Role of spiral artery Doppler to screen type 2 endometrial cancer cases

Soner Düzgüner[1], Mehmet Burak Özkan[1], Tuncay Küçüközkan[1], Enis Özkaya[1], Fadıl Kara[1], İpek Nur Balın[2], Vakkas Korkmaz[1], Mehmet Fatih Karslı[1], Burak Gültekin[1]

[1]Department of Obstetrics and Gynecology, Dr. Sami Ulus Maternity and Children Training and Research Hospital, Ankara, Turkey

[2]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Gynaecological Diseases Training and Research Hospital, Ankara, Turkey

Abstract

Objective: The purpose of this study was to determine the value of endometrial blood flow assessment in predicting type 2 endometrial carcinoma.

Material and Methods: Sixty-five consecutive post-menopoausal women who had vaginal bleeding were enrolled in the study. All subjects were directed to transvaginal sonography to determine endometrial blood flow and underwent endometrial biopsy. Doppler findings were analysed to predict endometrial pathology. Subjects with unsatisfactory Doppler analyses were excluded from the study.

Results: Mean age of the study population was 50.1±6.9 years (42-73). Mean endometrial thickness was 10.1±2.9 mm (4-15 mm) and mean cancer antigen 125 (CA125) level was 20.1±17.4 U/mL (3-92). Histopathological evaluation revealed 14 cases of type 2 endometrial cancer and 18 cases of endometrial hyperplasia without atypia, while the other 33 cases had normal endometrial tissue. CA125 (Area under curve (AUC)=0.853, p=0.000), spiral artery resistance index (AUC=0.905, p=0.000), and spiral artery peak systolic velocity (AUC=0.822, p=0.000) were significant predictors for the type 2 endometrial cancer cases. Endometrial thickness did not significantly predict pathologic cases (p>0.05). Hyperplasia cases were not predicted by any of these diagnostic modalities (p>0.05).

Conclusion: In patients with postmenopausal bleeding, spiral artery Doppler ultrasound, could play a role in refining the diagnosis of type 2 endometrial carcinoma; however, its predictive value should be evaluated with further studies. (J Turk Ger Gynecol Assoc 2014; 15: 1-5)

Key words: Type 2 endometrial cancer, post-menopausal woman, spiral artery Doppler

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Introduction

Endometrial carcinoma is predominantly a disease of postmenopausal women and the presenting sign is vaginal bleeding in more than 90%. Type II endometrial neoplasms account for 10 to 20 percent of endometrial carcinomas (1, 2). They have non-endometrioid histology (usually serous or clear cell) with an aggressive clinical course. These tumours are often high-grade, have a poor prognosis, and are not clearly associated with oestrogen stimulation. A precursor lesion is rarely identified. Type II neoplasms are generally associated with more aggressive clinical behaviour than type I tumours. An office endometrial biopsy is a sensitive test but the correct histology may not be identified in all cases (3). For these reasons, we focused this study on predicting type 2 endometrial cancer. In women with postmenopausal bleeding, an evaluation of endometrial morphology and vascularisation by using Doppler ultrasound imaging can be used to further refine the estimation of risk of pathology and, in particular, the risk of endometrial cancer (4-6).

Spiral artery is the end artery located just beneath the endometrial wall. To establish the fact in terms of endometrial histopathology, a Doppler study of the spiral arteries using resistance index (RI), pulsatility index (PI), peak systolic velocity (PSV) can be useful.

We hypothesised that vascular characteristics may correlate with the histopathology of the endometrium, knowledge that could be of value in assessment of the preoperative tumour and perhaps be used for risk evaluation. The aim of the study was to describe spiral artery Doppler sonographic features of the endometrium and relate the findings to predicting type 2 endometrial cancer.

Material and Methods

Patients

Between November 2009 and July 2013, 1523 postmenopausal women consulting for vaginal bleeding, underwent examination prospectively by two-dimensional grey-scale transvaginal sonography (TVS), colour and power Doppler.

Address for Correspondence: *Soner Düzgüner, Department of Obstetrics and Gynecology, Dr. Sami Ulus Maternity and Children Training and Research Hospital, Ankara, Turkey. Phone: +90 532 440 45 17 e.mail: sonerduzguner@yahoo.com*

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Inclusion criteria were as follows: 1) Women with measurable spiral artery Doppler; 2) transvaginal sonography with a measurable endometrial thickness; 3) not taking hormone replacement therapy or tamoxifen; and 4) a definitive type 2 endometrial carcinoma histological diagnosis obtained at our centre. Of 1523 women with postmenopausal bleeding, 65 were eligible for inclusion, but 1458 were excluded (Figure 1).

After obtaining ethical approval and patient informed consent, a structured history was taken following a standardised research protocol regarding parity, age at menopause, history of polycystic ovarian syndrome (PCOS), diabetes, hypertension, height, weight, medicine usage and any genetic disease. None of these patients was receiving treatment with a hormone replacement regimen. Doppler characteristics of the endometrial spiral artery were recorded and all patients were scheduled for a diagnostic procedure by sampling endometrial tissue with the method of Dilatation & Curettage (D&C). The sonographic findings were compared with the histopathological diagnostics.

Sonography

Ultrasound examination of all patients was performed by same radiologist, transvaginally, before endometrial sampling, after completely emptied their bladders. The blood flow of endometrial spiral artery and endometrial thickness were performed by transvaginal 8 MHz ultrasonography (LOGIQ S6; General Electric, Milwaukee, USA). In order to describe the sonographic features of the endometrium, measurements were performed according to a consensus opinion from the International Endometrial Tumour Analysis (IETA) group (7). Endometrial blood flow was detected by intra-endometrial or the adjacent sub-endometrial regions within 10 mm of the echogenic endometrial borders. Double thickness of the endometrium was measured (maximum distance between each myometrial/endometrial interface). Thereafter, colour Doppler energy was superimposed on the 2-D Doppler studies that were performed on the selected area. The pulsatility index (PI), resistance index (RI) and peak systolic velocity (PSV, cm/s) of the endometrial spiral arteries were calculated when three similar, consecutive waveforms of good quality were obtained (pulse repetition frequency 0.8 kHz, wall filter 40 Hz, colour power Doppler gain was reduced until all colour artefacts disappeared) (7). The parameters were analysed for: (i) RI: the difference between maximal systolic blood flow and minimal diastolic flow divided by the peak systolic flow (S-D/S); (ii) PI: the difference between maximal systolic blood flow and minimal diastolic flow divided by the mean flow throughout the cycle (S-D/mean); and (iii) PSV.

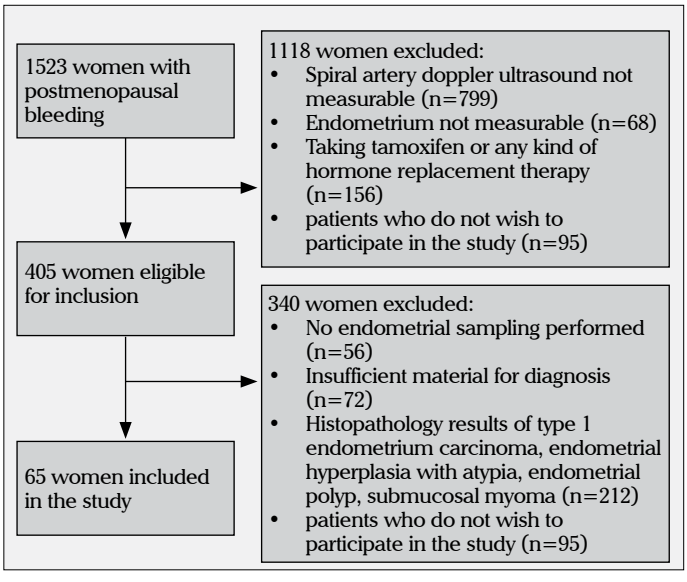

Figure 1. Algorithm showing the selection of the study population

Sample Size and Power

Sample size was calculated with 80% power and 95% confidence interval according to the previous study by Wang et al. (8).

Statistical Analysis

Data were entered to SPSS version 15; all data were presented as mean and standard deviation. The student t test was used to compare groups, correlation analyses were used to show association between variables and linear regression analyses were used to calculate adjusted associations. Receiver Operating Characteristic (ROC) analyses were used to assess the value of the test to predict abnormal cases. P value <0.05 was accepted to be statistically significant.

Results

One thousand five hundred and twenty three women with postmenopausal bleeding were screened from November 2009 to July 2013. The mean age of the study population was 50.1±6.9 years (42-73), and Body mass index (BMI) was 29.3±3.9 kg/m^2 (22.3-37.8). Mean CA125 level was found to be 20.1±17.4 U/mL (3-92). All women had postmenopausal bleeding. Mean endometrial thickness was 10.1±2.8 mm (4-15). Out of 65 postmenopausal women, 2 had diabetes mellitus, while 10 women had hypertension. Thirteen women were smokers in the study population. Endometrial tissue sample histopathological evaluation revealed 14 (21.5%) cases of type 2 endometrial cancer and 18 (27.7%) cases of endometrial hyperplasia without atypia. Another 33 women had proliferative, secretory or atrophic endometrium. In correlation analysis, age was found to be significantly correlated with endometrial biopsy histopathological results (r=0.513, p<0.001) and the spiral artery resistance index (r=0.284, p=0.029). Smoking was negatively correlated with spiral artery resistance index (r=-0.270, p=0.039), CA125 level (r=-0.274, p=0.027) and endometrial cancer (r=-0.270, p=0.039). Endometrial thickness was negatively correlated with the CA125 levels (r=-0.440, p<0.001). CA125 level was significantly correlated with endometrial cancer (r=0.516, p=0.001). Mean age, BMI, CA125, and spiral artery Doppler results of women with and without endometrial cancer are shown in Table 1. The predictive value of different variables to predict cancer cases are shown in Table 2. The optimal cut off value for PSV was 40.5 with 93% sensitivity and 60% specificity, and for RI was 0.73 with 86% sensitivity and 87% specificity; the cut-off value for CA125 was 19.5 with 86% sensitivity and 78% specificity (Figure 2).

Table 1. Clinical data and ultrasound results for patients with benign and malignant endometrium in the study

		N	Mean	Std. Deviation	*p* value
Patients Age (years)	N-H	51	47.7	3.8	<0.001
	EC	14	58.9	8.6	
BMI (kg/m^2)	N-H	51	29.2	4.3	NS
	EC	14	29.6	2.0	
Endometrial Thickness (mm)	N-H	51	10.4	2.4	NS
	EC	14	9.2	3.7	
CA125 Level	N-H	51	15.1	9.9	0.004
	EC	14	38.6	25.4	
Spiral Artery Doppler Resistance Index	N-H	51	0.68	0.12	<0.001
	EC	14	0.81	0.07	
Spiral Artery Doppler Pulsatility Index	N-H	51	0.99	0.20	NS
	EC	14	1.10	0.20	
Spiral Artery Doppler Peak Systolic Velocity	N-H	51	40.8	11.6	<0.001
	EC	14	52.6	7.2	

EC: Endometrial cancer; N-H: Normal endometrium and endometrial hyperplasia; NS: Not significant; BMI: Body mass index

Table 2. ROC curve statistics results of different variables to predict endometrial cancer cases

	Area	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Spiral Artery Doppler Resistance Index	0.905	0.000	0.824	0.986
Spiral Artery Doppler Peak Systolic Velocity	0.822	0.000	0.717	0.928
CA125 Level	0.853	0.000	0.742	0.965
Patients Age (years)	0.859	0.000	0.730	0.987
Endometrial Thickness (mm)	0.431	0.438	0.219	0.642

[b]Null Hypothesis

In multivariate regression analyses, Age (R^2=0.82, beta=0.409, p=0.009), CA 125 (R^2=0.82, beta=0.256, p=0.01), spiral artery Doppler resistance index (R^2=0.82, beta=0.207, p=0.02) and the spiral artery peak systolic velocity values (R^2=0.82, beta=0.316, p<0.001) were significantly associated with the endometrial cancer cases.

Discussion

The best combination of clinical and cost-effective diagnostic methods are not yet defined in the evaluation of postmenopausal bleeding (9). There are a lot of studies that have constructed some sonographic methods and multivariate logistic regression models for the prediction and diagnosis of endometrial malignancy. Endometrial thickness, vascular patterns, fluid content of the endometrial cavity, and blood flow indices of the uterine artery are some of those that have been used in different models (4, 6, 10). Re-evaluating and adding further individual risk factors to the logistic regression model might improve its diagnostic performance. In this study, we focused on predicting type 2 endometrial cancer, a rare entity without well known risk factors, by means of spiral artery blood flow assessment.

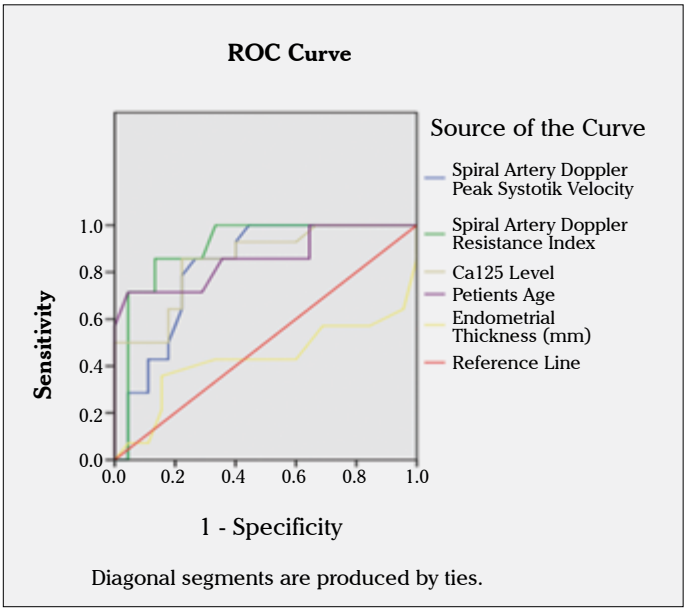

Figure 2. ROC curve of age, endometrial thickness, spiral artery RI and the PSV to predict endometrial cancer cases

Our study showed that endometrial spiral artery Doppler ultrasound examination can contribute to the correct prediction of type 2 endometrial malignancy, irrespective of endometrial thickness. We measured the resistance index in the spiral artery of 14 cases with type 2 endometrial carcinoma and found a significantly higher value for the spiral artery resistance index (RI=0.81±0.07) compared to that of normal and premalignant endometrium (RI=0.68±0.12). This is in contrast to a previous study in which velocimetric parameters (RI, PI, PSV) were not statistically different among different histopathologies (11). This may be explained by the high mean age of the study population with a wide range of distribution (47-83 years) and, in addition, the histopathological type of endometrial cancer was not mentioned in that study. Our study included a specific histopathological type of endometrial cancer (type 2) that may cause this kind of controversy. One study has shown that the median spiral artery RI (0.40) in 24 patients with endometrial carcinoma was significantly lower in comparison with the median spiral artery RI (0.61) of 82 patients with benign histopathologies (12). In that study, the authors found low vascular resistance in malignant cases; the reasons for this may be the variation in sonographic methods used to evaluate the endometrial lesions by transvaginal colour Doppler ultrasound and the assessment of both histopathological types of endometrial cancer. In our study, conversely, the mean value of PI was 1.10±0.20 in patients with type 2 endometrial cancer.

In the present data, there were only two postmenopausal women with an endometrial thickness of ≤5 mm. We saw that it was difficult to obtain data from the thin or indistinct endometrial stripe. In our series, no significant correlation was shown between the mean endometrial thickness and type 2 endometrium carcinoma (p=0.438). None of the spiral artery Doppler findings (RI, PI, PSV) were correlated with endometrial thickness (p>0.05).

In the beginning, we planned this study to evaluate Doppler measurements of type 2 endometrial cancer, which mainly originates from atrophic endometrium. Therefore, those cases with endometrial hyperplasia were grouped as the control. Thereafter, we showed that endometrial spiral artery Doppler ultrasound examination can contribute to a correct prediction of type 2 endometrial malignancy, irrespective of endometrial thickness. Additionally, our modalities (Doppler measurements) were not able to predict those cases with endometrial hyperplasia.

The results obtained by spectral Doppler procedures correlated with age and other measurements of BMI, such as CA125 levels. When regression analysis was performed by showing a causal relationship, high CA125 levels and advanced age were significantly associated with spiral artery RI and PSV; however, we did not find any significant association between spiral artery RI and BMI. The interpretation of CA125 levels has been based on a normal value of <35 U/mL (13). One study suggests that CA125 appears to be a significant independent predictor of the advanced stage of the disease (14). In our series, CA125 levels of patients with carcinoma were significantly higher (Mean value=38.6±25.4, p=0.004) than in patients with normal and premalignant histopathology. Ferrazi and co-workers found that the risk of endometrial cancer increased with increasing BMI (15). We did not find a positive correlation between BMI and type 2 endometrium carcinoma in this study (p>0.05). Also, there was no correlation between spiral artery RI and BMI (p>0.05).

Spiral artery Doppler analyses are satisfactory only in 30% of women within 1-5 years post-menopause (16). In our study, spiral artery Doppler analyses were optimal in a few number of women with normal and hyperplasic histopathological results; therefore, few women were left in the control group, while all analyses were satisfactory in the group with cancer. This result led us to conclude that satisfactory spiral artery Doppler assessment in late postmenopausal years necessitates further investigation for the higher risk for malignancy in postmenopausal women.

It is a strength that sonographic measurements (machine settings, qualitative assessment of the endometrium, colour and power Doppler assessment) were performed according to a consensus opinion from IETA (7). Since we used a standardised terminology, it would allow comparisons between future studies on the endometrium. The differences in results between studies can probably be explained by differences in the experience of the examiners and ultrasound equipment. Three-dimensional ultrasound imaging might also prove useful in the diagnosis of endometrial pathology, but in this study we limited ourselves to colour Doppler flow imaging and two dimensional grey-scale ultrasound.

In conclusion, although our series was relatively small, our data indicate that spiral artery Doppler ultrasound may play a role in refining the diagnosis of type 2 endometrium carcinoma in patients with post-menopausal bleeding. Further studies in larger series are needed to confirm or refute these preliminary data.

Ethics Committee Approval: *Ethics committee approval was received for this study.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

Author contributions: *Concept - E.Ö., S.D.; Design - T.K., S.D.; Supervision - M.F.K., T.K.; Resource - M.B.Ö., S.D.; Materials - M.B.Ö., B.G.; Data Collection&/or Processing - V.K., M.F.K.; Analysis&/or Interpretation - E.Ö., S.D.; Literature Search - İ.N.B., S.D., B.K.; Writing - S.D., E.Ö.; Critical Reviews - S.D., F.K., T.K.*

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