

Evidence-Based Case Report

Vaginal Estrogen Cream in Menopausal Women Using Pessary to Reduce Bacterial Vaginosis

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Abstract

Vaginal estrogen cream has widely been used for vaginal atrophy in menopausal women. However, the effectiveness in preventing bacterial vaginosis (BV) in women with pessary is limited. The study aims to evaluate the effectiveness of vaginal estrogen cream in preventing bacterial vaginosis in menopausal uterine prolapse women with a pessary. A literature search was conducted on PubMed®, Scopus®, and google scholar® before May 2022 using MeSH. Two investigators searched, extracted, and appraised the evidence. The studies were appraised using the Centre for Evidence-Based Medicine, University of Oxford, randomized controlled trial appraisal tools. There were two articles appropriate to the inclusion and exclusion criteria. Both studies were valid, important and applicable to our case. The relative risk of bacterial vaginosis after locally applied vaginal estrogen was 0.91-0.92, with a number needed to treat (NNT) 63.3-186.6. Estrogen vaginal cream did not reduce the risk of BV for menopausal women with pessary in the short term; however, BV incidence is reduced in the longer term.

Keywords: Estrogen vaginal cream, pelvic organ prolapse, pessary, menopause.

Penggunaan Krim Vagina Estrogen pada Wanita Menopause yang Menggunakan Pessarium untuk Mengurangi Kejadian Vaginosis Bakterialis

Abstrak

Krim estrogen vagina telah banyak digunakan untuk atrofi vagina pada wanita menopause. Namun, efektivitas dalam mencegah vaginosis bakterialis (BV) pada wanita dengan pessarium terbatas. Penelitian ini bertujuan untuk mengevaluasi efektivitas krim estrogen vagina dalam mencegah vaginosis bakterialis pada wanita prolaps uteri menopause dengan pessarium. Pencarian literatur dilakukan di PubMed®, Scopus®, dan google Scholar® sebelum Mei 2022 menggunakan MeSH. Dua penyelidik mencari, mengekstrak, dan menilai studi. Studi dinilai menggunakan Centre for Evidence-Based Medicine, Universitas Oxford, Randomized Clinical Trial Appraisal Tools. Ada dua artikel yang sesuai dengan kriteria inklusi dan eksklusi. Kedua penelitian tersebut valid, penting dan dapat diterapkan pada kasus kami. Risiko relatif vaginosis bakterial setelah pemberian estrogen vagina secara lokal adalah 0,91-0,92, dengan Number Needed to Treat (NNT) 63,3-186,6. Krim vagina estrogen tidak mengurangi risiko BV untuk wanita menopause dengan pessary dalam jangka pendek; namun, ada penurunan insiden BV dalam jangka panjang.

Kata kunci: krim vagina estrogen, prolaps organ panggul, pessarium, menopause.

Introduction

Pelvic Organ Prolapse (POP) is a protrusion of a pelvic organ into the vaginal wall or outside that may cause the symptom of bulging, pain or discomfort sensation, and pelvic floor dysfunction.¹ The weakened pelvic floor structure and muscle are considered the aetiology, and multiple risk factors such as age, menopause, parity, obesity, and genetic factor have been identified for POP.^{2,3} Although it rarely becomes fatal, the symptoms may harm a woman's quality of life (QoL), especially at older ages.^{4,5} Currently, gynaecologists manage pelvic organ prolapse with conservative and surgical treatment based on the patient's preference and state of health.

Conservative management, such as pessary, is commonly used since it is less invasive, effective and inexpensive.^{6,7} Pessary, with its varying type and shape, must be cleaned and changed regularly to prevent complications such as erosion, discharge, slipping, and infection.^{8,9} It is thought that vaginal atrophy in menopause may predispose women to bacterial vaginosis (BV) because of the decreased estrogen level.¹⁰

Vaginal estrogen cream could induce vaginal mucosa maturation and thickness and reduce the pH of the vagina, thus effective in reducing women's symptoms of atrophy.¹¹ Some studies have provided evidence for vaginal estrogen use in vaginal atrophy and genitourinary syndrome of menopause.^{11,12} A prospective study by Bulchandani et al¹³ found that women with pessary had fewer ulcerations when using vaginal estrogen than without (RR 0.11; 95% CI 0.01-0.83, p=0.03). Other studies by Dessie et al¹⁴ found the use of vaginal estrogen is associated with a higher incidence of pessary continuity and a lower incidence of vaginal discharge (HR 0.31; 95% CI 0.17-0.58, p=0.007).

This study aims to evaluate the effectiveness of vaginal estrogen use in menopausal women to prevent the incidence of bacterial vaginosis.

Case

A-65-year-old woman came into the urogynecology clinic with a chief complaint of vaginal bulging two years ago. She realized that her bulging was increasing six months ago, and sometimes she complained of discomfort in her vagina. The woman also complained of stress urinary incontinence symptoms but without fecal incontinence. Her husband was still alive and sexually active. Her medical history was multiple spontaneous vaginal deliveries and diabetes without insulin use. In physical examination, a bulging red

mass protrudes out from the vagina. Based on POP examination, she was diagnosed with uterine prolapse grade III, cystocele grade II, and rectocele grade II. Her ultrasound and pap smear results were unremarkable. She preferred to use pessary for her prolapse treatment and will undergo a fitting test for a few weeks. However, she is worried since she had recurrent bacterial vaginosis.

Clinical Question

Based on the case above, we formulized a clinical question that study on the population of postmenopausal women with pessary, with an intervention of estrogen vaginal cream to reduce the incidence of bacterial vaginosis. The clinical question will be, does the use of estrogen vaginal cream prevent the incidence of bacterial vaginosis in menopausal women with pessary?

Methods

We searched for evidence on Pubmed®, Scopus®, and google scholar and collected all literature before May 2022. Keywords such as Vaginal, estrogen/oestrogen [MeSH], pessary, complication, and trial were used to discover the studies. There were 176 articles found after removing some duplicates. We screened the studies based on the inclusion and exclusion criteria. Our study inclusion criteria were written in English, women with a pessary, a study comparing vaginal estrogen and without. We excluded studies that did not have appropriate design and studies with different outcomes/comparisons. The search steps were provided in PRISMA Figure 1.

Two investigators (RS) and (APK) actively searched, screened, and appraised the collected studies. A third investigator (SH) was asked when there were disputes in agreement for the study's appraisal. We used Oxford Center for Evidence-based Medicine Randomized Clinical Trial Appraisal Sheet to appraise the studies.

Result

Up to May 2022, there were 205 studies across three databases (google scholar, PubMed, Scopus). We appraise two RCT studies by Chiengtong et al¹⁵ and Coelho et al¹⁶ We excluded Meriwether et al¹⁷, Tontivuthikul et al¹⁸, Dessie et al¹⁹, and Bulchandani et al²⁰ since they use different interventions, different outcomes, and inappropriate method. PRISMA Figure 1 describes the search steps, and the details of the two RCT studies are in Table 1.

Both studies were valid and important based on the Oxford Center for Evidence-based Medicine Randomized Clinical Trial Appraisal Sheet. However, Chiengthong et al¹⁵ study did not mention if the investigator was blinded to the patient's allocation. Both studies discovered that vaginal estrogen cream might not be able to prevent the incidence of bacterial vaginosis. Chiengthong et al¹⁵ showed no difference in bacterial vaginosis between both groups at two weeks of treatment (p=0.609) and 14 weeks of

treatment (p=0.926). Similar to Chiengthong et al¹⁵, in longer follow-up, Coelho et al¹⁶ found no significant difference between both groups at 12 weeks of treatment (p=0.53) but a significant difference on six months followed-up (p=0.014). We analyzed the important aspect of the study within the range of 3 months since Chiengthong et al¹⁵ study did not observe further, which would be incomparable. Both of the study results could be applied to our patients. The critical appraisal details are in Table 3.

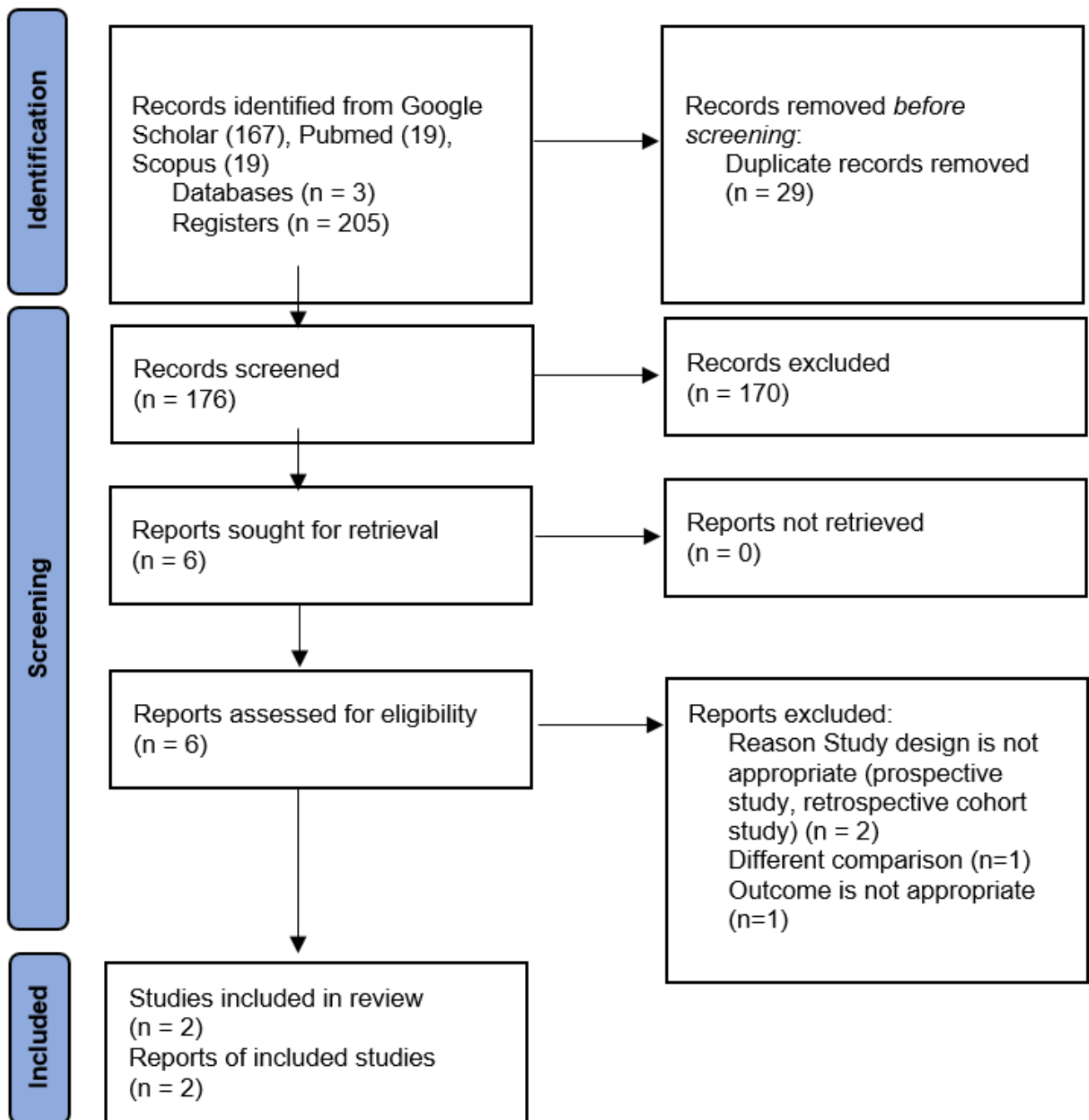


Figure 1. PRISMA Figure Of Literature Search

Table 1. Two Randomized Controlled Trial Study Characteristics

Study	Population	Location	Time	Inclusion and Exclusion criteria	Intervention group	Control group	Outcome criteria	Study Result
Chiangthong et al. ¹⁵	80 women	Female Pelvic Medicine and Reconstructive Clinic at King Chulalongkorn Memorial Hospital, Bangkok, Thaiian	April 2018-August 2020	<p>Inclusion Criteria</p> <ul style="list-style-type: none"> - Menopausal Thai women with symptomatic pelvic organ prolapse - Capable of completing a questionnaire - Had undergone successful pessary fitting <p>Exclusion Criteria</p> <ul style="list-style-type: none"> - Vaginal bleeding of unknown origin - Estrogen dependent cancers - Immunosuppression - Clinically manifested Sexually transmitted diseases - Bacterial vaginosis - Trichomoniasis - Vulvovaginal candidiasis - Known hypersensitivity to the anti-infective agent or test preparation 	Intravaginal estriol 0.03 mg + <i>Lactobacillus acidophilus</i> 100 million viable cell vaginal tablets daily for 12 days and followed up twice per week for 12 weeks	Standard instruction to remove and clean the pessary every day	<p>A single investigator obtained the vaginal discharge sample from the vaginal wall</p> <p>Bacterial vaginosis was diagnosed by three out of four Amsel criteria were met after 14 weeks</p>	<p>Within 14 weeks 5.7% patient in intervention group vs 6.2% patient in control group (p>0.05)</p>
Coelho et al. ¹⁶	98 women	Urogynecology Outpatient clinic of the University of Campinas, Brazil	August 2018 – October 2019	<p>Inclusion criteria</p> <ul style="list-style-type: none"> - Menopausal Women - POP grade 3/4 - Informed consent signed - Use vaginal pessary <p>Exclusion criteria</p> <ul style="list-style-type: none"> - Contraindication for local estrogen use - Use systematic hormonal therapy - Patients who could not follow the protocol - Uncontrolled/untreated psychiatric disorders 	Topical estrogen cream (10 mg/g promestriene cream, 0.5 g 3 times per week)	Without any vaginal cream or other lubricants during their pessary use	<p>A single investigator collected all the vaginal content with a swab applied to the left vaginal wall</p> <p>Bacteria Vaginosis was diagnosed when three of the four Amsel criteria were present</p>	<p>Within 3 months 18.4% patient in intervention group VS 20% patient in control group (p=0.55)</p> <p>Within six months 7.8% patient intervention group vs 30% patient in control group (p=0.007)</p>

Table 2. Validity, Importance, and Applicability assesment based on the Oxford CEBM of the RCT studies

Assessment	Chiengthong et al ¹⁵	Coelho et al ¹⁶
Validity		
Randomized Allocation	Yes	Yes
Similar Population	Yes	Yes
Equally treated between groups	Yes	Yes
All patients were accounted for	Yes	Yes
Outcome objectives/ blinded	Unclear	Yes
Importance		
Relative Risk	0.91	0.92
Absolute Relative Risk	-0.005	0.02
Relative Risk Reduction	0.09	0.08
The number needed to treat	186.6	63.3
Applicability		
Different Patient	Yes	Yes
Feasibility	Yes	Yes
Potential Benefits outweigh the harm	Unclear	Unclear

Discussion

Vaginal atrophy is commonly found in women, with a prevalence of 45% in menopausal women.²⁰ Estrogen plays a significant role in maintaining the vaginal microbiome and the symptoms and signs of atrophy. Estrogen contributes to the deposit of glycogen in vaginal epithelium, which is critical for epithelium maturation. Furthermore, glycogen will be metabolized by the normal microbiome of the vagina, such as *Lactobacillus spp*, to be organic acids. Those acids maintain vaginal pH and protect the genital tract.^{21,22} In prolapsed women, the genital tract protrudes out, exposing itself to the outside environment, and added by the insertion of foreign material such as pessary may increase the chance of bacterial vaginosis in menopausal women. With recent evidence of local estrogen use in minimizing the vaginal atrophy symptoms and signs, we predict that it would have a protective effect in menopausal women with a pessary.²²

The study aimed to evaluate the benefit of vaginal estrogen cream in preventing bacterial vaginosis in menopausal women with a pessary. However, our review found no use of estrogen cream in reducing the rate of bacterial vaginosis, with a relative rate of 0.91 and 0.92 with 95% CI in around three months of topical estrogen cream. Chiengthong et al¹⁵, in their study, discovered within 14 weeks, the incidence of bacterial vaginosis was 5.7% in the intervention group (2/35) and 6.2% in the control group (2/32) with $p=0.93$.¹⁵ Similar to Chiengthong et al¹⁵, Coelho et al¹⁶ observed

women within three months after local estrogen therapy and found that 18.4% of women in the intervention group (7/38) and 20% of women in the control group (8/40) had bacterial vaginosis with $p=0.547$.¹⁶ However, with a longer follow-up of 6 months, Coelho et al. found a significant reduction in the incidence of bacterial vaginosis in the intervention group with 7.8% (3/38) vs 30% (12/40) $p=0.007$.¹⁶ Thus, it raises whether three months of local estrogen treatment is insufficient to show improvement.

There were several hypotheses why estrogen cream treatment was not associated with less incidence of bacterial vaginosis. First, a strict protocol of clearing pessary and standard treatment of vaginal hygiene is good enough to prevent an infection. In Chiengthong et al.¹⁵ studies, both groups needed to clean their pessary daily; perhaps that protocol could reduce the incidence of BV.¹⁵ They also stated that vaginal estrogen did not positively affect pessary use, and perhaps the pessary itself might prevent vaginal atrophy and thus reducing the incidence of BV. Vaginal pessary could increase vaginal blood flow by mechanical pressure onto the vaginal wall, similar to regular sexual activity or a vaginal dilator.¹⁸ However, if the pessary is too large and not regularly maintained, the pressure on the vaginal wall is continuously high, resulting in vaginal erosion or ulcer.²³

Vaginal estrogen also did not significantly reduce vaginal abrasion/erosion rate, discharge, symptoms, or bleeding.^{15,16,18,19} However, a

retrospective cohort study by Dessie et al. found estrogen cream topically could increase the incidence of continued pessary use (30.6% vs 58.5% $p < 0.001$ rates of discontinuation). Both groups discontinue the pessary in a similar median time of around 12 months after fitting. Both groups have no significant differences, seemingly unrelated to vaginal estrogen cream.¹⁴

With the advancing population of older women, the prevalence of menopausal women and pelvic organ prolapse will be more frequent, so it will be expected that estrogen vaginal cream and ordinary vaginal lubricant will be more common. The increasing usage of estrogen cream could highlight the risk of potential side effects of estrogen cream. It is commonly known that additional estrogen preparation is contraindicated in patients with a history of estrogen-related cancer (some form of breast and uterine cancer).²⁵ However, patients with a history of thrombosis or embolism could use estrogen intravaginally. Intravaginal estrogen is expected to cause a low estrogen level in blood and thus may not be significant enough to cause any systematic effect.²⁶ Moreover, in the RCT studies we analyzed, there were no major side effects or significant complications that should be wary.^{15,16} Tontivuthikul et al. measured the endometrial thickness after 24 weeks of vaginal estrogen treatment. They discovered no significant difference in endometrial thickness between women that used vaginal estrogen and those who did not.¹⁸

Our study's limitation is that there was minimal evidence of RCT that studied estrogen vaginal cream to prevent pessary complications. Furthermore, the studies reviewed had a small sample size; Chiengthong et al.¹⁵ stated that other complications except BV were not statistically different since the lack of power calculations.¹⁵ Coelho et al. also declared that some patients had discontinued using pessary because extrusion could impair the sample size and power calculations.¹⁶ studies with more samples and longer follow-ups could further clarify the benefit of estrogen in menopausal women with a pessary. On the other side, this study review studies with a robust methodological RCT. To our knowledge, this is the first review to evaluate the use of estrogen cream to prevent BV in women with a pessary.

Conclusion

Estrogen vaginal cream did not reduce the risk of BV in menopausal women with pessary up to 14 weeks of treatment. However, a longer six-month follow-up found a significant BV reduction. There

were no significant side effects or complications from the RCT reviewed. A longer follow-up with a larger population could be beneficial to determine the impact of topical estrogen treatment in preventing complications of pessary in menopausal women.

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