Three dimensional transvaginal sonography and power Doppler angiography in the differentiation between endometrial hyperplasia and endometrial carcinoma in postmenopausal women with abnormal uterine bleeding

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Objective: The aim of this study was to evaluate the accuracy of 3D transvaginal sonography and power Doppler in the differentiation between endometrial hyperplasia and endometrial carcinoma.

Patients and methods: Forty-two women suffering from abnormal uterine bleeding (AUB) were examined by 3D TV sonography and power Doppler angiography and all the sonographic findings and Doppler indices were recorded and evaluated. Lesions were then classified as benign or malignant according to imaging findings and the results were then correlated with histopathology results.

Results: Significant improvement of the sensitivity and specificity was found in differentiating between endometrial hyperplasia and endometrial carcinoma when we combined the imaging findings of 3D TV sonography and the indices of power Doppler.

Conclusion: Adding power Doppler to 3D TV sonography has added value in the differentiation between endometrial carcinoma and hyperplasia.

1. Introduction

Postmenopausal bleeding is a common problem which occurs in about 10% of the postmenopausal women. Vaginal bleeding in women after menopause occurs in 90% of endometrial cancer. Endometrial cancer is most common cause of death in cancers which only affect women, behind ovarian and cervical cancer. It is the most common cancer of the female reproductive tract in developed countries [1].

The leading treatment option for endometrial cancer is abdominal hysterectomy and bilateral salpingo-oophorectomy. In more advanced cases, chemotherapy, radiation therapy or hormone therapy may be recommended. If the disease is diagnosed at an early stage, the outcome is favorable.

Endometrial hyperplasia is a significant risk factor for the development or even co-existence of endometrial cancer. Treatment of endometrial hyperplasia is individualized, and may include hormonal therapy, such as cyclic or continuous progestin therapy, or hysterectomy [2].
Several approaches have been proved to be clinically useful screening methods for early detection of endometrial abnormality in women with irregular uterine bleeding, and these include dilatation and curettage (D&C), hysteroscopy, and sonohysterography, and transvaginal sonography (TVS) with the measurement of endometrial thickness [3].

The objective was to evaluate the accuracy of 3D transvaginal sonography and power Doppler in the differentiation between endometrial hyperplasia and endometrial carcinoma.

2. Patients and methods

2.1. Patient characteristics

This is a retrospective study conducted at Ain Shams University Hospital during the period from January 2014 to January 2015. The study population consisted of 42 women suffering from abnormal uterine bleeding and scheduled for hysteroscopy and endometrial sampling. The mean age of the patients was 62 years (range, 42–84 years). Twelve patients were nulliparous, and 11 patients suffered from medical disorders as diabetes and essential hypertension.

The exclusion criteria included uterine fibroids, adenomyosis, endometrial polyps, and any general diseases, hormones or medications that could affect pelvic blood flow.

Post-menopause was defined as at least one entire year of menstrual stoppage after the age of 40. Verbal informed consents and full history were taken from all cases and then followed by general and local examinations.

3D ultrasonography together with power Doppler angiography study was done to all patients. The 3D power Doppler indices included “endometrial volume” (EV), “endometrial thickness” (ET), “flow index” (FI), “vascularization index” (VI), “vascularization-flow index” (VFI), and intratumoral “resistive index” (RI) were measured.

Endometrial sampling was carried out by formal dilatation and curettage for all the patients. Fifteen out of forty-two patients (36%) had benign endometrium and 27/42 (64%) had malignant endometrium (atypical hyperplasia and carcinoma).

The histopathological results were compared with 3D ultrasonography and 3D power Doppler indices findings.

Patients with endometrial hyperplasia received medical treatment but the patients diagnosed as hyperplasia with cytological atypia or diagnosed as endometrial carcinoma were treated surgically by TAH and BSO “total abdominal hysterectomy with bilateral salpingo-oophorectomy”. Lymph node dissection (para-aortic or pelvic nodes) in cases with carcinoma was also performed. Detailed histopathological reports were recorded. According to International Federation of Gynecology and Obstetrics criteria, all tumors were staged.

2.2. Three-dimensional sonography and power doppler angiography technique

Patients lied in lithotomy position during the examination. The system used was Voluson 730 system with a transvaginal multifrequency probe (3–9 MHz) (Kretztechnikiberca SA, Madrid, Spain).

At first, uterus and ovaries were examined in B-mode scan where endometrial thickness (maximum thickness) was measured and measurement should be in mid-sagittal plane and between the interfaces of myometrium with endometrium.

The ultrasound was then switched to the 3D mode with power Doppler. The Doppler window should be placed over the subendometrial area. Color gain was about 3.4 with normal color quality and PRF of 600 (pulse repetition frequency) and wall filter was 50 Hz. The most intense color signal was identified and the sample volume placed over it to obtain arterial flow wave. Resistive index (RI) was then calculated automatically and we took the lowest value. 3D endometrial volume then was captured with 90° sweeping angle. The 3D acquisition box was put over the window of the power Doppler.

Manual reformation of images was done by VOCAL program in coronal planes using rotational technique 90° step getting 20 endometrial slices from the fundus to the cervical internal os outlining the myometrial-endometrial interface.

The 3D power Doppler indices were measured: VI, FI, and VFI. The VI is “the measurement of the number of color voxels in the volume”, and this represents the tissue vessels, and the number was expressed as percentage. The FI is calculated as the “mean color value in the color voxels”, and it is an indication of the “average intensity of blood flow” (number from 0 to 100). The VFI is “the mean color value in all the voxels in the volume”, and so, it is mixed expression of both blood flow and tissue vascularity (number from 0 to 100). All indices were automatically calculated with The VOCAL program as well as the EV.

3. Statistical analysis

The Mann–Whitney U test was used to compare the endometrial volume and 3D power Doppler indices. The evaluation of the individual ability of the different parameters used in the differentiation between endometrial hyperplasia and carcinoma was done by “Receiver operating characteristic” (ROC) curves and these curves were also used to evaluate the best cutoff value calculated for each test, and this value was defined as the one corresponding to the point on the ROC curve situated farthest away from the reference line (Fig. 1). The different indices and RI were evaluated and compared to the stage of the tumor and its grading as well as myometrial infiltration together with metastases to lymph nodes. Analysis of variance was used for comparisons, except the VFI, for which we used the “Mann–Whitney U test”. A P-value < .05 was used in all tests as a significance level (see Figs. 2–5).

4. Results

Fifteen out of forty-two cases (36%) included in the study had endometrial hyperplasia while 27/42 cases (64%) had endometrial carcinoma, out of which 9 patients
were grade I (well differentiated), 15 were grade II (moderately differentiated) and 3 were grade III (poorly differentiated). There was cellular atypia in 4 cases. Endometrioid carcinoma was the most common type of carcinoma found in 24/27 cases (88.9%) and other types about 11.1%.

On comparing the cases of hyperplasia and carcinoma, we found that the EV was significantly higher in carcinoma

**Fig. 1.** ROC curves for ET, EV, VI, FI and VFI.

**Fig. 2.** 51 year old female with abnormal uterine bleeding caused by endometrial hyperplasia, endometrial volume was 5.3 cc, VI = 0.062%, VFI = 0.014 and FI 23.041. All indices were below the cutoff values of malignancy.
Fig. 3. 59 year old female with abnormal uterine bleeding proved pathologically to be high grade endometrioid carcinoma with metastasis, ET = 24 mm, EV = 19.14 cc, VI = 0.27 %, VFI = 15.906 and FI = 58.621. Notice the very high values of the Doppler indices in keep with the high grade malignancy.

Fig. 4. 60 year old female with abnormal uterine bleeding proved pathologically to be low grade endometrioid carcinoma with no metastasis, ET = 26.4 mm, EV = 14.48 cc, VI = 0.26 %, VFI = 0.086 and FI = 32.969.
than hyperplasia as well as different Doppler indices (VI, FI, and VFI). The results on combining both were more accurate in diagnosis. The resistive index was much lower in cases of carcinoma. For endometrial carcinoma prediction, cutoff values for different indices were obtained. The best cutoff value of malignancy was for VFI = 0.22, VI = 0.7%, FI = 25.

As regards the sonographic measurements, for endometrial thickness (ET) (best cutoff value 17 mm) and endometrial volume (best cutoff value 7 cc).

VFI was found the most accurate index in prediction of malignancy more than the other indices.

Tumor stage was best correlated with VI and FI.

Myometrial invasion more than 50% elevates all the indices and all lesions confirmed to have high grade malignancy were found to have low RI as well as cases with myometrial invasion or metastatic nodal deposits.

Different power Doppler indices values in benign and malignant endometrial lesions are detailed in Table 1

Diagnostic cutoff values for malignancy and statistical analysis are detailed in Table 2

Table 1
Different power Doppler indices in benign and malignant endometrial lesions.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
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<tbody>
<tr>
<td>ET (mm)</td>
<td>7.1 ± 6.5</td>
<td>20.1 ± 10.8</td>
</tr>
<tr>
<td>RI</td>
<td>1 ± 1.8</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>EV (cm³)</td>
<td>3.1 ± 2.8</td>
<td>9.1 ± 15.9</td>
</tr>
<tr>
<td>Endometrial VI (%)</td>
<td>0.3 ± 0.4</td>
<td>1.0 ± 0.83</td>
</tr>
<tr>
<td>Endometrial FI (0–100)</td>
<td>21.9 ± 5.5</td>
<td>24.1 ± 9.562</td>
</tr>
<tr>
<td>Endometrial VFI (0–100)</td>
<td>0.1 ± 0.17</td>
<td>0.042 ± 0.092</td>
</tr>
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Table 2
Diagnostic performance of ultrasound and Doppler markers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ET</th>
<th>EV</th>
<th>Endometrial VI</th>
<th>Endometrial VFI</th>
<th>Endometrial FI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff value</td>
<td>17 mm</td>
<td>7 cm³</td>
<td>0.7%</td>
<td>0.22</td>
<td>25</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80</td>
<td>92</td>
<td>90</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Specificity</td>
<td>70</td>
<td>82</td>
<td>88</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>PPV</td>
<td>30</td>
<td>43</td>
<td>53</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>NPV</td>
<td>95</td>
<td>98</td>
<td>98</td>
<td>96</td>
<td>98</td>
</tr>
<tr>
<td>AUC</td>
<td>0.750</td>
<td>0.870</td>
<td>0.890</td>
<td>0.740</td>
<td>0.890</td>
</tr>
<tr>
<td>( p )-Value</td>
<td>0.012 (S)</td>
<td>&lt;0.001 (HS)</td>
<td>0.023 (S)</td>
<td>( p &lt; 0.001 ) (HS)</td>
<td>&lt;0.001 (HS)</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.
5. Discussion

Differentiating endometrial hyperplasia from carcinoma is a very important subject in cases of abnormal uterine bleeding as it is crucial in changing the management plan. Also, predicting the degree of invasiveness and stage of the tumor prior to surgery affects the management and type of surgery and predicts the patient’s prognosis [4].

In cases of postmenopausal bleeding, thin endometrium less than or equal to 4 mm usually rules out endometrial carcinoma; yet, still some cases with early carcinoma may present with thin endometrium [5]. According to the results of this study, ET values alone are overlapping in hyperplasia and endometrial carcinoma and for this reason the Doppler indices would help in accurate diagnosis. Change from endometrial hyperplasia to carcinoma is accompanied with neovascularization and angiogenesis and these changes can be evaluated by power Doppler sonography. With increasing grade or invasiveness of the tumor there is more angiogenesis which also could be detected by the power Doppler indices. This is important for preoperative evaluation to predict tumoral extension. 3D sonography with power Doppler study of the endometrial and uterine arteries proved to be more accurate in differentiation between endometrial lesions [6]. RI values of endometrial hyperplasia and carcinoma show significant difference.

The signal amplitude is the dependent factor for power Doppler not the Doppler frequency and so blood flow depiction will be sensitive for markedly low velocities. The angle of insonation is not a factor for power Doppler indices determination and so there is no aliasing. With these features, very small vessels or vessels with irregular course can be accurately evaluated by power Doppler which are features of malignancy and so, the Doppler indices were high in endometrial cancer especially in cases with borderline endometrial thickness [7].

Many studies were done to evaluate the accuracy of ET, EV and power Doppler indices in differentiating benign and malignant cases of post menopausal bleeding.

In 1996 Gruboeck et al. made a study to evaluate endometrial thickness and volume and their relation to malignancy and found that endometrial volume was a more accurate measure than endometrial thickness in evaluation of endometrium and diagnosis of malignancy. The best cutoff value of endometrial thickening in his study for malignancy diagnosis was 15 mm. The best cutoff level of 13 cc for endometrial volume and he found sensitivity of 100% and a positive predictive value of 91.7% for this value. Late and poorly-differentiated malignancies have more thickness and volume [8]. These results were matching the results of our study as regards the thickness and showed a lower endometrial volume cutoff value for malignancy with cutoff for ET = 17 and EV = 7.

In 2006 Merce et al. made a study evaluating the 3D Doppler indices as well as ET and EV and found significantly high indices and EV in carcinoma than hyperplasia with VFI of 2.07 as best cutoff for detection of carcinoma, with a sensitivity of 76.5% and specificity of 80.8%. For endometrial thickness, no statistically significant differences were found [9].

In our study the calculated best cutoff value for VFI was 0.22, and this value was higher with high grade or invasive malignancies. The statistical values were close to our study (p < 0.001).

In 2007, Odeh et al. found that mean thickness was 15.5 mm, and a mean volume of 15.5 cc, mean VI of 2.95% and FI was 23.6 while VFI 0.89 in the malignant lesions [10].

In 2010, Opolskiene et al. showed that the accuracy for differentiating benign and malignant endometrium by 3D ultrasonography was not better than endometrial thickness assessed by B-mode ultrasonography, and also found that 3D power Doppler has no significant added value than endometrial thickness or volume; yet, the Doppler indices were generally higher in malignant lesions [11].

Galván et al. in 2010 stated that EV and VI were related independently to myometrial infiltration and tumor stage in endometrial carcinoma; VI was associated alone with tumor grade and EV had a correlation with lymph node metastases [12]. Saarelainen et al. in 2012 suggested that endometrial indices and EV correlate with the myometrial invasion depth of endometrial carcinoma [13]. These results match completely with our results.

Also, our study results showed that ET alone is not accurate in the differentiation between malignant and benign endometrial lesions. EV is more accurate than ET (p < 0.001).

Moreover, power Doppler indices give more accuracy in discrimination between the malignant and benign endometrial and this will help in early management and better prognosis for the patient’s condition.

Malignant cases showed statistically significant increase in power Doppler indices values and high EV (p < 0.001). There is significant reduction in RI values in malignant cases. RI value also becomes lower with higher grade malignancy. All the 3D power Doppler indices increased significantly with myometrial invasion; yet, VI was the only increased index in stages greater than grade I. The cutoff value (0.51) was found to be the best value for RI to differentiate benign from malignant lesion; yet, it was found to be of lower accuracy when compared to the power Doppler indices as the Doppler indices have better accuracy in the diagnosis of endometrial carcinoma.

The differences between our study results and the previous studies can be explained by the differences in populations, the study design as well as differences in methods used to calculate and evaluate sonographic and Doppler indices as well as the software used.

6. Conclusion

3DUS with power Doppler angiography considered important complementary techniques serves in noninvasive differentiation between endometrial hyperplasia and carcinoma with more accurate results found on using Doppler indices than EV alone and power Doppler indices and
RI adds the ability to predict tumor grade and spread by simple technique prior surgery.

ET was found to be non-accurate compared to the accuracy of RI and power Doppler indices in differentiation between benign and malignant lesions and moreover, spread of metastasis can be predicted by the power Doppler indices.

Conflict of interest

We have no conflict of interest to declare.

References


