Research Article

Accuracy of endometrial volume by 3 D ultrasound in prediction of endometrial carcinoma in patients with peri-menopausal bleeding

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Abstract
Introduction: The most commonly used technique for detecting endometrial disease in women with AUB is 2D and 3D transvaginal ultrasound. **The aim of the work**: is to measure endometrial thickness, volume, RI and PI in women with peri-\postmenopausal bleeding and correlate it with histopathological results to discriminate between benign and malignant endometrial lesions. **Patients and methods:** This study is a controlled clinical trial that was conducted in El-Minia University Maternity Hospital, Egypt. Cases were collected from the outpatient clinic and inpatient gynecological department and 132 pre-&postmenopausal women were included in this study. All cases presented by AUB. The study was conducted between August 2017 and August 2019.The study was approved by the hospital ethical committee. The aim of this work is to measure endometrial thickness, volume ,RI and PI in women with peri-\postmenopausal bleeding and correlate it with histopathological results to discriminate between benign and malignant endometrial lesions. **Results:** In our study by comparing the AUCs of ET is 0.859 ,EV is 0.875 , PI is 0.902 and RI is 0.930, the best variable to predict malignancy is RI followed by PI followed by EV and lastly ET. **Conclusion:** 3D ultrasonography and Doppler, especially RI, may be useful for discrimination between benign and malignant endometrium in women with AUB.
Keywords: endometrial disease, transvaginal, ultrasound

Introduction
AUB is a common gynecological complaint in outpatient clinic, but is often complex and difficult to be diagnosed.[1] AUB is diagnosed when there is a substantial change in frequency, duration, or amount of bleeding during or between periods[2].

There are many benign causes of PMB including: atrophic endometrium (50%), hyperplasia (13%) and polyps (10%). However, 10% probability of endometrial cancer in women with PMB.[3].

Endometrial cancer represents the sixth most common malignancy worldwide. The cumulative risk of endometrial cancer up to the age of 75 years estimated as 1.6% for high-resource regions and 0.7% for low-resource countries[4]. Elevated estrogen levels are known to be the most common cause of the increased risk of endometrial cancer for postmenopausal obese women.[5]

The most commonly used technique for detecting endometrial disease in women with abnormal vaginal bleeding is 2D transvaginal ultrasound[6]. Previous studies have reported a relationship between endometrial thickness and histoathologic diagnosis of endometrial cancer in peri-\postmenopausal women[7,8].

Although the sensitivity of 2D ultrasound in detecting endometrial cancer has been considered good, it is associated with low false-negative rate[9,10].

As the tumor growth depends upon angio-genesis process, the Doppler ultrasound has been used to enhance the ultrasound specificity for endometrial cancer[11]. The value of Doppler and color Doppler U/S is to discriminate benign from malignant endometrial disease is controversial[12].

EV measurements using a 3D ultrasound machine has been considered moderately

satisfactory[13]. However, another study by several of the same authors published 2 years later has good inter-observer reliability for endometrial volume[14]. Histological characteristics of endometrial biopsy remains the gold standard for the clinical diagnosis of endometrial pathology[15].

The aim of this work is to measure endometrial thickness, volume RI and PI in women with peri-\postmenopausal bleeding and correlate it with histopathological results to discriminate between benign and malignant endometrial lesions.

Patients & Methods

This study is a controlled clinical trial that was conducted in El-Minia University Hospital, Egypt. Cases were collected from the outpatient clinic and inpatient gynecological department and 132 pre- & postmenopausal women were included in this study. All cases presented by AUB. The study was conducted between August 2017 and August 2019.The study was approved by the hospital ethics committee. An informed consent was obtained from all participants

Inclusion criteria:

1. Age group above 40 years.
2. Abnormal uterine bleeding
3. Definitive endometrial histological diagnosis was obtained.

Exclusion criteria:

1. Evident general cause that can cause vaginal bleeding.
2. Presence of vaginal, vulval or cervical causes of bleeding.
3. Pregnancy.
4. Contraception use.
5. Any gross uterine or ovarian pathology.
6. Endometrial thickness less than 4 mm.

Each patient was subjected to:

(A) ***Complete history***:

With assessmentof: age, parity, menopausal status and medical disorders.

(B) ***Clinical examination***

1. BMI
2. Abdominal examination
3. Speculum examination : to rule out tumors of the cervix, vagina or vulva.

(C)***2 D-Transvaginal ultrasound examination***

Using Voluson S8,ultrasonography was performed to measure maximal endometrial thickness (double layer) and then 2-DPD gate was activated to assess (RI) and (PI) along ascending branch of the uterine artery.

(D)***3-Dimensional ultrasound examination***

3-Dimensional volumes were activated. With VOCAL program, endometrial area was evaluated manually in the coronal or C plane. The VOCAL program automatically calculates EV .

(E***)Endometrial sampling***

Within 1 week after ultrasound examination, all patients underwent endometrial sampling or hysterectomy. Definitive histological diagnosis was obtained in all cases

Statistical Analysis

Statistical analysis was done on a personal computer using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 13 (MedCalc© Software bvba, Ostend, Belgium).

Results

Patients in our study were divided in to two groups according to histopathological results; (A) Benign group: containing 108 patients (81.8%)., (B) Malignant group: containing 24 patients (18.2%).

			N=132
	Malignant		24(18.2%)
	Bengin		108(81.8%)
Histopathology	***Malignant***	***Endometrioid adencarc. G.I***	12(9.1%)
		Endometrioid adencarc. G.II	6(4.5%)
		Clear cell carcinoma	1(0.8%)
		Papillary sero. adenocarcinoma	1(0.8%)
		Squamous cell carcinoma	4(3%)
	Bengin	***Atrphic endometrium***	51(38.6%)
		Complex endometr. hyperplasia	6(4.5%)
		Simple endometr. hyperplasia	18(13.6%)
		Disordered proliferative endom.	18(13.6%)
		Endometritis	6(4.5%)
		Hyperplastic polyp	6(4.5%)
		Secretory endometrium	3(2.3%)

Table (2) :Shows comparison of the histopathological results(benign &malignant) with each variable

		All cases	**Histopathology**		**P value**
			Bengin	**Malignant**	
			N=108	**N=24**	
ET	***Range***	(4-20)	(4-14)	(7-20)	***<0.001****
	Mean ± SD	9±3.7	7.9±2.4	13.8±4.5	
	Median / IQR	8 / (7-10.8)	8 / (6-9)	14.1 / (9.5-18.3)	
EV	***Range***	(3.1-19.2)	(3.1-9.5)	(4.4-19.2)	***<0.001****
	Mean ± SD	7.6±3.7	6.2±1.4	13.5±4.7	
	Median / IQR	6.3 / (5.5-8.4)	6.1 / (5.3-7)	14.1 / (10.1-17.7)	
RI	***Range***	(0.3-1.6)	(0.3-1.2)	(0.5-1.6)	***<0.001****
	Mean ± SD	0.7±0.3	0.6±0.2	1.2±0.3	
	Median / IQR	0.6 / (0.4-0.8)	0.5 / (0.4-0.7)	1.2 / (0.9-1.5)	
PI	***Range***	(0.8-2.2)	(0.8-1.7)	(1-2.2)	***<0.001****
	Mean ± SD	1.2±0.4	1±0.2	1.7±0.4	

Table (3) : Receiver-operating characteristic (ROC) curve analysis for prediction of malignant lesions using different parameters measured.

	ET	**EV**	**RI**	**PI**
Cutoff point	> 10	> 8.5	> 0.89	> 1.3
AUC	0.859	0.875	0.930	0.902
95% CI	0.788-0.914	0.806-0.926	0.872-0.967	0.838-0.947
P value	***<0.001****	***<0.001****	***<0.001****	***<0.001****
Sensitivity	75	83.33	83.33	79.17
Specificity	86.11	93.52	93.52	92.59
PPV	54.5	74.1	74.1	70.4
NPV	93.9	96.2	96.2	95.2
Accuracy	84.1	91.67	91.67	90.15

Table (4):Comparison of the areas under the ROC curves (AUCs) associated with various predictors.

Comparison	ΔAUC	Standard error	95% CI	Z	P value
ET vs EV	0.0152	0.0374	-0.0581 to 0.0885	0.408	0.6836
ET vs RI	0.0704	0.0303	0.0109 to 0.130	2.321	0.0203*
ETvs PI	0.0426	0.0225	-0.00148 to 0.0867	1.894	0.0582
EV vs RI	0.0552	0.0371	-0.0176 to 0.128	1.486	0.1372
EVvs PI	0.0274	0.0458	-0.0625 to 0.117	0.598	0.5501
RI vs PI	0.0278	0.0281	-0.0273 to 0.0828	0.989	0.3226

Discussion

In our study as regarding the ET, the median endometrial thickness of whole study population was 8 mm with interquartile range (7-10.8), in benign group the median was 8 mm with interquartile range(6-9), while in malignant group it was much higher 14.1 mm with interquartile range (9.5-18.3), which denotes high statistical significance (P<0.001) (Table 2). When the endometrial thickness cut- off to predict malignancy was 10mm the AUC was 0.859, sensitivity 75% , specificity 86.11%, PPV 54.5% and NPV 93.9%. table (3). Our results come in agreement with the reults of Granberg et al.,[16] who concluded by measuring the endometrial thickness in 205 women complaining of postmenopausal bleeding that there were no cases of cancer with an ET< 9 mm.. In contrast our results aren't consistent with the study of Saha et al.,[17] who found that vaginal ultrasonographic evaluation of ET is not valuable to predict malignancy in females of AUB and the study of Tabor et al.,[18] who found that ET cut-off <4 mm alone to exclude malignancy isn't a reliable parameter as 4% of malignancy would still be missed, with false-positive rate as high as 50%.

As regards endometrial volume in our study, the median EV of the whole study population was 6.3 with IQR of (5.5 -8.4) while the median of benign group was 6.1 with IQR of (5.3-7) which is lower than that of malignant one which was 14.1 with IQR of (10.1-17.7) these results show high statistical significance (P<0.001) table (2)

In our study using EV cut-off >8.5 is reliable for predicting malignancy with AUC of 0.875, sensitivity of 83.33%, specificity 93.52%, PPV of 74.1%, NPV of 96.2% and (P <0.001) which denotes high statistical significance Table (3). The results of our study are in agreement with those of Gruboeck et al.,[19] We are also in agreement with the study of Odeh et al.,[20]

Comparing AUCs of ROC curve between endometrial thickness and endometrial volume Table (4) showed no significance (P=0.6836). Yet endometrial volume tended to be superior to endometrial thickness (Table 3). An opposite result was reported by Opolskiene et al.,[21]

As regarding median RI of benign group was 0.5, IQR (0.4 -0.7) and malignant group 1.2, IQR (0.9-1.5) denoting statistical difference (P<0.001) (table 2). By using RI cut -off >0.89 to predict malignancy had AUC 0.930, sensitivity 83.3%, specificity 93.52%, PPV of 74.1%, NPV of 96.2% and (P<0.001). table (2). The results are in disagreement with those of Kupesic & Kurjak[22].

As regarding mean PI of the benign group was 1.0, range (0.8 -1.7) and malignant group was 1.7, range (1-2.2) which denotes that there is statistical difference (P<0.001). table (2). By using PI cut -off >1.3 to predict malignancy had AUC 0.902 sensitivity 79.17%, specificity 92.59%, PPV 70.4%, NPV 95.2% and (P<0.001) table (3). These results are in agreement with those of Amit et al.,[23]. In disagreement with our results was with El-Sharkawy et al., 2016[24]

Our results showed that endometrial thickness, volume and Doppler velocimetry (RI, PI), may discriminate between endometrial cancer

and benign conditions as their values were higher in malignant endometrial lesions than those with benign endometrium. In our study by comparing the AUCs of ET is 0.859, EV is 0.875, PI is 0.902 and RI is 0.930 (Table), the best variable to predict malignancy is RI followed by PI followed by EV and EVT. (Table 4).

Conclusion

This study showed that the use of three-dimensional sonography and Doppler angiography can complement the conventional two dimensional ultrasound in assessing the endometrial lesions. This may be a possible new ultrasound marker in the diagnosis of endometrial malignancy, and it is worthy of further researches.

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