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Original article

The risk of endometrial (pre)malignancy in women having postmenopausal uterine bleeding at Tu Du Hospital

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Abstract: ***Introduction*:** Endometrial cancer and endometrial atypical hyperplasia, futher referred to as endometrial (pre)malignancy in approximately 8.3-17.6% of cases depending on different studies. The incidence of abnormal endometrium increases during the postmenopausal period, especially endometrial (pre)malignancy. There are limited data regarding endometrial (pre)malignant disorders in patients with postmenopausal uterine bleeding. ***Purpose***: The aim of this study is to investigate the risk of endometrial cancer and atypical hyperplasia in the women who had postmenopausal uterine bleeding (PUB) and assess the risk factors associated with such cases. ***Methods***: A cross-sectional study was conducted on 164 women with PUB used vacuum aspirator with Karman canula to evaluate endometrial pathology, underwent treatment at deparment of Gynaegology, Tu Du hospital through a set of questionaires and case file reports completed from February to June of 2020. ***Results:*** In Bayesian inference, the risk of endometrial (pre)malignancy was 17.5%, CI (credible interval) 95% of 14.1 to 21.1%. There was a significant association between the risk and the duration of bleeding (OR = 1.02, CI 95% 1.01 to 1.03, LR+ 1.96, LR- 0.37), number of live births (OR = 0.79, CI 95% 0.66 to 0.95, LR+ 2.41, LR- 0.76), endometrial thickness (OR = 1.08, CI 95% 1.01 to 1.16, LR+ 1.16, LR- 0.77) and the presence of abnormal intracavitary mass in transvaginal ultrasound (OR = 9.12, CI 95% 4.09 to 20.33, LR+ 3.65, LR- 0.4). ***Conclusions***: Using manual vacuum aspirator with Karman canula showed the risk of (pre)malignancy in women having PUB and this risk depends on the presence of the risk factors.

Keywords: postmenopausal uterine bleeding (PUB); endometrial (pre)malignancy; manual vacuum aspirator with Karman canula; Bayesian inference.

1. INTRODUCTION

Postmenopausal uterine bleeding (PUB) is an important symptom of both benign and serious gyaecological disease. In which, endometrial (pre)malignancy defined as atypical hyperplasia and endometrial cancer in approximately 8.3-17.6% of cases depending on different studies [1] [2] [3]. There are many factors that influence (pre)malignancy such as older age, late age natural menopause, obesity, the duration of bleeding, number of live births, endometrial thickness, long-term use unopposed estrogen and internal diseases: hypertension, type 2 diabetes [4]. In 2011, Đ.N.X. Trang reported that the most common pathologic diagnosis of PUB was endometrial atrophy (74.66%), followed by endometritis (4.45%), typical hyperplasia (2.72%), polyp (1.37%), endometrial cancer and atypical hyperplasia (13.6%) [5]. For

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decades, endometrial biopsy by dialtion and curettage (D&C) is a gold standard procedure for diagnosis of endometrial pathology. This technique has been replaced by endometrial biopsy, which can be done in out-patient clinic such as: vabra aspirator, pipelle, manual vacuum aspirator with Karman canula. The diagnostic accuracy of endometrial biopsy by Karman canula at 97% [6] when compared with subsequent findings at D&C. Most previous researches on endometrial pathology in Viet Nam had endometrial sampling device is D&C. The aim of this study is to estimate the risk of the (pre)malignancy and the likelihood ratio (LR) of the risk factors in women with PUB who had endometrial sampling by manual vacuum aspirator with Karman canula.

2. MATERIALS AND METHOD

2.1. Study setting

The study was conducted at Gynecologic Department of Tu Du hospital which is one of the two National OBGYN hospitals in Viet Nam, from February to June 2020.

2.2. Study design and participants

Study design

This study used a cross-sectional design.

Study participants

Data of this study was collected between February and June 2020. Participants of this study were PUB patients who underwent treatment at the Gynecologic Department of Tu Du hospital. Inclusion criteria included (1) having diagnosis of menopause was made using the WHO criteria when one completed year of amenorrhoea [7], (2) having abnormal uterine bleeding based on clinical examination. All of participants were checked pap smear test. Exclusion criteria consisted of patients known abnormal Pap smear, used anti-coagulation therapy or coagulopathy diseases. In addition, we also excluded the patients who refused endometrial biopsy or had an unclear endometrial biopsy report.

Data colection and tool

At Gynecologic Department, one a patient was confirmed as having PUB by attending physician, she would be invited to participate in the study. Written Informed consent was obtained from all participants. Then, the interview would be performed in a private room within the same Department to ensure privacy and confidentialy. Participation was voluntary and the participant could quit the interview at any time without fasing any consequences. During each interview, the interviewer asked the participant questions in the structured questionnaire based on data from demographic and medical history of the participants.

The baseline questionaire elicited data on demographic characteristics including age, geography, BMI, marital status; reproductive history including age at menarch, age at menopause, time since menopause, regularity of menstrual, frequency of bleeding, duration of bleeding, and number of live births; transvaginal ultrasound charactersistics, including endometrial thickness and abnormal intracavitary mass. Endometrial biopsy was done irrespective of endometrial thickness. Endometrial tissue was obtained by a manual vacuum aspiration syringe with Karman canula. Analysis of histopathology report was done and results were obtained in case file reports. Histopathological results were grouped according to the presence or absence endometrial (pre)malignanc. Endometrial thickness and abnormal intracavitary mass were also collected from ultrasound report in case file reports.

"Age" was calculated as year study minus year of birth. "Age at menarch" was calculated as year having the first menstrual period. "Age at menopause" was the age at the last menstrual bleeding determined after at least 12 months of amenorrhea. "Marital status" was a binary variable with two values of married and never married. "Time since menopause" was the period of time between age and age at menopause. "Regularity of menstrual" was a binary variable with two values of regular variation and irregular. Regular was when the shortest to longest cycle variation is below 7-9 days. "Frequency of bleeding" was a binary variable with two values of single episode and recurrent episode. Recurrent episode was defined as any repeat presentation of bleeding after previously being investigated. "Duration of bleeding" was calculated as the number of days having bleeding in the current bleeding episode, was a binary variable with two values of ≤ 4 days and >4 days. "Number of liver birth" referred to the number of births excluding stillbirths, was a binary variable with two values of < 2 and ≥ 2."Use HRT" standing for use hormone replacement therapy. Hypertension, was based on JNC 7 (The Seventh Report of the Joint National Committee), defined as a systolic pressure $\geq$140 mmHg and/or a diatolic pressure $\geq$90 mmHg or history of hypertension. "Diabetes" was based on ADA (American Diabetes Association). "Use HRT", "Hypertension", "Diabetes" and "Abnormal intracavitary mass" was a binary variable with to values yes and no. "Endometrial thickness" (mm) was a continuous variable.

2.3. Sample size and sampling

Sample size

The sample size was caculated based on the formula:

$$N = Z^2_{1-\alpha/2}P(1\text{-}P)/d^2$$

In that formula: tolerated margin of error d = 0.05, type I error is α = 0.05 for a confidence level of 95%, so the critical value is 1.96 and the propotion of endometrial (pre)malignant from data of previous study was P = 11% [5].

We caculated minium sample size of the study is N = 150.

Sampling

Convenience sampling technique was used.

2.4. Statistical method

All statistical analyses were performed using RStudio software. Distribution of variables were examined using descriptive analyses. Mean and standard deviation were continuous variables. Frequency and proportion were categorical variables. The risk of endometrial (pre)malignancy in PUB was inferred from the proportion of (pre)malignancy of endometrium by Bayesian inference. To identify factors associated with presence of (pre)malignancy, multivariate logistic regression was used and expressed as odds ratios (ORs) with confidence intervals (CIs). We used P value under 0.05 were considered significant statistically. Beta-binomial distribution was used to express the degree of

effects to the presence of (pre)malignancy of endometrium by Likelihood ratios (LRs).

2.5. Ethical considerations

This study was approved by the local ethics committee of Ho Chi Minh Medicine and Pharmacy University with registration number 604/ĐHYD-HĐĐĐ and Tu Du hospital. All participants were explained and requested for written informed consent.

3. RESULTS

From February to June 2020, a total of 166 paticipants were collected. Two cases were excluded because one case did not agree endometrial biopsy, and another had an unclear biopsy result. So that, 164 patients were included in our study and taken for analysis.

Demographic of paticipants is presented in Table 1. The mean age of the study is 63 years old which 88.4% of them are older than 55 years old. Of them, 62.2 % for BMI 18.5-24.9, 33.5% for BMI >25 kg/m2. That means patients had overweight (BMI 25.0-<30.0 kg/m2) and obesity (BMI ≥ 30 kg/m2) containing a third of participants. Almost patients have lived at small town and got married.

Table 1. Demographic Characteristics of Participants.

Characteristics	Paticipants (N=164)
Age – yr (SD)	63 (6.59)
Age group – no. (%)	
<55	19 (11.6)
≥55	145 (88.4)
BMI – group – no. (%)	
<18.5	6 (3.7)
18.5-24.9	102 (62.2)
25-29.9	40 (24.4)
>29.9	15 (9.1)
Geography	48 (29.3)
Ho Chi Minh city	116 (70.7)
Others	
Marital status – no. (%)	
Married	154 (93.9)
Never married	10 (6.1)

BMI: body mass index

Table 2. Clinical characteristics of participants

Characteristics	Paticipants (N=164)
Age at menarch – years	14.8±1.98
Age at menopause – years (SD)	51.7 (3.45)
Time since menopause – years (SD)	11.3±7.8
Regularity of menstrual – no. (%)	
Regular variation	158 (96.3)
Irregular	6 (3.7)
Frequency of bleeding – no. (%)	
Single episode	129 (73.2)
Recurrent episode	44 (26.8)
Duration of bleeding – days	18± 33.5
Duration of bleeding group – no. (%)	
≤4 days	84 (51.2)
>4 days	80 (48.8)
Number of live births – no. (%)	
<2	32 (19.5)
≥2	132 (80.5)
Use HRT	0
Hypertension – no. (%)	
Yes	89 (54.3)
No	75 (45.7)
Diabetes – no. (%)	
Yes	27 (16.5)
No	137 (83.5)
Endometrial thickness (mm) (n= 127)	7.21±5.56
Endometrial thickness group – no. (%)	
<5 mm	51 (40.0)
≥5 mm	76 (60.0)
Abnormal intracavitary mass – no. (%)	
Yes	50 (30.5)
No	114 (69.5)

HRT: hormone replacement therapy

Table 2 shows clinical characteristics. The mean age at menarche is 14.8±1.98 and at menopause is 51.7±3.45. The years of postmenopausal is 11.3±7.8. In the past, almost participants had regularity of menstrual and had 2 or more children. There were 26.8% having repeated abnormal vaginal bleeding and 48.8% having more 4 days of bleeding. None of

them had used hormone therapy but more than a half were hypertension and 16.5% were diabetes. In 127 pts, a mean endometrial thickness of 7.21±5.56 mm while 37 others could not be measured. Another sonographic sign was abnormal mass in uterine cavity which was seen in 50 pts.

Out of 164 participants, endometrial (pre)malignancy was found in 40 cases, accounting for 24.4% with a 95%CI of 18.2% to 31.8%, including atypical hyperplasia in 3 (1.8%) and endometrial cancer was obtained in 37 (22.6%). Benign pathology was found in 124 (75.6%) participants of total cases. Chronic endometritis was the commonest benign cause comprising total 47 (28.7%) cases followed by endometrial atrophy with 34 (20.7%) cases, endometrial polyp with 22 (13.4%) cases, acute endometritis with 8 (4.9%) cases. Typical hyperplasia in 13 (7.9%), including simple typical hyperplasia in 9 (5.5%) and complex typical hyperplasia in 4 (2.4%). In our study, there was no case of insufficient tissue (Table 3).

Table 3. Distribution of histopathological results

Histology	Paticipants (N=164)
(Pre)malinancy	40 (24.4)
Endometrial cancer	3 (1.8)
Atypical hyperplasia	37 (22.6)
Others	124 (75.6)
Chronic imflammation	47 (28.7)
Atrophic endometrium	34 (20.7)
Endometrial poplyp	22 (13.4)
Acute imflammation	8 (4.9)
Typical hyperplasia	4 (2.4)

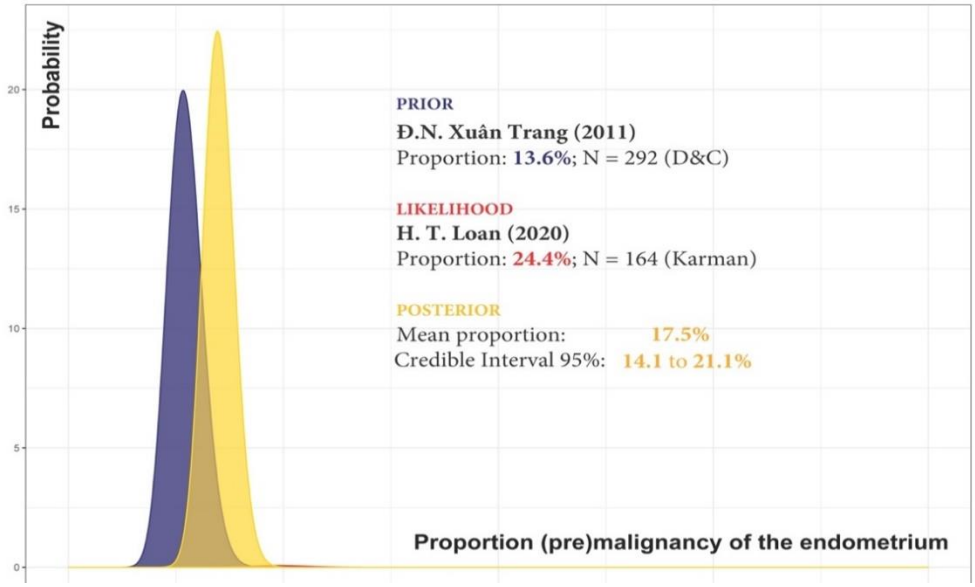

Figure 1. The risk of endometrium (pre)malignancy in PUB

Table 4. The association between the reproductive factors and endometrial (pre)malignancy

Characteristics (N=164)	ORs	95% CI	P-value
Age (years)	1.01	0.96-1.06	0.69
Age at menopause (years)	1.07	0.96-1.19	0.189
Time since menopause (years)	0.99	0.95-1.04	0.89
Frequency of bleeding	0.73	0.43-1.22	0.173
Duration of bleeding (days)	**1.02**	**1.01-1.03**	**<0.001**
Number of liver births	**0.79**	**0.66-0.95**	**0.009**
Hypertension	0.75	0.36-1.66	0.436
Diabetes	0.55	0.18-1.70	0.273
Endometrial thickness (mm) (n=127)	**1.08**	**1.01-1.16**	**0.0032**
Abnormal intracavitary mass	**9.12**	**4.09-20.33**	**<0.001**

Table 5. Sensitivity, specificity, likelihood ratios of endometrial (pre)malignancy at different risk factors

Characteristics	Sensitivity (%)	Specitivity (%)	LR+	LR-
Duration of bleeding ≥ 5 days	77.5	60.5	1.96	0.37
Number of liver birth <2	65	85.5	4.48	0.41
Endometrial thickness ≥ 5 mm	68.2	61.5	1.77	0.52
Abnormal intracavitary mass	67.5	81.5	3.65	0.40

LR+ = Likelihood ratio of positive test, LR- = Likelihood ratio of negative test

In Bayesian inference, the risk of endometrial (pre)malignancy in PUB was 17.5% with a 95% *credible interval* of 14.1% to 21.1% (Figure 1).

In multivariable logistic regression analyses, there were no statistically significant associations with age, age at menopause, time since menopause, frequency of bleeding,

hypertension, or diabetes and endometrial (pre)malignancy. There was a statistically significant increasing the risk of endometrial (pre)malignancy with duration of bleeding, number of live births, endometrial thickness and the presence of abnormal intracavitary mass with OR = 1.02 (95% CI 1.01-1.03), OR = 0.79 (CI 95% 0.66 to 0.95), OR = 1.08 (CI 95% 1.01 to 1.16) and OR = 9.12 (CI 95% 4.09 to 20.33), respectively (Table 4).

Bayesian inference was used to express the degree of impact of four risk factors including duration of bleeding, number of live births, endometrial thickness and the presence of abnormal intracavitary mass to the presence of (pre)malignancy of endometrium with sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were as followed: 77.5%, 60.5%, 1.96, 0.37 for cut-off value was ≥5 days; 65%, 85.5%, 2.41, 0.76 for cut-off value was below 2; 68.25, 61.5%, 1.16, 0.77 for cut-off value was ≥5 mm and 67.5%, 81.5%, 3.65, 0.4 for cut-off value was to have presence of abnormal intracavitary mass (Table 5).

4. DISCUSSION

Endometrial sampling is performed to exclude endometrial cancer in women having uterine bleeding during the postmenopausal period. There are many different methods of endometrial biopsy that include D&C, endometrial aspiration biopsy using a Pipelle, and manual vacuum aspirator with Karman canula. In present study, the histopathological examination of 164 samples obtained by using manual vacuum aspirator with Karman canula that the diagnostic accuracy at 97% [6] when compared with subsequent findings at D&C. Besides, this method seems safe without the added risk of general anesthesia, infection, and perforation. In published data because there is no clear consensus regarding what assign to endometrial biopsy. Not only PUB but also clinical examination findings, endometrial thickness and experience of the clinician are relevant for this decision. In our study, endometrial biopsy was done despite endometrial thickness. This is suitable for advertisement of the Society of Radiologists in Ultrasound that endometrial sampling or transvaginal ultrasonography is effective as a first diagnostic step [8] in a woman with postmenopausal bleeding.

Using manual vacuum aspirator with Karman canula, Shaker et al. (1991), Kairavi et al. (2014) and Cheryyil et al. (2016) reported the prevalence of endometrial (pre)malignancy in PUB was 11%, 17.6%, and 8.3%, respectively [1] [2] [3]. Reid et al. reported the prevalence of endometrial (pre)malignancy in PUB was 11% with endometrial aspiration biopsy using a Pipelle [9]. Gredmark et al. (1995), Gull et al. (2003), and Đ.N.X.Trang et al. (2011) reported the rate of endometrial (pre)malignancy in PUB was 9.8%, 13%, and 13.6% obtained by D&C, respectively [10] [11] [5]. In our study, the risk of endometrial (pre)malignancy in PUB was 24.4%, 95% CI (18.2-31.8%). This result is obviously very high because ninety-one percent of women with endometrial cancer had postmenopausal bleeding. Nearly 94% of postmenopausal bleeding cases was in North America, and 90% in Western Asia and Eastern Asia [12]. Another reason for high rate of endometrial (pre)malignancy as a cause of PUB in our study compared to others might be the limitations of our study design. We performed a cross-sectional study in Gynecologic department, Tu Du hospital – the leading hospital in the field of obstetrics and gynecology treatment of the Southern Vietnam in particular and the country in general. Every day, the hospital receives a large of patients from all over the area of country to take a gynecology exam with many problems, especially PUB. This selection bias can lead to the higher proportion.

In Bayesian inference, to estimate the posterior proportion (the risk) of endometrial (pre)malignancy in PUB, we use beta-binomial distribution to calculate the proportion of endometrial (pre)malignancy in PUB from the study of Đ.N.X. Trang et al [5], as refer to prior proportion of endometrial (pre)malignancy in PUB was 13.6% (N = 162 participants). The estimated mean posterior proportion of endometrial (pre)malignancy in PUB was 17.5% with a 95% credible interval of 14.1% to 21.1% (Figure 1). This means a patient who admit Gynecologic Department has PUB, there is a 95% probability that this patient's true risk of endometrial (pre)malignancy would lie within the interval from 14.1% to 21.1% and the highest risk is 17.5% (Figure 1). Using this interpretation of credible interval seems more practical in clinical practice to explain the risk of endometrial (pre)malignancy for patients. However, in Bayesian inference, the posterior proportion depends on likelihood from our study result and the prior proportion calculated from Đ.N.X. Trang's study result. Figure 1 shows the weights of our and theirs study, the effects of each to final results.

According to the likelihood ratios of endometrial (pre)malignancy at different risk factors, using Bayesian nomogram we can estimate the corresponding risk of endometrial (pre)malignancy (Table 5). For example, if a PUB patient has a prior risk 17.5% and endometrial thickness is ≥5mm (LR+ 1.77), she will have the posterior risk of endometrial (pre)malignancy 25% based on Bayesian nomogram. Conversely, if she has endometrial thickness <5mm (LR- 0.52), she will have the posterior risk of endometrial (pre)malignancy 10%. This improves that PUB combined endometrial thickness is a good indicator of pre(malignancy).

Conclusion

Using manual vacuum aspirator with Karman canula showed the risk of (pre)malignancy in women having PUB and this risk depends on the presence of the risk factors.

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