Thai Journal of Obstetrics and Gynaecology
April 2020, Vol. 28, No. 2, pp. 71-78

GYNECOLOGY

The Association between Herbal Substances and Endometrial Neoplasia in Thai Women with Postmenopausal Bleeding: A case-control study at Maharat Nakhon Ratchasima Hospital

Pete Wisodsongkram, M.D.*,
Siraya Kitiyodom, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, Thailand*

ABSTRACT

Objectives: The purpose was to study the association of herbal-medicine users on the endometrial pathology of patients who were diagnosed with postmenopausal bleeding.

Materials and Methods: This research was a retrospective case control study conducted on 170 patients with postmenopausal bleeding who received treatment and underwent endometrial biopsy for pathological examination at Maharat Nakhon Ratchasima Hospital during September 1, 2016 to September 30, 2017. Data were collected from medical records and telephone interviews to obtain information about their baseline characteristics and history of herbal medicine use.

Results: Regarding the age of the onset of postmenopausal bleeding, there were statistically different between the two groups: patients with pathological diagnosis of endometrial neoplasia had a mean age of 59 years, which was higher than those with pathological diagnosis of other benign conditions that had a mean age of 56 years. In addition, the mean age at menopause of patients with pathological diagnosis of endometrial neoplasia was 52 years, which was significantly higher than patients with pathological diagnosis of other benign conditions that had a mean age at menopause of 50 years. With respect to body mass index (BMI), it was evident that there was a larger number of patients with endometrial neoplasia who had a BMI of over or equal to 30 kg/m^2 than patients with other benign conditions, with statistical significance. After controlling for BMI and age at menopause, patients with pathological diagnosis of endometrial neoplasia had 4.11 times higher rates of herbal medicine user than patients with pathological diagnosis of other benign conditions (95% confidence interval 1.76-9.59).

Conclusion: Patients who were diagnosed with endometrial neoplasia had 4.11 times higher rate of herbal medicine use than those with pathological diagnosis of other benign conditions after controlling for BMI and age at menopause.

Keywords: herbal medicines, postmenopausal bleeding, endometrial hyperplasia, endometrial cancer.

Correspondence to: *Pete Wisodsongkram, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand, E-mail: pete.v97@gmail.com*

Received: 27 September 2018, **Revised:** 3 January, 2019, **Accepted:** 3 January 2019

ความสัมพันธ์ของการรับประทานยาสมุนไพรต่อเยื่อบุโพรงมดลูกในสตรีที่มีเลือดออกหลังหมดประจำเดือนในโรงพยาบาลมหาราชนครราชสีมา

พิชญ์ วิโสจสงคราม, สิรยา กิติโยดม

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลทางพยาธิวิทยาเยื่อบุโพรงมดลูกของสตรีที่มีภาวะเลือดออกหลังหมดประจำเดือน ในสตรีที่ใช้และไม่ใช้ยาสมุนไพรสำหรับสตรี*

วัสดุและวิธีการ: *เป็นการศึกษาแบบ retrospective case control study design ในสตรีที่มีภาวะเลือดออกทางช่องคลอดหลังหมดประจำเดือนที่เข้ารับการตรวจหรือรักษาในโรงพยาบาลมหาราชนครราชสีมา และต้องได้รับการตรวจวินิจฉัยเก็บเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยา ตั้งแต่วันที่ 1 กันยายน 2559 ถึงวันที่ 30 กันยายน 2560 จำนวน 170 คน โดยใช้ข้อมูลจากเวชระเบียนโรงพยาบาลและการสัมภาษณ์ทางโทรศัพท์ตามแบบสอบถาม เกี่ยวกับข้อมูลพื้นฐานต่างๆ รวมถึงประวัติการใช้ยาสมุนไพรสำหรับสตรี*

ผลการศึกษา: *ในสตรีที่มีภาวะเลือดออกทางช่องคลอดหลังหมดประจำเดือนพบว่า อายุขณะที่มีอาการเลือดออกทางช่องคลอดหลังหมดประจำเดือนในกลุ่มที่มีผลของพยาธิวิทยาเยื่อบุโพรงมดลูกตั้งแต่ระดับ hyperplasia ขึ้นไปเฉลี่ย 59 ปี ซึ่งมากกว่าสตรีที่มีผลของพยาธิวิทยาเยื่อบุโพรงมดลูกเป็นอย่างอื่นเฉลี่ย 55 ปี อย่างมีนัยสำคัญทางสถิติ นอกจากนี้พบว่าอายุที่หมดประจำเดือนนั้นเฉลี่ย 52 ปี ในกลุ่มสตรีมีผลของพยาธิวิทยาของเยื่อบุโพรงมดลูกตั้งแต่ระดับ hyperplasia ขึ้นไปมากกว่าสตรีที่ผลของพยาธิวิทยาของเยื่อบุโพรงมดลูกเป็นอย่างอื่นเฉลี่ย 50 ปี อย่างมีนัยสำคัญทางสถิติ อีกทั้งยังพบว่าสตรีที่มีผลของพยาธิวิทยาของเยื่อบุโพรงมดลูกร้ายแรงตั้งแต่ระดับ hyperplasia ขึ้นไป มีการใช้ยาสมุนไพรสำหรับสตรีมากกว่าสตรีที่มีผลของพยาธิวิทยาของเยื่อบุโพรงมดลูกเป็นอย่างอื่นถึง 4.11 เท่า (95% confidence interval 1.76-9.59) เมื่อควบคุมปัจจัยด้านดัชนีมวลกายและอายุที่สตรีในกลุ่มตัวอย่างหมดประจำเดือน*

สรุป: *การศึกษาพบว่า ผลชิ้นเนื้อทางพยาธิวิทยาของเยื่อบุโพรงมดลูกในสตรีที่มีภาวะเลือดออกทางช่องคลอดหลังหมดประจำเดือนเป็น hyperplasia ขึ้นไป มีประวัติการใช้ยาสมุนไพรสำหรับสตรีมากเป็น 4.11 เท่า อย่างมีนัยสำคัญทางสถิติ หากควบคุมปัจจัยด้านดัชนีมวลกายและอายุที่สตรีในกลุ่มตัวอย่างหมดประจำเดือน เมื่อเปรียบเทียบกับสตรีที่มีผลชิ้นเนื้อทางพยาธิวิทยาของเยื่อบุโพรงมดลูกเป็นอย่างอื่น*

คำสำคัญ: *ยาสมุนไพรสำหรับสตรี, เลือดออกหลังหมดประจำเดือน, การเจริญเกินของเยื่อบุโพรงมดลูก, มะเร็งเยื่อบุโพรงมดลูก*

Introduction

Endometrial cancer is a type of cancer that affects female reproductive organs and is the third most common gynecologic cancer in Thailand. According to WHO, the incidence rate of endometrial cancer in Thailand is 4.3 per 100,000 female population[1]. Based on the data obtained from Maharat Nakhon Ratchasima Hospital[2], there were 479 female patients diagnosed with postmenopausal bleeding during October 1, 2008 to September 30, 2011, whereby endometrial cancer and endometrial hyperplasia were found in 13.6% and 8.6% of the patients, respectively.

It is widely known that the risk factors for endometrial neoplasia are associated with age (above 50 years), obesity, diabetes, nulliparity, menstruation span, and intake of estrogen[3-5]. An intake of estrogen without progesterone affects the regeneration and growth of the endometrium, which subsequently increases the risk of endometrial cancer[6-8].

On the contrary, estrogen deficiency affects emotions and contributes to decreased bone mass, vaginal dryness, metabolic dysfunction, and amenorrhea[9]. In Thailand, there are a variety of herbal medicines available in the market, many of which claim to nourish the body and alleviate menopause symptoms, as well as brighten the skin and treat hormonal imbalances. Nonetheless, it is possible that these herbal medicines contain environmental estrogenic contaminants. A previous study[10] found that the uterus of oophorectomized mice receiving extracts of Thai herbs was heavier than of their counterparts.

Materials and Methods

This research was a retrospective case control study aimed to examine the association of herbal-medicine users on the endometrial pathology of female patients who were diagnosed with postmenopausal bleeding.

The research was conducted on a sample of 170 female patients with postmenopausal bleeding who were diagnosed or treated at Maharat Nakhon Ratchasima Hospital during September 1, 2016 to September 30, 2017 and had been approved by the Research Ethics Committee of Maharat Nakhon Ratchasima Hospital. The sample was randomly selected by the order of the date of visit. Data were collected from the medical records of the hospital. In addition, telephone interviews were conducted with patients upon their consent and according to the designed questionnaire. To minimize bias, the interviews were performed by one interviewer. Data pertaining to baseline characteristics and risk factors for endometrial neoplasia, such as age, age at menarche, age at menopause, gravidity, diabetes mellitus, use of oral contraceptive pills, and history of herbal medicine use, were obtained. Herbal medicines selected for this research were those that claimed to treat menopausal symptoms (such as irritability, skin dullness, bone loss, mild uterine prolapse, low libido, vaginal dryness, and sagging of breasts) and contained safflower, oriental motherwort, sappanwood, Java ginger, Szechuan lovage, pink and blue ginger, and Molineria latifolia as the main ingredients. A previous study[11] found that these herbs are the essential ingredients of herbal medicines for women.

The inclusion criteria of this research were: 1) patients with postmenopausal bleeding who were diagnosed or treated at Maharat Nakhon Ratchasima Hospital and 2) patients with pathological results obtained from endometrial sampling or curettage. In addition, the exclusion were 1) patients who underwent hormone replacement therapy; 2) patients with postmenopausal bleeding of which the causes were not related to endometrial abnormalities, such as vaginal injuries or inflammation, uterine leiomyomas, cervical cancer, vulvar cancer, thyroid disorders, and coagulopathy; 3) patients who had difficulty communicating or responding to the interview questions, such as those with cognitive impairment; 4) patients who were not willing to participate in the research; 5) patients who did not have pathological information; 6) patients whose treatment could not be monitored continuously; and 7) patients who discontinued the use of herbal medicines for more than 1 year.

The sample size was determined from the pilot study conducted during December 1, 2016 to March

31, 2017 and was calculated using a 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. In addition, the parameters were set on the basis of the low incidence rate of endometrial neoplasia in postmenopausal bleeding patients, as follows: α = 0.05, power = 80%, and control: case ratio = 4:1. According to the pilot study conducted on 100 patients, the prevalence of exposure among controls and cases were 0.03 and 0.2, respectively.

Upon calculation, the minimum sample size was found to be 170, whereby the sample was divided into 34 patients with pathological diagnosis of endometrial neoplasia and 136 patients with pathological diagnosis of other benign conditions. Based on the pilot study and the assumption that 30% of prospective participants cannot be reached or are not willing to participate in the telephone interview, a minimum of 221 patients were required for the research.

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 12.0 was used for statistical data analysis. The results were considered statistically significant when p value < 0.05.

Results

At the time of study, there were a total of 300 patients diagnosed with postmenopausal bleeding during September 1, 2016 to September 30, 2017. There were 69 patients who did not meet the sampling criteria, comprising 46 patients who could not be reached, 1 patient who did not have pathological information, 19 patients with postmenopausal bleeding of which the causes were not related to endometrial abnormalities, and 3 patients who were not willing to provide information. Thus, a total of 231 patients were included in the research. The sample was further divided into two groups: 40 patients with endometrial neoplasia and 191 patients with other benign conditions. After that, the sample was randomly selected by the order of the date of visit until 34 patients with endometrial neoplasia and 136 patients with other benign conditions were obtained (Fig. 1).

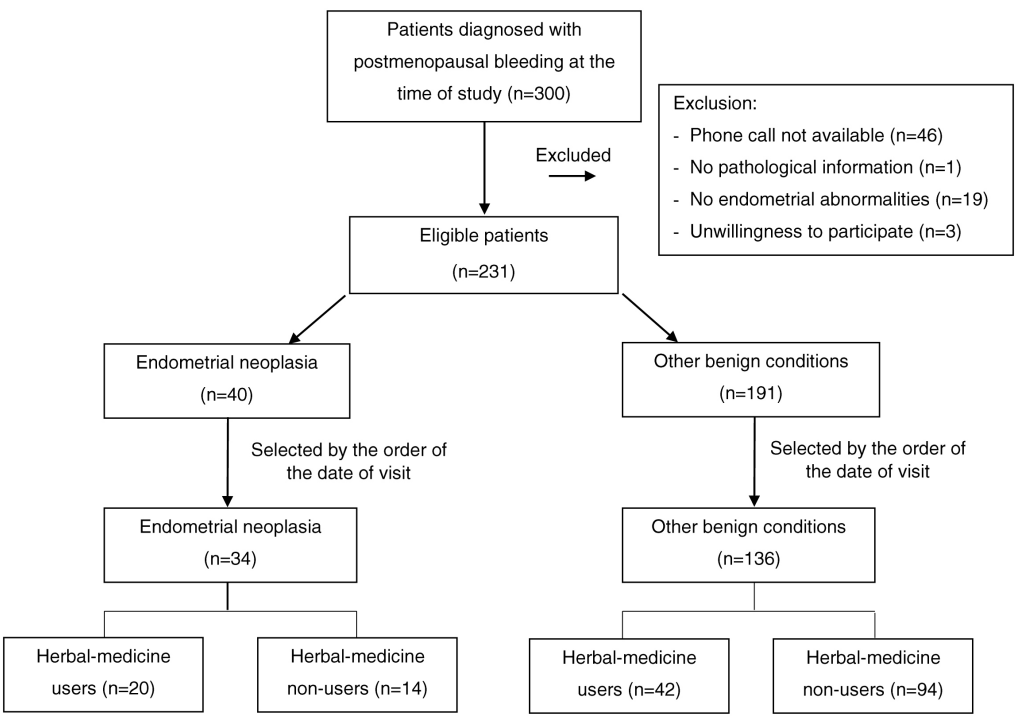

Fig. 1. Participant enrollment.

Regarding the demographic characteristics of the sample, it was found that there were statistically different between the two groups in terms of age, age at menopause and body mass index (BMI). The mean age of patients with pathological diagnosis of endometrial neoplasia was 59 years (±8, range 49 - 79 years), which was higher than patients with pathological diagnosis of other benign conditions that had a mean age of 56 years (±8.8, range 44-89 years) with p value = 0.047. With respect to the age at menopause, patients with pathological diagnosis of endometrial neoplasia had a mean age at menopause of 52 years (±3.6, range 47-63 years), which was higher than patients with pathological diagnosis of other benign conditions that had a mean age at menopause of 50 years (±3.3, range 43-6o years) with p value < 0.001. Moreover, across patients with pathological diagnosis of endometrial neoplasia, 23 patients had BMI ≥ 30 kg/m^2 (67.6%). This was statistically significantly higher than patients with pathological diagnosis of other benign conditions, of which 62 patients were found to have BMI ≥ 30 kg/m^2 (45.6%) with p value = 0.034. Alternatively, there were no statistically significant differences between the two groups in terms of age at menarche, gravidity, diabetes mellitus, and use of oral contraceptive pills (Table 1).

Table 1. Demographic Characteristics.

Characteristics	Endometrial neoplasia (n = 34)	Other benign conditions (n = 136)	p value
Age (years)	59.1 ± 8.0	55.8 ± 8.8	0.047
Age at menarche (years)	11.9 ± 1.7	11.9 ± 2.6	0.936
Age at menopause (years)	52.1 ± 3.6	50.0 ± 3.3	< 0.001
BMI			
< 30 kg/m^2	11 (32.4)	74 (54.4)	0.034
≥ 30 kg/m^2	23 (67.6)	62 (45.6)	
Gravidity			
0-1	8 (23.5)	25 (18.4)	0.823
2	14 (41.2)	59 (43.4)	
≥ 3	12 (35.3)	52 (38.2)	
DM	9 (26.5)	20 (14.7)	0.126
History of OCP use			
None	21 (61.8)	84 (61.8)	0.614
< 5 years	12 (35.2)	41 (30.1)	
≥ 5 years	1 (3)	11 (8.1)	

Data were presented as mean ± standard deviation and n (%)
BMI: body mass index, DM: diabetes mellitus, OCP: oral contraceptive pills

Concerning the duration of herbal medicine use, the mean duration of herbal medicine use in patients with pathological diagnosis of endometrial neoplasia was 4.35 years (± 3.17, range 1 - 15 years).

Upon endometrial biopsy, it was found that there were 34 patients with pathological diagnosis of endometrial neoplasia, 20 of whom had a history of herbal medicine use. Meanwhile, there were 136 patients with pathological diagnosis of other benign conditions, of which 42 patients had a history of herbal medicine use. The endometrial pathology of patients was demonstrated in Table 2.

Table 2. Histology of endometrium of 170 women with postmenopausal bleeding.

Pathology	Herbal medicine users (n = 62)	Herbal medicine non-users (n = 108)
Benign endometrial condition		
Atrophic endometrium	9 (14.5)	25 (23.1)
Proliferative pattern	6 (9.7)	23 (21.3)
Secretory pattern	5 (8.1)	21 (19.4)
Endometritis	5 (8.1)	9 (8.3)
Stromal or glandular breakdown	8 (12.9)	6 (5.6)
Endometrial polyp	5 (8.1)	6 (5.6)
Hormonal effect	4 (6.5)	4 (3.7)
Endometrial neoplasia		
Simple hyperplasia without atypia	2 (3.2)	7 (6.5)
Complex hyperplasia with atypia	2 (3.2)	1 (0.9)
Endometrioid carcinoma	8 (12.9)	4 (3.7)
Adenocarcinoma	4 (6.5)	1 (0.9)
Clear cell carcinoma	1 (1.6)	1 (0.9)
Endometrial stromal sarcoma	1 (1.6)	0 (0.0)
Serous carcinoma	1 (1.6)	0 (0.0)
Mixed serous and endometrioid carcinoma	1 (1.6)	0 (0.0)

Data were presented as n (%)

Upon analysis of data with multiple logistic regression and after controlling for BMI and age at menopause, it was evident that patients with pathological diagnosis of endometrial neoplasia had 4.11 times higher rate of herbal medicine use than patients with pathological diagnosis of other benign conditions (95% confidence interval (CI) 1.76-9.59) (Table 3).

Table 3. Relationship between herbal medicine use and endometrial pathology of postmenopausal bleeding.

Herbal medicine use	Neoplasia	Other benign Conditions	Unadjusted ORs (95%CI)	Adjusted ORs (95%CI)
Use (%)	20 (58.8)	42 (30.9)	3.67 (1.64 - 8.20)	4.11 (1.76-9.59)
Non-use (%)	14 (41.2)	94 (69.1)	1.00 (reference)	1.00 (reference)

[#]Adjusted for body mass index, and age at menopause
ORs: odds ratio, CI: confidence interval

Discussion

This research applied fundamental knowledge on factors that contribute to the incidence of endometrial neoplasia and, importantly, the continuous use of estrogen[6-8]. The research was conducted under the assumption that the herbal medicines available in Thailand may be environmentally estrogen contaminated and carry putative claims of health benefits. This was consistent with previous studies[12,13], conducted on healthy postmenopausal women who were given

Pueraria mirifica pills at a daily dose of 20, 30, and 50 mg for a period of 24 weeks. After comparing the results with the placebo group, it was evident that Pueraria mirifica was able to treat vaginal dryness, dyspareunia, and vaginal atrophy, as well as reducing the level of bone-specific alkaline phosphatase and the rate of bone turnover. Moreover, previous studies suggested that Pueraria mirifica may be effective in inhibiting bone resorption by acting as an antiresorptive agent.

This research found that, after controlling for BMI and age at menopause, the historical use of herbal medicines amongst patients with postmenopausal bleeding was 4.11 times higher in patients with pathological diagnosis of endometrial neoplasia than in patients with pathological diagnosis of other benign conditions (95%CI 1.76-9.59). Regarding the duration of herbal medicine use, the mean duration of herbal medicine use in patients with pathological diagnosis of endometrial neoplasia was 4.35 years (± 3.17, range 1-15 years). These results were consistent with a previous randomized, double-blind, placebo-controlled study[14], which found that an intake of phytoestrogen had an endometrial effect on women and contributed to the formation of endometrial hyperplasia with statistical significance.

In the aspect of the patients' age, there were statistically different between the two groups: patients with pathological diagnosis of endometrial neoplasia had a mean age of 59 years (± 8, range 49-79 years), which was significantly higher than patients with pathological diagnosis of other benign conditions that had a mean age of 56 years (± 8.7, range 44-89 years) ($p = 0.047$). Moreover, the mean age at menopause of patients with pathological diagnosis of endometrial neoplasia was 52 years (± 3.6, range 47-63 years), which was significantly higher than those with pathological diagnosis of other benign conditions that had a mean age at menopause of 50 years (± 3.3, range 43-60 years) with $p < 0.001$. These results conformed to previous studies[15-18], which found that aging and late-onset menopause were correlated with the incidence of endometrial cancer with statistical significance.

Regarding the BMI of patients with endometrial neoplasia, there were 23 patients with BMI ≥ 30 kg/m^2 (67.6%) and 11 patients with BMI < 30 kg/m^2 (32.4%). Meanwhile, across patients with other benign conditions, 62 had BMI ≥ 30 kg/m^2 (45.6%) and 74 had BMI < 30 kg/m^2 (54.5%). Accordingly, it can be inferred that there were statistically significant higher number of patients with BMI ≥ 30kg/m^2 in the endometrial neoplasia group at the p value of 0.034, which conforms to the previous study[19]. On the contrary, there were no statistically significant differences between the two groups in terms of age at menopause, gravidity, diabetes mellitus and contraceptive use.

Concerning the limitations of this research, there were some underlying errors in connection with the patients' responses to research questions, particularly when they were inquired of their past events. Moreover, patients may provide inaccurate responses to shorten the length of time spent in the telephone interview or attempt to provide responses that correspond to the interviewer's expectations, which subsequently leads to response bias. According to previous studies[20,21], close-ended questions that are short, concise, and straightforward were found to give more accurate responses than open-ended questions. Hence, close-ended questions were employed in the telephone interview to minimize errors in this research and the interview were performed by one interviewer. Furthermore, the sample was selected at the time of the patients' most recent visit to Maharat Nakhon Ratchasima Hospital, whereby patients with more than 1-year withdrawal from herbal-medicine use and patients with intellectual disability were excluded from the research. Although this research was a preliminary study, the findings of this research could be used as a guideline for future researches on the use of herbal medicines.

Conclusion

There are multiple risk factors for endometrial neoplasia, one of which includes the intake of estrogens. As far as this research is concerned, herbal medicines available in Thailand may contain an unknown amount

of phytoestrogens, which may contribute to the increased risk of endometrial neoplasia. Based on the results of this research, female patients with pathological diagnosis of endometrial neoplasia had a significantly higher rate of herbal medicine use than those with pathological diagnosis of other benign conditions. Therefore, the safety aspects of long-term herbal medicine use amongst postmenopausal women should be taken into consideration.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBACAN 2008. Int J Cancer 2010;127:2892-916.
2. Kitiyodom S. The Endometrial Histological Findings in Women with Postmenopausal Bleeding at Maharat Nakhon Ratchasima Hospital: 3-Year experience. Nakhon Ratch Med Bull 2011;35:152-3.
3. Centers for Disease Control and Prevention. Uterine cancer. Atlanta: CDC 2018
4. American cancer society. Endometrial cancer risk factors. USA [internet]. 2016 [cited 2018 sep 19]; available from: https://www.cancer.org/cancer/endometrial-cancer/causes-risks-prevention/risk-factors.html.
5. Dowdy SC, Mariani A, Lurain JR. Uterine cancer. In Berek JS, Berek DL, editors. Berek & Novak's gynecology. 15th ed. United States of America: Lippincott Williams and Wilkins 2012;1251-4.
6. Fournier A, Dossus L, Mesrine S, Vilier A, Rault MCB, Chapelon FC, et al. Risks of endometrial cancer associated with different hormone replacement therapies in the E3N cohort, 1992-2008. Am J Epidemiol 2014;180:508-17.
7. Trabert B, Wentzensen N, Yang HP, Sherman ME, Hollenbeck AR, Park Y, et al. Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? Int J Cancer 2012;132;417-26.
8. Brinton LA, Felix AS. Menopausal hormone therapy and risk of endometrial cancer. J Steroid Biochem Mol Biol 2013;142:83-9.
9. Burger HG. Physiology and endocrinology of the menopause. Med J 2006;34:27-30.
10. Wongbutdee J, Kamdang S, Joomprabutra S, Chaaroenchai L. Study of estrogenic effect on estrogen-dependent tissues of phytoestrogen extraction of Thai medicinal plants in Ubon Ratchatani province. IJPS 2012;8:34-8.
11. Kanchanapoo J, Kaewamatawong R, Khamdang S, Chinsai K, Ubolwat S, Jandee K. Effects of Thai herbs used in traditional women remedies on the uterine contraction. Thai Pharmaceutical Health Sci J 2011;3:203.
12. Virojchaiwong P, Suvithayasiri V, Itharat A. Comparison of Pueraria mirifica 25 and 50 mg for menopausal symptoms. Arch Gynecol Obstet 2011;284:411-9.
13. Manonai J, Chittacharoen A, Udomsubpayakul U, Theppisai H, Theppisai U. Effects and safety of Pueraria mirifica on lipid profiles and biochemical markers of bone turnover rates in healthy postmenopausal women. Menopause 2008;15:530-5.
14. Unfer v, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril 2004;82:145-7.
15. Dangal G. A study of endometrium of patients with abnormal uterine bleeding at Chitwan valley. Kathmandu Univ Med J 2003;1:110-2.
16. Hileeto D, Fadare O, Martel M, Zheng W. Age dependent association of endometrial polyps with increased risk of cancer involvement. World J Surg Oncol 2005;3-6.
17. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2001;15:341-54.
18. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, Dai Q, et al. Menstrual and reproductive factors and endometrial cancer risk: results from a population-based case-control study in urban Shanghai. Int J Cancer 2004;108:613-9.
19. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study. BMJ 2007; 335:1-11.
20. Carr ECJ, Worth A. The use of the telephone interview for research. NT Res 2001;6:513-9.
21. Mathiyazhagan T, Nandan D. Survey research method. Media Mimansa 2010;43-4.