ORIGINAL ARTICLE

Role of Three-Dimensional Ultrasound and Three-Dimensional Doppler in Imaging of Endometrium for Diagnosis of Bleeding in Women with Post-Menopausal Bleeding

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ABSTRACT

Objective: To determine whether the Three-Dimensional Ultrasound and Three Dimensional Doppler have a role in detection of Endometrial lesions in woman with post menopausal bleeding.

Methods: 36 woman in Zagazig University Obstetrics and Gynaecology Department outpatient clinics were recruited. Three-Dimensional Ultrasound and Doppler were done. Then after one week endometrial sampling was done & histological diagnosis was made. After tabulation, all data were analyzed using statistical procedures were carried with SPSS software.

Result: Twenty four patients were negative for atypia or cancer and Twelve patients were positive for atypia or cancer. Mean age was 58.1 years in benign endometrium and 62.2 year in malignant endometrium (p=0.1). The mean BMI was 24 in benign and 31.75 in malignant endometrium (p<0.001). Mean endometrial thickness was 11.1 m.m in benign and 26 mm in malignant endometrium (p<0.001). The mean endometrial Volume was 5.6 cc in benign and 54.8cc in malignant endometrium (p<0.001). The VI was 2.24%and 19.5% in the two groups respectively (p<0.001). The FI was 6.7 and 27.2 in two groups respectively (p<0.001). The VFI was 3.3 and 11.5 in two groups respectively (p<0.001). In this study using endometrial volume, vascularization index percent (VI) %, flow index (FI) and vascularization-flow index (VFI) rather than endometrial thickness provided a greater sensitivity for predicting atypia or malignancy.

Conclusion: The Three-Dimensional Ultrasound scanning of endometrial volume (3D-US) and Three-Dimensional Doppler Angiography (3D-DA) of the Vascular Indices (vascularization index percent, flow index, and vascularization-flow index), might predict endometrial cancer in women with postmenopausal bleeding and thickened endometrium at baseline ultrasound scanning.

INTRODUCTION

Post-menopausal bleeding is common problem representing 5% of all gynecological outpatient attendance.[1]

In most cases post-menopausal bleeding is caused by hormonal disorders, but it can also be an indirect sign of other more or less serious conditions such as (endometrial polyps, endometrial hyperplasia, or malignant lesions of the cervix or endometrium).[2] In both pre-and post-menopausal women the causes of these episodes are usually benign.[3]

Consequently, it is important to identify relatively non invasive, low cost methods that can be reliable in differentiation between cases that require surgical intervention and those related to hormonal or functional disorders.[3] Histopathological examination is done

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after hysterectomy or D&C, although this approach is invasive and expensive it is considered a gold standard for identifying uterine lesions associated with post-menopausal bleeding.[3] Other techniques for the assessment of uterine endometrium include Transvaginal Ultrasound (TVUS); Two Dimensional Ultrasound, Three Dimensional Ultrasound and Three Dimensional Doppler.[4]

Ultrasound is currently the first level of examination of post- menopausal bleeding. It is well tolerated, non invasive & relatively inexpensive, it provides adequate information on the thickness and homogeneity of the endometrium and presence of gross focal lesions.[4]

In some cases, (TVUS) is not reliable in identification of the nature of the lesion seen whether it is benign proliferation, hyperplasia, polyps, neoplasia.[5] Besides (TVUS) frequently misses certain types of lesions such as tiny polyps, submucosal leiomyomas and other small lesions.[5] Three Dimensional Ultrasound and Three Dimensional Doppler offer even better visualization of endometrium and more accurate assessment of the uterine cavity as well as improved visualization of uterine anatomy which is particularly useful in cases of congenital anomalies.[6] The Three Dimensional Ultrasound and Three Dimensional Doppler elaboration requires only few seconds to reconstruct the entire volume of uterine walls and cavity.[6]

METHODS

Thirty six women in Zagazig University obstetrics and gynecology department outpatient clinics with complaints of postmenopausal bleeding were recruited between January 2010 and August 2012, and were included in this prospective observational study.

Natural menopause established, defined as 1 year of absence of menstruation in women who were older than 45 years with baseline transvaginal sonography that showed a double layer endometrial thickness of ≥4 mm were included in this study. Definitive endometrial histologic diagnosis that was obtained. exclusion criteria were used for the study was endometrial thickness < 4 mm, use of tamoxifen citrate or any kind of hormone replacement therapy. Presence of intracavitary fluid collection at ultrasound examination. Diagnostic work-up included complete medical History taking included age, years since menopause, smoking, and presence or absence of any medical disorders such as diabetes mellitus or hypertension, and transvaginal ultrasound examination. Sonographic examinations were performed with a Voluson 730 Expert (GE Healthcare, Milwaukee, WI) that was equipped with a multifrequency (3-9 MHz) endovaginal probe, according to a determined scanning protocol. Briefly, first a conventional gray-scale

sonography was performed that obtained longitudinal and transverse sections of the uterus and adnexa. Maximal endometrial thickness (double layer) was measured in the longitudinal plane.

The method used for volume measurement is the three distance method in which the volume was obtained by multiplying maximal diameter in transverse, vertical, and frontal axis by the same factor, i.e. volume (ml) = distance1 (length)× distance 2 (height)× distance 3 (width)×0.5236.[7]

Measurement with the three distance method was performed in fundal height where the endometrium is expanded (Figure 1)

Volumes were stored and evaluated later in a personal computer. With the virtual organ computer aided analysis (4 D VIEW VOCAL) program. The program automatically calculates the three 3-Dimensional 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, all patients underwent endometrial sampling by Dilation and curettage.

Definitive histological diagnosis was obtained from cases that were included in this study. Benign histological findings included cystic atrophy, endometrial polyp,
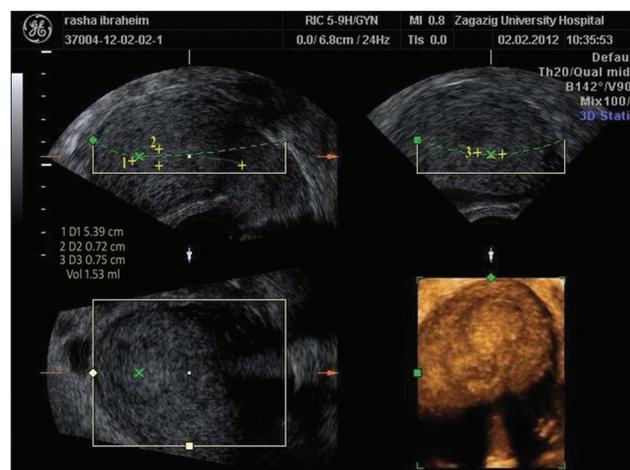

Figure 1: Three-dimensional endometrial volume estimation, using the three distance method

and submucous myoma and endometrial hyperplasia. Malignant histological findings included endometrial carcinoma, clear cell carcinoma, and endometrioid adenocarcinoma. Institutional review board approval was obtained, and all patients gave verbal informed consent.

Statistical Analysis

After tabulation, all data were analyzed using statistical procedures were carried with SPSS software. The p value (<0.001) was considered as Statistically significant.

RESULTS

This study was conducted in the period from 2010 - 2012; thirty six women with postmenopausal bleeding were evaluated at Zagazig university obstetrics and gynecology department outpatient clinics.

In this study Patient mean ±SD age was 59.4±7.2 years (range, 48-75 years), endometrial thickness was 16.1 ± 10.7 mm (range1.5-43.2 mm),endometrial volume was 22± 33.7 ml (range 0.7-120 ml), vascularization index percent (VI)%was 8 ±9.8 (range 0-36.8), flow index (FI) was 13.5 ±12.8 (range 0-39.4), vascularization-flow index (VFI) was 6.1 ±5.3 (range 0-16.7).

In this study Patient median age was 59 years, endometrial thickness was 12.8, endometrial volume was 7.2, vascularization index percent (VI) % 2.4, flow index (FI) was 10.35, vascularization-flow index (VFI) was 4.9. (Table 1)

Twenty four patients were negative for atypia or cancer; mean ±SD age was 58.1±6.9 years (range, 48-75 years), BMI was 24 ± 3.8 (range, 18-35 kg/m^2), endometrial thickness was 11.1 ± 6.1 mm (range 1.5-25.2 mm), endometrial volume was 5.6± 6.3 ml (range 0.7-25.9 ml), vascularization index percent (VI)% was 2.24 ±3.1 (range 0-13.6), flow index (FI) was 6.7 ±6.6 (range 0-21.6), vascularization-flow index (VFI) was 3.3 ±3.96 (range 0-14.2). (Table 2) (Figure 2).

Twelve patients were positive for atypia or cancer; mean ±SD age was 62.2±7.1 years (range, 49-71 years), BMI was 31.75 ± 5.36 (range, 19-40 kg/m^2), endometrial thickness was 26 ± 11.2 mm (range 5.2-43.2 mm), endometrial volume was 54.8± 42 ml (range 0.8-120 ml), vascularization index percent (VI)% was 19.5 ±8.4 (range 3.6-36.8), flow index (FI) was 27.2±11.3(range 3.6-39.4), vascularization-flow index (VFI) was 11.5 ±2.9 (range 5.8-16.7). (Table 2) (Figure-2).

Age was not statistically different between the patient with bengin endometrium and those with malignant endometrium. On the contrary BMI and endometrial thickness was significantly increased in the patient with malignant endometrium than those with benign endometrium. Endometrial volume was larger and flow vascular indices were higher in patients with malignant endometrium than in those with benign endometrium (Table 2), (Figure 2).

Twenty four patients were negative for atypia or cancer; parity percent was 37.5% in patient with parity from zero to

Table 1: General criteria for all participants

| Parameter	N=36
Age (years)	
Mean±SD	59.4±7.2
Range	48-75
Median	59
Endometrial thickness	
Mean±SD	16.1±10.7
Range	1.5-43.2
Median	12.8
Endometrial volume	
Mean±SD	22±33.7
Range	0.7-120
Median	7.2
Parity %	
Parity=0-2	N=18 (50%)
Parity>2	N=18 (50%)
Vascularization index (VI), %	
Mean±SD	8±9.8
Range	0-36.8
Median	2.4
Flow index (FI)	
Mean±SD	13.5±12.8
Range	0-39.4
Median	10.35
Vascularization-flow index (VFI)	
Mean±SD	6.1±5.3
Range	0-16.7
Median	4.9
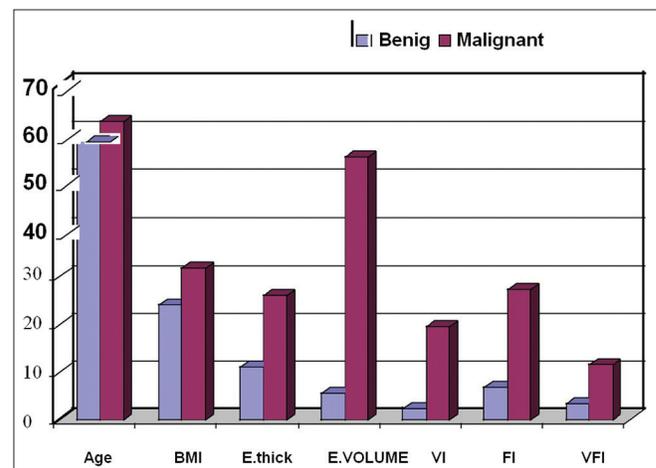
Figure 2: Comparison between benign and malignant endometrium

two, and 62.5% in patient with parity more than two.Twelve patients were positive for atypia or cancer; parity percent was 75% in patient with parity from zero to two, and 25% in patient with parity more than two (Table 3).

This table show that the percentage of malignant conditions were higher in nulliparous patients and patients with parity < 2 than in those with parity >2.

This table shows the correlation between the endometrial thickness and age, parity, BMI and their significance. (Table 4).

Endometrial thickness negatively correlated with age and parity positively correlated with BMI. (Table 4).

There was no correlation between endometrial thickness and age; on the other hand there is good correlation between sonographically estimated endometrial thickness and both parity and BMI as the incidence of malignant endometrium increase in patient with low parity and in patient with high BMI (Table 4).

This curve shows the negative correlation between endometrial thickness and the parity (Figure 3).

This curve shows the positive correlation between endometrial thickness and the BMI (Figure 4).

This table shows the correlation between the endometrial volume and age, parity, BMI and their significant (Table 5).

Endometrial volume negatively correlated with age and parity positively correlated with BMI (Table 5).

There was no correlation between endometrial volume and age; on the other hand there is good correlation between sonographically calculated endometrial volume and both parity and BMI as the incidence of malignant endometrium
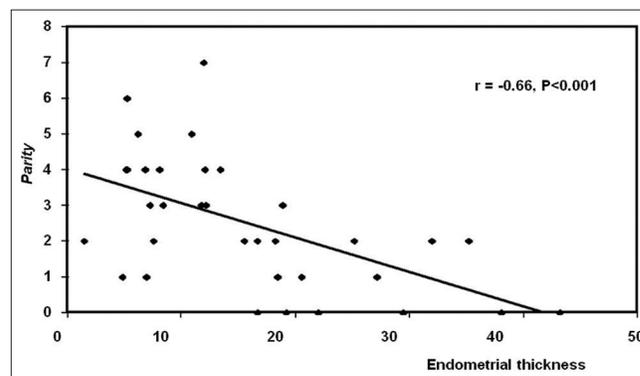
Table 2: Comparison between benign and malignant endometrium

Parameter	Benign N=24	Malignant N=12	t test	P value
Age (years)				
Mean±SD	58.1±6.9	62.2±7.1	1.64	0.1
Range	48-75	49-71		
BMI				
Mean±SD	24±3.8	31.75±5.36	4.97	0.001
Range	18-35	15-40		
Endometrial thickness				
Mean±SD	11.1±6.1	26±11.2	12.9	<0.001
Range	11.5-25.2	5.2-43.2		
Endometrial volume				
Mean±SD	5.6±6.3	54.8±42	13.2	<0.001
Range	0.7-25.9	0.8-120		
Vascularization index (VI), %				
Mean±SD	2.24±3.1	19.5±8.4	22.4	<0.001
Range	0-13.6	3.6-36.8		
Flow index (FI)				
Mean±SD	6.7±6.6	27.2±11.3	6.91	<0.001
Range	0-21.6	3.6-39.4		
Vascularization flow index (VFI)				
Mean±SD	3.3±3.96	11.5±2.9	17.49	<0.001
Range	0-14.2	5.8-16.7		

Table 3: Comparison between benign and malignant endometrium

Parameter	Benign N=24 (%)	Malignant N=12 (%)	χ^2	P value
Parity %				
Parity=0-2	N=9 (37.5)	N=9 (75)	4.5	0.03
Parity>2	N= 15 (62.5)	N=3 (25)		

This table show that the percentage of malignant conditions were higher in nulliparous patients and patients with parity <2 than in those with parity >2

Table 4: Correlation of the endometrial thickness, age, parity, and BMI

Correlation of endometrial thickness	r	p	Significance
Age	−0.24	>0.05	Not significant
Parity	−0.66	<0.001	Highly significant
BMI	0.69	<0.001	Highly significant

Figure 3: Correlation of the endometrial thickness and parity
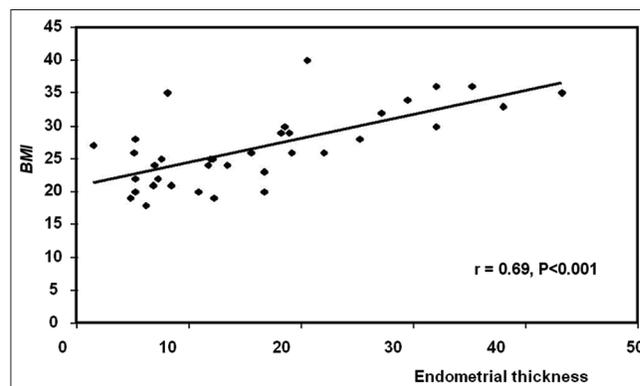

Figure 4: Correlation of the endometrial thickness and BMI

increase in patient with low parity and in patient with high BMI (Table 4).

This curve shows the negative correlation between endometrial volume and the parity (Figure 5).

This curve shows the positive correlation between endometrial volume and the BMI (Figure 6).

The sensitivity revealed that using endometrial volume, vascularization index percent (VI)%, flow index (FI) and vascularization-flow index (VFI) rather than endometrial thickness provided a greater sensitivity for predicting atypia or malignancy. Overall, sensitivity was 75% using endometrial thickness, 83.3% using endometrial volume, 91.7% using vascularization index percent (VI)%, 83.3% using flow index (FI), and 100% using vascularization-flow index (VFI).(Table 6) (Figures 7-13).

DISCUSSION

Abnormal vaginal bleeding is one of the most common presenting complaints in women of any age seeking gynecologic care.[8] The most worrisome cause of abnormal bleeding is endometrial carcinoma. Two of the most frequently used diagnostic tests to investigate the cause of bleeding are endometrial biopsy and Transvaginal Ultrasound.[8] Studies examining screening methods for endometrial carcinoma in asymptomatic postmenopausal women have accepted ultrasound determined endometrial thickness as an indication of risk. The thickest anteroposterior diameter of the endometrium is measured using 2D ultrasound, and a cutoff value of ≥4 mm is considered predictive of pathologic changes.[8] Three-Dimensional Ultrasound

scanning and Three-Dimensional Doppler Angiography recently have been introduced in the clinical practice. This technique overcomes some of the limitations of conventional B-mode and color/power Doppler ultrasound scanning.

This study included 36 cases complaining of postmenopusal bleeding and showing increased endometial Thickness, Three-Dimentional Ultrasound and Three Dimensional Doppler were done to measure endometrial volume and the whole endometrial vascularization, with the calculation of three Vascular Indices (vascularization
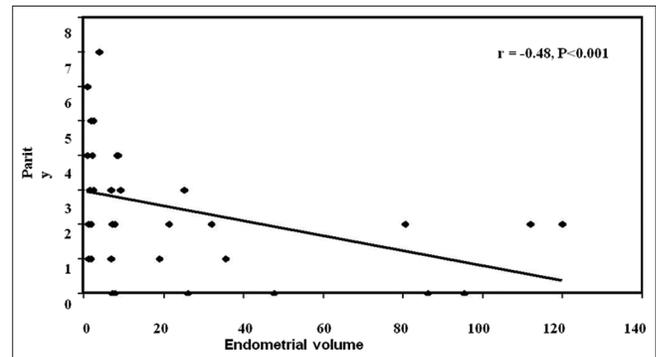

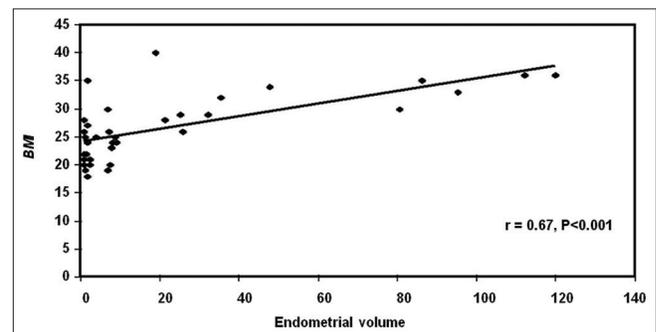**Figure 5:** Correlation of the endometrial volume and parity

Figure 6: Correlation of the endometrial volume and BMI

Figure 7: Showing the microscopic picture of atrophic endometrium

Table 5: Correlation of the endometrial volume, age, parity, and BMI

Correlation of endometrial volume	r	p	Significance
Age	−0.1	>0.05	Not significant
Parity	−0.48	<0.001	Highly significant
BMI	0.67	<0.001	Highly significant

Table 6: Validity of different indices

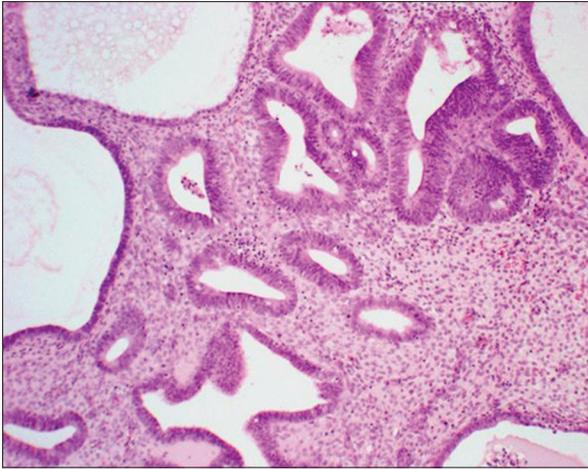| Indices	Sensitivity, %	Specificity, %	Predictive value, %		Accuracy, %
			+ve	-ve	
Endometrial thickness	75	91.7	81.8	88	86.1
Endometrial volume	83.3	91.7	83.3	91.7	88.9
VI, %	91.7	91.7	74.6	95.9	91.7
FI	83.3	87.5	76.9	91.3	86.1
VFI	100	91.7	85.7	100	94.4

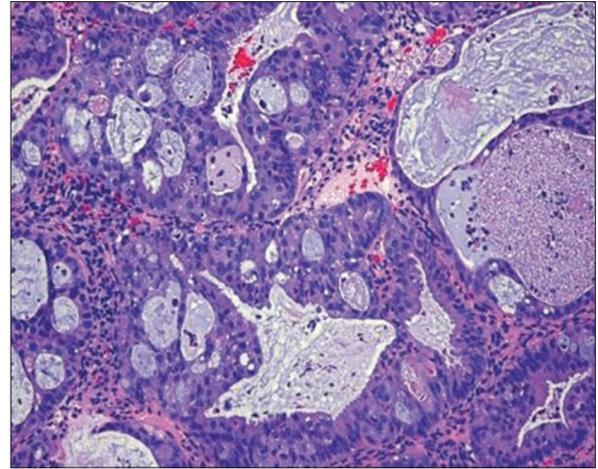**Figure 8:** Showing the endometrial polyp

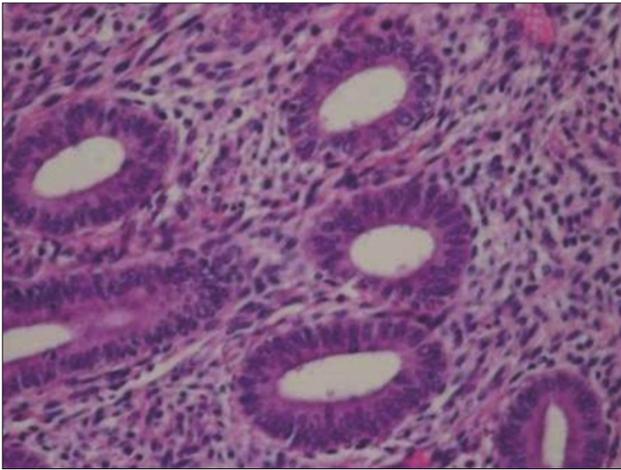**Figure 11:** Showing the complex atypical hyperplasia

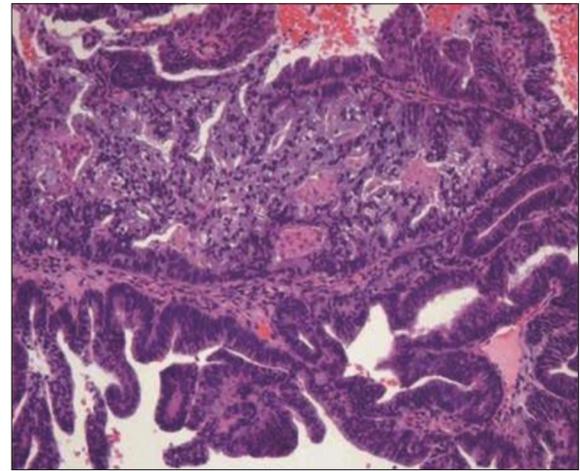**Figure 9:** Showing thesimple endometrium hyperplasia

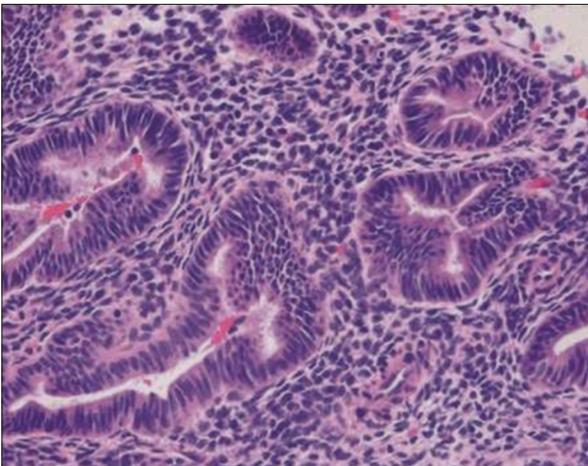**Figure 12:** Showing the endometrioid adenocarcinoma

Figure 10: Showing the complex endometrial hyperplasia without atypia
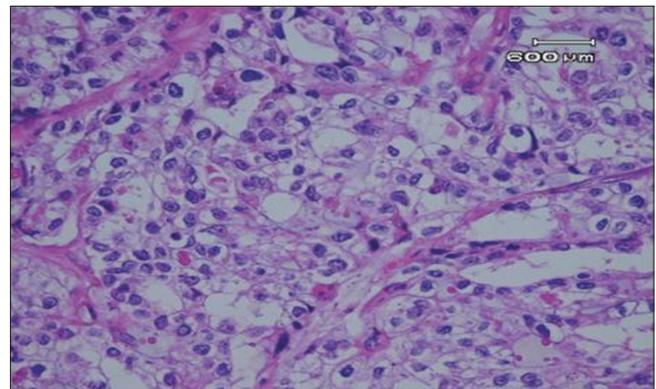

Figure 13: Showing clear cell carcinoma

index percent, flow index, and vascularization-flow index), then The results were compared to histopathological examination of endometrial biopsies taken from the participant women.

In this study, patient's age is not significant as the patients proved to be positive or negative for endometrial atypia or cancer at different ages.

It was found that there is no statistical difference between the study and control groups regarding age.[8]

However Merce LT et al. reported that age was significantly greater in endometrial carcinoma than endometrial hyperplasia.[10] G. Opolskiene et al reported that the patients with malignant endometrium tended to be older.[11]

In this study, patient's parity and BMI significantly greater for the study patients proved to be positive for endometrial atypia or cancer, than those proved to be negative for endometrial atypia or cancer.

Similarly, it was found that the patients with malignant endometrium had a higher body mass index.[11]

However Merce et al. reported that parity and BMI had no significance difference in endometrial carcinoma than endometrial hyperplasia.[10]

It was found that there is no statistical difference between the study and control groups regarding parity and BMI.[8]

In this study, endometrial thickness was increased proved to be positive for endometrial atypia or cancer, negative for endometrial atypia or cancer. Similarly, Luis T. Me et al reported that the endometrial thickness increased for the study patients proved to be positive for endometrial hyperplasia, and those proved to be positive for endometrial carcinoma.[10] in concordance, G. Opolskiene et al assumed that the endometrial thickness was not statistically different among different endometrial diseases except for endometrial cancer.[11] Regarding endometrial volume in this study, it was significantly larger for the study patients proved to be positive for endometrial atypia or cancer, proved to be negative for endometrial atypia or cancer. Going with the previous results, Luis T. Mercé et al showed that the endometrial volume was significantly increased, in endometrial carcinoma when compared with endometrial hyperplasia.[10]

Also, Mansour et al found that the endometrial volume was lower in patients proved to be negative for endometrial atypia or cancer, and higher in patients proved to be positive for endometrial atypia or cancer.[8]

Similarly, Alcazar et al found that the endometrial volume was significantly larger in endometrial cancer, compared with all other benign diseases.[9]

It was found that the endometrial volume has a great value for the detection of endometrial cancer in a series of 97 women with postmenopausal bleeding.[12]

In this study, vascularization index percent (VI)%, flow index (FI), and vascularization-flow index (VFI) were significantly high for the study patients proved to be positive for endometrial atypia or cancer, than those proved to be negative for endometrial atypia or cancer.

In concordance with the previous results, Luis T. Mercé et al showed that the 3D power Doppler indices were significantly increased, in endometrial carcinoma when compared with endometrial hyperplasia.[10]

Also, Alcazar et al found that the VI% and VFI were significantly higher in endometrial cancer, compared with all other benign diseases. FI was significantly higher in endometrial cancer, compared with endometrial polyp and hyperplasia.[9]

Similarly, Odeh et al observed that the 3-dimensional VIs are higher in endometrial cancer, compared with endometrial hyperplasia, during the assessment of endometrial vascularization by three dimensional Doppler.[7]

However G. Opolskiene et al found that the flow indices were significantly higher in malignant than in benign endometria, and the flow indices measurements will not discriminated well between benign and malignant endometria, and the 3D measurements was not clearly superior to simple endometrial thickness measurements taken using 2D ultrasound examination.[11]

In this study, a higher cutoff value of endometrial thickness ((≥ 20 mm), of endometrial volume (≥15 ml) of vascularization index (≥5) of flow index (≥15) and of vascularization flow index (≥5) were predict for atypia or Malignancy.

Luis T. Mercé et al reported that a cutoff value of endometrial volume (≥ 6.86mL), of vascularization index (≥6 85), of flow index (≥ 25 42) and of vascularization-flow index (≥ 2.7) were predictive for atypia or malignancy.[10] Gruboeck et al reported that an endometrial volume of ≥13 0 mL would detect all endometrial cancers, with a false-positive rate of 1.2%.[12]

In this study using endometrial volume, vascularization index percent (VI)%, flow index (FI) and vascularization-flow index (VFI) rather than endometrial thickness provided a greater sensitivity for predicting atypia or malignancy.

In concordance with the previous results, Luis T. Mercé et al reported that the using of endometrial volume, vascularization index percent (VI)%, flow index (FI) and vascularization-flow index (VFI) provided a greater sensitivity for predicting atypia or malignancy.[10]

CONCLUSION

In conclusion the Three-Dimensional Ultrasound scanning of endometrial volume (3D-US) and Three-Dimensional Doppler Angiography (3D-DA) of the Vascular Indices (vascularization index percent, flow index, and vascularization-flow index), might predict endometrial cancer in women with postmenopausal bleeding and thickened endometrium at baseline ultrasound scanning. This technique deserves future investigation in larger series to establish its actual role.

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