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The Prognostic Value of BMI, Serum Glucose, Endometrial Echo Pattern and Uterine Artery Doppler Velocimetry as a Predictor for Endometrial Pathology in Women with Postmenopausal Bleeding (Prospective Observational Study)

Yehia A. Wafa, Ahmed T. Abd Alfattah, Mohammed Sayed Korany

Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
Email: egy_77@yahoo.com

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Abstract

Background: Post-menopausal bleeding is a warning sign that accounts for about 5% of all outpatient gynaecologic visits and is a common indication for referral to rapid access clinics because of the fear of underlying malignancy. Endometrial malignancies differ from other malignancies in that early symptomization is common, allowing early cure. **Patients and Methods:** During the study period, 100 women with post-menopausal bleeding having inclusion criteria were evaluated in Al-Hussein University Hospital. For each patient full history, general, abdominal and pelvic examination was performed. Routine pre-operative investigations were done. Patients were divided into four groups: Group 1 included 29 patients with endometrial polyp. Group 2 included 34 patients with endometrial hyperplasia. Group 3 included 21 patients with atrophic endometrium. Group 4 included 16 patients with endometrial carcinoma. **Results:** As regards the predictive value of BMI, in the study there was a high statistical significance in comparison between the endometrial carcinoma group and all other benign groups. When discussing the predictive value of blood glucose level, in the study there was a high statistical significance in comparison between the endometrial carcinoma group and all other benign groups. It is worth to mention that the predictive value of endometrial thickness, in the study, was with high statistical significance in comparison between the endometrial carcinoma group and all other benign groups providing the highest specificity and sensitivity. At the last the predic-

tive value of uterine artery velocimetry, in the study, was with high statistical significance in comparison between the endometrial carcinoma group and all other benign groups. **Conclusion:** BMI, blood glucose level, endometrial thickness and uterine artery velocimetry indices, improve the prediction of endometrial carcinoma in women with post-menopausal bleeding.

Keywords

BMI, Serum Glucose, Endometrial Echo Pattern, Uterine Artery Doppler Velocimetry, Endometrial Pathology, Postmenopausal Bleeding

1. Introduction

Postmenopausal bleeding (PMB) is defined as bleeding recurring in menopausal women at least 1 year after cessation of cycles [1].

Although PMB may be associated with a number of different conditions, it must always be investigated because many causes are premalignant and malignant. The most common premalignant and malignant causes are complex hyperplasia with atypia and carcinoma of the endometrium. These disorders are present in as many as 1/3 of the patients evaluated for PMB in many series [2].

A large variety of lesions are noted, and the most common single cause is proved to be atrophic vaginitis. It is wisely counselled even though an apparent benign cause of bleeding is found.

Women with PMB deserve a thorough evaluation to rule out malignancy that may also be present [3].

Endometrial cancer usually affects postmenopausal women, and is rare before the age of 40. Only less than 20% of endometrial cancers occur before menopause [4].

The risk of endometrial cancer increases with obesity, diabetes, hypertension, nulliparity, hormone replacement therapy and tamoxifen therapy. Increasing age and a family history of hereditary non-polyposis colorectal cancer syndrome are also risk factors for endometrial cancer [5].

Endometrial cancer was among the first cancers identified as being obesity-related [6].

Although the risk of endometrial cancer is slightly increased with type 2 diabetes mellitus this increase is consistent and significant [7].

Transvaginal ultrasound is considered as the initial investigation to diagnose the cause of postmenopausal bleeding [8].

TVUS using a 3-mm cut off has high sensitivity for detecting endometrial cancer and can identify women with PMB who are highly unlikely to have endometrial cancer, thereby avoiding more invasive endometrial biopsy [9].

With the advent of hysteroscopy in the last two decades, focus has shifted from endometrial biopsy to hysteroscopic-guided biopsy as a gold standard diagnostic tool in the evaluation of postmenopausal bleeding [10].

2. Aim of the Work

This study aims to assess the prognostic value of BMI, serum glucose, endometrial echo pattern and uterine artery Doppler velocimetry as a predictor for endometrial pathology in women with postmenopausal bleeding.

3. Patients and Methods

After the study protocol and the whole related documents have been presented for the research ethical committee, Faculty of Medicine, Al-Azhar University. The details of the procedure, aim of the work, benefit and risk of trial have been explained to all patients, this prospective observational study was conducted. During the study period, 100 women with post-menopausal bleeding after fulfilling inclusion criteria at Al-Hussein University Hospital.

Group 1 included 29 patients with endometrial polyp. Group 2 included 34 patients with endometrial hyperplasia. Group 3 included 21 patients with atrophic endometrium. Group 4 included 16 patients with endometrial carcinoma.

The study included menopausal women with natural menopause defined as absence of menstruation for 1 year in women older than 40 years provided that the amenorrhea was not explained by medication or disease or pregnancy. Patients complaining of postmenopausal bleeding and patients with endometrial thickness more than 4 mm by transvaginal sonography were included.

While patients with bleeding tendency, patients with liver cell failure, patients with congenital anomalies in the uterus, Patients taking anticoagulant drugs as warfarin or heparin, Patients using tamoxifen citrate and patients using any kind of hormonal replacement therapy were excluded from the study.

3.1. Patient Consent

All participants signed informed consent (written consent) after explaining benefits and risks of the trial and have the right to leave the study at any time.

All patients are subjected to the following: A-Detailed history: including the following points. Present history of bleeding including onset, course, duration, and criteria of bleeding pattern. History of recent hormonal contraception and particular drug intake. History of bleeding tendency or general cause of bleeding. Past history of operations or blood transfusion. Family history of similar condition. Last menstrual history and amount of bleeding. B-Examination: General examination; Weight, height, general appearance and Body mass index calculation. Body mass index is a measure of body fat based on height and weight that applies to adults, Abbreviated by BMI. BMI is a person's weight in kilograms (kg) divided by his or her height in meters squared.

The following table which is approved by the WHO was applied:

Meaning	BMI
Normal weight	19 - 24.9
Overweight	25 - 29.9

Continued

Obesity level I	30 - 34.9
Obesity level II	35 - 39.9
Obesity level III	≥40

Vital signs (blood pressure and pulse), pallor and manifestations of anaemia. Abdominal examination and **Local examination:** Inspection of external genitalia. Bimanual examination to detect uterine size, mobility, tenderness and adnexal masses. Speculum examinations for cervical masses, erosions, hypertrophy, ulcers or vaginal lesions. **C-Laboratory investigations:** Complete blood count. Coagulation profile. Random blood sugar. Liver and kidney functions. **D-Ultrasound examination:** With an empty bladder, the patient examined in the lithotomy position, Transvaginal ultrasound has been done to study uterine size, endometrial thickness, uterine artery Doppler velocimetry and to exclude any uterine or ovarian pathology. **E-Histopathological examination** ***Patients will be subjected to one of the following*****:** Dilatation and curettage—Hysteroscopy with endometrial biopsy.

3.2. Statistical Analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: A one-way analysis of variance (ANOVA) when comparing between more than two means. Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: Probability (P-value) P-value < 0.05 was considered significant. P-value < 0.001 was considered as highly significant. P-value > 0.05 was considered insignificant.

4. Results

Table 1 shows that women age in years in the study group ranged from 49 - 80 with mean 59.78 ± 6.36. Table 2 shows that women BMI (kg/m^2) in the study group ranged from 20.8 - 48.8 with mean 29.84 ± 6.63. Table 3 shows that the mean blood glucose level is 136.15 ± 65.79 and mean of HbA1c is 8.13 ± 1.35 in the study group population. Table 4 shows that the endometrial thickness of the study group population ranged from 5 - 25 mm with mean 11.58 ± 5.23. Table 5 shows that the uterine artery peak systolic velocity in the study group population ranged from 2.5 - 26.5 (cm/sec) with mean 11.17 ± 4.65. Table 6 shows the histological types of the biopsies taken from the uterus of the study group population, the number and percentage of each type. Endometrial polyp 29 (29%), Endometrial hyperplasia without atypia 24 (24%), Atrophic endometrium 21

Table 1. Age (years) distribution of the study group.

Age (years)	Total (n = 100)
Range	49 - 80
Mean ± *SD*	59.78 ± 6.36
Median (*IQR*)	60 (9)

Table 2. BMI distribution of the study group.

BMI (kg/M2)	Total (n = 100)
Normal 18.5 - 25	22 (22%)
Overweight 25 - 30	43 (43%)
Obese >30	35 (35%)
Range [*Mean* ± *SD*]	20.8 - 48.8 [29.84 ± 6.63]

Table 3. Blood glucose level and HbA1c descriptive of the patients group.

	Total (n = 100)
Blood glucose level	
Range	70 - 377
Mean ± *SD*	136.15 ± 65.79
HbA1c	
Range	5.7 - 10.9
Mean ± *SD*	8.13 ± 1.35

Table 4. Endometrial thickness descriptive of the patients group.

Endometrial thickness (mm)	Total (n = 100)
Range	5-25
Mean ± *SD*	11.58 ± 5.23

Table 5. Uterine artery peak systolic velocity descriptive of the patients group.

Uterine artery peak systolic velocity (cm/S)	Total (n = 100)
Rt uterine artery peak systolic velocity (cm/s)	
Range	3 - 27
Mean ± *SD*	11.13 ± 4.67
Lt Uterine artery peak systolic velocity (cm/S)	
Range	2 - 26
Mean ± *SD*	11.22 ± 4.69
Uterine artery peak systolic velocity (cm/S)	
Range	2.5 - 26.5
Mean ± *SD*	11.17 ± 4.65

(21%), Endometrial carcinoma 16 (16%) and Endometrial hyperplasia with atypia 10 (10%) of histopathology. Table 7 shows that there is no statistically significant difference between histopathology and age (years) of the study group. However Table 8 that compares between histopathology and BMI of the study group population shows statistically significant difference between histopathology of benign lesions and malignant lesions with increasing BMI in the study group. Also Table 9 shows statistically significant difference between histopathology of benign lesions and malignant lesions with increasing blood glucose level and HbA1c in the study group. Table 10 shows statistically significant difference between histopathology of benign lesions and malignant lesions with increasing endometrial thickness in the study group. As most of the later indices Table 11 shows statistically significant difference between histopathology of benign lesions and malignant lesions with increasing uterine artery peak systolic velocity (cm/S) in the study group. Table 12 shows the different parameter indices for endometrial carcinoma.

Figure 1 shows Receiver operator characteristics (ROC) curves constructed for parameters indices of endometrial carcinoma [Endometrial thickness (mm), Rt uterine artery peak systolic velocity (cm/s), Lt Uterine artery peak systolic velocity (cm/S) and Uterine artery peak systolic velocity (cm/S)] as predictors of endometrial carcinoma in included women. All items indices were significant

Table 6. Histopathology distribution of the patients group.

Histopathology	Total (n = 100)
Endometrial polyp	29 (29%)
Endometrial hyperplasia without atypia	24 (24%)
Atrophic endometrium	21 (21%)
Endometrial carcinoma	16 (16%)
Endometrial hyperplasia with atypia	10 (10%)

Table 7. Comparison between histopathology and age (years) of the study group.

Age (years)	Atrophic endometrium (*n* = 21)	Endometrial polyp (*n* = 29)	Endometrial hyperplasia (*n* = 34)	Endometrial carcinoma (*n* = 16)	ANOVA	p-value
Mean ± SD	60.24 ± 5.09	58.48 ± 6.66	58.79 ± 6.08	63.63 ± 6.82	1.808	0.144
Range	51 - 70	49 - 73	49 - 69	50 - 80		

Table 8. Comparison between histopathology and BMI of the study group.

BMI (kg/M2)	Atrophic endometrium (*n* = 21)	Endometrial polyp (*n* = 29)	Endometrial hyperplasia (*n* = 34)	Endometrial carcinoma (*n* = 16)	ANOVA	p-value
Mean ± SD	27.85 ± 3.59	26.32 ± 3.95	30.20 ± 5.44ab	38.07 ± 8.76abc	17.346	<0.001**
Range	22.5 - 34.2	20.8 - 39	20.8 - 40.6	22.2 - 48.8		

Table 9. Comparison between histopathology and blood glucose level and HbA1c of the study group.

	Atrophic endometrium (n = 21)	Endometrial polyp (n = 29)	Endometrial hyperplasia (n = 34)	Endometrial carcinoma (n = 16)	ANOVA	p-value
Blood glucose level						
Mean ± SD	103.71 ± 25.43	110.28 ± 27.49	140.85 ± 66.11ab	215.63 ± 84.42abc	16.078	<0.001**
Range	77 - 189	70 - 189	78 - 290	95 - 377		
HbA1c						
Mean ± SD	7.30 ± 0	6.43 ± 0.53a	7.73 ± 0.76b	9.04 ± 1.31abc	8.066	<0.001**
Range	7.3 - 7.3	5.7 - 6.9	6.7 - 9.1	7.1 - 10.9		

Table 10. Comparison between histopathology and endometrial thickness (mm) of the study group.

Endometrial thickness (mm)	Atrophic endometrium (n = 21)	Endometrial polyp (n = 29)	Endometrial hyperplasia (n = 34)	Endometrial carcinoma (n = 16)	ANOVA	p-value
Mean ± SD	5.43 ± 0.68	10.31 ± 2.94a	12.94 ± 3.82ab	19.06 ± 3.43abc	63.292	<0.001**
Range	5 - 7	6 - 17	8 - 21	12 - 25		

Table 11. Comparison between histopathology and uterine artery peak systolic velocity (cm/S) of the study group.

Uterine artery peak systolic velocity (cm/S)	Atrophic endometrium (n = 21)	Endometrial polyp (n = 29)	Endometrial hyperplasia (n = 34)	Endometrial carcinoma (n = 16)	ANOVA	p-value
Rt uterine artery peak systolic velocity (cm/s)						
Mean ± SD	8.48 ± 2.54	10.86 ± 5.13a	10.62 ± 2.45a	16.19 ± 5.90abc	11.455	<0.001**
Range	4 - 15	3 - 19	6 - 17	9 - 27		
Lt Uterine artery peak systolic velocity (cm/S)						
Mean ± SD	8.81 ± 2.69	10.90 ± 5.08a	10.68 ± 3.07a	16.13 ± 5.64abc	10.042	<0.001**
Range	5 - 15	2 - 20	2 - 18	9 - 26		
Uterine artery peak systolic velocity (cm/S)						
Mean ± SD	8.64 ± 2.59	10.88 ± 5.08a	10.62 ± 2.72a	16.16 ± 5.75abc	10.903	<0.001**
Range	4.5 - 15	2.5 - 19.5	5 - 17.5	9 - 26.5		

Table 12. The different parameter indices for endometrial carcinoma.

Items	Cut-off	Sen.	Spec.	PPV	NPV	Accuracy	p-value
Endometrial thickness (mm)	**>14**	87.5%	84.5%	51.9%	97.3%	94.1%	<0.001**
Rt uterine artery peak systolic velocity (cm/s)	**>15**	56.3%	89.3%	50.0%	91.5%	79.6%	<0.001**
Lt Uterine artery peak systolic velocity (cm/S)	**>13**	62.5%	83.3%	41.7%	92.1%	79.3%	<0.001**
Uterine artery peak systolic velocity (cm/S)	**>15**	56.3%	88.1%	47.4%	91.4%	79.6%	<0.001**

predictors as denoted by the significantly large area under the curves (AUCs); with endometrial thickness being the most significant predictor.

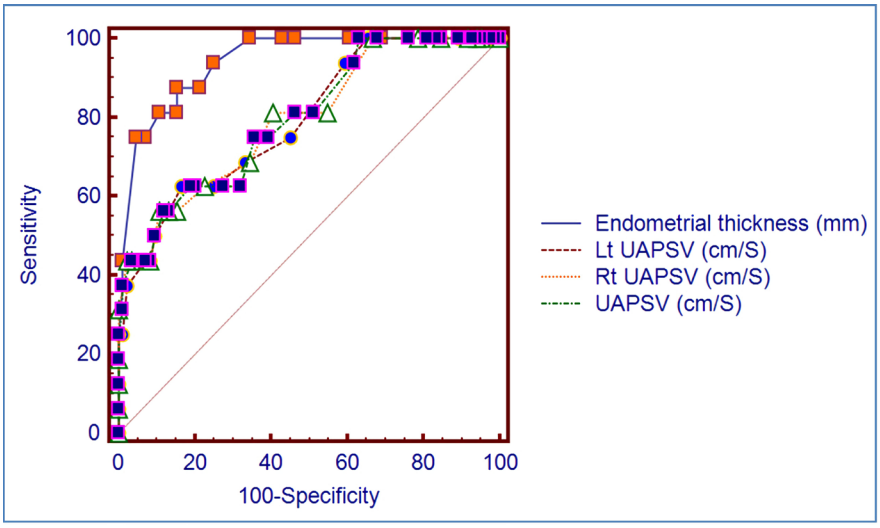

Figure 1. Receiver-operating characteristic (ROC) curve for prediction of endometrial carcinoma using the endometrial thickness and uterine artery peak systolic velocity.

5. Discussion

Endometrial cancer is the most common malignancy of the female genital tract in developed countries. Unlike other malignancies, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by Hysterectomy. Survival decreases with increased staging and lower histological differentiation, thus accurate and timely diagnosis is important and should preferably be carried out by a safe, simple and minimally invasive method [11].

In the modern era transvaginal ultrasound is considered as the first line approach and has been replaced dilatation and curettage as a first line [12].

Transvaginal ultrasound may have predictive value for endometrial cancer among post-menopausal women. Meta-analysis of 5892 symptomatic women (*i.e.*, with postmenopausal bleeding) in 35 published studies showed that an endometrial thickness of 5 mm or greater identified 95% of all endometrial cancers. Conversely, in this population, women with an endometrial thickness of less than 4mm had only a 1% probability of cancer. Among post-menopausal women, endometrium thickness > 1 cm as assessed by transvaginal ultrasound is correlated with an increased risk of endometrial cancer [13].

This study aims to assess the accuracy of BMI, level of blood glucose, endometrial echo pattern and uterine artery velocimetry in prediction of endometrial cancer in women with postmenopausal bleeding in comparison with histopathology. This prospective observational study conducted on 107 with post-menopausal bleeding and endometrial thickness ≥ 4 mm were potentially eligible for inclusion in our study. During the study period, 100 women with postmenopausal bleeding were evaluated, five patients were excluded due to power Doppler artefacts and very poor image quality and two were excluded to histopathology result of insufficient sample.

One hundred women were included; patient mean age was 59.78 years (range

49 - 80 years). Mean body mass index BMI was 29.84 (range 20.8 - 48.8). patient mean blood glucose level was 136.15 (range 70 - 377 mg/dl). Mean endometrial thickness was 11.42 (range 4 - 25). Mean uterine artery peak systolic velocity was 11.17 (range 2.5 - 26.5 cm/sec). Histopathological diagnosis were endometrial cancer (16 cases; 16%), endometrial hyperplasia with atypia (10 cases; 10%), endometrial hyperplasia without atypia (24 cases; 24%), endometrial polyp (29 cases; 29%) and atrophic endometrium was (21 cases; 21%).

As regarding body mass index (BMI) the study shows that BMI was statistically significant lower in patients with benign lesions. BMI was the same in patients with polyp (mean 26.32 ± 3.95) and atrophic endometrium (mean 27.85 ± 3.59). However BMI was higher in patients with endometrial hyperplasia (mean 30.20 ± 5.44).

As regarding blood glucose level the study shows that blood glucose level was statistically significant lower in patients with benign lesions. Blood glucose level was nearly the same in patients with polyp (mean 110.28 ± 27.49) and atrophic endometrium (mean 103.71 ± 25.43). However blood glucose level was higher in patients with endometrial hyperplasia (mean 140.85 ± 66.11).

As regarding endometrial thickness the study shows that endometrial thickness was statistically significant lower in patients with benign lesions. Endometrial thickness was nearly the same in patients with polyp (mean 10.31 ± 2.94) and endometrial hyperplasia (mean 12.94 ± 3.82) .However endometrial thickness in patients with atrophic endometrium was (mean 4.67 ± 1.28) this was less than other benign lesions. Endometrial thickness less than 5 mm was associated always with atrophic endometrium. However there was overlap between cases who have benign or malignant lesions. **The best cut-off for diagnosis of carcinoma was >14 mm with sensitivity of 87.5% and specificity 84.5%.**

As regarding the uterine artery peak systolic velocimetry; the study shows that uterine artery peak systolic velocimetry was statistically significant lower in patients with benign lesions. Uterine artery peak systolic velocimetry was nearly the same in patients with polyp (mean 10.88 ± 5.08) and endometrial hyperplasia (mean 10.62 ± 2.72). However uterine artery peak systolic velocimetry in patients with atrophic endometrium was (mean 8.64 ± 2.59); this was less than other benign lesions. **The best cut-off for diagnosis of carcinoma was >15 cm/sec with sensitivity of 56.3% and specificity 88.1%.**

Revision of the published literature revealed many studies assessing the prediction of endometrial carcinoma through BMI, blood glucose level or the presence of medical condition *i.e.*, Diabetes, endometrial thickness and uterine increased vascularization however none of them took all our variables in one study.

A similar prospective observational study that was conducted by [12] included 165 women with post-menopausal bleeding addressing the correlation of clinical characteristics with histopathological pattern of endometrium in the prediction of endometrial carcinoma in women with post-menopausal bleeding and concluded **similar results** to our study regarding the clinical significance between the presence of diabetes, increased BMI and increased endometrial thickness and

the prediction of endometrial cancer in post-menopausal women. This similarity may be attributed to the relative small number of both studies.

Another prospective observational study that agreed was our study conducted by [14] regarding the prediction value of the endometrial thickness and vascular indices in predicting malignancy in postmenopausal women with vaginal bleeding. Although they used in their study over the 174 women they chose, the 2D/3D power Doppler the final conclusion of that the increased endometrial vascularity can positively predict endometrial malignancy still can support the results of our study.

[15] agreed with our study regarding the clinically significant correlation between diabetes & obesity and endometrial cancer after conducted a large population based prospective cohort study that included 36,773 women, 225 endometrial cancer patients was diagnosed. This study contained many variables diabetes and obesity (increased BMI) were among these variables. [15] suggested that women with diabetes had a statistically significant ~2 fold higher risk for developing endometrial cancer. This risk was increased > 6 fold among obese diabetic women compared with normal weight women without diabetes.

Another study [16] agreed with our study in the predictive value of endometrial thickness and increased endometrial vascularity indices using power Doppler ultrasound after conducting a small study in Sweden over 83 postmenopausal women with vaginal bleeding.

[17] who developed a risk scoring model including recurrent vaginal bleeding, endometrial thickness > 8 mm, presence of hypertension, and age > 65 called RHEA, which provided a moderate diagnostic accuracy for the prediction of intrauterine malignancies among post-menopausal women at risk of endometrial cancer, agreed with us about the predictive value of endometrial thickness. However he disagreed with our study in the value of BMI and diabetes in the prediction of endometrial cancer in postmenopausal women suffering of post-menopausal bleeding.

6. Conclusion

BMI, blood glucose level, endometrial thickness and uterine artery velocimetry indices, improve the prediction of endometrial carcinoma in women with post-menopausal bleeding. It is worth to mention that the endometrial thickness was the most accurate variable; however the small number included in this study limits its value although it's supported by the results of similar studies giving the conclusions. Larger studies may be carried on the same indices to confirm that results aiming to develop a risk scoring model provide high diagnostic accuracy for the prediction of intrauterine malignancies among post-menopausal women.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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