Clinical Effects of 17 Beta-Estradiol and Norethisterone Acetate in Postmenopausal Thai Women

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Abstract

Objective : To compare the climacteric symptoms, the bleeding patterns, side effects, endometrial thickness, serum follicular stimulating hormone (FSH) and estradiol level in postmenopause Thai women who received this drug and placebo.

Study design : Double blind, randomized placebo controlled trial.

Material and Method : Sixty postmenopausal women attending the menopause clinic at Chulalongkorn Hospital from July, 1996 to December, 1996, were enrolled in the study. The patients were randomized to receive the placebo or drug (17 beta-estradiol 2 mg and norethisterone acetate 1 mg) continuously. After 12 months, 13 patients in the drug group were switched to have placebo and 13 patients in the placebo were switched to the drug group. Recording of patient characteristics, physical and gynecologic examination, pap smear, breast examination and mammogram, climacteric symptom scores, transvaginal ultrasonography, serum FSH and Estradiol level were performed prior to the study. Physical examinations, breast palpitations, measurement of body weight and blood pressure, climacteric symptom scores and side effects were repeated at 3, 6, 12, 18 months. Gynecologic examination, pap smear, serum FSH and estradiol, transvaginal ultrasonography, were repeated at 12 months.

Results : The women in the drug group had fewer climacteric symptoms than baseline after 6 months. The incidence of amenorrhea was 74.0 per cent at 12 months. The incidence of abnormal uterine bleeding (spotting and breakthrough bleeding) was 37.0 per cent at 3 months, 29.6 per cent at 6 months, 25.9 per cent at 12 months and 7.1 per cent at 18 months. The women in the drug group had fewer climacteric symptoms than baseline after 6 months. Breast tenderness was the most common side effect. The endometrial thickness decreased significantly in the drug group. Serum FSH decreased and serum estradiol increased significantly in the drug group.

Conclusion : This combined regimen was more effective in relieving the climacteric symptoms in women who used the drug than those who used the placebo. There was a high incidence of amennorhœa after 12 months. But there was also a high frequency of abnormal bleeding in the first 3 months of treatment. Counseling on the bleeding pattern and common side effects

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should be conducted before starting the treatment to increase the compliance. This combined regimen proved to be a useful alternative for postmenopausal Thai women who prefer to avoid cyclic bleeding from sequential therapy.

Key word : Combined Continued HRT, Postmenopause

LIMPAPHAYOM K & BUNYAVEJCHEVIN S
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Estrogen replacement therapy (ERT) can prevent vasomotor symptoms and urogenital atrophy and protect postmenopausal women from osteoporosis[1]. To prevent the risk of endometrial hyperplasia and carcinoma due to prolonged unopposed estrogen,[2,3] progestogen is added to ERT for the last 10 days of each month[4-9]. However, this sequential regimen of estrogen and progestogen can produce menstruation–like vaginal bleeding and spotting which can be unacceptable to some women [10]. A continuous combined regimen comprising a daily dose of estrogen and progestogen has been introduced which can lead to atrophic endometrium and amenorrhoea[11,12]. But with this continuous regimen, a high incidence of bleeding irregularities has been observed during the first 3 cycles[13-15]. After a 3 month-period, there was a higher incidence of amenorrhoea[1,13,15-17]. This regimen can help increase acceptability in menopausal women who want to avoid episodes of bleeding. Furthermore, a continuous combined regimen was found to reduce symptoms sometimes associated with cyclic hormonal therapies, such as bloating, depression and irritability[18,19]. Among many progestogens, noresthisterone acetate was the most effective in preventing bone loss and inducing amenorrhoea during long- term treatments[16,20-22]. Hence, the combination of 17 beta-estradiol and norethisterone acetate should be useful not only for the treatment of menopausal symptoms and prevention of osteoporosis but also for increasing compliance to long-term treatment.

Up to now, there has been no report on this combination in postmenopausal Thai women. Therefore, this study was conducted to compare the climacteric symptoms, bleeding patterns, side effects, endometrial thickness, serum follicular stimulating hormone (FSH) and estradiol level in postmenopausal Thai women receiving this drug *vs* placebo. The changes in metabolic parameters were also studied. Because of the large amount of data relating to other parameters such as bone density, lipid measurements, and liver function parameters, these will be reported in future articles.

MATERIAL AND METHOD

Permission to conduct this study was given by the Faculty of Medicine, Chulalongkorn University (Research and Ethics Committee). It was designed as a prospective randomized controlled study. Sixty postmenopausal women attending the menopause clinic at Chulalongkorn Hospital between July and December, 1996, were enrolled in the study. Their ages ranged between 45 and 65 years with intact uterus and menopause diagnosed on the basis of amenorrhoea for at least 12 months, Follicle Stimulating Hormones (FSH) > 35 IU/L, Estradiol (E_2) < 50 pmol/L. Exclusion criteria were history of estrogen-dependent tumor, active or chronic liver disease or history of liver disease where the liver function tests had failed to return to normal, deep vein thrombosis, thromboembolic disorders, cerebrovascular accidents or past history of these conditions associated with estrogen use, abnormal genital bleeding of unknown etiology, porphyria, hormone replacement therapy within the previous year, uncontrolled hypertension or diabetes mellitus.

All patients were randomly assigned into either the placebo or the drug group. During the first three months, 7 cases withdrew from the study

(4 in the drug group and 3 in the placebo group). The reasons were; change of residence to another city (3 cases), lack of time for participation (2 cases) and failure to keep appointments (2 cases). The study group continuously received 2 mg of 17 beta-estradiol and 1 mg of norethisterone acetate daily. After a 12 month period, 13 patients in the drug group were switched to placebo and 13 patients of the placebo group were switched to the drug (Fig. 1). All the patients continued with the treatments until the end of the 18-month period.

Patient characteristics, physical and gynecological examination, breast examination and mammogram, climacteric symptom scores, transvaginal ultrasonography, serum FSH and estradiol levels were performed prior to the study. The measurements of the FSH and estradiol level were carried out by using the time-resolved fluoroimmunoassay (FIA) method. The subjects were instructed to record in a diary every occurrence of bleeding during the treatment cycles. Bleeding and spotting were defined as vaginal bleeding that either did or did not require sanitary protection. The following definitions were used for data analysis. Amenorrhoea was defined as absence of any bleeding or spotting during medication. Irregular bleeding and spotting were defined as bleeding and spotting that occurred at any time during the study.

Physical examinations, breast palpation, measurement of body weight and blood pressure, climacteric symptom scores and side effects were repeated at 3-, 6-, 12-, and 18-month intervals. Gynecological examination, Pap smear, serum FSH and estradiol, transvaginal ultrasonography, were repeated at 12-month intervals. Endometrial biopsy, using the Pipelle aspiration technique,[23] was performed in cases of suspected malignancy or of abnormal bleeding persisting for 12 months.

Statistical analysis of patient characteristics was carried out between groups using the unpaired student T-test and within the same group by using the one-way-analysis of variance (ANOVA) and paired *t*-test. A statistics program, SPSS® version 7.5 for Microsoft Windows® 98, was used for statistical analysis.

RESULTS

There was no statistically significant difference between the groups with respect to any patient characteristics (Table 1). The climacteric score decreased significantly from 23.6 at month 0 to 14.7 after 6 months, 13.8 after 12 months and

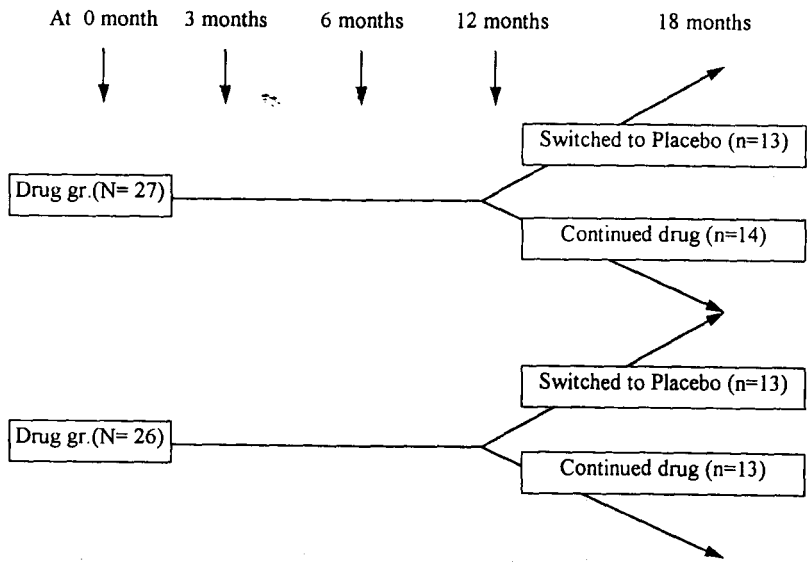

Fig. 1. Study Design.

Table 1. Patients characteristics.

Characteristics	Drug (N=27)		Placebo (N= 26)	
	Mean ± SD.	Range	Mean ± SD.	Range
Age (years)	53.4 ± 5.2	46-62	53.7 ± 4.6	45-64
Duration of menopause (years)	4.8 ± 3.8	1-17	4.9 ± 4.0	1-15
Menarche (years)	13.7 ± 1.7	11-18	14.1 ± 1.5	12-18
Age at menopause (years)	48.6 ± 3.7	42-56	48.8 ± 3.4	42-54
Weight (kg)	55.2 ± 7.2	40-68	57.5 ± 9.4	44-83
Height (cm)	152.0 ± 4.8	141.5-161	152.6 ± 4.0	144-161
Systolic blood pressure (mmHg)	118.9 ± 9.8	100-140	117.3 ± 14.6	90-140
Diastolic blood pressure (mmHg)	75.3 ± 7.3	60-90	76.5 ± 9.4	60-88
Parity	2.4 ± 1.5	0-6	2.6 ± 1.4	0-5
	N	%	N	%
Breast feeding				
• Yes	3	11.1	3	11.5
• No	24	88.9	23	88.5
Regular exercise				
• Yes	17	63.0	23	88.5
• No	10	37.0	3	11.5
Profession				
• Employee	8	29.6	2	7.7
• Government officer	4	14.8	10	38.5
• Business	2	7.4	3	11.5
• Housewife	13	48.1	11	42.3
Income (Bath)				
• < 5,000	5	18.5	6	23.1
• 5,000-10,000	6	22.2	4	15.4
• 10,001-20,000	5	18.5	3	11.5
• 20,001-50,000	9	33.3	9	34.6
• >50,001	2	7.4	4	15.4

Table 2. Climacteric symptom score (mean ± SD.)

Group	At month 0	At month 3	At month 6	At month 12	At month 18	At month 18 (Drug switched to Placebo during 12 –18 mo.)	At month 18 (Placebo switched to drug during 12 –18 mo.)
Drug	23.6±16.9 (N=27)	17.7±14.4 (N=27)	14.7±11.7* (N=27)	13.8±9.58*, ** (N=27)	12.7±6.0*, ** (N=14)	21.5±9.6 (N=13)	-
Placebo	23.5±15.2 (N=26)	21.0±14.1 (N=26)	19.5±14.5 (N=26)	20.5±13.7** (N=26)	20.92±11.2** (N=13)	-	17.5±13.0 (N=13)

* Significant statistical difference at $p < 0.05$ when compared to the 0 month period within the same groups.
** Significant statistical difference at $p < 0.05$ when compared between groups.

continued to decrease after 18 months (mean score = 12.7) when compared within groups. But in those patients who switched to placebo after 12 months, the score (21.5) was increased to one close to the pre-treatment level (23.6). Whereas, in the placebo groups, there was no significant difference within the groups. In those cases who switched to the drug, the score showed a trend to decrease. Upon comparing the groups, there were statistically significant differences after 12 and 18 months (Table 2). Table 3 summarizes the bleeding pattern. The incidence of amennorhoea increased with time, 74.1 per cent after 12 months and 92.9 per cent after 18 months. The irregular spotting and bleeding also decreased with time. Irregular spotting within the first 3 months decreased from 25.9 per cent to 18.5 per cent after 12 months. Irregular bleeding decreased from 11.1 per cent after 3 months to 7.4 per cent after 12 months and was not found after 18 months. There was one case in the drug group that still had spotting after 18 months. Endometrial biopsy was performed in this case and an atrophic endometrial pattern was found. The mean of bleeding days was 10.3 days within the first 3 months and decreased to 8.5 days after 12 months. In this group, the women who switched to placebo after 12 months had no bleeding after 18 months. In the placebo group, there was only one case of spotting which lasted for two days (Table 2).

There were two cases of mild pelvic pain in the drug group which responded to analgesic treatment. Six and three cases of nausea and vomiting, respectively, were noted after 3 and 6 months in the drug group. Twenty-four cases had breast tenderness within the first three months which decreased with time. The breast examinations were within normal limits (Table 4).

Transvaginal ultrasonogram revealed a decrease of endometrial thickness in the drug group after 12 months (5.0 *vs* 4.1 mms), whereas, there was no change in the placebo group (Table 5).

After 12 months, serum FSH decreased and estradiol increased significantly in the drug group in response to the treatment level. There was no significant change in the placebo group (Table 6).

Table 3. Bleeding pattern.

Abnormal uterine bleeding	Drug				Drug Switched to Placebo during 12-18 mo.	Placebo				Placebo Switched to Placebo during 12-18 mo.
	At month 3 (N=27)	At month 6 (N=27)	At month 12 (N=27)	At month 18 (N=27)	At month 18 (N=27)	At month 3 (N=27)	At month 6 (N=27)	At month 12 (N=27)	At month 18 (N=27)	At month 18 (N=27)
Incidence (%)										
• Amenorrhoea	17 (63.0)	19 (70.4)	20 (74.1)	13 (92.9)	13 (100.0)	26 (100.0)	25 (96.2)	26 (100.0)	13 (100.0)	8 (61.5)
• Irregular spotting	7 (25.9)	7 (25.9)	5 (18.5)	1 (7.1)	-	-	1 (3.8)	-	-	4 (30.8)
• Irregular bleeding	3 (11.1)	1 (3.7)	2 (7.4)	-	-	-	-	-	-	1 (7.7)
Mean and SD. of Bleeding days (days/ month)	10.3±8.9	10.4±8.9	8.5±9.91	28±0	-	-	2±0	-	-	5.5±1.2
Range (days)	2-28	2-28	3-28	-	-	-	-	-	-	3-9

DISCUSSION

The continuous regimen applied has the advantage of preventing the regular bleeding seen during sequential therapy. According to this study,

Table 4. Side effects.

	Drug				Drug Switched to Placebo during 12-18 mo.	Placebo				Placebo Switched to drug during 12-18 mo.
	At month 3 (N=27) n(%)	At month 6 (N=27) n(%)	At month 12 (N=27) n(%)	At month 18 (N=27) n(%)	At month 18 (N=27) n(%)	At month 3 (N=27) n(%)	At month 6 (N=27) n(%)	At month 12 (N=27) n(%)	At month 18 (N=27) n(%)	At month 18 (N=27) n(%)
Pelvic pain										
• No	26 (96.3)	25 (92.6)	25 (92.6)	12 (85.7)	13 (100)	26 (100.0)	26 (100.0)	26 (100.0)	13 (100.0)	11 (84.6)
• Yes	1 (3.7)	2 (7.4)	2 (7.4)	2 (14.3)	-	-	-	-	-	2 (15.4)
Nausea and vomiting										
• No	21 (77.8)	24 (88.9)	27 (100)	14 (100)	13 (100)	26 (100.0)	26 (100.0)	26 (100.0)	13 (100.0)	12 (92.3)
• Yes	6 (22.2)	3 (11.1)	-	-	-	-	-	-	-	1 (1.7)
Breast tenderness										
• No	3 (11.1)	18 (66.7)	21 (77.8)	8 (57.1)	12 (92.3)	23 (88.5)	24 (92.3)	24 (92.3)	13 (100.0)	5 (38.5)
• Yes	24 (88.9)	9 (33.3)	6 (22.2)	6 (22.2)	1 (7.7)	3 (11.5)	2 (7.7)	2 (7.7)	-	8 (61.5)
	-									
Weight gain										
• No	13 (48.1)	22 (81.5)	20 (74.1)	11 (78.6)	13 (100)	21 (80.8)	17 (65.4)	24 (92.3)	7 (53.8)	8 (61.5)
• Yes	14 (51.9)	5 (18.5)	7 25.9)	3 (21.4)	-	5 (19.2)	9 (34.6)	2 (7.7)	6 (46.2)	5 (38.5)
Headache										
• No	26 (96.3)	26 (96.3)	23 (85.2)	12 (85.7)	10 (76.9)	23 (96.2)	25 (96.2)	26 (100.0)	12 (92.3)	13 (100.0)
• Yes	1 (3.7)	1 (7.3)	4 (14.8)	2 (14.3)	3 (23.1)	1 (3.8)	1 (3.8)	-	1 (7.7)	-

Table 5. Endometrial thickness performed by transvaginal ultrasound.

Endometrial thickness (mm)	Drug (N=27)		Placebo (N=26)	
	0 month	12 months	0 month	12 months
Mean ± SD	5.0 ± 1.7	4.1 ± 2.1 *	3.8 ± 1.9	3.8 ± 1.5
Range	5.1 1-9	0.01-8	0.5-8.7	0.5-6.7

(*) Significant statistical difference at $p < 0.05$ when compared within groups.

Table 6. Serum FSH and estradiol level.

Group	0 month		12 months	
	FSH (IU/L)	Estradiol (pmol/L)	FSH (IU/L)	Estradiol (pmol/L)
Drug	64.9 ± 28.3	40.1 ± 43.1	11.6 ± 19.3*, **	334.6 ± 138.7*, **
Placebo	68.0 ± 22.4	34.0 ± 17.9	68.4 ± 26.9**	33.4 ± 52.0**

(*) Significant statistical difference at $p < 0.05$ when compared within the same groups.
(**) Significant statistical difference at $p < 0.05$ when compared between groups.

Thai women experienced abnormal bleeding (25.9% irregular spotting and 11.1% bleeding) within the first three months which decreased with time. This data was similar to other reports[13,15-17,24]. There was one case of abnormal uterine bleeding in the drug group which continued up to 18 months. This irregular spotting required no tampon. This case necessitated endometrial biopsy an the pathology revealed an atrophic pattern. No one in the drug group wanted to withdraw from the study due to abnormal bleeding. After six months of treatment, there was a higher probability of achieving amenorrhoea. It is very important to counsel postmenopausal Thai women about this bleeding pattern during the first year of use. This abnormal bleeding pattern can be explained by local factors in the endometrium[13]. Its occurrence could not be predicted on the basis of the endometrium status before treatment[13] and an endometrial atrophic pattern has been demonstrated even in women with bleeding irregularities during treatment[25,26].

The control of climacteric symptoms improved significantly after 6 months in the drug group (Table 3). The hormonal control effect disappeared after the women switched to placebo after 12 months and the climacteric symptom score returned to pre-treatment level. The climacteric symptoms decreased significantly in the drug group showing a greater effect than placebo after 12 months. This was in keeping with other findings as to continuous low dose estrogen and progestogen regimens for reduction of climacteric symptoms[27-29].

Breast tenderness was a common side effect found in many sequential and continuous regimens[30]. This was also noted as the most common complaint in our study. This side effect was also evident in the placebo group who switched to the drug. This side effect decreased with time. Patients should be informed about it before beginning the treatment.

The endometrial thickness decreased and there was evidence of an atrophic endometrium by transvaginal ultrasound at the one-year follow-up. In this study, we decided not to use endometrial biopsy for pretreatment and follow- up due to the pain and discomfort experienced during Pipelle endometrial sampling by postmenopausal Thai women. Endometrial biopsy for baseline and follow-up studies has been suggested to be unnecessary[15].

Due to its high accuracy and sensitivity, transvaginal ultrasonography was recommended to detect endometrial hyperplasia in menopausal women receiving hormone replacement therapy[31-33].

According to this study, the dosage of 2 mg 17 beta-estradiol is enough to increase the

estradiol blood level of to 334.6±38.7 pmol/l which was similar to other studies in European women[13, 26]. The decreased level of FSH due to the suppressive effect of pregesterone was also noted in the drug group.

In summary, this dosage of combined estrogen and progesterone was found effective in the treatment of climacteric symptoms in postmenopausal Thai women. The frequency of spotting and bleeding was high during the first 6 months of treatment. Counseling on the bleeding pattern and side effects should be performed before starting the treatment. This combined hormonal therapy appeared to be a useful alternative for postmenopausal Thai women who prefer to avoid cyclic bleeding resulting from sequential treatment.

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การศึกษาผลทางคลินิกในสตรีไทยวัยหลังหมดประจำเดือนที่ได้รับยา 17 beta-estradiol and norethisterone acetate เทียบกับยาหลอก

คุณหญิงกอบจิตต์ ลิมปพยอม, พ.บ.,*
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วัตถุประสงค์ เพื่อศึกษาเปรียบเทียบ อาการในวัยหมดระดู ลักษณะเลือดออกผิดปกติ ภาวะข้างเคียง ความหนาของเยื่อบุโพรงมดลูก และระดับ FSH และ estradiol ในกระแสเลือด ในสตรีไทยวัยหลังหมดประจำเดือนที่ได้รับยา 17 beta-estradiol and norethisterone acetate เทียบกับยาหลอก.

รูปแบบการศึกษา Double blind, randomized placebo controlled trial

วัสดุและวิธีการ ทำการสุ่มแบ่งกลุ่มสตรีไทยวัยหลังหมดประจำเดือนจำนวน 60 คนที่มารับบริการที่คลินิกวัยหมดระดู ระหว่างเดือนกรกฎาคม ถึงเดือนธันวาคม พ.ศ. 2539 เป็นสองกลุ่ม โดยผู้รับบริการจะได้รับยาหลอก หรือ 17 beta-estradiol 2 มก. และ norethisterone acetate 1 มก. อย่างต่อเนื่อง เมื่อครบ 12 เดือน ผู้รับบริการ 13 รายที่ได้รับยาหลอก จะได้รับการเปลี่ยนเป็นยาจริง และผู้รับบริการ 13 รายที่ได้รับยาจริง จะได้รับการเปลี่ยนเป็นยาหลอก จะทำการบันทึกข้อมูลทั่วไป การตรวจร่างกายทั่วไปและการตรวจทางนรีเวช การตรวจแพพสเมียร์ การตรวจเต้านม อาการวัยหมดระดู ความหนาของเยื่อบุโพรงมดลูก และระดับ FSH และ estradiol ในกระแสเลือดก่อนเริ่มการศึกษา จากนั้นจะบันทึกข้อมูลทั่วไป การตรวจร่างกายทั่วไป และการตรวจเต้านม อาการวัยหมดระดูที่เวลา 3, 6, 12, 18 เดือน ภายหลังได้รับยา ทำการตรวจทางนรีเวช การตรวจแพพสเมียร์ ระดับ FSH และ estradiol ในกระแสเลือด และความหนาของเยื่อบุโพรงมดลูกที่เวลา 12 เดือนภายหลังได้รับยา

ผลการศึกษา สตรีที่ได้รับยาจริงมีอาการวัยหมดระดูน้อยกว่าก่อนรับยาอย่างมีนัยสำคัญทางสถิติที่เวลา 6 เดือน พบอุบัติการณ์ของการไม่มีระดู 74.0% ที่เวลา 12 เดือน พบภาวะเลือดออกผิดปกติ 37.0% ที่เวลา 3 เดือน 29.6% ที่เวลา 6 เดือน 25.9% ที่เวลา 12 เดือน และ 7.1% ที่เวลา 18 เดือน อาการคัดตึงเต้านมเป็นผลข้างเคียงที่พบมากที่สุด ความหนาของเยื่อบุโพรงมดลูกลดลงอย่างมีนัยสำคัญทางสถิติในกลุ่มที่ได้รับยา ค่า estradiol ในกระแสเลือดลดลง และค่า estradiol ในกระแสเลือดเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ

สรุปผลการศึกษา รูปแบบฮอร์โมนรวมนี้มีประสิทธิภาพดีในการรักษาอาการวัยหมดระดู ดีกว่ายาหลอก สตรีส่วนใหญ่จะไม่มีระดูเมื่อเวลา 12 เดือนของการรักษา แต่อาจพบอุบัติการณ์ของภาวะเลือดออกผิดปกติในระยะเวลา 3 เดือนแรกของการรักษาได้ ควรให้คำปรึกษาเกี่ยวกับลักษณะเลือดออกผิดปกติที่อาจพบได้และภาวะข้างเคียงก่อนเริ่มการรักษาเพื่อเพิ่มการต่อเนื่องของการรักษา รูปแบบฮอร์โมนรวมนี้จัดเป็นวิธีเลือกหนึ่งที่มีประโยชน์ต่อสตรีวัยหมดระดู ที่ต้องการหลีกเลี่ยงการมีเลือดประจำเดือนออกจากการใช้ฮอร์โมนชนิดกินเป็นระยะ

คำสำคัญ : Combined Continued HRT, Postmenopause

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