Application of transvaginal three-dimensional power Doppler ultrasound in benign and malignant endometrial diseases

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Abstract
To investigate the value of transvaginal three-dimensional (3D) power Doppler ultrasound in the diagnosis of benign and malignant endometrial diseases.

A total of 144 patients with endometrial thickness ≥4 mm were enrolled. Endometrial thickness was measured by transvaginal 3D B-mode ultrasound, while blood signals were detected by 3D power Doppler ultrasound. Endometrial volume (EV), vascularization index (VI), blood flow index (FI), and vascularization flow index (VFI) were calculated. All histopathological diagnoses of endometrium were obtained.

There were 86 benign and 58 malignant cases. There were statistically significant differences between two groups in endometrial thickness [1.50 (1.30, 1.80) vs 2.30 (1.80, 3.20), P < .001], EV [10.62 (7.14, 17.36) vs 28.94 (9.59, 67.96), P < .001], VI [6.07 (3.61, 10.33) vs 12.01 (7.50, 19.87), P = .001], FI [27.42 (24.45, 31.33) vs 32.98 (30.22, 35.40), P < .001], and VFI [1.58 (0.92, 3.32) vs 4.28 (2.24, 6.41), P < .001]. Sensitivity and specificity of endometrial thickness were relatively high [endometrial thickness (86.2%, 76.1%), EV (48.3%, 97.7%), VI (72.4%, 69.8%), FI (72.4%, 74.4%), and VFI (72.4%, 74.4%)]. There was no significant difference in any parameters of the endometrium between different stages (Ia, Ib, II, and above) or phases (G1, G2, and G3) of the phase of endometrial cancer (all P > .05).

Transvaginal 3D power Doppler ultrasound is valuable in the differentiating benign and malignant endometrial lesions.

Abbreviations: 2D/3D = two-dimensional/three-dimensional, EV = endometrial volume, FI = blood flow index, G1/G2/G3 = Grade 1/Grade 2/Grade 3, NCCN = National Comprehensive Cancer Network, PD = power Doppler, Rflow = Radiantflow, ROC = receiver operating characteristic, TVS = transvaginal ultrasound, VFI = vascularization flow index, VI = vascularization index.

Keywords: endometrial cancer grading, endometrial cancer staging, endometrial lesions, three-dimensional power Doppler
Therefore, the accurate clinical stage of endometrial cancer can significantly reduce the incidence of over-treatment.

2. Materials and methods

2.1. Patients

Our study is a prospective study, and 144 patients with endometrial lesions from October 2018 to April 2019 in Yuhuangding Hospital in Yantai were enrolled; all have been first diagnosed with suspicious endometrial abnormalities by transvaginal 3D power Doppler ultrasound and were performed with hysteroscopy examination or diagnostic curettage later. Those patients with benign pathological classification would only have direct curettage or hysteroscopic electrotomy, while those with malignant pathology would have further surgical treatment.

Fifty-eight patients were diagnosed with endometrial cancer. The median age in malignant cases was 59 (28–77) years old. Among which 52 cases were attended to the hospital due to irregular vaginal bleeding or vaginal bleeding after menopause, 2 with vaginal discharge, 2 with increased menstrual volume, and 2 with routine follow up of endometrial dysplasia. Eighty-six patients with benign endometrial lesions were confirmed by hysteroscopic pathological diagnosis, with a median age of 45 (26–78) years old. Among them, 81 case came to the clinic due to irregular vaginal bleeding or vaginal bleeding after menopause, 1 for accidental discovery in ultrasound examination, 3 cases for routine follow up after using tamoxifen after breast cancer, and 1 with follow-up after being treated for hydatidiform mole since 10 months ago.

All patients underwent transvaginal 3D power Doppler ultrasound examination. Inclusion criteria: endometrial thickness was more than 0.4 cm, with both detailed ultrasound and clinical data. Exclusion criteria: history of endometrial trauma such as hysteroscopy operation or curettage.

The study was approved by the Hospital Medical Ethics Committee and written informed consents of patients were obtained.

2.2. Ultrasonographic examination

All ultrasound examinations were performed with cavity volume probe with frequency of 5–9 MHz (Voluson E10, General Electric Company, GE, United States). Rflow stereo flow imaging technology were applied. Gynecological GLASS BODY and VOCAL software packages were used to analyse the images.

2.3. Methods

Under the bladder lithotomy position, endometrial thickness of patients was measured by 2D ultrasound. The standard of endometrial thickening was >0.4 cm. After the conventional colour Doppler flow imaging, the color blood flow is obtained under the new Rflow stereo flow imaging mode. Then the 3D power Doppler mode was turned on, with the sampling frame size and the scanning angle adjusted appropriately (at 100–120°) and pulse repetition frequency at 0.8. VOCAL software (manual

Figure 1. A 56-year-old patient. (1) Thickened endometrium and invasion of the deep myometrium on the longitudinal section of transvaginal two-dimensional ultrasound; (2) two-dimensional transverse section of the lesion; (3) flow parameters at the lesion site of transvaginal three-dimensional power Doppler ultrasound: vascularization index (VI), flow index (FI), and vascularization flow index (VFI).

Figure 2. (1) A colored flow diagram; (2) a colored flow diagram under Rflow conditions, which is more stereoscopic and intuitive than (1); (3) an power flow diagram, which is more abundant than (1) or (2).
vascularization, also known as tissue perfusion.12 Background voxels), representing the sum of blood flow and measure related parameters: vascularization index (VI), blood flow index (FI), and vascularization flow index (VFI). Expressed as a percentage, VI equaled to the color voxel/total element (background voxel), which indicates the number of blood vessels in the tissue. FI was weighted color voxel/color voxel, indicating the blood flow intensity during the 3D scanning period. VFI was calculated by weighted color voxels/whole metabolic background voxels, representing the sum of blood flow and vascularization, also known as tissue perfusion.13

No infiltration of the muscular layer was defined as the boundary between the basal layer and the muscular layer of the endometrium remaining intact. Myometrial invasion was defined that the basal layer was blurred or disappeared, and the echo of the intima invaded the muscular layer, displayed as serrated or finger-like. Take the normal thickness of the uterus myometrium in the deepest lesion infiltrating plane as numerator, the ratio of >0.5 was defined as the superficial myometrial invasion; the ratio of 0.5 or less was classified as the deep myometrial infiltration.

Surgery-pathological typing was based on the criteria recommended by the International Federation of Obstetricians and Gynecologists (FIGO) in 2009.14 Stage I tumor is the one which confined to the uterus: depth of tumor invasion <1/2 muscle layer is stage Ia, depth of invasion ≥1/2 muscle layer is stage Ib. Stage II tumor is defined as tumor invades cervical interstitial, but no uterine in vitro is involved. Stage III means tumor with or without regional spread. Stage IIIa is the tumor involving the serosal layer and/or accessory, stage IIIb includes vaginal with/without parametral involvment, and stage IIIc is pelvic lymph node and/or paraaortic lymph node metastasis. Stage IV means the tumor invades the bladder and/or rectal mucosa, with/without distant metastasis; stage IVa is bladder or (rectal) metastasis and stage IVb is intra-abdominal with/without inguinal lymph node distant metastasis.

According to FIGO standards,15 tumor histology is divided into 3 levels: Grade 1 (G1) is defined as more than 95% of glandular tumor area; Grade 2 (G2) is defined as 5 to 50% solid content of tumor; Grade 3 (G3) is defined as a solidity of more than 50% of the internal components of the tumor.

2.4. Statistical methods

Statistical analysis was performed using software SPSS 22.0. In the comparison of parameters of benign and malignant lesions, t-test and chi-square test were used for age and postmenopausal status analysis. Rank sum test was used for endometrial volume (EV), VI, FI, VFI, and endometrial thickness analysis. The receiver operating characteristic (ROC) curve evaluates the accuracy of the diagnostic indicators, and the optimal cutoff point is determined by the Yoden index (sensitivity + specificity – 1). Rank sum test was used to compare endometrial cancer between groups. The difference was statistically significant at P < .05. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, taking pathological classification as the gold standard.

3. Results

A total of 144 patients were included in this study, whose endometrial thickness were all higher than the normal value (0.4 cm). There were 86 cases of benign lesions (86/144, 59.7%), including 34 cases of polyps, 40 cases of polypoid hyperplasia, 4 cases of submucosal myoma, 4 cases of proliferative endometrium, and 4 cases of secretory endometrium. There were 58 cases of malignant lesions (58/144, 40.3%) and 10 cases of malignant cases being excluded during the research, including 4 mixed cancer, 2 cancer confined to the mucosa, 2 complex hyperplasia with locally differentiated adenocarcinoma, and 2 cases who gave up further examination and treatment. Of the remaining 48 malignant cases, 34 cases were stage Ia (8 cases of G1, 20 cases of G2, 6 cases of G3), 6 cases were stage Ib (2 cases of G2, 4 cases of G3), 2 cases were stage II (both IIaG2), and 6 cases were stage III (2 cases of IIIaG3, 4 cases of IIIcG2). There were statistically significant differences between benign and malignant groups in age (P < .001) and postmenopausal status (menopausal years, P = .003) (Table 1). There were also significant differences in blood flow parameters between benign and malignant lesions including EV (P < .001), VI (P < .001), FI (P < .001), VFI (P < .001), and endometrial thickness (P < .001) (Table 2). The ROC curve (Fig. 3) and curve analysis (Table 3) of the above five diagnostic indicators showed that the sensitivity (86.2%) and specificity (72.1%) of the endometrial thickness were relatively higher, with the area under the curve of 0.839, indicating a high diagnostic value. Other index including EV (48.3%, 97.7%), VI (72.4%, 69.8%), FI (72.4%, 74.4%), VFI (72.4%, 74.4%) were not satisfying in sensitivity and specificity.

There was no significant difference in the parameters of the membrane parameters in different stages (Table 4): endometrial thickness (P = .283), EV (P = .438), VI (P = .776), FI (P = .913), and VFI (P = .799). In the different grades (G1, G2, G3) of Ia phase of endometrial cancer, there was either no significant difference in all parameters: endometrial thickness (P = .222), EV (P = .146), VI (P = .572), FI (P = .788), and VFI (P = .547) (Table 5).

We compared the diagnostic value of transvaginal ultrasound (TVS), transvaginal ultrasound (RLow+TVS), and transvaginal 3D energy Doppler ultrasound (3D+PD+TVS). The numbers of

| Table 1 | Baseline data comparison. |
|---|---|---|---|
| Index | Benign (n = 86) | Malignant (n = 58) | P |
| Age | 41.63 (13.70) | 59.24 (10.14) | < .001 |
| Postmenopausal state | 2.05 (6.27) | 7.90 (8.50) | .003 |

Mean (standard deviation) or number of cases (constituent ratio).

| Table 2 | Comparison of endometrial parameters between benign and malignant endometrial lesions in 144 cases. |
|---|---|---|---|
| Index | Benign (n = 86) | Malignant (n = 58) | Z | P |
| EV | 10.62 (7.14, 17.36) | 28.94 (6.59, 76.96) | -3.61 | < .001 |
| VI | 6.07 (3.61, 10.33) | 12.01 (7.50, 19.87) | -3.39 | .001 |
| FI | 27.42 (24.45, 31.33) | 32.98 (20.22, 35.40) | -3.91 | < .001 |
| VFI | 1.58 (0.92, 3.32) | 4.28 (2.24, 6.41) | -3.51 | < .001 |
| Endometrial thickness | 1.50 (1.30, 1.80) | 2.30 (1.80, 3.20) | -4.87 | < .001 |

EV = endometrial volume, FI = blood flow index, VFI = vascularization flow index, VI = vascularization index.
Figure 3. Comparison of areas under the five receiver operator characteristic (ROC) curves.

### Table 3

ROC curve analysis of five diagnostic indicators in diagnosis of endometrial lesions.

| Index        | Area under ROC curve (95% CI) | Optimal cutoff point | Sensitivity (%) | Specificity (%) |
|--------------|--------------------------------|----------------------|----------------|---------------|
| EV           | 0.752 (0.632, 0.872)          | 30.32                | 48.3           | 97.7          |
| VI           | 0.737 (0.617, 0.856)          | 8.3645               | 72.4           | 69.8          |
| FI           | 0.773 (0.666, 0.881)          | 30.866               | 72.4           | 74.4          |
| VFI          | 0.745 (0.625, 0.866)          | 2.706                | 72.4           | 74.4          |
| Endometrial thickness | 0.839 (0.744, 0.933) | 1.75                | 86.2           | 72.1          |

EV = endometrial volume, FI = flow index, VFI = vascularization flow index, VI = vascularization index.

### Table 4

Comparison of endometrial parameters in different stages [M (P25, P75)].

| Endometrial parameters | Stage IA (n = 34) | Stage IB (n = 6) | Stage II and above (n = 8) | $\chi^2$ | P     |
|------------------------|-------------------|------------------|---------------------------|---------|-------|
| EV                     | 28.94 (13.26, 38.69) | 9.31 (8.54, 21.31) | 37.94 (9.01, 70.37) | 1.649   | .438  |
| VI                     | 14.52 (8.76, 20.24)  | 15.43 (12.20, 22.90) | 9.59 (5.22, 26.16) | 0.507   | .776  |
| FI                     | 32.98 (31.00, 35.60) | 31.26 (31.08, 33.19) | 33.08 (27.87, 38.53) | 0.183   | .913  |
| VFI                    | 4.81 (2.82, 6.52)   | 5.42 (4.10, 7.45)  | 3.17 (1.51, 10.77) | 0.449   | .799  |
| Endometrial thickness  | 2.60 (1.80, 3.20)   | 1.80 (1.60, 2.00)  | 2.35 (1.95, 3.35) | 2.527   | .283  |

EV = endometrial volume, FI = flow index, VFI = vascularization flow index, VI = vascularization index.

### Table 5

Comparison of endometrial parameters of three grades (G1, G2, G3) in stage IA [M (P25, P75)].

| Endometrial parameters | G1 (n = 8) | G2 (n = 20) | G3 (n = 6) | $\chi^2$ | P     |
|------------------------|------------|------------|------------|---------|-------|
| EV                     | 53.35 (33.86, 105.35) | 17.63 (13.24, 32.51) | 22.24 (15.17, 76.68) | 3.850   | .146  |
| VI                     | 11.22 (7.05, 16.40)   | 16.45 (8.76, 19.50)  | 21.88 (12.13, 22.94) | 1.117   | .572  |
| FI                     | 33.14 (30.05, 36.03)  | 32.02 (31.00, 35.20) | 35.66 (31.48, 36.72) | 0.478   | .788  |
| VFI                    | 4.06 (2.35, 5.47)     | 5.12 (2.82, 6.52)   | 7.80 (4.23, 10.49)   | 1.205   | .547  |
| Endometrial thickness  | 3.00 (2.75, 4.20)     | 2.25 (1.80, 3.20)   | 1.80 (1.60, 3.30)    | 3.007   | .222  |

EV = endometrial volume, FI = flow index, VFI = vascularization flow index, VI = vascularization index.
benign lesions misdiagnosed as malignant were respectively 8, 4, and 2 by TVS, Rflow+TVS and 3D+PD+TVS. The numbers of malignant lesions misdiagnosed as benign were respectively 18, 8 and 4, respectively (Table 6). The sensitivity, specificity, PPV, and NPV of these three methods for the diagnosis of benign and malignant endometrial lesions were analyzed (Table 7).

4. Discussion

Endometrial lesions are one of the most common gynecological diseases. Most patients come to hospital due to abnormal vaginal bleeding. Seventy-six (76/86, 88.4%) benign cases and 52 (52/58, 89.7%) malignant cases in our study had irregular vaginal bleeding. Most endometrial cancers are localized lesions. In our study, 40 patients (40/48, 83.3%) remained in stage I.

Studies[6–8] have shown that patients with well-differentiated or moderately differentiated endometrial cancer, including stage Ia (G1, G2, and G3) and stage Ib (grades G1 and G2), may undergo endoscopic hysterectomy and bilateral accessory resection. The long-term effect is similar to that of conventional surgery, while significantly reduces the surgical trauma and shortens the perioperative course. Accurate clinical staging of endometrial cancer not only reduces complications caused by inadequate or over-treatment, but is also a guarantee for the retention of fertility in young patients with highly differentiated endometrioid adenocarcinoma. Two patients in our study (median age 28.5 years) had the diagnostic curettage showing endometrial complex hyperplasia with dysplasia, partly with highly differentiated endometrioid adenocarcinoma. Conservative treatments were performed due to these two patients’ strong fertility requirements.

Studies of Di Cello et al.[6–8] showed that patients with inconsistent histopathological results before and after surgery had poor prognosis, resulting that some clinical centers try to apply rapid intraoperative freezing pathology to improve the pathological information of endometrial cancer, in order to solve the problem of inconsistent pathological results before and after surgery. Therefore, it is of great clinical significance to improve the differential diagnosis of endometrial benign and malignant lesions before surgery and to assess the degree of myometrial invasion of malignant lesions as early as possible. In our study, endometrial thickness, volume, and blood flow index (VI, FI, VFI) of malignant patients were all higher than those of benign patients, which was in consistent with Hanafi et al.[9] and Pandey et al.[10] Besides, Pandey et al showed that VI, FI, and VFI had no significant difference in different staging and grading of malignant cases. This is consistent with the results of our study. It was considered that 3D ultrasound has a good ability to distinguish benign and malignant endometrial lesions and can be used as a screening tool. However, further studies are needed to apply it to distinguish tumor characteristics.

The myometrium is the first invasive part of endometrial cancer. As the contrast between the basal layer and the muscular layer of the endometrium is low, conventional 2D and 3D ultrasonography is difficult to distinguish the boundary between the muscular layer and the lesion, making it hard to evaluate the degree of infiltration of the muscular layer. The blood flow parameters provide a relatively reliable basis for the assessment of myometrial invasion. Saarelainen et al.[11] showed that larger EV and FI were associated with deep muscle infiltration. Galván et al.[12] showed that EV and VI were associated with myometrial invasion and tumor staging. VI was associated with tumor grade, and EV was associated with lymph node metastasis. At present, there are few studies on endometrial blood flow parameters, and the results of myometrial invasion and pelvic metastasis of endometrial malignant lesions are quite different. The reason for the difference in the evaluation of the degree of myometrial invasion in this study may be that the sample size is small (the number of cases in stage II and above is less; only 2 cases in stage II, only 6 cases in stage III, and no cases in stage IV). Besides, intra-group variety and differentiation were large. In the future work, the sample size should be expanded and differences within the group should be minimized. Tumor invasion should be further studied to provide a reliable basis for the choice of clinical treatment and surgical methods, so that the quality of life of patients can be effectively guaranteed.

In short, the application of transvaginal 3D energy Doppler ultrasound is more intuitive and accurate, and has certain application value for the diagnosis of endometrial lesions.
Author contributions

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