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Gray scale 2D Ultrasound in Relation to Coagulation Profile and Uterine Artery Doppler Indices in Women with Postmenopausal Bleeding

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ORIGINAL ARTICLE

Gray Scale Two-dimensional Ultrasound in Relation to Coagulation Profile and Uterine Artery Doppler Indices in Women with Postmenopausal Bleeding

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Abstract

Background: **Abnormal uterine bleeding (AUB) in postmenopausal women is a common complaint in general gynecological practice. Progression and prognosis of AUB primarily rely on invasive surgery and pathology so our research aimed to evaluate the use of non-invasive procedures such as uterine artery Doppler indices and coagulation profile in detecting some underlying causes of AUB.**

Aim and objectives: **To evaluate the coagulation profile (prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet count) in women with postmenopausal bleeding in relation to two-dimensional ultrasound endometrial thickness and uterine artery Doppler.**

Patients and methods: **This longitudinal observational study was performed at the departments of Obstetrics and Gynecology at AL-Zahraa University Hospital and El-Salam Specialized Hospital and it was carried out from January 2022 to September 2022 and included 80 women with postmenopausal AUB as a sample size using Transvaginal Ultrasound (Siemens Acuson NX2 Ultrasound machine).**

Conclusion: **Coagulation profile and Transvaginal ultrasound measurement of endometrial thickness are reliable methods of screening women with postmenopausal AUB. The measurement of endometrial thickness can serve as a noninvasive screening instrument for the evaluation of AUB. In malignant conditions, Color Doppler can detect neovascularization and decreased pulsatility index and resistive index in uterine vessels. D-dimer is a basic biomarker for detecting an abnormal coagulation profile in AUB cases.**

Keywords: Abnormal uterine bleeding, Coagulation profile, D-dimer, Postmenopausal bleeding, Uterine artery doppler

1. Introduction

General gynecologists often hear women complain about abnormal uterine bleeding (AUB). About 10 % of postmenopausal women get AUB in the first year after menopause. Postmenopausal AUB is associated with endometrial cancer in roughly 10 % of cases.[1]

One of the most common types of gynecologic cancer is endometrial cancer. Among American women, it ranks as the fourth most common cancer. Unopposed estrogen medication, early menarche, late menopause, tamoxifen therapy, nulliparity, infertility or failure to ovulate, and polycystic ovarian syndrome (PCOS) are all risk factors for prolonged exposure to estrogen without any counteracting hormones.[3]

Endometrial cancer risk is greatly increased by both advancing age and excess body fat. Both work by stimulating endometrial growth via estrogen in the absence of progesterone. The likelihood of mutations in both oncogene and tumor suppressor genes rises during proliferation. Without apoptosis to stop them, cells with these mutations can continue to replicate clonally and acquire further mutations that fuel carcinogenesis.[2]

About 10 % of postmenopausal women who experience AUB should be tested for endometrial carcinoma because this potentially lethal disease accounts for 90 % of all episodes of hemorrhage.[1]

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If the bleeding is severe, a complete blood count, prothrombin time, and partial thromboplastin time should be run to rule out other diseases in postmenopausal women. Most standards suggest either transvaginal ultrasound (TVUS) or endometrial biopsy as the first step in diagnosis.[3]

Potentially affecting coagulation variables are the preanalytical circumstances. Stress (both mental and physical), the time of day, hormone levels, and even one's posture when blood is drawn can all play a role. Several coagulation factors, including FVIII and fibrinogen, are seen in increased concentrations in healthy postmenopausal women, likely as a result of age and estrogen status.[4]

Serum fibrinogen and D-dimer concentrations shift in response to alterations in coagulation function. There is mounting evidence to imply a link between these factors and tumor stage and prognosis across a variety of cancer types. Carcinoma tumor growth and development are both significantly correlated with a hypercoagulable microenvironment.[5]

Hypercoagulability of the blood is caused by tumor cells' procoagulants, tissue factors, and inflammatory mediators even in the early stages of the disease. Therefore, cancers may raise serum fibrinogen and D-dimer levels. Several studies have shown that their levels are related to a patient's prognosis when they have cancer.[5]

Due to its availability, cost-effectiveness, and high sensitivity, transvaginal ultrasonography is typically the first diagnostic test of choice for endometrial cancer. Transvaginal ultrasonography is a reliable method for gauging endometrial thickness. Transvaginal ultrasonography is considered normal if the endometrial thickness is 4 mm or less, according to a new American College of Obstetricians and Gynecologists (ACOG) committee decision. Three patients with malignant endometrium had lower impedance in their uterine arteries, myometrium, and endometrium. Patients with malignant histology have significantly lower pulsatility and resistance indices (RI) than those without malignant histopathology. Uterine artery cutoff criteria were determined to be a pulsatility index (PI) of 1.450 and an RI of 0.71.[6]

AUB in postmenopausal women should be evaluated with dilatation and curettage. If the patient is not a good candidate for general anesthesia or refuses the procedure, an alternative may be transvaginal ultrasonography or saline-infusion sono-hysterography with guided endometrial biopsy. Surgical options for treatment range from hysterectomy to uterus-sparing procedures.[7]

The goal of this study was to correlate two-dimensional ultrasonography endometrial thickness and uterine artery Doppler velocity with coagulation profile (prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer, and platelet count) in women with postmenopausal AUB.

2. Patients and methods

This longitudinal observational research was conducted among January 2022 and September 2022 at the departments of Obstetrics and Gynecology at AL-Zahraa University hospital and El-Salam Specialized hospital, with a sample size of 80 women with postmenopausal AUB using TVUS Probe 7.5 MHz of Siemens Acuson NX2 Ultrasound machine.

The eighty women who completed the investigation were separated into two groups based on histopathological findings:

(1) Group 1 (71 women): 88.7 % pathology was benign.
(2) Group 2 (9 females): 11.3 % malignant pathology.

The benign group consisted of 40 women with endometrial hyperplasia, 16 women with polyps, five women with endometrial hyperplasia with atypia, and 10 women with endometrial atrophy.

Bengtsen *et al.* (2020)[8] estimated the sample size based on the prevalence of endometrial cancer among women with hospital-diagnosed postmenopausal AUB to be ~5 %. Therefore, we dealt with 73 women experiencing postmenopausal AUB. As a result, 80 postmenopausal women were recruited for the study.

Ethical approval: prior to participation in this investigation, approval from the ethical committee and written consent from all subjects were obtained.

Inclusion criteria: individuals aged 50–65 years, with abnormal postmenopausal vaginal hemorrhage, and with hypertension or diabetes.

Exclusion criteria: individuals that declined to participate in the study and those with chronic cardiac disease. Cases with any medical condition affecting coagulation profile, cases receiving anticoagulant or antithrombotic medication for any reason, and cases receiving hormonal therapy for any reason.

Every individual were subjected to the following: before participating in the study, each participant provided written informed consent, full history taking: examination (general examination and local examination), TVUS Examination using Probe 7.5 MHz (Siemens Acuson NX2 Ultrasound machine) with Uterine Artery Doppler indices,

Laboratory examination (complete blood count, PT, PTT, INR, and D-dimer), fractional curettage and histopathology examination, and, data management and analysis.

Analytical statistics: the normality of distribution parameters was determined using the one-sample Kolmogrovo-Smirnov test, followed by the Independent-Samples T Test, the one-way analysis of variance A test, the one-way analysis of variance Post Hoc Tests, the receiver operating characteristic Curve, the χ^2 test, and Fisher's exact χ^2 test for normal distribution.

P value: level of significance ($P > 0.05$: nonsignificant (NS), $P \leq 0.05$: Significant (S) and $P \leq 0.01$: Highly significant (HS)).

3. Results

Table 1.

The average age of group 2 was much older than that of group 1 (as seen in the table). However, there was no discernible variation in mean BMI among the groups. Group 1 (consisting of 53.5 % of the sample) favored Multiparty, whereas Group 2 (consisting of 66.7 % of the sample) favored Nulliparity, creating a striking dichotomy. The prevalence of diabetes mellitus (55.6 % in group 2) and hypertension (77.8 % in group 2) was statistically substantially higher in group 2 compared with group 1 Table 2.

According to this data, the average endometrial thickness (ET) for the cancer group was greater than that of the benign group. There was a statistically significant distinction there. The presence of endometrial polyps was more common among the benign group (25.4 %), compared with the malignant group (11.1 %) Table 3.

The average PI for the benign group was greater than that of the malignant group, as seen in the table. There was a statistically significant distinction ($P < 0.001$). The benign group had a mean RI that was greater than the malignant group. There was a difference with statistical significance ($P < 0.001$) Table 4.

There were no statistically significant differences among the groups in this table with respect to HB (P1: 0.369, P2: 0.160). When comparing platelets (PLT) among groups, no significant changes were found ($P = 0.218$, $P = 0.159$) Table 5.

In comparison to the pre-malignant and benign groups, the malignant group had a significantly greater mean PTT (see table). Neither of those dissimilarities reached statistical significance ($P = 0.162$, $P = 0.082$). The malignant group had the greatest mean PT. There was statistical evidence for those distinctions. Malignant versus benign and premalignant showed statistically significant differences (P1: 0.042, P2: 0.011). Nonetheless, 'pre malignant versus benign' showed no statistically noteworthy differences. The malignant group had the highest mean INR. Malignant versus benign and premalignant conditions showed statistically significant differences (P1: 0.043, P2: 0.012).

Table 1. Demographic data of the studied patients.

	Group 1 (Benign: 71)		Group 2 (Malignant: 9)		*P* Value	Significance
Age	*Min.*	Max.	Min.	Max.	<0.001	HS
Range	*48.0*	74.0	61.0	78.0		
Mean	*57.1 + 5.3*		68.2 + 5.9			
BMI					0.371	NS
Range	*23.5*	*48.8*	30.2	38.9		
Mean	*34.o +5*		35.6 + 3.5			
Parity					<0.001	HS
0	4(5.6 %)		6(66.7 %)			
<4	29(40.8 %)		3(33.3 %)			
≥4	38(53.5 %)		0			
Work					0.676	NS
NO	55(77.5 %)		8(88.9 %)			
Yes	16(22.5 %)		1(11.1 %)			
Marriage					<0.001	HS
Not married	2(2.8 %)		6(66.7 %)			
Married	51(71.8 %)		3(33.3 %)			
Divorced	5(7.0 %)		0			
Widow	13(18.3 %)		0			
DM					0.031	S
Present	14(19.7 %)		5(55.6 %)			
Absent	57(80.3 %)		4(44.4 %)			
HTN					0.026	S
Present	25(35.2 %)		7(77.8 %)			
Absent	46(64.8 %)		2(22.2 %)			

Table 2. Sonographic assessment of endometrial cavity of the studied groups.

	Group 1 (Benign: 71)		Group 2 (Malignant: 9)		*P* Value	Significance
Endometrial thickness						
Range	Min.	Max.	Min.	Max.	<0.001	HS
	3.o	18.4	14.7	21.2		
Mean + SD	10.1 + 3.4		17.3 + 2.o			
Polyp						
Present	18 (25.4 %)		1 (11.1 %)		<0.001	HS
Absent	53 (74.6 %)		8 (88.9 %)			

Table 3. Doppler assessment of uterine arteries among the studied patients.

	Group 1 (Benign: 71)		Group 2 (Malignant: 9)	*P* Value	Sig.
	Benign $N = 66$	Premalignant $N = 5$			
PI Mean + SD	1.85 + 0.52		0.92 + 0.28	<0.001	HS
	1.90 + 0.50	1.17 + 0.39			
RI Mean + SD	0.75 + 0.13		0.51 + 0.03	<0.001	HS
	0.75 + 0.13	0.69 + 0.10			

Table 4. Comparison of studied patients regarding Hemoglobin Concentration and Platelet count.

	Group 1 (Benign: 71)		Group 2 (Malignant: 9)	*P* Value	Significance
	Benign $N = 66$	Premalignant $N = 5$			
HB Mean + SD	1.85 + 0.52		11.3 + 0.7	0.369*	NS
	12 + 1.6	12.1 + 0.9		0.160**	
PLT Mean + SD	318.3 + 69.3		283.2 + 72.2	0.218*	NS
	320.6 + 70.9	287 + 34.9		0.159**	

PLT, platelets.

Table 5. Coagulation Profile of the studied cases.

	Group 1 (Benign: 71)		Premalignant $N = 5$	*P* Value	Significance
	Benign $N = 66$	Group 2 (Malignant: 9)			
PT Mean +SD	11.6 + 1.1		12.9 + 2.9	0.042*	S
	11.6 + 1.1	11.7 + 1.8		0.011**	
PTT Mean +SD	33.4 + 4.1		35.9 + 2.4	0.162*	NS
	33.5 + 4.1	32.0 + 4.2		0.082**	
INR Mean +SD	1.05 + 0.12		1.16 + 0.27	0.043*	S
	1.05 + 0.09	1.05 + 0.14		0.012**	
D-dimer Mean +SD	0.24 + 0.08		0.51 + 0.09	<0.001	HS
	23 + 0.09	0.34 + 0.1			

INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Nonetheless, 'pre malignant versus Benign' showed no statistically important differences.

D-dimer means were highest in the cancerous group, then the premalignant, and finally the benign. The statistical significance of the differences was substantial. Malignant versus benign and pre-malignant conditions showed statistically significant differences. Furthermore, there were distinguishable variations between the 'pre malignant vs. benign' categories. The noncancerous group had a lower mean D-dimer level than the cancerous group. The statistical significance of that difference was high. *P* less than 0.001, Figs. 1–3.

According to this table D-dimer has the highest specificity while PI and RI with the highest sensitivity.

Although in our study platelet count PTT were statically insignificant in some cases it was highly abnormal which prompted us to take a closer look at these cases.

3.1. Case study (1)

A 68 years old G3P3 NVD, menopausal for 20 years. She had abnormal vaginal bleeding for 8 months not responding for hormonal treatment.

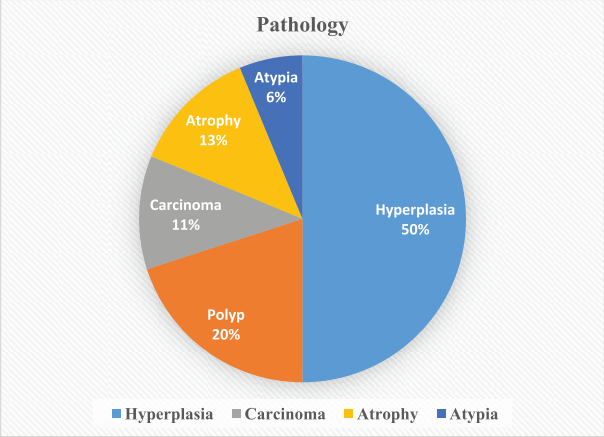

Fig. 1. Pie chart describing different endometrial pathologies.

BMI: 32.5, PLT: 80.000, PT: 14.8, activated partial thromboplastin time (APTT): 38, INR: 1.37, D-dimer: 0.88 ET: 16.2 mm, Doppler finding (PI: 1.6, RI: 0.48) D and C was performed.

Histopathology: high grade endometrial adenocarcinoma on top of complex endometrial hyperplasia with atypia Fig. 4.

Results of the investigations in this case were correlating with the findings of our study except for platelet count and APTT. It was noted that ET and D-dimer were exceeding the cut-off values of the current study.

3.2. Case study (2)

A 58 years old Nullipara she had vaginal bleeding for the last 2 years, hypertensive on bisoprolol for the last 10 years. Her BMI: 35.35, Hb: 7.5, PLT: 72, PT: 15, APTT: 41, INR: 1.94, D-dimer: 0.41 ET: 20.1 mm, Doppler findings (PI: 0.93, RI: 0.58) D and C was performed.

Histopathology: Disordered Proliferative Endometrium Fig. 5.

4. Discussion

Endometrial carcinoma was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide in 2012, with an estimated 3 21 000 new cases and 76 000 deaths.[9]

Hyperplasia (40 women), polyps (16 women), atrophy (11 women), and atypia (5 women) were the most common endometrial histologist among the 71 women with benign illnesses, whereas 9 were diagnosed with endometrial cancer.

Researchers gathered data from people aged 48 to 78 (mean +SD = 67 + 5.9). Participants who reported postmenopausal AUB ranged in age from 45 to 75 (mean = 53 + 6.7 years), which is consistentwith the results of a study by Nidhi Elizabeth *et al.*[10]

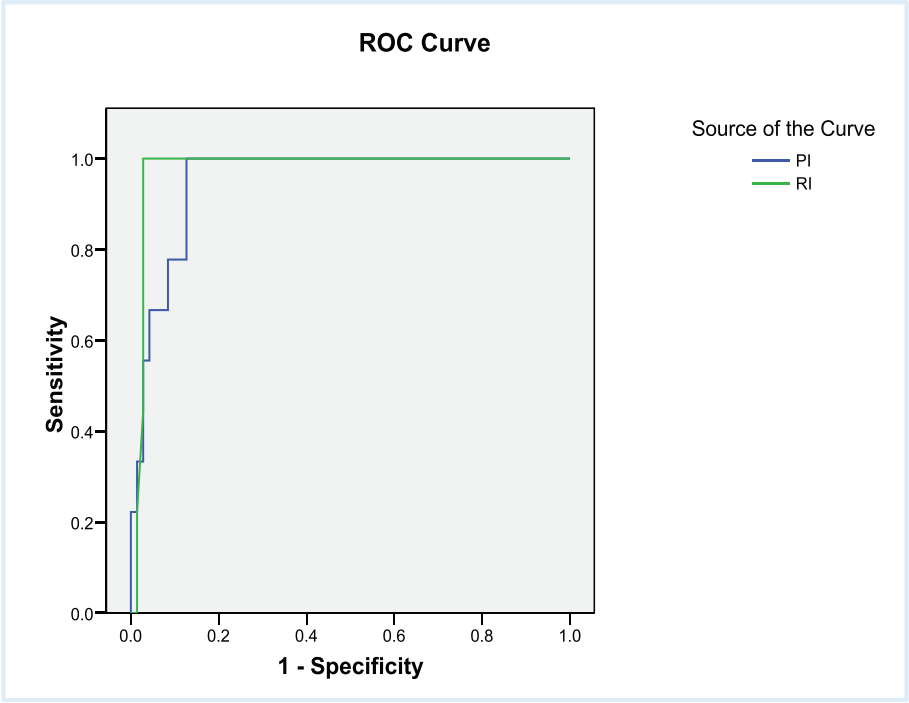

Fig. 2. Receiver operating characteristic curve shows comparison among benign and malignant regards pulsatility index and resistance index.

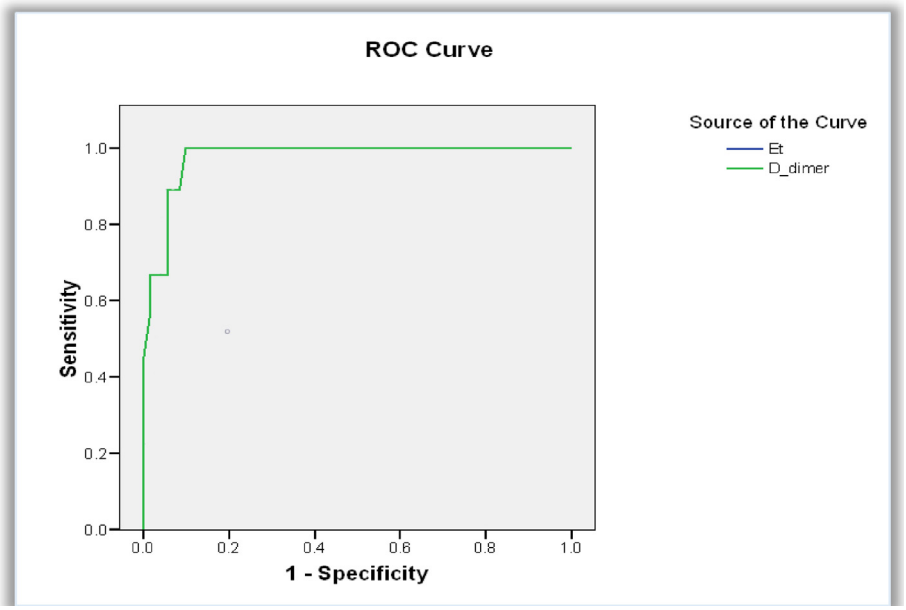

Fig. 3. Receiver operating characteristic curve showing comparison between benign and malignant regards D-dimer.

In the research conducted by Mulic-Lutvica *et al.* 60 women reported symptoms of postmenopausal AUB, and their average age was 60 + 4.8 years (mean +standard deviation). Estrogen has been related to type 1 endometrial cancers, which make up over 80 % of all endometrial malignancies.[10,11] An increasing number of postmenopausal women are using exogenous estrogens, and changes in endogenous estrogen exposure (nulliparity, fewer births, earlier age at menarche, and obesity) may explain much of the observed increase in endometrial cancer.[12]

The prevalence of DM was higher in the malignant group (55.6 % vs. 19.7 %) among postmenopausal women. The evidence indicated that the differences were significant.

Peripheral estrogen production in diabetic women's adipose tissue was shown to be 72 % higher than that in women without diabetes, according to other research.[13]

Hypertension was more common among the malignant (73.8 %) than the benign (35.2 %) group. This difference was significantly different from zero ($P = 0.026$)

There is inconsistent evidence linking hypertension to an increased risk of endometrial cancer. The association between hypertension and endometrial cancer was slight but significant.[14]

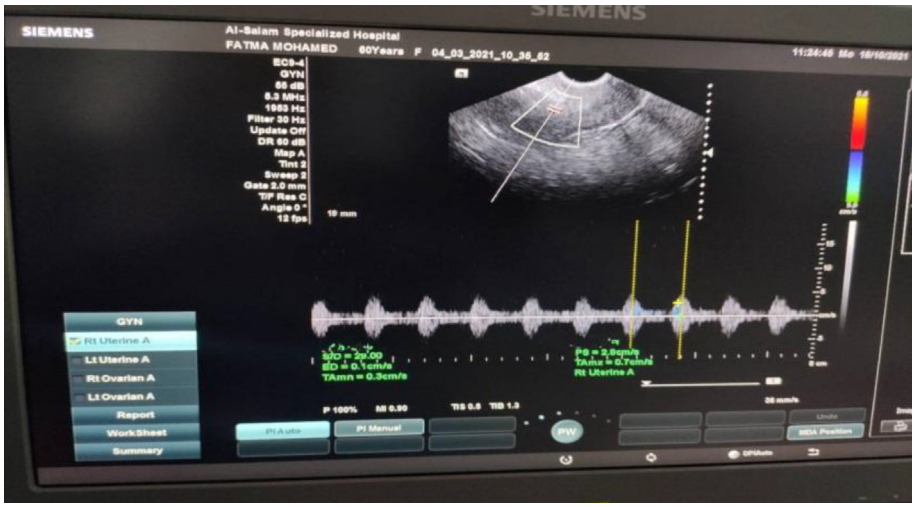

Fig. 4. Doppler US of Case study 1.

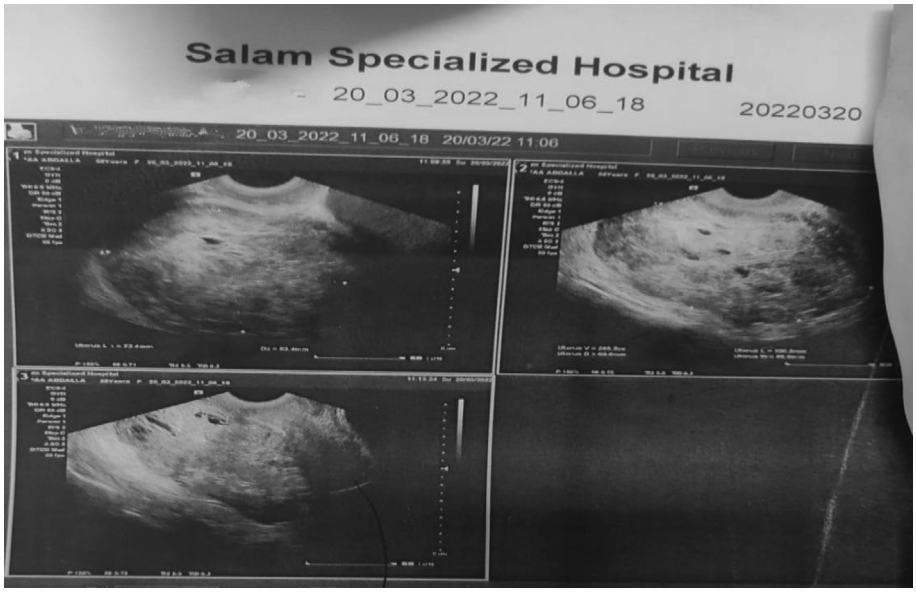

Fig. 5. Ultrasonography of case study 2.

Important risk factors for both hypertension and endometrial cancer, such as obesity and diabetes, may complicate the relationship between the two diseases.[14]

In our study, we used a receiver operating characteristic curve to assess the accuracy of ET by TVUS in making a diagnosis of endometrial disorders in AUB in postmenopausal women. The average thickness of benign pathology was 10.1 mm, while the average thickness of endometrial cancer was 17.3 mm. Based on this measurement, a threshold of 14.7 mm was established.

The best combination of sensitivity and specificity is at an ET of 14.7 mm. The sensitivity and specificity of ET were 88 % and 92 %, respectively ($P < 0.001$).

The findings of our study are congruent with those of Nidhi Elizabeth *et al.* who found that the median size of endometrial cancers was 21 mm. A total of 7 Cancer cases also had a median ET of 16.4 mm, while benign cases had a median ET of 4.1 mm.[15]

Malek *et al.*'s investigation of 150 women yielded comparable findings; like ours, 76 % of the women in their study had benign endometrial lesions and 24 % had endometrial cancer. Endometrial cancer sufferers were significantly older (62.2 + 4.9 vs. 60.7 = 4.3 years; $P = 0.005$) and had thicker endometrium (15.8 + 7.7 vs. 9.9 + 5.9 mm; $P < 0.001$) than those with benign endometrial lesions.[16]

We analyzed the differences among benign and malignant endometrial lesions in terms of their coagulation characteristics. In the current study, laboratory analysis indicated that D-dimer was substantially higher in cancer lesions than in benign ones (mean +SD, 0.24 + 0.09, higher value, 0.51 + 0.09). Hemoglobin, platelet, and PTT counts were not statistically significant (P values of 0.369, 0.218, and 0.162, respectively)

Cancer and benign lesions show a somewhat different distribution of PT values (mean +SD of PT in cancer 12.9 + 2.9, premalignant 11.7 + 1.8, and benign lesions 11.6 + 1.1), as shown in (Table 6). The correlation between PT and INR is marginally significant. The median INR for cancerous lesions was 1.16 + 0.27, while the median INR for benign lesions was 1.05 + 0.09.

The average preoperative D-dimer level for 176 cases with endometrial cancer was 0.42 mg/l, with a specificity of 63.7 % and a sensitivity of 63.4 %, as reported by Huang and Li.[17]

Choudhary *et al.* identified notable differences between the coagulation parameters of the two groups. Malignant cases have abnormal coagulation parameters compared with a control group. Platelet counts ranged from 250 ± 61 in the control group to 375 ± 100 in the case group. In comparison to the case group's average PT of 15.2 ± 1.2 s, the control group's PT was 14.1 ± 6 s.[18]

In the present research, we analyzed the accuracy of endometrial thickness, Doppler indices, and D-

Table 6. Diagnostic Accuracy of the tested parameters.

Variable	Mean ± SD		Cut off	Sensitivity	Specificity
	Benign	Malignant			
ET	10.1 ± 3.4	17.3 ± 2.0	14.7	88 %	92 %
PI	1.85 ± 0.52	0.92 ± 0.28	1.26	100 %	87 %
RI	0.75 ± 0.13	0.51 ± 0.03	0.56	100 %	91.2 %
D-dimer	0.24 ± 0.08	0.51 ± 0.09	0.45	67 %	94 %

ET, endometrial thickness.

dimer as diagnostic tools. ET cutoff readings had a sensitivity of 88 % and a specificity of 92 %. ET is a reliable predictor of EC, as was found by Nguyen *et al.* Using an ET larger than 12.5 mm as the threshold value resulted in a sensitivity of 93.8 and a specificity of 78 % for AUB postmenopausal.[19]

The sensitivity and specificity of a cutoff of 1.26 for PI are both 100 %, while those of 0.56 are both 91.2 %. Nguyen *et al.* found that the PI was significantly lower in the malignant group than in the benign group. Sensitivity and specificity for the uterine artery were 91.3 % and 83.3 %, respectively, at threshold values of RI less than or equal to 0.73 and PI less than or equal to 1.42.[19]

Using a cutoff value of 0.45, the sensitivity and specificity for D-dimer were 67 % and 94 %, respectively. In agreement with Huang and Li determined that a cutoff value of 0.42 mg/l for D-dimer levels would yield a specificity of 63.7 % and a sensitivity of 63.4 %.[17]

Platelet count may be useful in forecasting the phases or prognosis of cases with known malignant and benign illnesses, as observed in case 1, despite our statistical analysis suggesting that it was not useful in separating benign from premalignant to malignant instances.

4.1. Conclusion

Effective screening tools for women experiencing AUB after menopause include the coagulation profile and TVUS evaluation of endometrial thickness. We can use endometrial thickness measurement as a noninvasive screening method for assessing AUB. Neovascularization, as well as a reduced pulsatility index and resistive index in the uterine vasculature, are detectable with color Doppler in malignant situations. D-dimer is a straightforward biomarker for identifying a coagulation profile deviation in AUB cases.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

The authors declared that there were NO conflicts of Interest.

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