29 (93.5)	
Parity			0.11
Nulliparous	4 (12.1)	0	
Parous	29 (87.9)	31 (100)	
Post-Menopausal status			0.01
Yes	17 (51.5)	25 (80.6)	
No	16 (48.5)	6 (19.4)	
Presence of DM/HTN			0.35
Yes	5 (15.2)	8 (25.8)	
No	28 (84.8)	23 (74.2)	

endometrial cancer in India, Mahantshetty et al. observed that endometrial cancers were seen in relatively younger population (mean age 54 years) and the trend was towards incomplete staging when surgery was performed by non-oncologists [5]. Pre-operative identification of the risk status in terms of type, grade (differentiation) and stage of the cancer, aids in effective planning for optimal surgery in consultation with an oncologist. Although endometrial biopsy and Magnetic Resonance Imaging (MRI) could provide this information, a non-invasive sonological evaluation may possibly be an alternative option.

With this background in mind, the present study was designed to find the utility of 3-D and Power Doppler sonography parameters in differentiating benign and malignant endometrial lesions and to find the correlation of 3-D and Power Doppler sonography with the type, grade and stage of endometrial cancer.

Patients and methods

A prospective study among gynaecology out-patient attendees of a tertiary care hospital in South India was conducted over a period of two years. Ethical approval was obtained from the Institutional Ethics Committee (IEC 274/2012) and written informed consent was obtained from all the participants. Women with postmenopausal bleeding and with one or more sonological features (endometrial thickness $\geq$5 mm, indistinct endo-myometrial junction, cystic spaces in endometrium, hyperechoic areas and irregular endometrium) or one or more risk factors (obesity, diabetes, hypertension, nulliparity and family history of gynecologic/breast cancer); and women with perimenopausal abnormal uterine bleeding with risk factors and/or endometrial thickness $\geq$18 mm were eligible to be included in the study.

A total of 70 women were enrolled in the study during the stipulated time frame of two years. Women with inadequate histopathology at biopsy and did not wish to have further evaluation and those who were lost to follow up were excluded from the analysis. All the patients underwent meticulous history taking, clinical examination and a 2D transvaginal ultrasonography to measure endometrial thickness. Patients underwent a detailed trans-vaginal ultrasound examination, using Voluson 730 Expert (GE Healthcare, Milwaukee, WI, USA) which had a multi-frequency vaginal probe (3–9 MHz). All 64 cases were examined by a single consultant (Radiologist with >15 years' experience and having the necessary training and expertise to operate the 3D power Doppler). Grey scale assessment of uterus was done and endometrial thickness was measured in the sagittal plane including both layers at the level of maximum thickness. Volume acquisition was done by manually tracing the endometrium in the coronal, axial and mid sagittal planes. Power Doppler was applied over the endometrial and sub-endometrial area. Uniform settings in power Doppler were used, namely; normal frequency, pulse repetition frequency 0.6 kHz, gain 4.0 and low wall motion filter. Vascular patterns were subjectively interpreted and classified based on the International Endometrial Trial Analysis (IETA) group as, no vessels, single vessel, multiple focal vessels, multiple global vessels and scattered vessels [6].

Endometrium was traced manually in three planes, and VOCAL software was used to manually delineate the endometrial area and to calculate the volume and vascular indices (Vascularisation Index, Flow Index and Vascularization flow index). Vascularisation Index (VI) is a measure of the number of color coded voxels in a given volume and represents the number of vessels in a given volume. Flow Index (FI) is the intensity of the Doppler signal in the color coded voxels and is the average color of all voxels. Vascularization flow index (VFI) is a combination of VI and FI and is expressed as a range from 0 to 100.

The final diagnosis was made based on the histopathological report following endometrial curettage or surgery. In cases of endometrial carcinoma, the histopathology report included the

Table 2
VOCAL software characteristics of benign and malignant cases.

VOCAL software characteristics	Benign Median (IQR)	Malignant Median (IQR)
Endometrial volume (cc)	3.48 (2.15–7.79)	10.3° (4.02–25.23)
Vascular indices		
VI	0.49 (0.23–1.78)	11.92 (3.21–22.9)
FI	23.63 (21.18–28.21)	33.16 (26.68–37.45)
VFI	0.12 (0.05–0.42)	3.65 (1.02–10.76)

Table 3
Diagnostic performance of individual ultrasound variables of VOCAL[a].

Parameter	AUC	95% CI	Cut off	Sensitivity	Specificity
Endometrial Volume	0.755	0.63–0.87	4.52	74.2	60.6
Vascular indices					
VI	0.902	0.82–0.98	2.02	90.3	78.8
FI	0.820	0.71–0.92	26.18	80.6	66.7
VFI	0.904	0.82–0.98	0.76	90.3	81.8

[a] Fischer's exact test P value < 0.001.

grade of the tumor, type, myometrial infiltration, and lymph node metastases. The universally accepted 3-grade system of grading of carcinoma was followed, in which grade 1 carcinoma showed gland formation in more than 95% of the tumor, grade 2 showed solid growth pattern in 5%–50% of the tumor while grade 3 had solid growth pattern in more than 50% of the tumor. All tumors were staged according to International Federation of Gynecology and Obstetrics Committee on Gynecologic Oncology 2008 [7].

Endometrial histopathology was considered as the gold standard. Cases reported as malignant by curettage underwent surgical staging, and the hysterectomy specimen was analysed for myometrial invasion.

Ultrasound diagnosis was compared with the histopathological diagnosis for all the subjects. The four parameters considered in analysis were endometrial volume, VI, FI and VFI, for which cut off values separating benign and malignant lesions were obtained. A diagnosis of malignancy was made when the measured values exceeded the cut offs for at least three out of four parameters.

Statistical analysis was done using Statistical Package for Social Science (SPSS version 15). Data is expressed as percentages and proportions. Continuous data pertaining to USG parameters is expressed as median and inter-quartile range (IQR). Univariate analysis for categorical data was done using chi-square test. Multivariate logistic regression was used to identify the significant predictors of malignant lesions. p value < 0.05 was considered to be statistically significant. Receiver Operating Characteristic (ROC) curve was used to determine the sensitivity and specificity of the USG parameters.

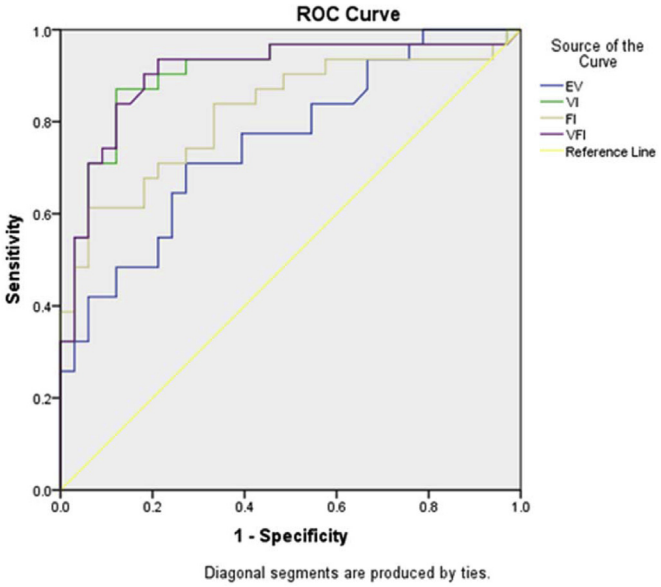

Fig. 1. Receiver Operating Characteristic curve for ultrasound parameters.

Results

A total of 70 women were enrolled in the study from August 2012 to July 2014. Six cases were excluded; four women with inadequate histopathology at biopsy did not wish to have further evaluation and were lost to follow up; two women had histopathology report as uterine sarcoma and cervical cancer with uterine extension, hence were excluded from the study. The results have been described for the remaining 64 participants. The clinical characteristics of the enrolled women are shown in Table 1. Malignant lesions were more commonly noted among women, in the post menopausal age group.

Histopathology identified 33 (51.6%) benign lesions of endometrium and 31 (48.4%) with endometrial carcinoma. Hyperplasia was the commonest (18/34) diagnosis in the benign group.

On evaluation by two dimensional ultrasound, endometrial thickness showed a wide range in the benign [median and IQR:12 mm (8,16 mm)] and malignant [20 mm (15, 32 mm)] groups.

Table 2 depicts the comparison of 3D ultrasound parameters among the benign and malignant endometrial lesions. Malignant cases had larger volume (median 10.3 cc v/s 3.4 cc, p value < 0.001) and higher Doppler indices.

Table 3 and Fig. 1 describe the results of the ROC Curve analysis for individual ultrasound parameters with respect to benign and malignant histology. All parameters had a statistically significant discriminatory potential in differentiating between benign and malignant lesions. Among the parameters, the best discriminatory potential was seen for VI and VFI, with Area Under Curve of 0.902 and 0.904 respectively. The sensitivity for both VI and VFI was 90.3% and specificity around 80%. The unadjusted odds for malignant lesions to have VI $\geq$ 2.02 and VFI $\geq$ 0.76 was 19.6 and 42 respectively as depicted in Table 4.

Multivariate logistic regression identified only VFI as the significant variable, associated with malignancy when adjusted for age and menopausal status (adjusted odds ratio 40.40; 95% CI – 8.46–192.88); p value < 0.001.

Study of vessel patterns showed multiple focal and global pattern in a majority of malignant cases (19/31, 61.3%). Multiple focal and global pattern correlated well with histopathology having a specificity of 93.9%, positive predictive value of 90.4% and negative predictive value of 72.1%, in spite of low sensitivity (61.2%) (Fisher's exact test p value of <0.001) (Fig 2).

The tumor characteristics showed predominant cases of stage greater than 1 b (12/31, 61.3%); two thirds of the cases (21/31, 67.7%) were well differentiated and majority of the cases were of endometrioid type (26/31, 83.9%). Among the five cases with non-endometrioid type, two each were adenosquamous and serous papillary types and one had a clear cell type.

Table 5 illustrates the three dimensional ultrasound parameters in the 31 endometrial carcinoma cases with respect to the stage, grade and type of malignancy. None of the parameters showed any association with the tumor characteristics, probably due to the small numbers in each categories. However, endometrial volume appears to be higher in higher stages, higher grade and non endometrioid types.

Discussion

Endometrial thickness is a time tested and well accepted method for screening for carcinoma endometrium [8,9]. However, it may not provide an accurate picture of the endometrium, especially when the lining is irregular or indistinct [10]. Endometrial volume calculated by VOCAL software along with flow indices and vascular patterns on 3D Power Doppler may be a good alternative in such situations to evaluate the endometrium.

Table 4
Performance of newly derived cut offs of 3D Power Doppler parameters with HPE outcomes.

USG Characteristics	HPE		Chi square value	p value	Unadjusted OR	95% CI
	Benign n (%)	Malignant n (%)				
EV			7.86	0.005	4.42	1.52–12.83
<4.52	20 (71.4)	08 (28.6)				
≥4.52	13 (36.1)	23 (63.9)				
VI			18.95	<0.001	19.67	4.01–96.54
<2.02	19 (90.5)	02 (9.5)				
≥2.02	14 (32.6)	29 (67.4)				
FI			0.95	0.32	1.96	1.54–2.51
<26.18	01 (100.0)	0				
≥26.18	32 (50.8)	31 (49.2)				
VFI			33.40	<0.001	42.00	9.52–185.11
<0.76	27 (90.0)	03 (10.0)				
≥0.76	06 (17.6)	28 (82.4)				

Observations of researchers has been conflicting regarding the usefulness of endometrial volume in differentiating benign from malignant endometrium [9,11–13]. In the present study, median endometrial volume was significantly higher in malignant endometrium (10.3 cc) than benign (3.4 cc).

Endometrial thickness as well as endometrial volume may be influenced by menopausal status of the women especially when lesions are benign. Hence, there can be significant overlap in the measurements, thereby making it difficult to have a single cut off value for malignancy in premenopausal as well as postmenopausal women. Power Doppler determined vascular indices could then be useful adjuncts. Concurring with other studies [1–4,10–14] the present study also identified that 3 D power Doppler indices were significantly higher in cases of carcinoma compared to the benign group. Though both VI and VFI had higher AUC, multiple regression analysis narrowed it down to VFI as the best indicator of malignancy with a cut off of 0.76. Other reporters observed that VI was the most reliable indicator of malignancy [1,12,14] whereas

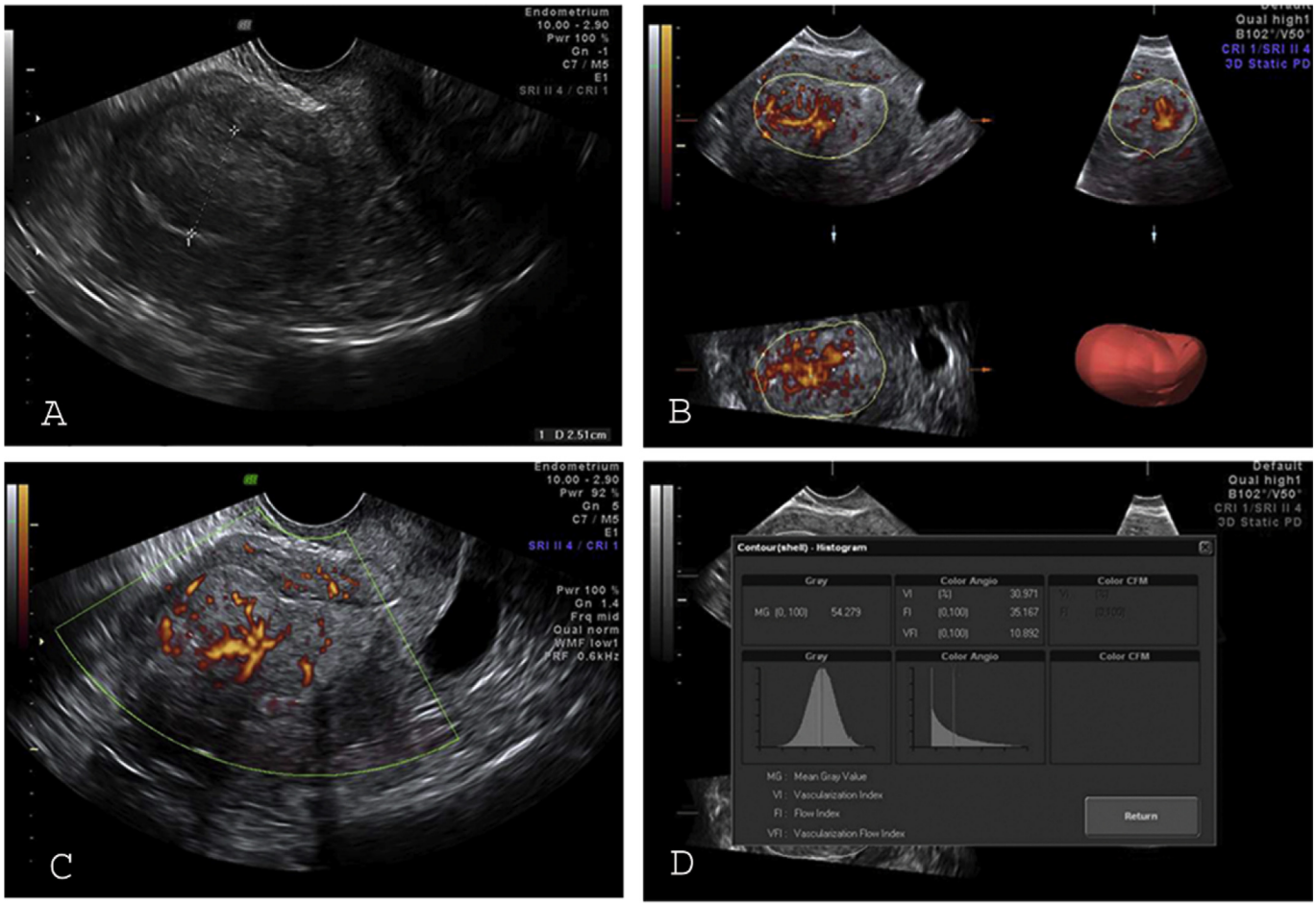

Fig. 2. 49 years, presented with postmenopausal bleeding. 2D ultrasound showed thickened endometrium (A). 3D ultrasound showed significantly increased endometrial volume (B) and multiple global vascular pattern on power Doppler (C). All vascular indices were elevated consistent with malignant pathology (D). Histopathology revealed endometrial carcinoma.

Table 5
Association of ultrasound parameters with tumour characteristics (n = 31)*.

USG parameters	Tumour characteristics								
	Staging			Grading			Type		
	1a	1b& beyond	p value[a]	1	2&3	p value[a]	Endo	Non-endo	p value[a]
Endometrial volume Median (IQR)	8.33 (3.26, 20.60)	19.58 (5.90, 33.58)	0.12	9.31 (3.28, 21.02)	25.23 (8.56, 69.20)	0.09	8.45 (3.32,20.74)	33.68 (17.7, 114.27)	0.01
VI Median (IQR)	11.34 (3.21, 22.90)	14.03 (3.48, 25.87)	0.79	12.27 (3.99, 26.76)	4.64 (2.88, 15.66)	0.21	11.98 (3.32, 24.19)	4.96 (1.77, 41.30)	0.54
FI Median (IQR)	33.57 (26.68, 37.82)	32.62 (27.37,37.40)	0.82	33.37 (26.56, 37.68)	32.88 (30.56,37.45)	0.87	33.02 (26.6, 37.42)	33.79 (27.63,42.95)	0.65
VFI Median (IQR)	3.08 (1.00, 7.99)	4.8 (1.16, 15.53)	0.58	4.03 (1.38, 10.86)	1.60 (0.97, 5.58)	0.25	3.79 (1.16, 10.79)	1.86 (0.56, 19.01)	0.58

[a] Fischer's exact test.

AbdElkhalek I et al. found VFI as the best predictor of malignancy [3] similar to present study results. The observations indicate that it is mainly the vascularisation and not the flow within the tumor that determines the malignant nature of the tumor.

Opolskiene et al., however, found that Doppler indices did not discriminate well between benign and malignant endometrial lesions [9]. This could be because their study population included only 13 cases of carcinoma, which were compared with 49 benign cases and does not include details about the stage and grade of carcinoma. It is possible that the 13 cases in their study were in the early stage, thus decreasing the difference between the values noted in the benign and malignant groups. Hanafi S reported the usefulness of vascular indices in women with postmenopausal bleeding, but concluded that it was no better than endometrial thickness or volume (AUC of endometrial thickness was 0.82, volume 0.78, VI 0.82 and VFI 0.82) [15].

In the present study, endometrial vascular patterns were also studied and classified as per the definitions set forth by the IETA group. Malignant endometrium had predominantly multiple global and multiple focal patterns than the scattered pattern. This in concordance with other studies [16,17]. Epstein et al. could not distinguish between benign and malignant lesions based on vessel morphology in their study when colour Doppler was used instead of power Doppler [14]. Power Doppler uses Doppler signal amplitude instead of Doppler signal frequency, and is hence much better at delineating small, tortuous vessels and thus gives a much clearer and more distinct picture of vessel patterns in malignant endometrial lesions. The present study used Power Doppler, classified vessel patterns into established, predefined groups similar to Alcazar et al., and had similar observations [18].

A study by Galvan R et al. explored the role of Power Doppler indices in defining tumor characteristics in 99 women with endometrial cancer [4]. Though they found correlation between tumor characteristics and Doppler parameters, they opined that due to some overlapping values it would be difficult to obtain a clinically useful cut off. With the cut off they obtained they could show only moderate diagnostic performance. AbdElkhalek I et al. [3] and Galvan R et al. [4] found VI and EV to be the best predictors of myometrial invasion. The present study could not determine a statistically significant association between the USG parameters with stage, differentiation and non endometrioid histology. This could be due to smaller numbers in each category. However, higher endometrial volume was identified in higher stage, higher grade and non-endometrioid types of tumors. These observations require further validation with a larger study sample and possibly explore other non-linear relation with tumour characteristics.

As the imaging was done by a single sonologist, inter observer variability was not a concern in the study. Well-designed prospective studies with adequate sample size is essential to compare reproducibility of three dimensional ultrasound against 2D ultrasound and pelvic MRI. It would also be worthwhile exploring the role of Power Doppler for establishing tumor characteristics in terms of stage, grade and type of endometrial malignancy; so that the extent of surgery as well as postoperative radiotherapy could be determined.

Conclusions

3D ultrasound and power Doppler are reliable tools for differentiating benign and malignant endometrial lesions, with VFI being the single most effective measure. However, utility of 3-D tool for differentiation between tumour characteristics needs further validation.

Conflict of interest statement

There is no financial or nonfinancial conflict of interest.

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