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Low-dose (0.3 mg) synthetic conjugated estrogens A is effective for managing atrophic vaginitis

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Abstract

Objective: Estrogen or combined hormone (estrogen-progestin) therapy is highly efficacious for managing the signs and symptoms of urogenital atrophy. A low, effective estrogen dose may enhance patient acceptance and reduce side effects. **Methods:** In this randomized, double-blind, multicenter clinical trial, 71 healthy postmenopausal women with vaginal atrophy (Vaginal Maturation Index ≤ 55) received either low-dose synthetic conjugated estrogens, A tablets (Cenestin^{®1}) (SCE-A), 0.3 mg once daily, or placebo for 16 weeks. **Results:** Treatment with SCE-A for 16 weeks resulted in a highly significant ($P < 0.0001$) mean increase of 17.7 in the Vaginal Maturation Index compared to a mean increase of 4.1 with placebo treatment. A significant estrogenic improvement was detected as early as 4 weeks (mean increase 14.6). Superficial cells were significantly increased from 2.1% at baseline to 15.9% at week 16 with SCE-A, and parabasal cells were significantly reduced from 23.0% at baseline to 1.6% at week 16 ($P < 0.01$ between treatments for both). Vaginal pH was significantly decreased from 6.2 at week -2 to 5.2 at week 16 with SCE-A compared to placebo ($P < 0.0001$). There were no significant differences between treatment groups in the incidence of treatment-emergent side effects or other measures of safety, except for urinary tract infection, which occurred more frequently in the placebo group. **Conclusions:** These results confirm the relatively rapid estrogenic effect and safety of a low-dose (0.3 mg/day) of slow-release SCE-A (Cenestin) in the treatment of vaginal atrophy in postmenopausal women.

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1. Introduction

Menopause is associated with senescence of the ovaries and a decline in follicular development. The resulting estrogen deprivation causes the vaginal mucosa and vulvar skin to become thinner; the labia to

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¹ Cenestin[®] is a registered trademark of Duramed Pharmaceuticals.

flatten and shrink; and the clitoris, uterus, and ovaries to decrease in size [1]. Common menopausal symptoms include hot flushes, menstrual irregularities, night sweats, chills, insomnia, paresthesia, palpitations, tachycardia, cold hands and feet, headache, anxiety, dizziness, nervousness, depression, irritability, impaired cognition, diminished libido, fatigue, gastrointestinal upset, and urinary difficulties [1–6]. The vaginal epithelium becomes dry and atrophic, which may cause inflammation, discomfort, itching, and dyspareunia [3]. Cytologic examination of the vaginal mucosa shows a decreased proportion of superficial cells and an increased proportion of parabasal cells [3,5,7]. With menopause, vaginal pH increases from the normal 3.5–4.0 (which favors lactobacilli) to 6.0–8.0 (which favors pathogenic organisms) [6,7].

Estrogen or combined hormone (estrogen-progestin) therapy is highly efficacious for managing the signs and symptoms of urogenital atrophy [8,9]. Various forms of estrogen-based therapies have been shown to effectively manage menopausal signs and symptoms, including those associated with vaginal atrophy [1–6,8,10,11]. Estrogen therapy decreases vaginal pH [3], thickens and revascularizes the vaginal epithelium [3], increases the number of superficial cells (thereby increasing the Vaginal Maturation Index) [7], and reverses vaginal atrophy [3]. The Vaginal Maturation Index is an indicator of the estrogenic effect on the vaginal wall, with a range of 0–49 indicating absent or low estrogenic effect, 50–64 moderate estrogenic effect, and 65–100 high estrogenic effect [9].

Despite the effectiveness of estrogen, concerns about side effects and safety have hindered its use by postmenopausal women. Lower dose estrogen therapy may enhance utilization and continuation by providing therapeutic efficacy while minimizing adverse effects. Literature supports the use of low dosages of estrogen therapy for effectively relieving symptoms and restoring healthy vaginal cytology in postmenopausal women with vaginal atrophy, but little is known about the length of treatment necessary to produce significant improvements [12–17]. The purpose of this study was to evaluate the effects on the urogenital tract of a lower dose of estrogen and the time course over which changes occur.

2. Methods

2.1. Study design

This trial was conducted at five clinical research sites in the US (Chicago, IL; Phoenix, AZ; Las Vegas, NV; San Antonio, TX; and Marietta, GA) and utilized a randomized, double-blind, placebo-controlled design. After screening, eligible subjects were assigned to one of two parallel treatment arms (SCE-A or placebo). There were six clinic visits: two pretreatment visits (screening at week –2 and baseline at week 0) and four treatment visits (weeks 4, 8, 12 and 16).

The protocol was reviewed and approved by an appropriately constituted Institutional Review Board (Schulman Associates, Inc., Cincinnati, OH), and procedures were conducted in accordance with regulations pertaining to Good Clinical Practice (International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline, Notice of Availability, Fed. Reg. 25692, May 6, 1997) and the Declaration of Helsinki (revised Edinburgh, 2000). Signed written informed consent was obtained from all subjects before protocol-specific procedures were carried out.

2.2. Subjects

Subjects were recruited from areas local to the study sites and included healthy and normally active females 30–80 years of age who had undergone spontaneous amenorrhea at least 12 months prior to screening, or had documented bilateral oophorectomy, with or without hysterectomy, at least 12 weeks prior to screening. Women with unilateral or no oophorectomy, but with a history of signs and/or symptoms of estrogen deficiency, and a circulating follicle stimulating hormone concentration >40 mIU/ml were also allowed entry into the study. Participants were required to have a clinically acceptable Papanicolaou smear (no evidence of malignancy or pre-malignancy), a clinically acceptable mammogram (no evidence of malignancy), endometrial thickness ≤ 4 mm (as measured by transvaginal ultrasound in those with a uterus), and vaginal examination consistent with postmenopausal status (pallor, dryness, and diminished rugosity of the vaginal mucosa). Eligible women had a body mass index between 18.0 and 35.0 kg/m², inclusive, and did not smoke or use tobacco

or nicotine (past smokers must have been free of any tobacco use for at least 3 months).

Subjects were excluded from participation in this study if they had a Vaginal Maturation Index >55 at screening, or a vaginal smear inconsistent with atrophy. Women were not allowed to use any oral, transdermal, or topical estrogen or progestin-containing product within 6 weeks of the screening visit (week -2). In addition, persons with known sensitivity or contraindications to natural or synthetic estrogens, progestins, or peanuts were ineligible. Women with known or suspected pregnancy were excluded, as were those with a recent history of vaginal bleeding of unknown cause, a current diagnosis of vaginal infection, recent history or current diagnosis of endometriosis, or history or current diagnosis of endometrial hyperplasia. Persons with a history or current diagnosis of thrombophlebitis, thromboembolic events, stroke, amaurosis fugax (a transient episode of monocular blindness or partial blindness lasting 10 min or less), or transient ischemic attack were also excluded. In addition, women with a history or current diagnosis of congestive heart failure, myocardial infarction, known coronary artery disease, undiagnosed chest pains, or any heart disease requiring antiarrhythmics or digitalis did not participate in the study. A fasting serum triglyceride value >300 mg/dl was exclusionary, as was systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg, or any abnormal laboratory value at screening. Women with a history of breast cancer or estrogen-dependent neoplasia (e.g. endometrial cancer) at any time before study entry, or other cancer (except basal cell carcinoma) within the last 5 years were not allowed study entry. Diabetes mellitus and a presence or history of other major diseases of the cardiovascular, hepatic, renal, gastrointestinal, pulmonary, or endocrine systems were also exclusionary. Persons with migraine headaches, asthma, epilepsy, or other conditions aggravated by fluid retention; any clinically significant mental illness; and those with a recent history (within past 12 months) or strong potential for alcohol or substance abuse were excluded.

2.3. Study products

Subjects received one of two randomly assigned treatments: synthetic conjugated estrogens, A tablets,

0.3 mg (Cenestin[®]) or matching placebo tablets (both provided by Barr Research) administered orally once daily for a 16-week treatment period. Subjects and all study personnel who handled data or communicated with the Investigators or subjects were blinded to study treatment assignment. All patients with an intact uterus were provided with a 14-day supply of progesterone (Prometrium[®]) at the end of the study.

2.4. Vaginal assessments

Vaginal cytology specimens were collected at screening (week -2) and at each treatment visit (weeks 4, 8, 12 and 16). Specimens were obtained by scraping the right and left lateral vaginal walls (midway between the fornix and introitus) with a wooden spatula. The cells and mucus that were collected were then mixed in a fixative to form a cell suspension. Cytology assessments were performed by Women's Pathology Services (Thousand Oaks, CA), and the results were blinded from the study Investigators. The number of superficial, intermediate, and parabasal cells were counted and the percentage of each cell type calculated. These percentages were utilized in the following equation to determine the Maturation Index of the vaginal mucosa [9].

Vaginal Maturation Index

$$= (\% \text{ Intermediate Cells} \times 0.5) \\ + \% \text{ Superficial Cells}$$

Vaginal pH was measured at screening (week -2) and at the end of treatment (week 16) by inserting standardized pH paper into the vagina and comparing the color change result to the manufacturer's color chart (pHEM-ALERT[®], Gynex Corporation, Redmond, WA).

2.5. Safety assessments

Safety and tolerability were assessed by standard laboratory evaluations (serum chemistry, hematology, and urinalysis) at screening (week -2) and end of treatment (week 16), and vital signs (blood pressure and heart rate), body weight, and adverse events at each clinic visit. Standard clinical laboratory analyses were conducted by Quest Diagnostics, Clinical Trials (Van Nuys, CA).

Physical examinations (general, including breast and pelvic examinations) were conducted at screening (week –2) and end of treatment (week 16). For entry criteria determinations at screening, Papanicolaou smears and urine pregnancy tests (for women with a uterus) were conducted, and in women at least 40 years of age, a mammogram was performed. Endometrial thickness was measured by transvaginal ultrasound at screening (week –2), and in subjects with an intact uterus, a follow-up transvaginal ultrasound was completed at the end of treatment (week 16). Women with an endometrial thickness >4 mm at the end of treatment were required to undergo an endometrial biopsy. Papanicolaou smears and endometrial biopsy specimens were analyzed by Women's Pathology Services (Thousand Oaks, CA).

2.6. Statistical methods

Seventy-one subjects were randomized in this trial, providing greater than 99% power to detect a standardized effect size of 1.17, assuming a standard deviation of 16.3 for the change from baseline in the Vaginal Maturation Index. These calculations were based on a previous trial of oral hormone medications conducted at the Chicago Center for Clinical Research (unpublished data).

Results presented in this paper are for the intent-to-treat (ITT) sample, which included subjects with at least one post-randomization assessment of vaginal cytology. Missing values were imputed utilizing the method of last observation carried forward. The safety population was the same as the ITT population and included all subjects who received at least one dose of the study medication and had at least one follow-up safety evaluation.

Potential differences between treatment groups at baseline were assessed using the χ^2 -test (for race) or analysis of variance models. Analysis of variance models were employed to assess possible differences between treatment groups for the change from screening (week –2) to subsequent clinic visits (weeks 4, 8, 12 and 16) in the Vaginal Maturation Index. The initial models included terms for treatment, center, and treatment-by-center interaction. If the interaction term was found to contribute substantially to the model ($P \leq 0.05$), the nature of the interaction was investigated and the appropriateness of inferences made re-

garding treatment main effects was evaluated. Models were reduced in a stepwise manner until only significant ($P \leq 0.05$) terms remained, or until treatment was the only term left in the model. A similar approach was taken in the analysis of the change from screening (week –2) to end of treatment (week 16) in vaginal pH, and the change from week –2 to weeks 4 and 16 in the vaginal mucosa cell types.

The Shapiro–Wilk test was applied to the residuals to test for normality. When the residuals did not follow a normal distribution ($P > 0.05$), the values were ranked and the analysis was performed on the ranked data. McNemar's test or the Stuart Maxwell test was utilized to assess significant changes in standard laboratory values from screening (week –2) to end of treatment (week 16). The Fisher's exact (2-tail) test was applied to assess differences between treatment groups in the frequency of adverse events. For those subjects who did not complete the study, time to discontinuation was analyzed by a Kaplan–Meier life table analysis.

3. Results

3.1. Subjects

A total of 71 subjects received either SCE-A ($n = 37$) or placebo ($n = 34$). Sixty-three subjects completed to week 16 of the study ($n = 34$ SCE-A, $n = 29$ Placebo). Reasons for discontinuation included: lost to follow-up ($n = 1$ SCE-A), adverse events ($n = 1$ SCE-A [nausea] and $n = 1$ placebo [vaginal symptoms]), non-compliance ($n = 1$ placebo), withdrew consent ($n = 1$ placebo), and other reasons ($n = 1$ SCE-A and $n = 2$ placebo). There was no significant difference between treatment groups in the number of subjects who completed the study or in the reasons for discontinuation. Furthermore, an analysis of the time to discontinuation indicated that there was no significant difference between SCE-A and placebo groups in the length of time prior to dropping from the study. Treatment compliance was measured by monitoring weekly drug accountability records. Mean compliance with study medication was 98.4% for SCE-A subjects and 98.7% for placebo subjects.

Overall, there were no major differences in the baseline characteristics between the two treatment groups (Table 1). Subjects had a mean age of approximately

Table 1
Baseline characteristics^a of subjects according to treatment with SCE-A or placebo

Characteristic	SCE-A (n = 37)	Placebo (n = 34 ^b)
Age (years)	57.1 ± 1.4	60.7 ± 1.5
Time since last menstrual period (month)	189.8 (28.7, 387.2)	150.3 (8.8, 439.1)
Hysterectomy (years)	20 (54.1%)	15 (44.1%)
Weight (kg)	71.3 ± 4.1	68.3 ± 3.7
Height (in)	64.8 ± 0.4	63.4 ± 0.4
Body mass index (kg/m ²)	26.3 ± 0.6	26.3 ± 0.8
Systolic blood pressure (mmHg)	119.2 ± 2.0	123.7 ± 2.3
Diastolic blood pressure (mmHg)	75.4 ± 1.3	77.3 ± 1.6
Pulse rate (bpm)	67.9 ± 1.3	72.2 ± 1.6
Race (%)		
Caucasian	54.1	67.6
Black	21.6	14.7
Hispanic	18.9	14.7
Asian	2.7	2.9
Other	2.7	0.0

^a No significant differences between treatment groups for any characteristic. Values are means ± standard error, except for time since last menses (medians [minimum, maximum]), hysterectomy (n, %), and race (%).

^b For placebo, n = 33 for height and body mass index.

59 years. Roughly half of the subjects had a previous hysterectomy, and mean time since last menses was 13–16 years.

3.2. Vaginal cytology

3.2.1. Maturation index

The results of the analyses of the change in Vaginal Maturation Index from weeks –2 to 4, 8, 12 and 16 are displayed in Table 2. SCE-A subjects exhibited a significant estrogenic effect as early as week 4, as observed by a mean increase of 14.6 in the Vaginal Maturation Index. The mean increase changed very little after week 4, reaching 17.7 at week 16. Placebo subjects had a mean increase of 4.1 from week –2 to week 16. There was a highly statistically significant ($P < 0.0001$) difference between SCE-A and placebo groups in the change from week –2 to each post-randomization clinic visit in the Vaginal Maturation Index. The mean values for the Vaginal Maturation Index at week –2 and each subsequent clinic visit are shown in Fig. 1.

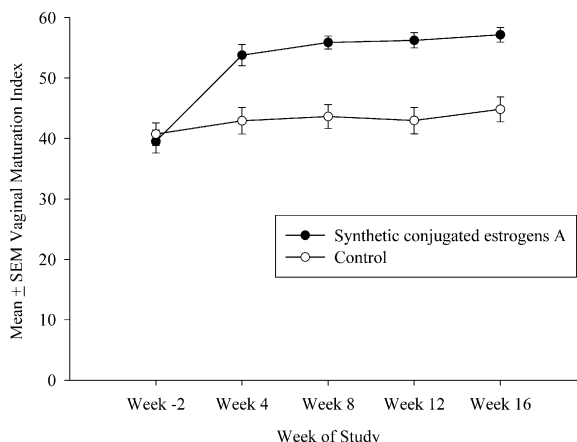


Fig. 1. Mean vaginal maturation index ± S.E.M. at screening (week –2) and weeks 4, 8, 12 and 16 according to treatment groups.

3.2.2. Cell types

The percentages of each of the individual cell types assessed at the clinic visits are shown in Table 2. Superficial cells significantly increased in the SCE-A group from 2.1% at baseline to 15.9% at week 16 ($P < 0.0001$ between treatments). There was also a significant increase in superficial cells in the placebo group (from 1.6 to 5.3%), though this was significantly less than the increase in the SCE-A group. The mean values for superficial cells for the SCE-A and placebo groups at each clinic visit are shown in Fig. 2. There

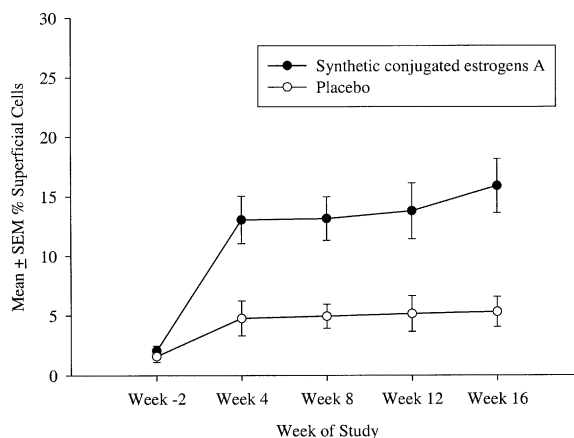


Fig. 2. Mean percentage of superficial cells ± S.E.M. at screening (week –2) and weeks 4, 8, 12 and 16 according to treatment groups.

Table 2

VMI, superficial, intermediate, and parabasal cells of the vaginal mucosa at week –2 (screening), and the change from weeks –2 to 4, 8, 12 and 16 according to treatment with SCE-A or placebo

Parameters	Study week	SCE-A (<i>n</i> = 37) Mean ± S.E.M.	Placebo (<i>n</i> = 34) Mean ± S.E.M.	<i>P</i> -value ^a
VMI ^b	Week –2	39.5 ± 1.9	40.7 ± 1.9	0.6531
	Δ week –2 to 4	14.6 ± 2.5	2.3 ± 1.9	< 0.0001
	Δ week –2 to 8	16.7 ± 2.3	3.5 ± 1.5	< 0.0001
	Δ week –2 to 12	17.0 ± 2.3	2.8 ± 1.7	< 0.0001
	Δ week –2 to 16	17.7 ± 2.4	4.1 ± 1.6	< 0.0001
Superficial (%)	Week –2	2.1 ± 0.4	1.6 ± 0.5	0.4644
	Δ week –2 to 4	11.0 ± 1.9	3.4 ± 1.4	0.0012
	Δ week –2 to 8	11.1 ± 1.7	3.3 ± 1.0	< 0.0001
	Δ week –2 to 12	11.8 ± 2.2	3.6 ± 1.4	0.0002
	Δ week –2 to 16	13.8 ± 2.2	3.7 ± 1.3	0.0001
Intermediate (%)	Week –2	74.9 ± 3.6	78.3 ± 3.4	0.5015
	Δ week –2 to 4	7.1 ± 3.3	–2.1 ± 3.1	0.0659
	Δ week –2 to 8	11.1 ± 3.6	0.3 ± 2.8	0.0629
	Δ week –2 to 12	10.5 ± 3.8	–1.4 ± 3.4	0.0242
	Δ week –2 to 16	7.6 ± 3.9	0.7 ± 2.6	0.2314
Parabasal (%)	Week –2	23.0 ± 3.7	20.2 ± 3.6	0.5752
	Δ week –2 to 4	–18.1 ± 3.8	–1.3 ± 3.2	0.0003
	Δ week –2 to 8	–22.2 ± 3.8	–3.7 ± 2.7	0.0004
	Δ week –2 to 12	–22.3 ± 3.7	–2.1 ± 3.1	< 0.0001
	Δ week –2 to 16	–21.5 ± 3.8	–4.5 ± 2.6	0.0004

^a *P*-value derived from analysis of variance of the ranked values to test for between treatment differences.

^b Pre-specified primary outcome variable.

was a significant increase in intermediate cells in the SCE-A group, but there was a significant difference between treatment groups in the proportion of intermediate cells only at week 12 ($P = 0.0242$). Parabasal cells were significantly reduced in the SCE-A group from 23.0% at baseline to 2.3% at week 16, compared to 20.2% at baseline to 15.7% at week 16 in the placebo group ($P < 0.001$ between treatments).

3.3. Vaginal pH

Vaginal pH decreased significantly from 6.2 to 5.2 in the SCE-A group and was essentially unchanged in the placebo group. The difference in response between treatment groups was highly statistically significant (17.1%, $P < 0.0001$).

3.4. Safety

Treatment-emergent adverse events were reported by 59 (83.1%) of the subjects enrolled in the study.

Of the subjects who received SCE-A, 32 (86.5%) reported at least one adverse event and of those who received placebo, 27 (79.4%) reported at least one adverse event. There was no significant difference between treatment groups in the overall incidence of treatment-emergent adverse events. In general, adverse events did not differ between groups with the exception of an increased incidence of urinary tract infection in the placebo group (6, 17.6%) compared with the SCE-A group (0, 0%) ($P = 0.009$). The body systems with the most reports of adverse events included: body as a whole, digestive, neurological, and urogenital. The most commonly reported adverse events were leukorrea (32% SCE-A, 15% placebo), vaginitis (24% SCE-A, 15% placebo), headache (11% SCE-A, 21% placebo), and endometrial thickening classified as >4 mm by transvaginal ultrasound (8% SCE-A, 9% placebo). There were three cases in each group where an endometrial biopsy at week 16 was indicated. In the SCE-A group, two of the biopsy results were normal, and in the other not enough tissue was obtained

to conduct a biopsy. In the placebo group, one biopsy was normal, and in two, a biopsy was not obtainable due to a stenotic cervical os.

There were no clinically important changes in serum chemistry, hematology, or urinalysis detected during treatment in either group. No adverse effects were noted in other safety assessments, including vital signs, body weight, and general physical and gynecological examinations.

4. Discussion

The primary objective of this study was to determine the effect of low-dose (0.3 mg once daily) SCE-A tablets (Cenestin) on vulvovaginal atrophy in healthy postmenopausal women. As early as 4 weeks and throughout the 16-week study, women treated with SCE-A had a highly significant improvement in vaginal cytology compared to placebo, as indicated by the Vaginal Maturation Index. This response of the vaginal mucosa to estrogen treatment was as anticipated [9]. A meta-analysis reviewing randomized, placebo-controlled trials published between 1969 and 1995 determined that estrogen therapy, as compared to placebo, was efficacious in the treatment of postmenopausal women with signs and symptoms of vaginal atrophy [10]. As the testing involved both a unique estrogen formulation (Cenestin, SCE-A), and a lower dose than had been previously evaluated, a placebo control was employed in order to determine the impact of therapy on vaginal histology and symptoms.

The Vaginal Maturation Index is a standardized scale utilized to express the proportion of the various vaginal cell types. The Vaginal Maturation Index typical of premenopausal women is comprised of 30–60% superficial cells, 40–70% intermediate, and 0% parabasal depending on cycle phase [9]. During early menopause, parabasal cells increase to ~65% and intermediate and superficial cells decrease to ~30 and 5%, respectively [9]. In some elderly women, all cells may be parabasal [9]. In the current trial, treatment with SCE-A resulted in a significant estrogenic improvement in the distribution of the vaginal cell types. The percentage of vaginal superficial cells increased significantly, the percentage of intermediate cells also increased, and the percentage of parabasal

cells decreased significantly, resulting in a vaginal cellular distribution similar to that of premenopause.

Notably, the improvements in vaginal cytology were demonstrated as early as 4 weeks following initiation of estrogen therapy. Though it may take up to 1 year to reverse the effects of urogenital atrophy using hormone replacement, the duration of treatment necessary to produce significant improvements in atrophy symptoms and vaginal pH and cytology measurements is significantly less [10]. Current standard oral doses of estrogen therapy are considered to be effective for vaginal atrophy after 1–3 months of treatment [10]. Less is known about lower doses of oral estrogen. In the Women's HOPE trial, which included a dose of 0.3 mg conjugated equine estrogens with and without medroxyprogesterone acetate at 1.5 mg/day, significant changes from baseline Vaginal Maturation Index were reported after 6 and 13 cycles [17], but there was no measure of the Maturation Index taken earlier than 6 cycles. The finding in the current trial has important clinical applications, relevant to the treatment expectations of the patient and her doctor.

An additional benefit of treatment with SCE-A was decreased vaginal pH. The decrease in circulating estrogen that occurs with menopause leads to a reduction in the glycogen content of epithelial cells, which in turn inhibits the production of lactic acid by lactobacilli [6]. Elevated vaginal pH breaks down the body's natural protective barrier against vaginal and urinary tract infections [6]. The reduced pH seen with SCE-A treatment would be expected to improve the vaginal defense against infection. As further evidence of the importance of this effect, there were no reports of urinary tract infections in the SCE-A group during the study, whereas there were six reports of urinary tract infection in the placebo group.

SCE-A tablets at 0.3 mg daily was well tolerated by the subjects. Mean compliance with study medication was high (>98%), and there were no differences in adverse events between treatment and placebo groups, except for an increased incidence of treatment-emergent urinary tract infection in the placebo group. The most commonly reported adverse events were leukorrhea, vaginitis, headache, and endometrial thickening (which was not classified as hyperplasia upon biopsy). Headache and endometrial thickening were reported less frequently among the synthetic conjugated estrogens, A subjects, while

vaginitis and leukorrhea were reported slightly more frequently in this group. The increased reports of leukorrhea observed in the SCE-A group may have actually been a result of increased lubrication from the estrogen treatment, which thickens and revascularizes the vaginal epithelium. Furthermore, assessments of vital signs, body weight, clinical laboratory values, and physical and gynecological examinations revealed no untoward effects of SCE-A treatment.

The data collected in this study agree closely with results of previous studies which have demonstrated estrogen's effectiveness for partially or completely restoring vaginal cytology, vaginal pH, and improving symptoms and physician assessments of vaginal atrophy [3,6,7,9,10,14,17]. Concerns about side effects and safety often prevent women from initiating or continuing estrogen or estrogen-progestin therapy [9]. As a result, there is much interest in determining whether low-doses of estrogen are effective for relieving menopausal symptoms, including vaginal atrophy. The lowest dosage of oral estrogen required to treat urogenital atrophy is not yet defined. The present study showed that Cenestin produced improvements in vaginal cytology within 4 weeks, and perhaps even earlier, though 4 weeks was the earliest timepoint measured.

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