Assessment of risk factors of uterine cancer in Saudi patients with postmenopausal bleeding

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ABSTRACT

Objective: To investigate whether postmenopausal bleeding (PMB) in our postmenopausal patients is a significant early symptom of uterine cancer (UC) and to assess risk factors for developing the disease in our population.

Methods: A retrospective observational study conducted at King Fahad National Guard Hospital (KFNGH), Riyadh, Kingdom of Saudi Arabia. A review of documents was carried out from PMB patients who were admitted to the hospital from January 1990 through to December 2000. Factors that are usually associated with UC were studied (age, body mass index, parity, menopausal duration, past medical history, ultrasound endometrial thickness, and number of PMB episodes).

Results: Forty-seven/one hundred and ninety-five patients (24.1%) were found to have UC. One hundred and forty-eight/one hundred and ninety-five patients (75.9%) had no pathology or a benign pathology. After adjustment for confounding variables, patient's is age >60-years and occurrence of ≥2 episodes of PMB were the risk factors significantly related to UC development. Age 61-70-years P=0.02, odds ratio (OR) 6.8, 95% confidence interval (CI) 1.4-32.9. Age >70-years P=0.001, OR 28.4, 95% CI 3.5-156.3. Occurrence of ≥ 2 episodes of PMB P=0.005, OR 4.5, 95% CI 1.6-11.8. Endometrial thickness >5mm, diabetes, hypertension and obesity were not found to be among the risk factors associated with UC development.

Conclusion: Patient's age >60-years and occurrence of ≥2 episodes of PMB were the risk factors significantly related to UC development in saudi patients with PMB. National risk factors assessment though case control study is required.

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Postmenopausal bleeding (PMB) is a worrisome complaint as of its association with endometrial cancer (EC) in 10% of cases,[1,2] and with complex endometrial hyperplasia which has been shown to progress to EC in 10-30% of the cases.[3] The standard clinical care for evaluation of such patients includes Pap smear, pelvic ultrasound scanning (USS), dilatation and curettage (D&C), fractional curettage, and hysteroscopic directed endometrial biopsy.[4-7] This universal sampling approach may have led to many uncomfortable, costly, and sometimes morbid procedures that can be a reason to prevent the patient from reporting her disease, while a more conservative and acceptable approach such as pipelle endometrial sampling carries a high sensitivity between 92-96% in diagnosing endometrial cancer.[8] The aim of this study is to investigate whether PMB in our postmenopausal patients is a significant early symptom of uterine cancer (UC), and assess risk factors in our population.

Methods. We performed a retrospective chart review from January 1990 through to December 2000 at King Fahad National Guard Hospital (KFNGH), Riyadh, Kingdom of Saudi Arabia (KSA), of cases of PMB that were admitted to the hospital for investigation and management. Only

patients with at least one year of menopause were included. Patients with unknown final histopathology either as they were referred to another hospital, they refused surgical management, or their medical condition did not allow surgical intervention, were excluded. Patients with insufficient endometrial biopsy for histopathology evaluation, who ceased to bleed during their follow up, were considered with no pathology. Repeated PMB meant that the patient had ≥2 episodes of bleeding regardless of the amount. Obesity was diagnosed when body mass index (BMI) was >25 kg/m² and excessive obesity when BMI >30 kg/ m². Ultrasound scanning endometrial thickness of ≤5 mm was considered normal, while thickness >5mm was considered to be abnormal. Due to the retrospective nature of the study, the approval of our Institutional Review Board was not required. During the study period, 256 patients were admitted with the presentation of PMB. Only 195 patients fulfilled the criteria for inclusion in the study. The data collected included patient's age, parity, duration of menopause, number of episodes of PMB whether single or repeated, medical history in particular diabetes and hypertension, USS endometrial thickness, and initial and final histopathology results. Various methods through which uterine cancer was diagnosed were assessed including pipelle endometrial sampling, hysteroscopy, hysteroscopic directed biopsy, dilatation and curettage, fractional curettage, and hysterectomy. The patients were divided into 2 groups. Group 1 included patients who were diagnosed with UC. Group 2 included patients who were found to have no uterine pathology or a benign pathology (such as simple and complex hyperplasia, complex hyperplasia with atypia, endometrial polyp, cervical polyp, adenomyosis, uterine fibroids and others). The difference between these 2 groups was studied.

Data analysis. Testing for normality was performed by Kolmogorov-Smirnov test. Using univariate logistic regression analysis, we calculated the rates of UC and determined the odds ratios (OR) with 95% confidence interval (CI) for the following factors: age, parity, BMI, menopausal duration, past medical history, ultrasound endometrial thickness, and number of episodes of PMB. Multivariate logistic regression analysis with stepwise selection of predictors was used to assess the significance of all variables that were related to UC. Fisher's exact and X^2-tests were used as appropriate. Two tailed tests were used, and p value ≤0.05 was considered statistically significant.

Results. During the 11-year study period, there were 256 patients who were admitted with the diagnosis of PMB. A total of 195 patients met the

Table 1 - Characteristics of 195 post menopausal patients. Group 1 patients with uterine cancer. Group 2 patients with benign pathology.

Patients characteristics	G1 (n=47)		G2 (n=148)	
Age (%)	63.8 ± 8.9*		57.9 ± 7.4	
<50	2	(4.3)	14	(9.5)
50-60	19	(40.4)	87	(58.8)
61-70	18	(38.3)	44	(29.7)
>70	8	(17)*	3	(2)
BMI (%)	29.5 ± 5.2		29.3 ± 6.2	
<25	18	(38.3)	41	(27.7)
26-30	13	(27.7)	50	(33.8)
>30	14	(29.8)	49	(33.1)
Unknown	2	(4.2)	8	(5.4)
Parity (%)	9 (range 0-9)		7 (range 5-15)	
0	2	(4.3)	1	(0.7)
1-3	10	(21.3)	14	(9.5)
4-5	9	(19.1)	21	(14.2)
>5	26	(55.3)	112	(75.6)*
Menopausal duration/year (%)	13.5 (range 1-37)		6 (range 1-35)	
1-4	6	(12.8)	57	(38.5)
5-10	11	(23.4)	29	(19.6)
11-20	12	(25.5)	34	(23)
>20	13	(27.7)*	15	(10.1)
Not known	5	(10.6)	13	(8.8)
Past medical history (%)				
None	13	(27.7)	33	(22.3)
Diabetes	6	(12.8)	30	(20.3)
Hypertension	7	(14.9)	28	(18.9)
Diabetes + Hypertension	16	(34)*	33	(22.3)
Hypothyroid	1	(2.1)	6	(4)
Others	4	(8.5)	18	(12.2)
USS endometrial thickness mm (%)	13 (range 4-43)		12 (range 3-36)	
<5	1	(2.1)	15	(10.1)
6-10	3	(6.4)	21	(14.2)
>10	32	(68.1)*	69	(46.6)
Not known	11	(23.4)	43	(29.1)
Number of episodes of PMB				
Single	5	(10.6)	52	(35.1)
≥2 episodes of PMB	42	(89.4)*	96	(64.9)

*p value ≤ 0.05
Values presented as means ± SD
BMI - body mass index in kg/m²
USS - ultrasound scanning, PMB - postmenopausal bleeding

Table 2 - Univariate logistic regression analysis for risk of uterine cancer in patients with postmenopausal bleeding.

Risk factor	Odds ratio	95% CI	p value
Age	1.1	1.05, 1.1	0.00*
Parity	0.8	0.7, 1.0	0.05*
BMI	1.0	0.9, 1.0	0.51
Menopausal duration	1.1	1.1. 1.2	0.00*
Number of episodes of PMB	4.6	1.7 12.3	0.002*
Past medical history	1.0	0.8, 1.2	0.94
USS endometrial thickness	1.1	1.0, 1.2	0.01*

*p value ≤0.05
BMI - body mass index in kg/m², USS - ultrasound scanning
PMB - post menopausal bleeding, CI - confidence intervals

Table 3 - Multiple logistic regression of risk factors of uterine cancer for patients with post menopausal bleeding.

Risk factor	OR	95% CI	*p* value
Age			
50-60	3.8	0.8-18	0.09
61-70	6.7	1.4-32.9	0.02
>70	28.4	4.1-198.5	0.001
Parity			
1-3	0.32	0.0-5.6	0.43
4-5	0.17	0.0-3	0.23
>5	0.10	0.0-1.6	0.11
Number of episodes of PMB	4.5	1.6-12.7	0.005
Repeated			

*p value ≤0.05
PMB - post menopausal bleeding
OR - odds ratio
CI - confidence interval

Table 4 - Diagnostic procedure.

Diagnostic procedure	Frequency	(%)
Pipelle endometrial biopsy only	7	3.6
D&C	64	32.8
Hysteroscopy D&C	45	23.1
Fractional curettage	49	25.1
Hysteroscopy, fractional curettage	22	11.3
Hysterectomy	2	1
Others	6	3.1
Total	**195**	**100**

D&C - dilatation and curettage

inclusion criteria and were available for analysis. Those patients were divided into 2 groups. Group 1 included patients who were diagnosed with UC 47/195 (24.1%). Group 2 148/195 (75.9%) included patients who were found to have no pathology or a benign pathology. Endometrial cancer occurred in 37/47 (78.7%) of uterine cancer patients while the remainder 10/47 (21.3%) were cases with uterine sarcomas. Following testing for normality by Kolmogorov-Smirnov test, age of the patients and their BMI were found to be normally distributed and were presented by their means ± SD, while patient's parity, menopausal duration and their USS endometrial thickness were not normally distributed and were presented by their medians and ranges **(Table 1)**

Age. The mean age for the studied patient was 59.4 ± 8.1 ranging between 42-85 years. Group I mean age was significantly higher 63.8 ± 8.9 compared with 57.9 ± 7.4 years for non-cancer patients. By applying student T test, the difference between the 2 groups was statistically significant. *P*=0.001 and that appeared mainly for the age group >70-years *P*=0.00 **(Table 1).**

Menopausal duration. Menopausal duration was divided into 5 main groups **(Table 1)** with a median duration of 9-years. The majority of patients 63/195 (32.3%) had menopausal duration of 1-4 years. Thirteen/fourty-seven (27.7%) UC patients had menopausal duration of >20-years compared with 15/148 (10.1%) in the benign group. The difference was statistically significant *P*=0.002.

Body mass index. The patients' BMI were distributed into 3 main groups as seen in **(Table 1)**. The majority of patients 126/195 (68.2%) had BMI >25 kg/m², mean BMI was 29.0 ± 5.9 ranging

between 19-51. Obesity and excessive obesity did not seem to affect the occurrence of UC, as there was no statistically significant difference between Groups 1 and 2.

Parity. The majority of patients 136/195 (70.5%) were more than para 5 **(Table 1).** It appeared that high parity (more than 5) was a protective factor from UC **(Table 2)**. Univariate logistic regression showed OR 0.8, *P*=0.05 and 95% CI 0.7-1.0. This finding was not confirmed by the multiple logistic regression **(Table 3)**.

Past medical history. Patient's past medical history was shown in **(Table 1)**. Fourty-six/one hundred and ninety-five (23.6%) patients had no medical disease, 36/195 (18.5%) were diabetic, 35/195 (17.9%) were hypertensive, and 49/195 (25.1%) had both diabetes and hypertension. By applying the chi square test, occurrence of diabetes and hypertension was a significant risk factor for UC development with *P*=0.04.

Ultrasound endometrial thickness. Ultrasound endometrial thickness endometrial thickness was classified into 4 main groups **(Table 1)**. 16/195 (8.2%) had endometrial thickness <5mm, 24/195 (12.3%) had endometrial thickness 6-10 mm, and 101/195 (51.8%) had endometrial thickness of >10 mm. Fifty-four/one hundred and ninety-five (27.7%) patients did not have their USS endometrial thickness assessed or documented in the file, 43/54 (79.6%) found to have benign pathology and 11/54 (20.4%) diagnosed with uterine cancer. There was a statistically significant difference between the studied groups for those with endometrial thickness >10mm by chi square test. *P*=0.04.

Number of episodes of postmenopausal bleeding. Fourty-two/fourty-seven (89.4%) UC

patients had 2 or more episodes of PMB, while 95/148 (64.2%) Group 2 patients had 2 or more episodes of PMB. The difference was statistically significant. *P*=0.001 **(Table 1)**. **Table 2** shows the results of the univariate logistic regression analysis. Age, parity, menopausal duration, number of episodes of PMB and USS endometrial thickness were the only factors associated with UC development, *P* value <0.05. Stepwise multivariate logistic regression was performed to identify the most important factors among the 5 variables significantly related to UC **(Table 3)**. Overall, the analysis revealed that patients in the age group 61-70 years carry 6.8 times more risk of developing UC while in those aged >70-years the risk increased >28 times. Age 61-70-years *P*=0.02, OR 6.8, 95% CI 1.4-32.9. Age >70 *p*=0.001, OR 28.4, 95% CI 3.5-156.3. On the other hand, the occurrence of ≥ 2 episodes of PMB increased the risk of UC by 4.5 times (*p*=0.005, OR 4.5, 95% CI 1.6-11.8).

Discussion. Early investigation of PMB aims mainly to detect UC at its early stages and should result in a significantly improved overall survival. Based on the knowledge that approximately 10% of PMB women have EC[1,2,9] all our patients were investigated by different methods of endometrial sampling **(Table 4)**. The resulting UC incidence in the investigated group was 47/195 (24.1%). This percentage was significantly higher than the known international incidence that can be explained, based on the international studies by the high incidence of obesity, diabetes, and hypertension in the studied population **(Table 1)**. King Fahad National Guard Hospital is a tertiary referral centre where suspected cancer patients are usually referred from different areas of KSA for investigation and management. However, such a small number of UC patients does not really reflect an active referral system to our Centre. Finally, 138/195 (70.8%) of the investigated patients had repeated episodes of PMB over a prolonged period of time. Of the UC patients 42/47 (89.4%) had repeated episodes of PMB. Hence patients' delayed attendance to the Hospital could be one of the explanations for the high incidence of UC in the studied group. Patients'age was a significant risk factor for UC development. *P*=0.001 **(Table 1)**. Univariate logistic regression and multivariate stepwise logistic regression has confirmed this significance. These findings were in correspondence with other studies.[10-12] Though statistically significant positive relation was found by chi square test between duration of menopause >20-years and uterine cancer diagnosis *P*=0.02 **(Table 1)**. This finding was not confirmed when univariate and multiple logistic regression were applied. This in fact does not agree with other published studies.[10-12] The reason could again be related to the late presentation of the patients

following repeated episodes of PMB without timed appropriate management prior to the progress into a frank cancer. There was no positive relation between UC diagnosis and obesity, diabetes and hypertension, despite their high incidence in the studied patients. This is unlike data published in other studies[11,12] **(Table 1)**. The same finding was noted for the relation between USS endometrial thickness >5 mm and UC, unlike the findings of others on a different population group.[10-15] This has confirmed the fact that the presence of symptoms (namely bleeding) seems to be more informative than endometrial thickness[16] particularly for patients who are attending late for investigating PMB. In view of this, and knowing that abnormal echogenicity has recently become an added criteria to the endometrial thickness in assessing PMB due to better prediction of atrophy and higher prediction for endometrial cancer,[17] these details, if are added to the future routine USS reports for cases of PMB, may improve its sensitivity and specificity for our patients. Repeated episodes of PMB (2 or more) were a leading risk factor for UC in the studied patients with 4.5 times increased risk. Such a result was not achieved in other published studies. The previous findings strongly reflect the difference between our population and the western population on which most of risk factors assessment studies were based. Saudi PMB women have a very high incidence of multiparity that is known to be protective against UC[10-12] while late reporting of PMB, and the resulting high percentage of thickened endometrium, high incidence of diabetes, hypertension, and obesity are known risk factors for the disease. Such factors might be counteracting each other resulting in such a unique difference. We strongly recommend UC risk factor assessment among Saudi PMB women.

In conclusion, age >60-years and occurrence of 2 or more episodes of PMB were the variables most strongly associated with uterine cancer development. This study has shown that saudi PMB population is at high risk of developing UC with risk factors that are different from the known published western ones. We strongly recommend national risk factor assessment through case control study. There is an urgent need for public education to explain the importance of early reporting of PMB in detecting the disease at its early stages, and significantly improve the overall survival of the UC population.

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