
Endometrial Volume as a Predictor of Endometrial Pathology in Perimenopausal Uterine Bleeding

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Abstract

Background: Transvaginal ultrasonography (TVS) imaging is a routine, non-invasive procedure in initial evaluation of patients with abnormal uterine bleeding in perimenopausal age. However, there is no yet a cutoff value to discriminate benign form malignant cases.

Aim of the Work: Is to assess the potential value of endometrial volume measurements by 2D TVS compared with that of endometrial thickness in prediction of different endometrial pathologies in women with perimenopausal uterine bleeding.

Patients and Methods: Ninety-two perimenopausal women presented with uterine bleeding were enrolled to the study after exclusion of general and local caused of bleeding as polyps and fibroids. TVS (2D) was done to measure endometrial thickness and volume using a specific formula. Endometrial biopsy was taken and the pathological results was correlated with the endometrial thickness and volume.

Results: There was a statistically noticeable difference between benign endometrial pathology compared to endometrial hyperplasia with atypia or endometrial carcinoma as regard age as well as body mass index. There was a high statistically significant difference between patients with benign endometrium pathology and malignant endometrial pathology regarding endometrial thickness and volume. That endometrial volume had a high predictive value as proved by an area under the ROC curve (AUC) of 0.826. The best cut-off value was an endometrial volume >11.675 cm³. While (ROC) curve analysis for differentiation of patients using endometrial volume and endometrial thickness into women with benign endometrial pathology or hyperplasia and those with endometrial carcinoma; Endometrial volume also had a higher predictive value than endometrial thickness as proved by an area under the ROC curve (AUC) of 0.871. The cut-off value was an endometrial volume >13.105 cm³. While using endometrial thickness cut-off value was an endometrial thickness > 14.5mm.

Conclusion: endometrial volume measured with inexpensive 2D TVS has a higher predictive value than measuring endometrial thickness in correspondence to the pathological results in patients with perimenopausal bleeding.

Keywords: Perimenopausal bleeding, endometrial volume, 2D transvaginal ultrasound.

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INTRODUCTION

Persistent changes to the bleeding patterns during the perimenopausal period may be dangerous and careful evaluation should be done. (Klein NA, 1998). The increasing prevalence of obesity and metabolic syndrome yielded to higher incidence of endometrial cancer. Between 1992-1994 and 2009-2011, the European age-standardized rates of uterine cancer in the UK have risen by 48% (CRUK, 2014).

Transvaginal ultrasound (TVS) is an inexpensive, non-invasive way to indirectly visualize the endometrial cavity. Therefore, it is recommended as a first diagnostic tool to assess uterine pathology in any woman presenting with AUB. There is continuing interest in the role of spectral and color Doppler imaging for the endometrium (Kotdawa-la, et al.2013).

Measuring of the endometrial thickness for determination of the cause of abnormal uterine bleeding in the perimenopausal women is not easy in absence of anatomical lesions. Anovulatory cycles are a common cause, but hyperplasia, submucous-myomas, and carcinoma are of the concern to the patients (Merce, et al. 1991).

Volumes are usually measured by 3D where data are retrieved and presented in multi-planer display mode which simultaneously displays three perpendicular planes on the screen for the volume calculation which done by built in computer program using VOCAL. The endometrial volume was measured in plane A by delineating the endometrial margin at the endometrial-myometrial interface from the fundus to the internal cervical in a number of parallel slices which are 1-2 mm apart (Elsokkary M, 2016). Endometrial volume also can be measured by 2D transvaginal sonography with easy and applicable procedure by 2D TVS ellipse help to predict endometrial pathology. The formula for determining the volume of the endometrium by using one diameter and ellipse or three diameters of the endometrium.

The basic limitation of all imaging techniques has been the diagnosis of cellular changes in the endometrium. As of now the best use of ultrasonography along with saline infusion sonography in pre-menopausal AUB is to rule out organic pathol-

ogies such as a fibroid, adenomyosis, polyp etc., It has been proposed to use the 'thick endometrium' as a screening tool to select patients for histological assessment (Tinelli R et al., 2008).

The cut off value for endometrial thickness is >12 mm is the most common used for screening but its use is not recommended as this has been found to be inaccurate and a blind adherence. In contrast, endometrial thickness >4 mm in post-menopausal bleeding has a better predictive value in diagnosis of about 99% patients with endometrial cancer. However, repeated episode of postmenopausal bleeding with a endometrial thickness <4 mm, a biopsy is done to exclude that 1% chance of endometrial cancer (Litta P et al., 2005).

Endometrial pathology should be evaluated in women with abnormal uterine bleeding that not responding to a course of therapy for three months. (Brand A et al., 2000).

Aim of the Work:

Is to assess the potential value of endometrial volume measurements by 2D TVS compared with that of endometrial thickness in prediction of different endometrial pathologies in women with perimenopausal uterine bleeding.

PATIENTS AND METHODS

A prospective observational study was conducted on perimenopausal women with abnormal uterine bleeding who attended to Obstetrics & Gynecology department at Mansoura university hospital.

Patients: From August 2017 till August 2018, ninety two patients who were admitted to Obstetrics & Gynecology department at Mansoura university hospital suffering from perimenopausal uterine bleeding were enrolled into the study. Age ranged from 45-55 years with symptoms of abnormal bleeding e.g. heavy menstrual bleeding, intermenstrual bleeding and polymenorrhea within the last six months. General causes of bleeding e.g. liver cell failure, coagulopathy, hereditary hemorrhagic telangiectasia patients were excluded. Moreover; local causes of bleeding e.g. fibroid, polyp and cervical lesion were also excluded as well as patients with history of drug intake like antiplatelets, anticoagulant or recent hormonal contraception.

Ethical consideration: Study protocol was submitted for approval by IRB. Informed verbal and written consent was obtained from each participant sharing in the study.

Methods: All patients were exposed to the following

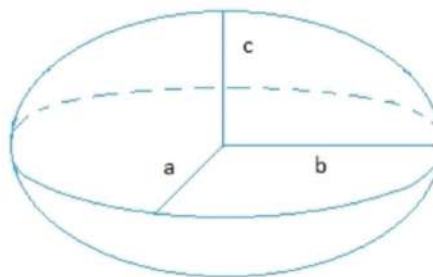
- Full history taking, General, abdominal and pelvic examination

2D-TVS measuring endometrial thickness by Sonoace R3medisone Samsung South Korea device) endometrial thickness is measured at its thickest part in the longitudinal plane. The surrounding more echo lucent layer (or “halo”) is considered to be the inner myometrium and is not included.



- Fig (1): 2D endometrial thickness by TVS SAMSUNG MEDISONE sonoace R3 South Korea device
- 2D-TVS measuring endometrial volume by the same device. The formula for determining the volume of the endometrium by using one diameter and ellipse reads as follow :

$$V = \frac{4}{3} \times \pi \times a \times b \times c$$



Volume of an ellipsoid



Fig (2): 2D endometrial volume by TVS SAMSUNG MEDISONE sonoace R3 South Korea device

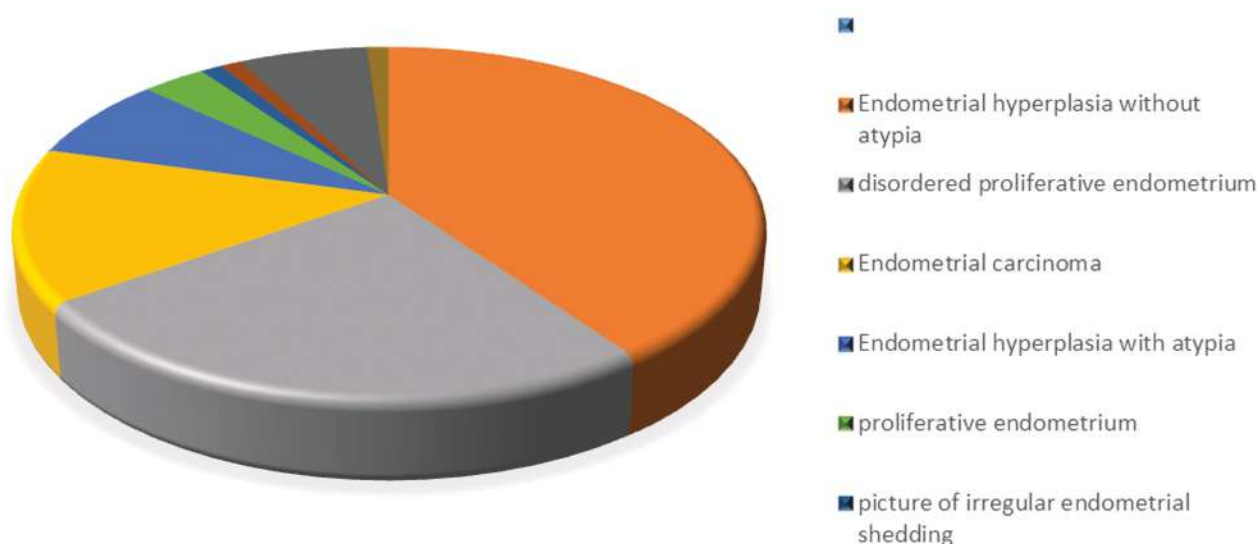
- Patients prepared for dilatation and curettage(one to two days following ultrasonic assessment) using sedating agents e.g. Propofol 2%, Midazolam, Fentanyl.
- Endometrial samples sent to Pathology department at Mansoura university for histopathological examination.
- Comparison of the endometrial thickness and volume obtained by 2D- TVS with the results of the histopathological examination of endometrial tissue.

Results:

The mean age of the patients was 50.53 ± 3.64 years. About third of them were diabetic patients, half of them were hypertensive, and 2.2% have had viral hepatitis.

Table (1): Distribution of the pathological results in women under study:

Result of pathology	No	%
Endometrial hyperplasia without atypia	37	40.2
Disordered proliferative endometrium	23	25.0
Endometrial carcinoma	13	14.1
Endometrial hyperplasia with atypia	7	7.6
Proliferative endometrium	3	3.3
picture of irregular endometrial shedding	1	1.1
Scanty endometrial tissue with occasional proliferative glands	1	1.1
Atrophic endometritis	6	6.5
Endometritis	1	1.1

**Figure (3):** Chart for the patients histopathological results

There was a statistically noticeable difference between benign endometrial pathology compared to endometrial hyperplasia with atypia or endometrial carcinoma as regard age [49.93 ± 3.58 and 52.70 ± 3.05 respectively], parity [3.74 ± 1.48 , 3.30 ± 1.59 respectively] and body mass index [35.49 ± 2.34 , 37.95 ± 1.61 respectively] using independent sample t-test.

Table (3): Endometrial volume and thickness in patients with benign endometrial pathology, endometrial hyperplasia and endometrial carcinoma ranging from the 1st and 3rd quartiles (interquartile range) using Kruskal-Wallis test.

	N	Endometrial thickness (mm) [median(range)]	Endometrial volume (cm3) [median(range)]
Benign endometrial pathology	35	9 (6 – 10)	9 (7.2 – 11.7)
Endometrial hyperplasia	44	10 (8 – 12)	12.2 (10.1 – 18.3)
Endometrial carcinoma	13	17 (13.5 – 30)	26 (16 – 52.5)
Kruskall-Wallis test	χ ²	23.222	26.682
	P	< 0.001*	< 0.001*

As regarding to endometrial volume and endometrial thickness there was a high statistically significant difference between patients with benign endometrium pathology and malignant endometrial pathology. That endometrial volume had a high predictive value as proved by an area under the ROC curve (AUC) of 0.826. The best cut-off value was an endometrial volume >11.675 cm³. This had a sensitivity of 95%, a specificity of 62.5%, +ve predictive value 41.3% and -ve predictive value 97.8% and endometrial thickness cut-off value was an endometrial thickness >10.5mm, evidenced by an area under the ROC curve (AUC) of 0.809. This had a sensitivity of 85%, a specificity of 69.4%, +ve predictive value 43.6% and -ve predictive value 94.3%.

Table (4): ROC curve analysis for differentiation of patient's pathology results into those with benign endometrial results and those with endometrial hyperplasia with atypia or carcinoma using measured endometrial volume

Variable	Volume
Cut off point	11.675
Area under the curve	0.826
Sensitivity	95%
Specificity	62.5%
Positive predictive value	41.3%
Negative predictive value	97.8%
Accuracy	69.6%
P value	< 0.001*

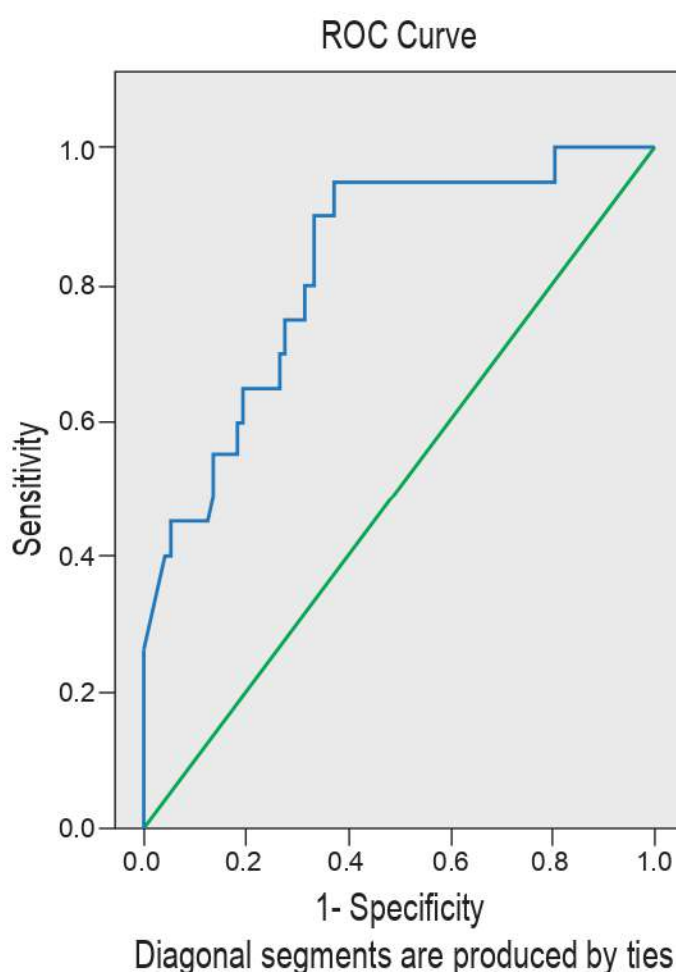
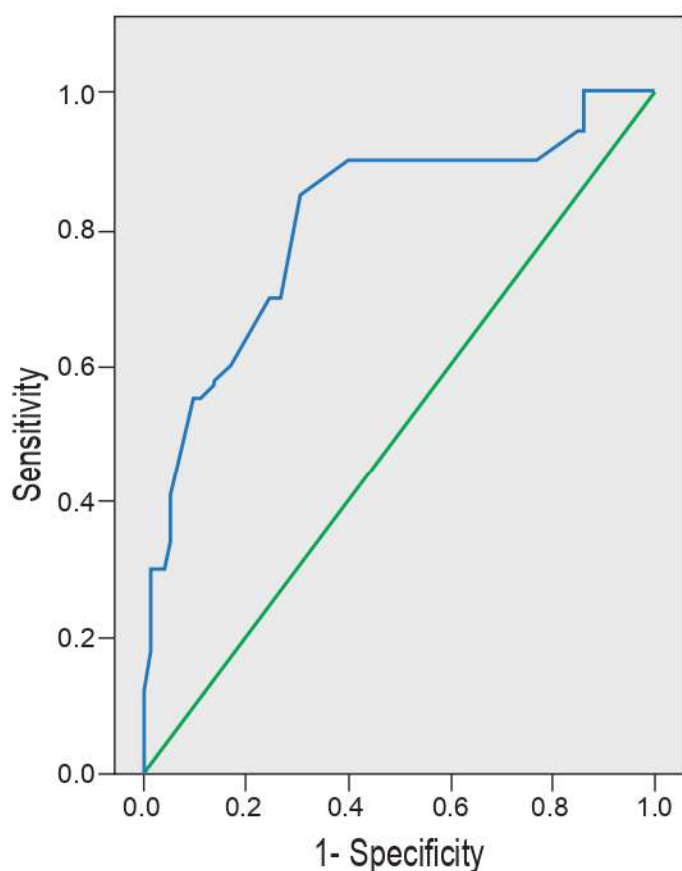


Table (5): ROC curve analysis for differentiation of patient's pathology results into those with benign endometrial pathology and those with endometrial hyperplasia with atypia or carcinoma using endometrial thickness.

	Thickness
Cut off point	10.5
Area under the curve	0.809
Sensitivity	85%
Specificity	69.4%
Positive predictive value	43.6%
Negative predictive value	94.3%
Accuracy	72.8%
P value	< 0.001*

ROC Curve



Diagonal segments are produced by ties

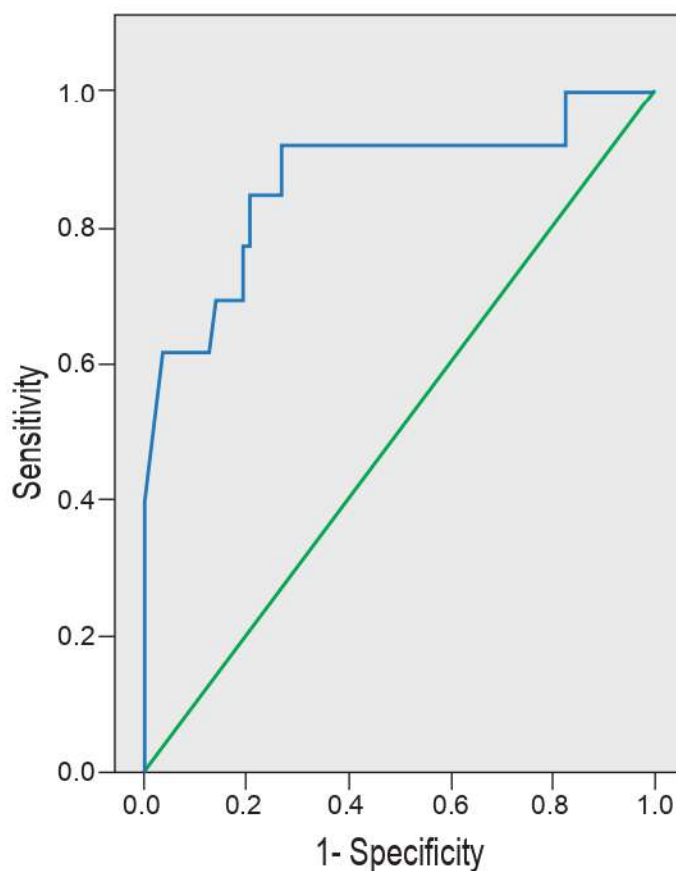
The results of the ROC curve analysis for differentiation of patient's pathology into benign endometrial pathology or hyperplasia and endometrial carcinoma using endometrial volume had shown also that endometrial volume had a good predictive value as proved by an area under the ROC curve (AUC) of 0.871. The best cut-off value was an endometrial volume >13.105 cm³. This had a sensitivity of 92.3% , a specificity of 73.4%, Positive predictive value 36.4% and negative predictive value 98.3%, using endometrial thickness cut-off value was an endometrial thickness >14.5mm,

proved by an area under the ROC curve (AUC) of 0.867 This had a sensitivity of 76.9%, a specificity of 89.9%, +ve predictive value 55.6% and -ve predictive value 96%.

Table (6): ROC curve analysis for differentiation of the patient's pathology into benign endometrial pathology or hyperplasia and endometrial carcinoma using endometrial volume at a cut off value of 13.105 cm³.

	Volume
Cut off point	13.105
Area under the curve	0.871
Sensitivity	92.3%
Specificity	73.4%
Positive predictive value	36.4%
Negative predictive value	98.3%
Accuracy	76.1%
P value	< 0.001*

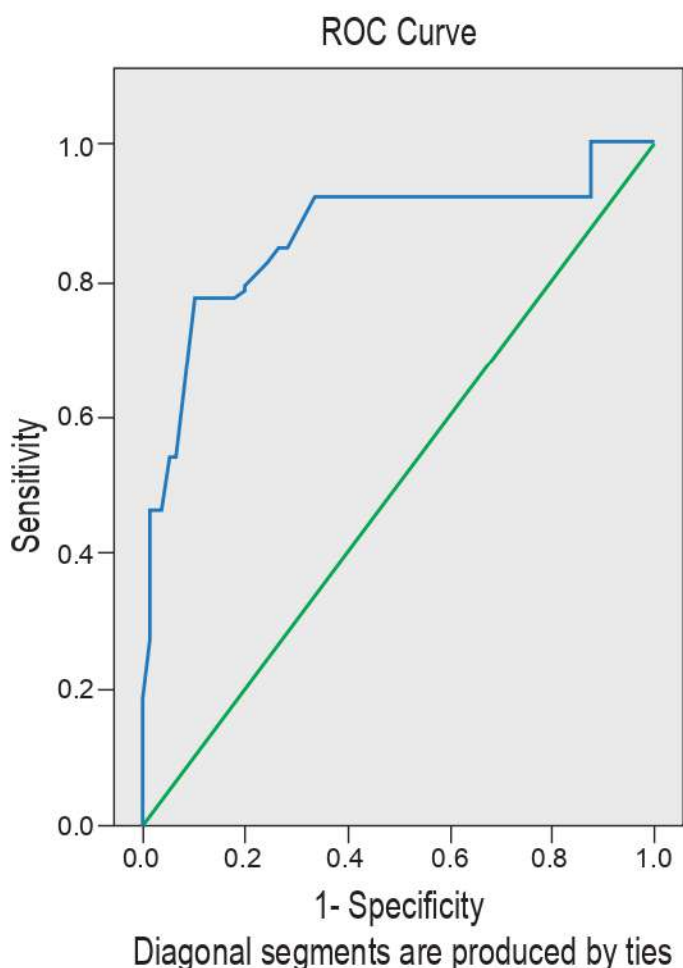
ROC Curve



Diagonal segments are produced by ties

Table (7): ROC curve analysis to differentiation of patient’s pathology into benign endometrial pathology or hyperplasia and endometrial carcinoma using endometrial thickness at a cut off value of 14.5mm

	Thickness
Cut off point	14.5
Area under the curve	0.867
Sensitivity	76.9%
Specificity	89.9%
Positive predictive value	55.6%
Negative predictive value	96%
Accuracy	88%
P value	< 0.001*



Discussion

Menstrual disorders affect the lifestyle in otherwise healthy women. Once bleeding occurs, investigation should be done to exclude benign and malignant causes (Munro M, 2014).In most studies about 43-66% of cases with hyperplasia were missed by D&C when comprising both women with perimenopausal and those with postmenopausal bleeding. (Karampl E et al., 2001).

Three-dimension ultrasound has been used to explore anatomical sections of the uterine cavity; the relations of myomas to the cavity, endometrial polyps can be diagnosed through it and endometrial volume measurement rather than thickness in women with AUB are feasible (Fleischer AC et al., 2003).

The current study aimed at assessment of the potential value of endometrial volume measurements by 2D transvaginal sonography compared with that of endometrial thickness in foretelling of different endometrial pathologies in women with perimenopausal uterine bleeding. The resultsshowed that there is higher predictive role of endometrial volume in prediction of different endometrial pathologies like hyperplasia or carcinoma that affect women with perimenopausal uterine bleeding and this comes consistent with findings from other studies(M. Odeh et al., 2007, Elsokkary M et al., 2016 and Wael .S. Nossair, 2017).

However, to the best of our knowledge, all studies concerned with assessment endometrial volume were done by 3D ultrasound machine. However,the financial burden and the limitation of the resources in many areas in the world made the idea of using 2D and getting accurate results looks glory and reasonable.

The histopathological results in the current study showed that 6.5% of specimen was atrophic endometritis, 25% was disordered proliferative endometrium, 40.2% was endometrial hyperplasia without atypia, 7.6% was with atypiaand 14.1% was endometrial carcinoma.This is different to another study that showed that myomas found in 32% of specimens, endometrial hyperplasia in 22% and endometrial carcinoma in only 4% of them(Pyari JW, et al., 2006).Low incidence of endometrial atrophy may be explained by the group

of enrolled patients that usually take hormonal replacement therapy in the perimenopausal period. There is similarity in the prevalence of endometrial carcinoma in the present study (14.1%) and that reported in another study (Khare A, 2012).

Regarding to endometrial volume there was a difference between cases with benign endometrial pathology, endometrial hyperplasia and endometrial carcinoma, the medians (IQR) were [9 (7.2 – 11.7), 12.2 (10.1 – 18.3) and 26 (16 – 52.5) cm³ respectively, using Kruskal-Wallis test. Similarly using the same test as regards endometrial thickness there was noticeable difference between them; the medians (IQR) were [9 (6 – 10), 10 (8 – 12) and 17 (13.5 – 30) mm respectively.

Results were consistent with other study done many years ago, (Kupesic S, et al., 1991), the mean value of the endometrial volume in hyperplasia was 7.82 ± 7.60 cc and was higher than the volume of patients with polyps (mean 2.63 ± 2.12 cc). Correspondingly; in a study done by M. Odeh et al. in 2007 the endometrial volume in patients with normal endometrium and pathologic endometrial were 6.87 ± 6.3 cc and 13.79 ± 13.2 cc respectively.

Endometrial volume in women with endometrial cancer was 18.1 cc and 11.2 cc in women with hyperplasia; both values were higher than in the normal. Their results showed difference than the current study results that may be explained by the heterogeneity in the group studied and the type of endometrial cancer present.

Discrimination of the results using ROC curve for endometrial volume and thickness into those with benign endometrium and those with endometrial hyperplasia with atypia or carcinoma; endometrial volume had a better predictive value than endometrial thickness as proved by an area under the ROC curve (AUC) of 0.826. The cut-off value was an endometrial volume >11.675 cm³. On the other hand, endometrial thickness cut-off value was 10.5 mm.

While (ROC) curve analysis for differentiation of patients using endometrial volume and endometrial thickness into women with benign endometrial pathology or hyperplasia and those with endometrial carcinoma; Endometrial volume also had a

higher predictive value than endometrial thickness as proved by an area under the ROC curve (AUC) of 0.871. The cut-off value was an endometrial volume >13.105 cm³. While using endometrial thickness cut-off value was an endometrial thickness > 14.5 mm.

In another study done to predict the carcinoma of the endometrium in women with postmenopausal bleeding by measuring the endometrial volume through vocal. Patients were classified into two groups of postmenopausal Women with and without bleeding the later was used for control. 50% of the patients had benign disease, 35% with atypia and 15% with cancer in the study group. Whereas in cases with atypia or cancer endometrial thickness was 9.61 ± 5.12 mm but endometrial volume was 3 ± 1.1 ml, in cases with benign endometrium they were 4.87 ± 3.43 mm and 1.52 ± 0.82 ml, respectively. While in the control group, endometrial volume was 1.15 ± 0.14 ml Endometrial volume with cutoff value of 1.35 ml was found to be with higher sensitivity than endometrial thickness in prediction of malignancy (Mansour GM et al., 2007).

Ebrashy et al., 2004; showed that 3D transvaginal sonography has higher accuracy than 2D transvaginal sonography in detection of endometrial pathology. While other studies assessing the value of ultrasound and hysteroscopy in diagnosis of intrauterine lesions showed there is higher sensitivity of combined 2D US and hysteroscopy than 2D US alone in diagnosis of perimenopausal bleeding. (Pasqualotto EB, et al., 2000, Bonnamy et al. 2002, Dery et al. in 2007).

Conclusion

Our study confirms that endometrial volume is a better diagnostic tool than endometrial thickness in foretelling carcinoma of the endometrium and hyperplasia in women with perimenopausal bleeding.

Recommendations:

- Endometrial volume is more sensitive than endometrial thickness for predicting malignancy in perimenopausal women
- The commonest pathology of the endometrium in women with perimenopausal bleeding is endometrial hyperplasia.
- Endometrial volume of 13.105 cm³ or greater may predict malignancy in women with perimenopausal bleeding. This has a sensitivity of 92.3% , a specificity of 73.4%, Positive predictive value 36.4% and negative predictive value 98.3%,
- Endometrial thickness cut-off value of benign rather malignant lesion in perimenopausal women is >14.5mm, This has a sensitivity of 76.9%, a specificity of 89.9%, +ve predictive value 55.6% and -ve predictive value 96%.

Limitation of the study

This study has some limitations. First, it may be, until the date submitting this work, the first observational study to assess the effect of 2D endometrial volume in foretelling of the endometrial pathology in the Mansoura university hospitals. Second, recruitment of a larger group of patients, multicentric studies may show different relations with different pathologies

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