



CROSS-SECTIONAL STUDY OF ASSOCIATION BETWEEN HERBAL MEDICINE CONTAINING PHYTOESTROGENS AND ENDOMETRIAL NEOPLASIA IN THAI WOMEN WITH POSTMENOPAUSAL VAGINAL BLEEDING AT MAHARAT NAKHON RATCHASIMA HOSPITAL

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ABSTRACT

The primary objective is aimed to study the association between the use of herbal medicine claimed to alleviate the postmenopausal symptoms, which are actions of the phytoestrogen and endometrial pathology in female outpatients with postmenopausal bleeding. The secondary objective is to evaluate the correlation of results derived from different techniques for endometrium thickening examination: transvaginal ultrasound and endometrial biopsy. This cross-sectional study was conducted at Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, Thailand from June 2019 to May 2020 and has obtained scientific ethical approval by the Research Ethics Committee of Maharat Nakhon Ratchasima Hospital. The total number of females who came to the Outpatient Department due to experiencing postmenopausal bleeding and underwent endometrial biopsy procedure for medical assessment was 175. The patient's demographic data, baseline characteristics, history on herbal medicine use and medical records were collected from the medical charts of the hospital. Statistical analysis was performed using Strata version 12. There were 51 out of 175 patients with postmenopausal bleeding who had used herbal medicines containing phytoestrogens. From the endometrial biopsy results, those who exposed to herbal medicines had 1.19 times higher rates of endometrial hyperplasia (95%CI = [0.44 - 3.17], p-value 0.722) and every 1 millimeter of endometrial thickening represent 1.12 times higher risk of endometrial hyperplasia (95 %CI = [1.06 - 1.18], p-value < 0.001*) compared to those who did not use herbal medicines. It is statistically significant after controlling factors including age, number of childhood duration of menstruation and contraception methods by Logistic regression analysis. We found that the patients who took herbal medicine claiming to alleviate postmenopausal symptoms, which are actions of the phytoestrogen, had the rate of endometrial neoplasia 1.19 times higher than those who did not take herbal medicine with no statistical significance. The research result also revealed that every 1-millimeter increase of the endometrial thickness associated with 1.12 times higher risk of endometrial hyperplasia neoplasia with statistical significance. Further study may need to collect data from more patients to see if there is any difference between the two groups.

KEYWORDS : herbal medicine, Phytoestrogen, postmenopausal bleeding, endometrial intraepithelial neoplasia

INTRODUCTION

Endometrial cancer is one of the most common types of cancers found in the elderly. According to the database during October 2008 to September 2011 of Maharat Nakhon Ratchasima hospital, 479 women suffering from the symptoms of postmenopausal bleeding; 13.6% of those were diagnosed with endometrial cancer and 8.6% were diagnosed with endometrial hyperplasia.⁽¹⁾ Regarding to the statistical data from Cancer in Thailand Vol.9, the incidence rate of endometrial cancer in Thailand is 4.5 per 100,000 female populations.⁽²⁾ Endometrial cancer ranks the fourth most common gynecologic malignancy in Thailand⁽³⁾ and the fifth most common cancer in women worldwide, followed by breast, colorectal, lung and cervical cancers. It is a disease that occurs primarily in postmenopausal women and is increasingly virulent with advancing age.^(16,17) and also the eight leading cause of death from malignancy in women.⁽⁴⁾

Prolonged unopposed estrogen is one of the major causes of endometrial hyperplasia which can lead to endometrial cancer for 1-29%.⁽⁵⁾ The factors that cause the hyperestrogenic stage in women include obesity, diabetes, nulliparity, menstruation span, polycystic ovarian syndrome and intake of estrogen.^(5,6) An estrogen intake without progesterone stimulates the regeneration and growth of the endometrium, which increases the risk of endometrial cancer about 4 - 8 times.⁽⁵⁻⁸⁾

On the other hands, estrogen deficiency in postmenopausal women leads to various symptoms including hot flash, vaginal dryness, skin dryness, bone mass decrease and metabolic dysfunction.⁽⁹⁾ In Thailand, there are many types and forms of herbal medicines claimed to alleviate the

menopausal symptom, boost female rejuvenation, and balance hormone level. These herbal medicines' function is similar to estrogen, namely Phytoestrogen, which is usually found in soybean, flax, black cohort and Shatavari.⁽¹⁰⁾ Regarding Thai culture, herbal medication is believed to be safe; however, many of Thai women consumed these products of Phytoestrogen with expectation to alleviate postmenopausal symptoms without awareness that the product may increase risk of endometrial cancer.

According to the study in mice,⁽¹¹⁾ the uterus of oophorectomized mice fed with Thai herbal extracts weighed heavier than their counterparts. The study in Maharat Nakhon Ratchasima hospital during September 2016 to September 2017 also revealed that patients with pathological diagnosis of endometrial neoplasia had 4.11 times higher rate of herbal medicine use.⁽¹²⁾

MATERIAL AND METHODS

This research was a cross-sectional study. The primary objective is to study the association of herbal medicine with Phytoestrogens on endometrial pathology in patients with postmenopausal bleeding and the secondary objective is to study the relationship between endometrial thickness, examined with transvaginal ultrasound, and pathological results, derived from endometrial biopsy.

The research was conducted on 227 women who came to Maharat Nakhon Ratchasima hospital with postmenopausal vaginal bleeding between June 2019 and May 2020 and had been approved by the Research Ethics Committee of Maharat Nakhon Ratchasima Hospital. Every woman who came to the Outpatient Department of Gynecologic and Obstetrics at

Maharat Nakhon Ratchasima Hospital with symptom of postmenopausal vaginal bleeding was requested for their consent and according to the designed questionnaire. Data on baseline characteristics and risk factors for endometrial neoplasia, such as body weight, age, menarche age, menopause age, parity, underlying disease, contraception method, family background related to cancer, hormonal therapy use and herbal-medicine use in the past 1 month.

The definition of herbal product in accordance with the Herbal Product Act B.E. 2562 (2019) are 1) Medicine from herbs including Thai traditional medicine, medicine developed from herbs, traditional medicine for human use as stated by medicine-related regulations, medicine from traditional medicine announced by the Minister through advising committee, which is for treatment, alleviation, or prevention in human. 2) Materials intended to be ingredients in the herbal product production. 3) Other materials announced by the Minister through advising committee.

The herbal medicines mentioned in this research are the herbal-containing products in several dosage forms, such as tablets, capsules, or powder which claimed to alleviate menopausal symptoms including irritable mood, hot flush, skin dullness, vaginal dryness, low libido and bone loss. According to the product claims, they inferred that the active ingredients include phytoestrogen either from beans, rice, flax, safflower, oriental motherwort, sappanwood, java ginger, Szechuan lovage, pink and blue ginger, Molineria, or Shatavari. After acquiring the permission, every patient at the outpatient department was asked to share their historical background after having physical examination and investigation with transvaginal ultrasound to record endometrial thickness and endometrial biopsy for pathological information.

This research inclusion criteria are 1) patients with clinical postmenopausal vaginal bleeding, diagnosed and treated at Maharat Nakhon Ratchasima hospital 2) patients with pathological results, which are obtained from endometrial sampling or uterine curettage and 3) patients with endometrium thickness via transvaginal ultrasound. The exclusion criteria include 1) patients treated with hormone replacement therapy 2) patients with postmenopausal bleeding that were diagnosed with other diseases, which is not related to endometrial abnormalities such as cervical cancer, uterine leiomyomas, vaginal injuries, vulva cancer, and coagulopathy 3) patients who were not willing to participate in this research 4) patients with no pathological information 5) patients whose pathological result shows inadequate tissue, reflecting unable to interpret.

The sample size was determined from the previous research and was calculated using power and sample size calculation software. The two independent proportions were selected as the proportion type, and Fisher's exact test was employed as the statistical test. Besides, the parameters were set based on the low incidence rate of endometrial neoplasia in the postmenopausal bleeding patients as follow $\alpha = 0.05$, power 80% and control: case 4:1. According to the earlier study conducted with 170 patients, the prevalence of exposure among controls and cases were 0.58 and 0.31, respectively.⁽¹²⁾ From the calculation, the minimum sample size was 160 patients, which are divided into 32 patients with herbal medicine use and 128 patients with no herbal medicine use.

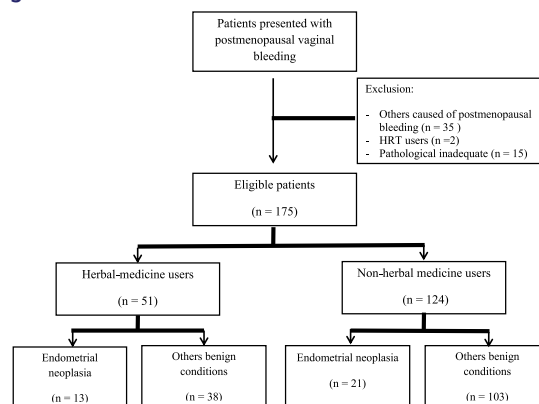
The statistical tests employed in this research consisted of Fisher's exact test for dichotomous variables and student's T-test for continuous variables. Moreover, Stata version 12 and SPSS Statistics version 25 was used for statistical data analysis. The result was considered statistically significant when p-value is lesser than 0.05.

RESULTS

At the time of study, a total of 227 patients were diagnosed with postmenopausal vaginal bleeding between June 2019 and May 2020. There were 52 patients excluded due to the exclusion criteria; 35 patients were diagnosed with other diseases unrelated to endometrial abnormalities. 2 patients took hormone replacement therapy, and 15 patients had been reported there were inadequate tissues in the pathological result. Consequently, the total of 175 patients were eligible for this research, including 51 patients who had the background of herbal medicine use and 124 patients that had no record of herbal medicine use. All patients in both groups have undergone the investigation with transvaginal ultrasound to track endometrial thickness and endometrial biopsy on the day they visit the hospital. In the herbal-medicine user group, the pathological findings revealed 13 of them have had endometrial neoplasia and 38 of them have had benign condition.

While in the non-herbal medicine user group, 21 of them were diagnosed with endometrial neoplasia and 103 of them were diagnosed having the benign condition, as illustrated in Figure 1.

Figure 1



Regarding the data from 170 patients, that mutual characteristic of both groups; herbal medicine users and non-herbal medicine users, are relatively similar except the average age of the first group, which is 61.8 ± 9.61 years while the second group is 58.75 ± 8.46 years with p-value 0.039. Where other risk factors, which can cause endometrial neoplasia, menopausal age, duration of menstruation, BMI, number of parity, underlying disease, contraception method and family background of malignancy in both groups, were found no statistically significant differences, as illustrated in Table 1.

Table 1 Demographic of post-menopausal bleeding in women with herbal-medicine users and non-users

Variables	Herbal-medicine users (n=51)	Herbal-medicine non-users (n=124)	p-value
Age (yr)	61.8 ± 9.61	58.75 ± 8.46	0.039*
Menarche (yr)	13.18 ± 1.16	13.35 ± 1.31	0.399
Menopause (yr)	50.2 ± 3.54	49.9 ± 3.87	0.633
Duration of menstruation (yr)	37.02 ± 3.97	36.54 ± 3.89	0.463
BMI kg/m² (%)			
<18	4 (7.8)	5 (4)	0.461
18-22.9	10 (19.6)	24 (19.4)	
23-24.9	12 (23.5)	21 (16.9)	
≥25	25 (49)	74 (59.7)	
Parity (%)			
0	4 (7.8)	13 (10.5)	0.236

1	9 (17.6)	14 (11.3)	
≥ 2	38 (74.5)	97 (78.2)	
Underlying (%)			
DM	16 (31.4)	24 (19.4)	0.085
CA breast	2 (3.9)	11 (8.9)	0.257
Contraception (%)			
None	20 (39.2)	54 (43.5)	0.773
OCP	9 (17.6)	14 (11.3)	
Others	22 (43.3)	56 (45.16)	
Family history of CA (%)	3 (5.9)	7 (0.56)	0.359

Regarding the endometrial biopsy findings, 13 patients out of 51 patients (25.5%) in the herbal medicine users group have had a pathological diagnosis with endometrial hyperplasia while 21 out of 124 patients (17%) in the non-herbal medicine users group have had a pathological diagnosis with endometrial neoplasia. The endometrial pathology of those patients was demonstrated in Table 2.

Table 2 Pathology of endometrium

Variables	Herbal-medicine users N (%) = 51	Non-herbal-medicine users N (%) = 124
Benign endometrial condition	38 (74.5)	103 (83)
No malignancy	24 (47.1)	54 (43.5)
Atrophic	5 (9.8)	20 (16.1)

Endometrial polyp	5 (9.8)	18 (14.5)
Hormonal effect	3 (5.9)	3 (2.4)
Endometritis	1 (2)	8 (6.5)
Endometrial neoplasia	13 (25.5)	21(17)
Simple hyperplasia without atypia	0 (0)	1 (0.8)
Complex hyperplasia with atypia	1 (2)	1 (0.8)
Endometriod carcinoma	7 (13.7)	14 (11.3)
Adenocarcinoma	4 (7.8)	3 (2.4)
Serous carcinoma	1 (2)	0 (0)
Endometrial stromal Sarcoma	0 (0)	1 (0.8)
Leiomyosarcoma	0 (0)	1 (0.8)

P-value by Chi-square test or Fisher's exact test.

The analysis of data with univariate distribution found there is no significant difference among the risk factors that cause endometrial cancer, BMI, underlying diseases, and family background of malignancy in both groups. However, the result after analyzing with the multiple logistic regression after setting the control function of the program for age, duration of menstruation, number of parity, contraception method and endometrial thickness, has presented that the patients with herbal medicine use have had rate of endometrial neoplasia 1.19 times higher than those in the non-herbal medicine users (95%CI 0.44 – 3.17, p-value = 0.722) with no statistical significance, as illustrated in Table 3.

Table 3 Factors associated with endometrial neoplasia on multivariate analysis

Variables	Univariate		Multivariate 1		Multivariate 2	
	Coef (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age ≥ 60	1.62 (0.78,2.45)	<0.001*	3.66 (1.42,9.50)	0.007*	3.89 (1.5,10.02)	0.005*
Duration of menstruation	0.78 (-0.01,1.57)	0.050*	1.74 (0.69,4.43)	0.240		
BMI	-0.51 (-1.27,0.25)	0.183				
Parity ≥ 2	-0.78 (-1.6,0.026)	0.054*	0.92 (0.31,2.81)	0.894		
Underlying						
DM	0.43 (-0.41, 1.28)	0.311				
CA breast	-0.3 (-1.85, 1.25)	0.702				
OCP users	-1.14 (-1.93, -0.36)	0.003*	0.38 (0.145,0.972)	0.044*	0.39 (0.16,0.97)	0.043*
Family history of CA	0.61 (-0.79, 2.02)	0.384				
Herbal-medicine use	0.517 (-0.27, 1.3)	0.194	1.21 (0.45,3.24)	0.691	1.19 (0.44,3.17)	0.722
Endometrial thickness	0.002 (0.014, 0.026)	<0.001*	1.14 (1.08,1.19)	<0.001*	1.12 (1.06,1.18)	<0.001*

Table 4 the association between endometrial thickness and endometrial neoplasia in women with herbal-medicine users and non-users

Endometrial thickness	Herbal-medicine users (n=51)		p-value	Non-herbal medicine users (n=124)		p-value
	Endometrial neoplasia (millimeters) (%) (n = 13)	Benign endometrial condition (millimeters) (%) (n = 38)		Endometrial neoplasia (millimeters) (%) (n = 21)	Benign endometrial condition (millimeters) (%) (n = 103)	
millimeters	17.03±12.29			8.47±6.59		<0.001*
<4	0 (0)	11 (28.9)	0.028*	0 (0)	26 (25.2)	0.010*
≥ 4	13 (100)	27 (71.1)		21 (100)	77 (74.8)	

Table 4 describes the association between endometrial thickness and endometrial neoplasia in herbal medicine user group and non-herbal medicine user group. In herbal medicine user group, the average endometrial thickness was 17.03 ± 12.29 millimeters meanwhile the average endometrial thickness of the non-herbal medicine user group was

8.47±6.59 millimeters with p-value <0.001*. There was no significant difference of the number of the patient diagnosed with endometrial neoplasia between both groups; 28.9 percentage and 25.2 percentage, respectively.

We also divided both herbal medicine user group and non-

herbal medicine user group into 2 subgroups, categorized by endometrial thickness less than 4 millimeters and more than or equal to 4 millimeters. In the herbal medicine user group, the data revealed that none of those patients has endometrial thickness less than 4 millimeters. In herbal medicine user group, there were 13 patients diagnosed with endometrial neoplasia, had endometrial thickness more than or equal to 4 millimeters and 27 patients with the benign condition with p-value 0.0028*. The pathological of benign condition in the herbal medicine user group was found in 38 patients; 11 of them have had endometrial thickness less than 4 millimeters and 27 endometrial thickness more than or equal to 4 millimeters. In the non-herbal medicine user group, there were 21 patients have had endometrial neoplasia and 77 patients have had benign conditions endometrial thickness more than or equal to 4 millimeters with p= value 0.010*.

DISCUSSION

This research has the purpose of exploring the relationship between phytoestrogen intake from Thai herbal medicine and endometrial neoplasia. The information regarding phytoestrogen amount could not be identified in the study, hence, further investigation for the association between the amount of phytoestrogen intake and endometrial neoplasia is suggested. According to the previous study⁽¹³⁻¹⁴⁾ related to herbal medicine consumption revealed that phytoestrogen intake could alleviate postmenopausal symptoms and phytoestrogen is generally perceived as a non-harmful substance for women health, however, the result of this research emphasizes that phytoestrogen should be considered as a potential risk factor which can cause endometrial neoplasia.

In this study, the incidence of endometrial neoplasia appeared to be higher than other reports in both group^(2,3). The possible reason of this incidence is that Maharat Nakhon Ratchasima Hospital is a tertiary care hospital where provides highly specialized medical care. Since most of the patients who visit Maharat Nakhon Ratchasima Hospital have already had advanced and complex diseases from 3 provinces including the population almost 5.5 million population.

After setting the control function of the program for age, duration of menstruation, number of parities, the use of combined oral contraceptive pill and endometrial thickness, we found that patients with background on herbal-medicine use to alleviate postmenopausal vaginal bleeding, had 1.19 times higher risk to have a pathological diagnosis as endometrial neoplasia (95%CI 0.44-3.17). From the previous research with case-control study,⁽¹²⁾ it was found that patients with a pathological diagnosis of endometrial neoplasia had 4.11 times higher rate than background on herbal medicine use with statistical significance (95 %CI 1.76-9.59). The study was conducted with 170 patients with postmenopausal bleeding aiming to investigate their background on the herbal medicine use through verbal conversation via phone, by this method, it could prevent any prejudice occurred during face-to-face investigation on their hospital visit. The result proves that the herbal medicine use had a higher rate of endometrial neoplasia, in accordance with the previous study,⁽¹²⁾ with no statistical difference and lower rate. However, the information could be misinterpreted due to relatively small sample size and bias occurred from patients not telling the truth to the doctor. The possible reason could be their beliefs that the patients should not inform the doctor about their herbal medicine intake.

After the multivariate analysis, the result showed that the patients with postmenopausal vaginal bleeding with the age more than 60 had higher rate of endometrial neoplasia at 3.89 with statistical significance (95 %CI 1.50 - 10.02). These results comply with the previous study which found that aging

is a factor correlated with the incidence of endometrial cancer.^(12,15-17)

Regarding the result of endometrial thickness, the previous study⁽¹⁸⁾ had shown that the endometrial thickness was correlated with endometrial neoplasia; the cut point is 4 millimeters. In this study, we found that every millimeter increase will have effect on 1.12 times higher rate of endometrial carcinoma. Primarily, we expected to analyze the data with less than 4 millimeters and more than or equal to 4 millimeters but from the result show that no patient with pathological diagnosis endometrial neoplasia had endometrial thickness less than 4 millimeters

The background on the combined oral contraceptive had a protective outcome for endometrial neoplasia with 0.39 times compared with the non-user patients (95 %CI 0.16-0.97), which is accorded with the previous study⁽¹⁹⁻²⁰⁾ that the patients who used combined oral contraceptive more than 5 years had lower risk of endometrial cancer.

As the result, patients with clinical postmenopausal vaginal bleeding in the age > 60 having high endometrial thickness should get the endometrial biopsy as they are likely to have a high risk of endometrial cancer.

The challenges of this research include the means to obtain the information on the risk factors, especially during the hospital visit at the outpatient department. Some patients might not tell the doctor that they were having herbal medicines since it could affect the doctor's prejudice. The solution is to change the tone of questions into close-ended ones or a questionnaire that let the patient fill the information themselves to support our process and gain the right information. Since this is a cross sectional study, the result shows the analysis in terms of mathematic means to see the association between the risk factor and endometrial cancer. In order to get more information on the effect of the herbal medicine use on the endometrial cancer, prospective cohort study may give more information.

CONCLUSION

There are many risk factors of endometrial neoplasia but mostly they are irreversible risks. External unopposed estrogen is the risk factor easy to control. The result of this study assures us that patients with background on herbal medicine use have effect on higher rate of endometrial neoplasia. Although it is not statistically significant, further study need to collect data from more patients to see if there is any difference between the two groups.

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