

Effect of Local Estrogen Cream on Vaginal Health after Pessary Use for Prolapsed Pelvic Organ: A Randomized Controlled Trial

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Background: Currently, there is no evidence whether local estrogen cream should always be used in conjunction with a pessary as atrophic prevention. There is still no consensus about the long-term safety of local estrogen cream. Therefore, it is recommended to use hormone for the shortest duration as possible.

Objective: Evaluate the effect of local estrogen cream on vaginal health in pessary use for pelvic organ prolapse.

Material and Method: Forty postmenopausal women with pelvic organ prolapse who had used a pessary in conjunction with local estrogen cream for six weeks were randomly selected to use vaginal conjugated equine estrogen (CEE) cream 0.5 g once a week (treatment group) or no treatment (control group) for 24 weeks. The primary outcome was vaginal health assessment composed of vaginal symptom score, vaginal pH, and vaginal maturation index. The secondary outcome measures were the difficulty to use pessary and the endometrial thickness.

Results: No statistical differences were found for all vaginal health assessment at baseline, 12, and 24 weeks among the treatment and the control groups. There was also no significant difference between the groups about the difficulty to insert and remove the pessary or the endometrial thickness.

Conclusion: Vaginal CEE cream 0.5 g once a week did not show any additional positive effect on vaginal health in pessary use.

Keywords: Pelvic organ prolapse, Pessary, Local estrogen cream, Vaginal health

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Vaginal pessary is a conservative treatment option for pelvic organ prolapse (POP). It can be used as the first line treatment for all POP especially in patients who have contraindications for surgery or declined surgery or still wanted to get pregnant^(1,2). Most studies have found that prolapse associated symptoms improved 80 to 90% with pessary use and patients satisfaction rates were high (70-92%)^(3,4). Pessary use in POP is effectively equivalent to surgical treatment in improving the quality of life⁽⁵⁾.

The common side effects of pessary use are vaginal discharge, foul odor, vaginal bleeding, and vaginal pain⁽⁶⁾. These are the results of vaginal irritation from pressure of the pessary. One of the risk factors that easily causes injury or irritation to vaginal tissue is vaginal atrophy due to estrogen deficiency. It typically occurs in postmenopausal women, which compose of the majority of POP patients. Currently,

there is no evidence whether a pessary should be used in conjunction with hormones to prevent vaginal atrophy^(7,8). Some studies suggested using a pessary in combination with hormones to reduce side effects^(9,10), but some suggested to only use hormones when atrophic related symptoms such as abrasion or vaginal discharge were present⁽¹¹⁾. If a hormone is needed, local vaginal estrogen is recommended rather than systemic estrogen therapy because it is more effective for the treatment of vaginal symptoms⁽¹²⁾. Moreover, local estrogen also avoids or minimizes systemic estrogen effects due to less absorption into the bloodstream. Therefore, it does not increase the risk of breast cancer⁽¹³⁾ and endometrial cancer^(12,14-16). However, some studies found that women using a local estrogen hormone had increased serum estradiol levels; therefore, systemic risks are possible⁽¹⁷⁻²⁰⁾. There is still no consensus on the potential risks of long-term local estrogen use because clinical trials to date have not followed women beyond one year⁽²¹⁾.

Currently, there is a lack of evidence on whether local estrogen is needed in pessary use, which seems to be used in long-term or even lifelong. The

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aim of the present study was to evaluate the effect of local estrogen hormone in pessary use on vaginal health compared to a placebo.

Material and Method

This randomized controlled study began after the approval was obtained from the Institutional Review Board of the Faculty of Medicine, Chiang Mai University. The inclusion criteria were postmenopausal women with POP who were able to give informed consent and answer treatment-related questions, and had used a pessary for six weeks and decided to continue using the pessary. Exclusion criteria were contraindications for local estrogen hormone such as known or suspected breast cancer, hormone-dependent tumor or thromboembolic disorder, and patients who could not follow the protocol.

After a successful fitting on the first visit, vaginal estrogen cream containing conjugated equine estrogen (CEE) 0.625 mg/g (Premarin[®], Wyeth, Philadelphia, PA, USA) was prescribed to all postmenopausal women to apply 0.5 g daily for two weeks, and subsequently, twice per week until their follow-up visit. They were advised to remove the pessary each night and reinsert it each morning. At six weeks after the fitting, patients who met the criteria were enrolled to the study. A computer-generated randomization table (block of ten) was used to allocate participants to either discontinue local estrogen (control group) or continue using local estrogen 0.5 g, once a week for the entire 24 weeks (treatment group). The trial design was presented in Fig. 1. The data were collected at the baseline, 12 and 24 weeks. At each visit, patients answered self-assessed treatment-related questions and underwent a speculum examination with vaginal sample collection. Endometrial safety was evaluated by transvaginal ultrasonography for endometrial thickness at the baseline and trial endpoint. In cases of severe adverse events either from the pessary itself or related to hormone/placebo effect the participant was discontinued from the study and received proper treatment.

The primary endpoint was the assessment of vaginal health by a vaginal symptom score (dryness, soreness, itching/irritation, and discharge), vaginal pH and vaginal cytology. The vaginal symptom score was self-assessed with a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Vaginal pH was measured by a pH indicator strip inserted into the vagina. For vaginal cytology, vaginal smears were taken from the upper third of the lateral vaginal wall and analyzed

blindly by the cytologist to determine the vaginal maturation index (VMI) which was calculated by the formula: $VMI = (0 \times \% \text{ parabasal cells}) + (0.5 \times \% \text{ intermediate cells}) + (1.0 \times \% \text{ superficial cells})^{(22)}$.

Secondary outcomes were the self-assessment of the difficulty to insert/remove a pessary based on a 4-point scale (0 = very easy, 1 = easy, 2 = difficult, 3 = very difficult), the endometrial thickness, and an adverse event such as vaginal abrasion/ulcer or vaginal bleeding.

The sample size would provide an 80% power in detecting a difference in change from baseline score of 0.5 between two groups for the primary endpoint (vaginal symptom score of vaginal dryness, soreness, itching/irritation and discharge). We calculated that 18 subjects each arm would be required to demonstrate a *p*-value of 0.05. Forty subjects were recruited, expecting 10% to drop out.

The SPSS version 16 for Windows (SPSS Inc., IL, USA) was used to perform statistical analysis. Baseline demographic characteristics were compared using independent sample *t*-test or Mann-Whitney *U* test based on data type and distribution. Friedman test and paired *t*-test was used to analyze changes from the baseline over time. A *p*-value <0.05 was considered statistically significant.

Results

Forty participants were enrolled in the present study and randomized into 20 patients in the treatment group that used vaginal estrogen cream (Premarin[®]) 0.5 g once a week for 24 weeks, and 20 patients in the

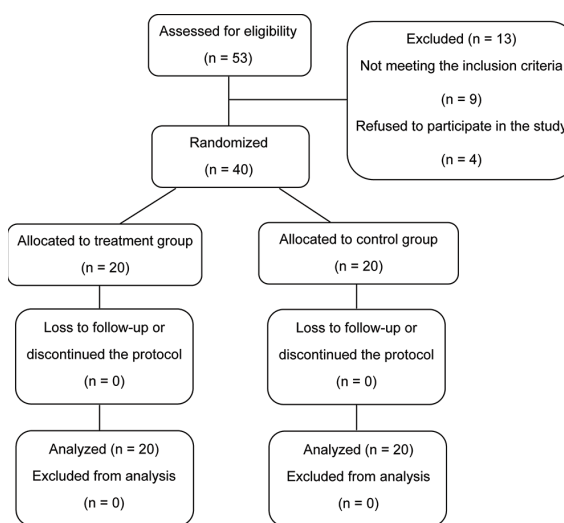


Fig. 1 Trial design.

control group with no treatment. All participants in both groups continued using a pessary and were followed until the endpoint.

Demographic characteristics were similar between the treatment group and the control group (Table 1). Additionally, baseline vaginal health, difficulty score to insert/remove pessary and endometrial thickness were also similar between groups (Table 2-4).

According to the vaginal symptom scores in the control group at the baseline, 20% of the patients complained of mild to moderate vaginal itching/irritation and 10% had mild to moderate vaginal

discharge (mean score = 0.47 ± 1.06). At 12 weeks, 5% reported mild vaginal dryness and soreness, 10% had mild vaginal itching/irritation and 15% had mild to moderate vaginal discharge (mean score = 0.64 ± 0.74). After 24 weeks, 5% indicated mild vaginal dryness and itching/irritation and 15% had mild vaginal discharge (mean score = 0.45 ± 0.69). In the treatment group at the baseline reported mild vaginal itching/irritation in 15% and 10% complained of mild vaginal discharge (mean score = 0.33 ± 0.49). At 12 weeks, 10% reported mild vaginal discharge (mean score = 0.14 ± 0.36). After 24 weeks, 5% had mild vaginal soreness and 15% had

Table 1. Demographic and baseline characteristics

Characteristics	Control group (n = 20) mean \pm SD or n (%)	Treatment group (n = 20) mean \pm SD or n (%)	p-value
Age (year) ^a	66.67 \pm 8.05	66.13 \pm 6.78	0.178
Parity ^b	4.0 \pm 2.5	2.9 \pm 1.1	0.553
Age of menopause (year) ^a	50.26 \pm 6.26	50.00 \pm 4.07	0.787
Body mass index (kg/m ²) ^a	22.48 \pm 3.55	24.63 \pm 3.97	0.463
Sexuality active ^b	3 (15)	2 (10)	0.624
Previous hysterectomy ^b	4 (20)	5 (25)	0.712
Medical disease ^b	8 (40)	10 (50)	0.456
Prolapse stage ^b			
Stage 2	5 (25)	3 (15)	0.757
Stage 3	10 (50)	9 (45)	
Stage 4	5 (25)	8 (40)	
Pessary type ^b			
Ring	15 (75)	17 (85)	0.289
Gellhorn	4 (20)	2 (10)	
Donut	1 (5)	1 (5)	

a Student's t-test, b Mann-Whitney U test

Table 2. Vaginal health assessment comparison: vaginal symptoms score, vaginal pH, and vaginal maturation index (VMI)

	Control group (n = 20), mean (SD)	Treatment group (n = 20), mean (SD)	p-value
Vaginal symptoms score			
Baseline	0.47 (1.06)	0.33 (0.49)	0.461
12 weeks	0.64 (0.74)	0.14 (0.36)	0.100
24 weeks	0.45 (0.69)	0.33 (0.65)	0.816
p-value	0.547	0.382	
Vaginal pH			
Baseline	5.55 (0.69)	5.25 (0.62)	0.472
12 weeks	5.54 (0.88)	5.14 (0.53)	0.375
24 weeks	5.39 (0.54)	5.17 (0.72)	0.398
p-value	0.675	0.314	
VMI			
Baseline	51.73 (4.37)	51.85 (3.08)	0.483
12 weeks	52.50 (3.26)	53.18 (4.39)	0.587
24 weeks	57.75 (1.02)	56.13 (6.72)	0.382
p-value	0.308	0.268	

Mann-Whitney U test or Friedman test

mild vaginal discharge (mean score = 0.33±0.65). The vaginal symptom scores were not different from the baseline, 12 and 24 weeks in both the treatment and control groups (Table 2).

No statistically significant differences were found for the mean vaginal pH at baseline, 12 and 24 weeks among the treatment and the control groups (Table 2).

The VMI indicated no statistically significant differences for VMI at the baseline, 12 and 24 weeks among the treatment and the control groups (Table 2).

All participants in both group revealed that it was very easy or easy to insert/remove the pessary. No one complained of any difficulties in using the pessary. No statistically significant differences were found for the difficulty score to insert/remove pessary at the baseline, 12 and 24 weeks among the treatment and the control groups (Table 3).

The analysis of the endometrial thickness at the baseline and 24 weeks in both the treatment and control groups revealed no statistically significant differences (Table 4).

Throughout the study period, only one adverse event was found in the control group. A post hysterectomy woman with a donut pessary reported at her 12-week visit vaginal spotting a few days prior to her visit. A speculum exam found a vaginal ulcer 0.5 cm. The treatment was to cease pessary use and apply vaginal estrogen cream daily for two weeks. After two weeks, the ulcer was healed and she continued to use pessary without problems until 24 weeks.

Table 3. Difficulty score to insert/remove pessary

	Control group (n = 20) mean (SD)	Treatment group (n = 20) mean (SD)	p-value
Baseline	0.33 (0.49)	0.13 (0.35)	0.195
12 weeks	0.14 (0.36)	0.29 (0.47)	0.357
24 weeks	0.09 (0.30)	0.25 (0.45)	0.315
p-value	0.250	0.585	

Mann-Whitney U test or Friedman test

Table 4. Endometrial thickness

	Control group (n = 16) mean (SD)	Treatment group (n = 15) mean (SD)	p-value
Baseline	2.85 (1.56)	3.14 (1.91)	0.741
24 weeks	2.02 (0.49)	2.92 (1.56)	0.502
p-value	0.578	0.386	

Student's t-test or paired t-test

Discussion

The most effective treatment option for atrophic related-vaginal symptoms is local vaginal estrogen. Although there were reports that the use of low-dose local estrogen was effective without systemic side effects⁽²³⁾, several studies have shown that vaginal estrogen administration can reach the systemic circulation^(20,24-26). Therefore, the North American Menopause Society (NAMS) recommended using the lowest dose of hormone for the shortest duration as possible to treat vulvovaginal atrophic symptoms⁽¹²⁾. Moreover, until now there were no reported clinical trials regarding the endometrial safety of local hormone use beyond one year, so it is always considered a systemic risk in cases of prolonged use.

Currently, there is widespread use of local estrogen in combination with POP patients who use a pessary as the prevention of vaginal atrophy due to atrophic vagina being associated with an increased incidence of vaginal abrasion in pessary use⁽²⁷⁾. However, there was no evidence regarding the use of local estrogen as prevention. The aim of the present study was to answer the question, is local estrogen needed in pessary use patients? To our knowledge, this is the first study on local estrogen in pessary use patients.

In our study, we compared the vaginal health in the pessary use patients that were randomized to use local estrogen versus no treatment. The vaginal health assessments were composed of a vaginal symptom score as subjective measurement, and vaginal pH and VMI as objective measurements. In our study, dyspareunia was excluded from the composite vaginal symptom because the majority of participants were sexually inactive. We found that all parameters of vaginal health were comparable in both groups at the beginning and throughout the study period. At 24 weeks, the mean vaginal pH was 5.39 and 5.17 and the mean VMI was 57.75 and 56.13 in the control group versus the treatment group, respectively, which did not fit the diagnostic criteria for atrophy. These showed that pessary itself might provide a preventive effect against vagina atrophy by mechanical stimulation of the vaginal wall to increase vaginal blood flow, which was the same mechanism as regular sexual activity or use of a vaginal dilator. Moreover, the use of local estrogen did not show any additional positive effect on vaginal health and did not affect the ease of pessary use. That the local estrogen would help prevent vaginal abrasion/ulcer caused by the use of pessary cannot be concluded because the sample size was not large

enough. In a study by Bulchandani et al⁽²⁸⁾ demonstrated that vaginal ulceration in all type pessary use for POP were more in no estrogen group compare to estrogen group (17.4%, 12/69 vs. 11.8%, 6/51, $p = 0.151$). Especially in “non-ring” subgroup (Shelf, Gellhorn or Shaatz), there were significantly higher risk of vaginal ulceration in no estrogen group compared to estrogen group (46.2%, 6/13 vs. 5.2%, 1/19, $p = 0.033$). It seemed to be that vaginal estrogen might lower risk of vaginal ulceration in pessary users especially in non-ring pessary. For endometrial safety, no case of uterine bleeding was reported throughout the study period and endometrial thickness was comparable from the baseline and at 24 weeks after the application of 0.5 g premarin vaginal cream once a week.

The limitation of the present study was that all participants received local estrogen six weeks prior to the study enrollment because we agreed that local estrogen played an important role in the initial success of fitting⁽⁹⁾. Therefore, we were concerned about the residual hormonal effect, but in theory, the half-life of hormone was not as long as 24 weeks.

In conclusion, the present study suggested that local estrogen was not useful for pessary use patients in the aspect of atrophic prevention. It should be used when indicated with moderate to severe symptoms of vulvovaginal atrophy or atrophic related vaginal abrasion/ulcers. However, longer duration studies are needed to confirm the long-term results especially on adverse events from the use or non-use of local estrogen. Moreover, a larger sample size is needed to explain the effect of local estrogen on the pessary related adverse events such as vaginal abrasion/ulcer, which is a rare event.

What is already known on this topic?

At present, local estrogen is always use in combination with pessary for POP to prevent or reduce atrophic related problem such as abrasion. However, there is no clear information about the safety of long-term local estrogen use. Therefore, it is not reasonable to always prescribe local estrogen to pessary use patients, which seem to become long-term use, even lifelong. Moreover, there is still no consensus on whether local estrogen is needed in pessary use.

What this study adds?

To our knowledge, this is the first study on local estrogen in pessary use patients. The study showed that long-term use of local estrogen did not have additional effect on vaginal health in pessary use

patients. The study suggested that short-term use of local estrogen, first six weeks of pessary use, is enough to improve vaginal health. After that, local estrogen should be use when indicated such as moderate to severe atrophic symptoms or atrophic related vaginal abrasion/ulcer.

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Potential conflicts of interest

None.

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การทดลองแบบสุ่มเพื่อทดสอบผลของการใช้เอสโตรเจนครีมทาเฉพาะที่ต่อสุขภาพช่องคลอดในผู้ป่วยอู้งเชิงกรานหย่อนที่รักษาโดยการใส่ห่วงพวงอู้งเชิงกราน

ภพรัด ดันดีคุณกุล, อุษณีย์ แสนหมี, สุปรียา วงษ์ตระหง่าน, ชัยเลิศ พงษ์นริศร

ภูมิหลัง: ปัจจุบันยังไม่มีข้อมูลที่ชัดเจนว่าในคนที่ใส่ห่วงพวงอู้งเชิงกรานเพื่อรักษาภาวะอู้งเชิงกรานหย่อนนั้นจำเป็นต้องได้รับเอสโตรเจนครีมทาเฉพาะที่ร่วมด้วยเสมอ และข้อมูลเกี่ยวกับความปลอดภัยในการใช้เอสโตรเจนครีมทาเฉพาะที่เป็นระยะเวลาสั้นๆ ยังไม่ชัดเจน ดังนั้นในปัจจุบันจึงแนะนำให้ใช้เอสโตรเจนครีมทาเฉพาะที่ในระยะเวลาสั้นที่สุดที่เป็นไปได้

วัตถุประสงค์: เพื่อศึกษาผลของเอสโตรเจนครีมทาเฉพาะที่ต่อสุขภาพช่องคลอดในผู้ป่วยอู้งเชิงกรานหย่อนที่รักษาโดยการใส่ห่วงพวงอู้งเชิงกราน เทียบกับกลุ่มที่ไม่ได้รับเอสโตรเจนครีมทาเฉพาะที่

วัสดุและวิธีการ: หญิงวัยหมดประจำเดือนที่มีภาวะอู้งเชิงกรานหย่อนและรักษาโดยการใส่ห่วงพวงอู้งเชิงกรานร่วมกับได้รับเอสโตรเจนครีมทาช่องคลอดมาเป็นเวลา 6 สัปดาห์ และต้องการใช้ห่วงพวงอู้งเชิงกรานต่อจำนวน 40 ราย ได้รับการสุ่มเป็นกลุ่มทดลองคือได้รับ conjugated equine estrogen (CEE) ครีมทาช่องคลอด 0.5 กรัม สัปดาห์ละครั้ง และกลุ่มควบคุมที่ไม่ได้รับครีมทาช่องคลอด จากนั้นเก็บข้อมูลในวันที่สุ่ม, 12 และ 24 สัปดาห์ โดยผลลัพธ์หลักที่สนใจศึกษาคือสุขภาพช่องคลอด โดยประเมินจาก vaginal symptom score, ความเป็นกรดต่างในช่องคลอด และ vaginal maturation index (VMI) ผลลัพธ์รองที่สนใจ ได้แก่ ความยากง่ายในการใส่/ถอดห่วงพวงอู้งเชิงกราน และการเปลี่ยนแปลงความหนาของเยื่อบุโพรงมดลูก

ผลการศึกษา: ผลการศึกษาไม่พบความแตกต่างทางสถิติในทุกผลลัพธ์ที่สนใจ ได้แก่ vaginal symptom score, ความเป็นกรดต่างในช่องคลอด, VMI, ความยากง่ายในการใส่/ถอดห่วงพวงอู้งเชิงกราน และการเปลี่ยนแปลงความหนาของเยื่อบุโพรงมดลูก ในกลุ่มศึกษาและกลุ่มทดลอง เมื่อติดตามไป 24 สัปดาห์

สรุป: CEE ครีมทาช่องคลอด 0.5 กรัม สัปดาห์ละครั้ง มีผลต่อสุขภาพช่องคลอดไม่ต่างจากกลุ่มที่ไม่ได้รับครีมทาช่องคลอดในคนที่ใส่ห่วงพวงอู้งเชิงกราน
