

Comparative study: Replens* versus local estrogen in menopausal women†

Lila E. Nachtigall, M.D.‡

New York University School of Medicine, New York, New York

As life expectancy in women increases and the age of menopause remains the same, the postmenopausal period will increase. This becomes very significant in the treatment of vaginal dryness, postmenopausal dyspareunia, vaginal infections, irritation and discomfort, and even some forms of incontinence. We have known for some time that the hypoestrogenic state leads to loss of cornification and loss of rugal folds in the vaginal epithelium. Estrogen replacement has been shown to increase cornification and return rugal folds to the premenopausal state. In addition, vaginal fluid volume, vaginal moisture, and vaginal pH levels are restored as well. In many cases sexual dysfunction is reversed. Until recently, no other agent has been able to reverse atrophy. As estrogen is not always indicated and sometimes contraindicated even when only used in the vagina, a search for a well-tolerated nonhormonal alternative has been ongoing. Recently, a nonhormonal local bioadhesive vaginal moisturizer (Replens; Parke-Davis, Morris Plains, NJ) became available. Leiblum et al. (1) have shown its superior efficacy when comparing it with a common lubricant. We believed it would be advantageous to compare Replens to Premarin Vaginal Cream (Wyeth-Ayerst Laboratories, Philadelphia, PA), the most widely used therapy for vaginal dryness.

MATERIALS AND METHODS

We began a 12-week study with 30 women. Eligible women were >1 year past their last menstrual

period, not on any other hormone therapy, cancer free, and experiencing vaginal discomfort or dyspareunia. Once selected, they were randomized to two groups, with 15 in each group. Group 1 was placed on Replens three times per week for 12 weeks, and group 2 was placed on 2 g of Premarin every day for 12 weeks.

Once the randomization was accomplished, the study proceeded as open label. All patients were seen by a physician once a week during the first month and then every 4 weeks for the next 2 months. A Papanicolaou (PAP) smear, using a brush, was done at every visit. The smear was read by the pathologist and reported as atrophic if the following findings were noted: [1] strands of cells with stretched appearance, [2] the cell nuclei appeared bland, or [3] cells appeared to have almost no fluid (2). Vaginal fluid pH was measured by using pH indicator strips (colorpHast; EM Science, Gibbstown, NJ). A previously published rating system (1), a vaginal health index, as modified (3), was completed by the physician. This index, shown in Table 1, allows for scoring of vaginal moisture, vaginal fluid volume, vaginal elasticity, and vaginal mucosa on a scale of 1 (poorest) to 5 (best). Statistical evaluations were performed using the Wilcoxon two-sample test for between-treatment group comparisons and the Wilcoxon matched-pairs signed-rank test for within-treatment group comparisons (4). All tests were two-sided, $\alpha = 0.05$.

RESULTS

Table 2 presents the changes scored in the various parameters of the vaginal health index. Both groups had a statistically significant return of vaginal moisture and vaginal fluid volume by week 4. This increase was maintained in both groups over the 12-week study period.

Received January 12, 1993; revised and accepted September 15, 1993.

* Replens, Parke-Davis, Morris Plains, New Jersey.

† Supported by Columbia Laboratories, Inc., Hollywood, Florida.

‡ Reprint requests: Lila E. Nachtigall, M.D., 231 East 33rd Street, New York, New York 10016.

Table 1 Vaginal Health Index

	Score				
	1	2	3	4	5
Vaginal moisture (coating)	None, surface inflamed	None, surface not inflamed	Minimal	Moderate	Normal
Vaginal fluid volume (pooling of secretions)	None	Scant amount, vault not entirely covered	Superficial amount, vault entirely covered	Moderate amount	Normal amount
Elasticity	None	Poor	Fair	Good	Excellent
Epithelial integrity (mucosa)	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable, thin epithelium	Normal
Vaginal pH	≥6.1	5.6 to 6.0	5.1 to 5.5	4.7 to 5.0	≤4.6

Vaginal elasticity also increased in both groups. In the estrogen group, this increase was statistically significant at week 4; in the Replens group, it was statistically significant at week 12. Both groups had returned to premenopausal pH levels by week 4 and both groups remained free of vaginal infections for the entire 12 weeks.

Papanicolaou smear results demonstrated that all patients on estrogen with reported vaginal atrophy at baseline had it reversed at the end of 12 weeks. Also, 60% of the Replens group with vaginal atrophy as seen on PAP smear at baseline had it reversed in 12 weeks as well. Estrogenic changes in cytology were seen in the Premarin group, but no such changes were noted in the Replens group. There were no serious side effects in either group.

DISCUSSION

A vaginal pH of 4 to 5 with the return of vaginal fluid volume, moisture, and elasticity is probably

satisfactory for prevention of vaginal infections and comfortable return of sexual function even without complete vaginal atrophy reversal and recornification. An acid vagina not only protects against secondary invaders but supports the beneficial vaginal flora as well (5). Recornification would not be expected, nor was it seen, with the nonhormonal gel, because this is a cellular reaction. The gradual increase in vaginal elasticity with continued use of the nonhormonal preparation was found also by Bachmann et al. (6).

SUMMARY

This was an open-label study comparing effects of a nonhormonal drug-free bioadhesive vaginal moisturizer to a local estrogen therapy in the treatment of vaginal dryness symptoms. There were 15 women evaluated in each treatment group during a 12-week period. Results indicated that the bioadhesive vaginal moisturizer was a safe and effective

Table 2 Results of Vaginal Therapies*

	Baseline	Week 4	Week 8	Week 12
Vaginal moisture				
Replens	2.63 ± 0.78	3.55 ± 0.50†	3.47 ± 0.81	3.67 ± 0.60†
Estrogen	2.13 ± 0.78	4.15 ± 0.66†	4.36 ± 0.61†	4.71 ± 0.45†
Vaginal fluid volume				
Replens	2.25 ± 0.75	3.36 ± 0.64‡	3.40 ± 0.71‡	3.67 ± 0.70‡
Estrogen	1.81 ± 0.63	3.85 ± 0.66‡	4.38 ± 0.74‡	4.71 ± 0.45‡
Vaginal elasticity				
Replens	2.69 ± 0.68	3.36 ± 0.64	3.33 ± 0.60	3.40 ± 0.71§
Estrogen	2.31 ± 0.58	3.92 ± 0.62§	4.00 ± 0.53§	4.50 ± 0.50§
Vaginal pH				
Replens	5.8 ± 0.18	4.8 ± 0.25‡	5.3 ± 0.28	4.8 ± 0.26‡
Estrogen	6.3 ± 0.20	4.7 ± 0.18‡	4.6 ± 0.12‡	4.4 ± 0.17‡

* Values are means ± SD.
† P < 0.005 compared with baseline.

‡ P < 0.05 compared with baseline.
§ P < 0.02 compared with baseline.

alternative to estrogen vaginal cream, with both therapies exhibiting statistically significant increases in vaginal moisture, vaginal fluid volume, and vaginal elasticity with a return of the premenopausal pH state.

Key Words: Vaginal, vaginal dryness, vaginal moisturization, nonhormonal vaginal therapy, hormonal vaginal therapy, vaginal pH.

REFERENCES

1. Leiblum S, Bachmann GA, Kemmann E, Coburn D, Swartzman L. Vaginal atrophy in the postmenopausal woman, the importance of sexual activity and hormones. *JAMA* 1983;249:2195-8.
2. Koss LG. *Diagnostic cytology and its histopathologic bases*. 4th ed. Philadelphia: JB Lippincott Company, 1992:279-80.
3. Bachmann GA, Notelovitz M, Gonzalez SJ, Thompson C, Morecraft BA. Vaginal dryness in menopausal women: clinical characteristics and non-hormonal treatment. *Clin Pract Sexuality* 1991;7:25-32.
4. Hollander M, Wolfe DA. *Nonparametric statistical methods*. New York: John Wiley and Sons, 1973.
5. Semmens JP, Wagner G. Estrogen deprivation and vaginal function in postmenopausal women. *JAMA* 1982;248:445-8.
6. Bachmann GA, Notelovitz M, Kelly SJ, Thompson C, Owens A. Long-term non-hormonal treatment of vaginal dryness. *Clin Pract Sexuality* 1992;8:12-7.