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Short term oral estriol treatment restores normal premenopausal vaginal flora to elderly women

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Abstract

Objective: Estriol is an estrogen with considerably weaker stimulatory effects on endometrial proliferation than estradiol. A study was conducted to determine the effects of oral estriol on vaginal flora and endometrial thickness. *Methods:* Fifty-nine postmenopausal women (50–75 years of age), complaining of pruritus or vaginal discharge, participated in the study. Vaginal flora and endometrial thickness were evaluated before treatment and after receiving oral estriol (2 mg/day) for 14 days. *Results:* Prior to treatment, lactobacilli were found in vaginal cultures from only six of the 59 study participants, whereas after treatment, the vaginal flora of 27 women showed a presence of lactobacilli ($P < 0.0001$). Endometrial thickness exceeded 5 mm in only five cases. No side effects were reported. *Conclusion:* Estriol, which has little effect on the endometrium, has the potential to be highly useful for the treatment of atrophic vaginitis.

Keywords: Estriol; Vagina; Flora; Hormone-replacement therapy; Bacterial vaginosis; Atrophic vaginitis

1. Introduction

Lactobacilli are the predominant microorganisms in the vaginal flora of healthy, fertile women, and their metabolic activity maintains an appropriately acidic vaginal pH. Following menopause, however, genitourinary atrophy, accompanied by a decline in *Lactobacillus*, often leads to colonization by pathogenic microorganisms, which may in turn cause vaginitis and a variety of symptoms that adversely affect the ease and quality of living [1]. Estriol is an estrogen with considerably weaker stimulatory effects on endometrial proliferation than estradiol. Accordingly, estriol therapy is less frequently associated with genital bleeding and may not require concomitant use of progestin. [2] The purpose of the present investigation was to determine whether oral estriol would restore the normal vaginal flora and improve the mucosa, thereby protecting against undesired colonization by potentially pathogenic microorganisms.

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2. Materials and methods

The study included 59 postmenopausal women, 50–75 years of age, complaining of pruritus or vaginal discharge; all had been climacteric and amenorrheic for at least 18 months, with no etiologic cause other than estrogen depletion due to aging. The patients had not had estrogens in the past 2 years. Extensive medical, surgical, psychological and sexual histories were taken to rule out any known contraindications to estrogen treatment, and a complete gynecologic examination excluded those with pelvic tumors or neoplastic disease. Finally, those with endometrial thicknesses of <4 mm, as measured by transvaginal ultrasonography, were enrolled in the study.

The study design and laboratory procedures were fully explained to each subject and informed consent was obtained. Estriol (Estriel®, Mochida Pharmaceutical Co. Ltd., Tokyo, Japan), which is synthesized to a purity of $>99\%$ and does not include estron or estradiol, was administered orally at a dose of 2 mg/day for 14 days. Samples of vaginal bacterial flora, obtained by rolling a swab across the vaginal wall, were collected upon enrollment in the study and after the 14 days of therapy. Aerobic and anaerobic cultures were then established, enabling identification of the bacteria. No participant ever developed withdrawal bleeding. The frequencies of detection of *Lactobacillus* before and after estriol administration were compared by chi-square analyses.

3. Results

The various organisms isolated and the number of times they were found are shown in Table 1. At the beginning of the study, only six of the 59 participants had vaginal cultures that were positive for lactobacilli. After 2 weeks of estriol therapy, however, lactobacilli were detected in cultures from 27 of the women (Table 2; $P<0.0001$). Moreover, prior to treatment, there were no women in whom *Lactobacillus* was the only bacterium found, whereas after treatment, *Lactobacillus* was the only bacteria detected in the vaginas of 12 of the women (Table 3; $P<0.001$). Endometrial thickening to >5 mm occurred in only five cases, and they returned to <4 mm after cessation of treatment. No adverse reactions were observed.

4. Discussion

In fertile women, estrogen causes proliferation of vaginal epithelial cells. Glycogen is deposited in the intermediate and superficial epithelial layers of the vagina, and lactobacilli proliferate and enzymatically break down the cellular glycogen. Subsequent metabolism of the glucose yields lactic acid and hydrogen peroxide, lowering the vaginal pH to 3.5 to 4.5, which is considered indicative of a properly-estrogenized vagina. However, extremely low estrogen production in women of late postmenopausal age may lead to atrophy of vaginal mucosa, accompanied by vaginitis, pruritus, dyspareunia and stenosis. The vaginal pH increases, lactobacilli disappear from the vaginal flora, and the vagina is colonized by various other bacteria, such as Enterobacteriaceae. Estrogen replacement restores the atrophic vaginal mucosa and lowers the vaginal pH. [1]

Conjugated estrogen or transdermal estradiol are the compounds often used in estrogen replacement therapy. It is suspected, however, that unopposed estrogen may increase the risk of developing endometrial cancer, and concomitant use of progestin is therefore recommended. Unfortunately, some women do not tolerate treatment with progestational hormones. Typical side effects include breast tenderness, bloating and depression, reactions that sometimes make it necessary to discontinue treatment. Occurrence of genital bleeding may be also distressing; therefore, hormone replacement regimens associated with amenorrhea are preferable. [1] In that regard, it has been suggested that estriol, the end product of estrogen metabolism, specifically affects the epithelium of the uterine cervix and vagina, and has little ability to induce endometrial proliferation [2].

We found that the use of estriol for 2 weeks was associated with a significant increase in the rate of vaginal colonization by lactobacilli. Be-

Table 1
Alteration in vaginal flora ($n = 59$)

	Pre-treatment	After 2 weeks of treatment
Lactobacillus		
Lactobacillus spp.	6	27
Bifidobacterium		
Bifidobacterium spp.	1	1
gram positive rods	4	6
Staphylococcus		
Staphylococcus spp.	4	4
Staphylococcus aureus	5	3
coagulase negative *Staphylococcus*	6	5
Micrococcus		
Micrococcus spp.	0	1
Streptococcus		
Streptococcus spp.	3	1
Streptococcus non-hemolyticus	7	5
Streptococcus alpha-hemolyticus	13	11
Streptococcus agalactiae	5	6
other *Streptococcus*	1	3
Enterococcus		
Enterococcus spp.	2	2
Enterococcus faecalis	1	2
Peptostreptococcus		
Peptostreptococcus spp.	1	0
Haemophilus		
Haemophilus vaginalis	7	8
Haemophilus influenza	3	0
Haemophilus parainfluenza	1	0
Escherichia		
Escherichia coli	11	2
gram negative rod *(fermentative)*	4	6
Krebsiella		
Krebsiella oxytoca	1	1
Citrobacter		
Citrobacter spp.	1	0
Bacteroides		
Bacteroides fragilis	0	1
Prevotella		
Prevotella spp.	1	0
Prevotella denticola	1	0
Prevotella bivia	2	1
Fusobacterium		
Fusobacterium spp.	0	1
Corynebacterium		
Corynebacterium spp.	7	6
Propionibacterium		
Propionibacterium spp.	0	1
Candida albicans	2	3
Proteus mirabilis	1	

Table 2
The frequencies of detection of *Lactobacillus* before and after estriol administration

	Pre-treatment	After 2 weeks of treatment
Lactobacillus spp. (+)	6	27
Lactobacillus spp. (−)	53	32

cause thickness of the postmenopausal endometrium correlates with the presence of pathology, an endometrial thickness of < 5 mm is reassuring and allows conservative management. [1] Among our study participants, endometrial thickness after treatment was < 5 mm in all but five cases. Brandberg et al. [3] reported that the vaginal flora of all 51 patients, after 4 weeks' treatment with a dosage of 3 mg/day of estriol, showed a dominance of lactobacilli. Nonetheless, long-term or large-dose treatment with estriol may significantly affect the endometrium. For instance, genital bleeding occurred in six of 29 elderly women (70–84 years of age) administered estriol at 2 mg/day for 10 months [4]; while histologically, estriol at doses of 6 mg/day for 3.5 months [5] or 8 mg/day for 4 weeks [6] had the same effect on the endometrium as other estrogens. It was reported in Sweden that oral use of estriol for at least 5 years increased the relative risk of endometrial cancer and endometrial atypical hyperplasia [7].

Some evidence has suggested that vaginal dryness responds somewhat more slowly to estrogen replacement therapy than do hot flashes. [8] When conjugated equine estrogens (Premarin) were administered, vaginal pH reached near premenopausal levels within one year, though changes in blood flow and transvaginal electropotential developed comparatively slowly, becoming maximal after 18–24 months. Those investigators concluded that restoration of vaginal tissue function requires 18–24 months, despite hormonal and cytological return to premenopausal values. It is thus very interesting to us that estriol therapy beneficially affected bacterial flora within only 2 weeks.

Table 3
The frequencies of detection of *Lactobacillus* only, before and after estriol administration

	Pre-treatment	After 2 weeks of treatment
only *Lactobacillus* spp.	0	12
any other bacteria with/without *Lactobacillus* spp.	59	47

Estriol has been referred to as a "terminal metabolite" or as a "weak hormone" [2]. Nevertheless, estriol restores atrophic vaginal, urethral and trigonal mucosa and reduces recurrent urinary tract infections in postmenopausal women [9]. In addition to its beneficial effects on the urogenital epithelium, estriol is reported to have beneficial effects on bone mineral density [10] and on climacteric vasomotor symptoms [11], and at doses of 8–16 mg, it significantly increases serum HDL-cholesterol levels [12]. In the present study, estriol restored vaginal flora, while the incidence of endometrial thickening was low, and compliance was good. We therefore conclude that estriol has the potential to be highly useful in the treatment and prophylaxis of atrophic vaginitis.

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