Assessment of the accuracy of endometrial volume and Doppler vascular indices in predicting endometrial carcinoma in women with postmenopausal bleeding

Thesis

Submitted for partial fulfillment of the master degree in

Obstetrics and Gynecology

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Mohamed Hassan Abdel Ati

Dedication

To the soul of

my father

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Introduction

Postmenopausal bleeding is an early clinical sign of endometrial malignancy. The finding of a thin (<5 mm) endometrium at transvaginal ultrasound examination in women with postmenopausal bleeding rules out about 99% of endometrial cancers ***(Gale and Dey, 2009).***

Therefore, endometrial sampling is usually considered necessary only in women with postmenopausal bleeding and endometrial thickness ≥5 mm ***(Gale and Dey, 2009 and Breijer et al., 2010).***

However, many women with postmenopausal bleeding and endometrial thickness ≥5 mm do not have endometrial cancer and some do not have any endometrial pathology at all, but will still undergo – perhaps unnecessarily – interventional diagnostic procedures such as dilatation and curettage (D&C) or hysteroscopy. In the high-risk group of women with post-menopausal bleeding and a thick endometrium, the thicker the endometrium the higher the risk of malignancy ***(Seebacher et al., 2010).***

Diagnostic methods other than a simple measurement of endometrial thickness, e.g. Doppler examination of the endometrium, might be helpful for discrimination between benign and malignant endometrium in women with postmenopausal bleeding and thick endometrium, and so be used to select those women who might best benefit from an invasive diagnostic procedure ***(Seebacher et al., 2010).***

Subjective evaluation of the colour content of the endometrial scan or of the morphology of endometrial blood vessels using conventional two-dimensional (2D) power Doppler ultrasound imaging can discriminate between benign and malignant endometrium, and, when added to gray-scale ultrasound imaging, may improve discrimination in women with postmenopausal bleeding and endometrial thickness=5 mm ***(Seebacher et al., 2010).***

However, these methods of assessing endometrial vascularity have the disadvantage of being purely subjective. The color content in a

representative 2D power Doppler image of the endometrium can also be quantified objectively using dedicated software ***(Seebacher et al., 2009).***

Moreover, a single power Doppler image is likely to reflect the vascularization of the endometrium less well than multiple power Doppler images in an endometrial volume obtained by three-dimensional (3D) power Doppler imaging. In theory, therefore, 3D power Dopplerultrasound examination might be superior to 2D power Doppler ultrasonography when estimating the risk of endometrial malignancy in a woman with postmenopausal bleeding. Some have claimed that endometrial volume measurements taken using 3D ultrasound imaging discriminate better between benign and malignant endometrium than do endometrial thickness measurements ***(Clark et al., 2006 and Coyne et al., 2008)****.*

Recently, the potential role of 3D Power Doppler has been explored as a mean to assess tumor vascularization, in endometrial hyperplasia and cancer, and the correlation with histoprognostic factors. It was found that endometrial cancer trends to express a higher vascularization than hyperplasia, and the deeply infiltrating, poorly differentiated and advanced staged endometrial cancers are more vascularized than their counterparts ***(Alcazar and Galvan, 2009).***

Aim of the Work

This study aims to assess the accuracy of endometrial volume and vascular indices measured by 3D ultrasonography in discrimination between benign and malignant endometreial lesions in women with postmenopausal bleeding.

Research hypothesis:

In women with postmenopausal bleeding, endometrial volume and power Doppler vascular indices measured by 3D ultrasound may discriminate between benign and malignant endometrial lesions.

Research question:

In women with postmenopausal bleeding, do the endometrial volume and power Doppler vascular indices discriminate between benign and malignant endometrial lesions?

Patients and Methods

This is an observational study in which 57 patients will be recruited from the outpatients attending gynecologic clinic in Ain Shams University maternity hospital including patients presenting with post-menopausal bleeding and thick endometrium >5mm by TVS .

Patients involved in this study will be subjected to the following:

- Full history taking with special attention to confirmation of the selection criteria.
- Comprehensive general examination.
- Pelvic examination.
- 3 D-transvaginal ultrasonography measuring endometrial volume using virtual organ computer aided analysis **(VOCAL**) program.
- Full endometrial curettage.
- Histopathological examination of endometrial tissue.

Comparison of the endometrial volume obtained by 3D-TVS and the results of the histopathological examination of the endometrial tissue to obtain the best cut-off of the endometrial volume to diagnose malignant endometria in post-menopausal women.

Inclusion criteria:

- Post-menopausal patients presenting with abnormal uterine bleeding (if she has reported absence of menstruation for at least one year after the age of forty.
- Endometrial thickness > 5 mm measured by two-dimensional Transvaginal ultrasound.
- Definitive endometrial histological diagnosis obtained at Early Cancer Detection Unit in Ain Shams University Maternity hospital.

Exclusion criteria:

- Enlarged uterus ≥ 12 weeks.
- Postmenopausal woman on HRT (Hormonal intake 3m before recruitment).
- Presence of general causes of bleeding as: (Uncontrolled hypertension, thyroid dysfunction).
- Bleeding tendency due to anti-coagulant treatment.
- Lesions that distort the endometrium eg. Polyp, septum, myoma

<u>For all included women the following will be done:</u>

A- Full history taking.

- Personal history:

Name, age, gravidity, parity, special habits

- Current problem / complaint (bleeding, pain).
- Menstrual and gynecological history:
- Past obstetric history:
  - Outcome of previous pregnancies in details including the abortions.
- Past medical and surgical history.
- Drug History.
- Family History.
  - Hereditary illness → Diabetes Mellitus, hypertension., thalassemia, sickle cell disease, hemophilia

B- Complete general, abdominal, and local examination.

<u>1) General examination:</u>

- General condition.

- Height, Weight. (BMI →Kg / m^2)

-Pulse → (tachycardia in case of bleeding).

-Blood pressure → (for diagnosis of hypertension).

2) Clinical examination.

1-Inspection:

- Size: huge in Fibroid uterus.
- Shape, striae, veins, scars, movement with respiration, pigmentations, hernial orifices.

2-Palpation:

- Bimanual examination.

3-Percussion → Ascites

Vaginal examination: Not done.

3) Investigations:

- Complete blood picture (CBC), Rhesus factor (RH), Blood group and blood sugar.
- Urine for: glucose, protein
- Kidney function tests, Liver functions tests (if indicated) .

C-Ultrasound Instrumentation:

Technique of Ultrasound and Doppler Examination:

Sonographic examinations were performed with a GE Voluson 730 Expert ultrasound system (GE Healthcare, Zipf, Austria) with transvaginal 5- to 9-MHz volume transducer.

First a conventional gray-scale sonography was performed to obtain longitudinal and transverse sections of the uterus and adnexa.

Maximal endometrial thickness (double layer) was measured in the longitudinal plane in order to include those patients with endometrial thickness of ≥ 5 mm.

After B-mode evaluation, a 2-dimensional power-Doppler gate was be activated to assess vascularization from the myometrium and endometrium. Then, 3-dimensional volume was activated to obtain a 3-dimensional box from the uterus. With a sweeping angle of 90 degrees, the acquisition box of 3-dimensional volume was placed over the power Doppler window.

Volumes will be stored to be evaluated later with the virtual organ computer aided analysis **(VOCAL**) program.

The **VOCAL** program automatically calculates the endometrial volume and three 3-dimensional power Doppler indices: vascularization index (**VI**), flow index (**FI**) and vascularization-flow index (**VFI**).

VI measures the number of color voxels in the volume, which represents the vessels in the tissue and is expressed as a percentage.

FI is the mean color value in the color voxels, which indicates the average intensity of blood flow and is expressed as an entire number from 0-100.

VFI is the mean color value in all the voxels in the volume, which represents both vascularization and blood flow and is also expressed as an entire number from 0-100.

Within 1 week after ultrasound examination, endometrial sampling by fractional curettage will be done.

Definitive histological diagnosis will be obtained in all of the cases included in this study.

Then Correlation between :

.The results of the histopathological examination of the endometrial tissue

.The endometrial thickness obtained by 2D_TVS

.The endometrial volume and vascular indices obtained by 3D-TVS so you can assess its accuracy.

Data Management and Analysis:

Sample size Calculation

- The required sample size has been calculated using the Power Analysis and Sample Size Software (PASS©) version 11.0.10 (NCSS©, LLC. Kaysville, Utah, USA).

- The primary outcome measure is the accuracy of endometrial volume and 3D power Doppler indices as measured by 3D ultrasound imaging combined with 3D multislice view of grayscale for discrimination between benign and malignant endometria in women with postmenopausal bleeding and endometrial thickness ≥5 mm.

- A previous study reported that the area under the ROC curve (AUC) for discrimination between benign and malignant endometria using the endometrial volume, VI, FI, or VFI was 0.749, 0.902, 0.704, or 0.868, respectively **(Alcazar & Galvan, 2009).** In that series, the prevalence of endometrial carcinoma among the studied cohort was 44%.

- So, it is estimated that a total sample size of 57 postmenopausal women with postmenopausal bleeding and endometrial thickness ≥5 mm would yield 25 (44%) women with endometrial carcinoma and 32 (56%) women with benign endometrial. This sample size would achieve a power of 81% (type II error, 0.19) to detect a difference of 0.204 between a null AUC (AUC_0) of 0.5 and an alternative AUC (AUC_1) in association with the FI of 0.704.

- The power of this sample size of 57 women to detect a statistically significant difference for alternative AUCs of 0.749, 0.868, or 0.902 in association with the endometrial volume, VFI, or VI, respectively, would be 93%, 100%, or 100%, in that order.

- These calculations used a two-sided z-test with a confidence level of 95% (type I error, 0.05) and assumed that the prevalence of endometrial carcinoma among the study cohort is 44%.

Statistical Methods

- Data will be collected, tabulated, then analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY).

- Normally distributed numerical data will be presented as mean and SD, and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage. Comparison of normally distributed numerical data in patients with benign or malignant endometria will be done using the unpaired Student *t* test. Skewed data will be compared using the Mann-Whitney U test. Categorical data will be compared using the chi-squared test, or Fisher's exact test when appropriate. Receiver-operating characteristic (ROC) curve analysis will be used to examine the diagnostic value of endometrial volume and 3D Power Doppler indices for discrimination between benign and malignant endometria. A two-sided p-value <0.05 will be considered statistically significant.**(Alcazar JL1, Galvan R 2009.)**

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001).** Data will be presented and suitable analysis will be done according to the type of data obtained for each parameter.

- **Descriptive statistics:**
  - Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and for non parametric numerical data.
  - Frequency and percentage of non-numerical data.

- **Analytical statistics:**

  - **Student T** Test will be used to assess the statistical significance of the difference between two study group means.

  - **Chi-Square test** will be used to examine the relationship between two qualitative variables