

## Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women

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### ABSTRACT

**Objective:** To assess the efficacy and safety of intravaginal estriol administration on urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women.

**Design:** Eighty-eight postmenopausal women with urogenital aging symptoms were enrolled in this prospective, randomized, placebo-controlled study. Participants were randomly divided into two groups, with each group consisting of 44 women. Women in the treatment group received intravaginal estriol ovules: 1 ovule (1 mg) once daily for 2 weeks and then 2 ovules once weekly for a total of 6 months as maintenance therapy. Women in the control group received inert placebo vaginal suppositories in a similar regimen. We evaluated urogenital symptomatology, urine cultures, colposcopic findings, urethral cytologic findings, urethral pressure profiles, and urethrocystometry before as well as after 6 months of treatment.

**Results:** After therapy, the symptoms and signs of urogenital atrophy significantly improved in the treatment group in comparison with the control group. Thirty (68%) of the treated participants, and only seven (16%) of the control participants registered a subjective improvement of their incontinence. In the treated participants, we observed significant improvements of colposcopic findings, and there were statistically significant increases in mean maximum urethral pressure, in mean urethral closure pressure as well as in the abdominal pressure transmission ratio to the proximal urethra. Urethrocystometry showed positive but not statistically significant modifications.

**Conclusions:** Our results show that intravaginal administration of estriol may represent a satisfactory therapeutic choice for those postmenopausal women with urogenital tract disturbances who have contraindications or refuse to undergo standard hormone therapy.

**Key Words:** Postmenopausal women – Urogenital atrophy – Recurrent urinary tract infections – Urinary incontinence – Vaginal estriol – Low-dose estrogen.

Symptoms and signs of urogenital integrity disorders involving the lower urinary tract, genital tract, and pelvic floor become evident after menopause, increasing with advancing age.<sup>1</sup> The effective prevalence of compromised urogenital

integrity is unknown. In fact, many women seek no treatment because they perceive it as an unavoidable effect of aging. Others feel embarrassed and do not talk with their physician about this problem. Recently, Greendale et al<sup>2</sup> reported that from 10% to 40% of all postmenopausal women were found to have symptoms related to urogenital atrophy, but only about 25% of these women presented the problem to their physicians, and very few underwent hormone therapy.<sup>3</sup> In the West, 8% of the total population has urogenital problems;<sup>4</sup> and in the United States, 20 million women, who do not undergo hormone therapy (HT), have these socially disabling symptoms.<sup>5</sup>

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The symptoms relating to urogenital aging may be categorized into two groups: those localized to the lower urinary tract (urethra and bladder) and those confined to the vagina and vulva. The first group includes frequency and urgency, nocturia, dysuria, recurrent urinary tract infections, and urinary incontinence; the second group includes vaginal dryness, itching, burning, and dyspareunia.

It is now well demonstrated that the urogenital organs are highly sensitive to the influence of estrogen. In fact, estrogen receptors have been found in the urethra and bladder trigone,<sup>6</sup> as well as in the round ligaments and levator ani muscles.<sup>5,7</sup> In the vagina, the progressive decline of estrogens during the climacteric induces atrophy of the mucosa, which becomes thinner. Similarly, in the urethra and bladder the reduction of estrogens produces atrophy of the mucosa, causing nocturia, dysuria, and urinary urgency. The atrophy of muscles and the reduction of collagen content may be important factors in the increased prevalence of urinary incontinence and urogenital prolapse.<sup>8,9</sup>

The efficacy of estrogen therapy on urogenital complaints has already been clearly demonstrated by numerous clinical studies.<sup>3,10-13</sup> In particular, estriol is a weak estrogen that has been successfully adopted to treat postmenopausal women in several countries for more than 30 years. Estriol is considered to be free of the potential risks associated with the systemic use of estrogenic therapy;<sup>14</sup> moreover, it has been definitively demonstrated that intravaginal estriol does not stimulate the proliferation of endometrium.<sup>15-17</sup> Its vaginal absorption is swift and effective and bypasses the first hepatic inactivation, and more stable circulating levels are achieved compared with the oral route.

Several studies have shown the efficacy of intravaginal estriol in the treatment of urogenital atrophy,<sup>16,18-23</sup> of recurrent urinary tract infections<sup>24,25</sup> and of climacteric symptoms.<sup>18,21,26,27</sup> Relatively few published studies have demonstrated the effect of intravaginal estriol therapy on urinary incontinence in postmenopausal women using different pharmaceutical preparations and doses.<sup>17,28-34</sup> The aim of the present study was to assess the efficacy and safety of intravaginal estriol administration on urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women.

## METHODS

### Study area

The study was carried out from May 1999 to April 2002 in Sassari, the largest district of northern Sardinia, with a population of 120,803 (Istituto Nazionale di Sta-

tistica, Rome, Italy, 2001)<sup>35</sup> and a density of 224 people per square kilometer. The population included 11,269 women between 55 and 70 years of age.

### Sampling

Sample size was calculated on the basis of prevalence of urinary incontinence, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women, and so they increased by 10%. Consequently, our estimates were safeguarded at an optimal level of precision (5%) against the possible effect of disease reduction since the previous study. The theoretical sample size was 434. All the women were given an information leaflet explaining the aim of the study and requesting their participation. Fifty-six (13%) women chose not to participate; hence, 378 (87%) women were evaluated.

An initial assessment (screening visit or visit 1) including the recent history of somatic symptoms, complete medical and surgical history, and a complete physical and gynecological examination were performed to determine each woman's suitability for the study in accordance with inclusion and exclusion criteria. If the woman were suitable for the study, an appointment was made for her to return for the baseline visit (visit 2). During the baseline visit, the determination of vaginal pH, colposcopic examination, vaginal and urethral smears, urodynamic examination, and a further check of her compliance with inclusion and exclusion criteria were performed. All participants presented symptoms and signs of urinary stress incontinence, vaginal atrophy, and histories of recurrent urinary tract infections. None had received estrogen treatment before the study. Exclusion criteria for the study were anatomical lesions of the urogenital tract, such as uterovaginal prolapse, cystocele, and rectocele of grade II or III, presence of severe systemic disorders, thromboembolic diseases, biliary lithiasis, previous breast or uterine cancer, abnormal uterine bleeding, and body mass index of 25 kg/m<sup>2</sup> or higher. The diagnosis of genuine stress incontinence (GSI) was confirmed by the direct visualization of loss of urine from the urethra during the standard stress test and by urodynamic investigation. Women with detrusor over activity and abnormal maximal cystometric capacity were excluded from the study. Hence, the study reports data on 88 postmenopausal women with urogenital aging symptoms.

At this point, the eligible women signed informed consent forms and were randomly assigned to a treatment or a control group. Each group consisted of 44 women. Randomization was obtained using sets of sequenced, sealed, opaque envelopes, each containing

the bottle number to be given to each participant. Women in the treatment group were given intravaginal estriol ovules: 1 ovule (1 mg) once daily for 2 weeks (Colpogyn, Angelini, Rome, Italy) and then 2 ovules once weekly as maintenance therapy for a total of 6 months. Women in the control group received inert placebo vaginal suppositories in a similar regimen. The placebo- and estriol-containing vaginal suppositories were identical in appearance. Participants and investigators were blinded to the drug being dispensed and to the assigned treatment group. We evaluated the urogenital symptomatology, urine cultures, colposcopic findings, urethral cytologic findings, urethral pressure profile, and urethrocystometry before as well as after 6 months of treatment. The same physician was involved in the clinical and gynecological examinations.

The women enrolled in the study complained of the main symptoms of stress urinary incontinence, such as urine loss with physical exertion, coughing, sneezing and intercourse, and symptoms of genital atrophy conditions, including vaginal dryness and dyspareunia. According to Ingelman-Sundberg<sup>36</sup> classification of stress incontinence symptoms, the participants were classified: grade I, 16 women; grade II, 61 women; and grade III, 11 women. The subjective evaluation of incontinence disorders was based on a woman's description of the effect of the incontinence with respect to activities at home and at work (Incontinence Impact Questionnaire).<sup>37</sup> The urinary incontinence complaints were assessed as none, mild, moderate, or severe. The therapeutic efficacy on urinary incontinence complaints was assessed as follows: women who changed from "mild/moderate/severe" to "none" were classified as "cured." Women who changed from "moderate" to "mild" or from "severe" to "moderate/mild" were classified as "improved." Women who did not change from pretreatment were classified as "no change." Women who changed from "none" to "mild/moderate/severe" or from "mild" to "moderate/severe" or from "moderate" to "severe" were classified as "worse." The symptoms relating to urogenital atrophy such as vaginal dryness and dyspareunia were classified as follows: none, moderate, or severe at each visit. Therapy efficacy on atrophic condition complaints was assessed as described above.

The gynecologic evaluation included vaginal atrophy and pH assessment. The authors visually assessed the degree of urogenital atrophy conditions as none, moderate, or severe at each visit, taking into account pallor, petechiae, friability, and vaginal dryness (no, yes) as objective evidence of estrogen deficiency. Vaginal pH was measured using an indicator strip, and

midstream urine specimens were obtained at the beginning of the study and after 6 months of treatment. Significant bacteriuria was considered to be present if the midstream urine culture yielded  $10^5$  colony-forming units or more per milliliter. The decrease in thickness of the epithelium of portio was subjectively assessed as present or absent. We performed Schiller's test in all participants and visually evaluated the possible presence of petechiae. Vaginal and urethral smears were taken during colposcopic examination by the cytobrush sampling technique from the upper lateral vaginal walls and from the distal urethral walls. After preparation with a cytology fixative, the smears were sent to the pathologist for preparation and staining according to Papanicolaou. The effect of estriol on the vaginal and urethral epithelium was estimated by means of the karyopyknotic index, defined as the percentage of superficial cells found in the total population of the squamous cells examined,<sup>38</sup> which is considered a reliable cellular index for the determination of estrogen activity.<sup>39</sup>

We calculated the urethral pressure profile and urethrocystometry at the beginning of the study and after 6 months of treatment according to the criteria of the International Continence Society, using the Phoenix Plus videourodynamic machine (Albyn Medical LTD, Dingwall, Scotland). Urethral and intravesical pressures were measured in the supine position by a catheter equipped with a microtransducer two-way standard (Albyn Medical LTD, Dingwall, Scotland). Vesical filling was performed with saline solution at a constant speed of 50 mL/min. The urethral pressure profile was measured after vesical filling to 250 mL. By three reproducible urethral pressure profiles, the mean maximum urethral pressure (MUP), the mean maximum urethral closure (MUCP), and the mean functional urethral length (FUL) were calculated. The abdominal pressure transmission ratio (PTR) to the urethra was calculated as  $a/b \times 100$  where  $a$  is the urethral pressure increase and  $b$  is the intravesical pressure increase during coughing.

At the beginning of the study, the women received a diary in which they were asked to record the occurrence of localized or systemic side effects. Six months later we reviewed these diaries to assess the treatment compliance.

Our Ethic Board Committee approved the study.

#### Statistical analysis

It is a common to have participants drop out of studies designed such as ours. Nevertheless, we decided to include the eventual dropouts in statistical analyses.

TABLE 1. Characteristics of the study group

	Treatment group (n = 44)	Control group (n = 44)
Age (y)	58 ± 4	56 ± 5
Height (cm)	161 ± 5	162 ± 7
Weight (kg)	62 ± 7	64 ± 8
BMI (kg/m <sup>2</sup> )	21.8 ± 4.5	22.4 ± 4.9
Race (white)	99%	98%
Vaginal parity	2.9 ± 1.8	2.6 ± 1.2
Duration of menopause (y)	7.5 ± 5.2	7.0 ± 4.8
Duration of urinary incontinence symptoms (y)	6.5 ± 4.4	5.7 ± 4.2
Duration of urogenital atrophy symptoms (y)	4.8 ± 5.0	5.0 ± 5.2

BMI, body mass index.

In the statistical elaboration of the data concerning the dropouts, the unavailable outcome data were assumed to be worst-case, ie, the parameters taken into account at the baseline were considered to have remained unchanged.

All the data were computed in a database. The analysis was carried out using an Anova one-way for means observation and  $\chi^2$  with collinearity for dichotomous variables. All statistical significance figures apply to the after-treatment measurements.

## RESULTS

The characteristics of the participants are summarized in Table 1.

The treatment and control groups were homogenous for age (58 ± 4 years and 56 ± 5 years, respectively), vaginal parity (2.9 ± 1.8 and 2.6 ± 1.2, respectively), menopause duration (7.5 ± 5.2 years and 7.0 ± 4.8, respectively), and duration of urinary incontinence (6.5 ± 4.4 years and 5.7 ± 4.2, respectively).

The dropout participants, who stopped the treatment before the 6 months established in the protocol, were four women in the treatment group and seven in the placebo group. Among them, four women (two in the treatment group and two in the placebo group) had experienced discomfort during vaginal treatment; three (two in the treatment group and one in the placebo group) experienced localized adverse reactions, such as vaginal irritation, burning and itching; and 4, all in the control group, did not benefit from therapy.

Before starting therapy, all of the women presented symptoms of stress incontinence ranging from mild to severe. After 6 months, 30 (68.2%) of the treated participants registered subjective improvement of their incontinence (7 totally continent and 23 significantly improved), whereas only 7 (16%) of the control participants reported this improvement ( $P < 0.01$ ) (Table 2).

At the beginning of the study, the women in the two groups were graded according to Ingelman-Sundberg as follows: in the treatment group, 8 women were grade I, 31 women were grade II, and 5 women were grade III; in the control group, 8 women were grade I, 30 women were grade II, and 6 women were grade III. After the 6-month treatment period, the women were graded as follows: in the treatment group, 7 women were considered cured, 25 women were in grade I, 8 were in grade II, and 4 were in grade III; in the control group, 11 women were grade I, 21 were grade II, and 12 were grade III.

Before starting therapy, all 88 women had presented with urogenital atrophy ranging from moderate to severe and had suffered from vaginal dryness; 38 in the treatment group and 37 in the control group reported symptoms of dyspareunia. Subsequently, on clinical examination, symptoms and signs of urogenital atrophy, vaginal dryness, and dyspareunia improved significantly in the treatment group in comparison with the control group (Table 2).

At baseline, 17 women (38.6%) had presented with significant bacteriuria (*Escherichia coli* in 12 cases, *Proteus mirabilis* in 5) in the treatment group, and 16 (36.3%) in the placebo group (*E. coli* in 10 cases, *P. mirabilis* in 6). After treatment, there was a significant bacteria in the urine of 6 treated (13.6%) and 20 control (45.4%) women ( $P < 0.001$ ).

The mean vaginal pH at baseline was 5.65 ± 0.97 for the treatment group and 5.47 ± 0.93 for the placebo group. After therapy, vaginal pH was 4.12 ± 0.96 and 5.30 ± 0.75 ( $P < 0.05$ ) (Table 2).

Among treated women, a statistically significant improvement of colposcopic parameters, and a significant rise in karyopyknotic index was found after treatment in the vaginal and urethral epithelium, in comparison with nontreated women (Table 3).

In the treated participants, there were statistically significant increases in mean MUP and MUCP, no significant change in mean FUL, and a significant increase in mean PTR in comparison with the control participants (Table 4).

Urethrocystometry showed positive modifications in the treatment group; however, they were not statistically significant (Table 5).

No systemic adverse reactions were observed.

## DISCUSSION

Vasomotor symptoms and dyspareunia due to urogenital atrophy are the main reasons that a menopausal woman requires HT.

# LOW-DOSE ESTRIOL AND UROGENITAL AGING

**TABLE 2.** Clinical modifications induced by intravaginal estriol therapy

Clinical variables	Treatment group (n = 44)		Control group (n = 44)		P
	Before treatment	After treatment	Before treatment	After treatment	
Subjective complaints of SUI	44/44	14/44	44/44	37/44	<0.01 <sup>a</sup>
Vaginal dryness	44/44	9/44	44/44	40/44	<0.001 <sup>a</sup>
Dyspareunia	38/44	9/44	37/44	38/44	<0.001 <sup>a</sup>
Urogenital atrophy	44/44	12/44	44/44	41/44	<0.01 <sup>a</sup>
Significant bacteriuria	17/44	6/44	16/44	20/44	<0.001 <sup>a</sup>
Vaginal pH	5.65 ± 0.97	4.12 ± 0.96	5.47 ± 0.93	5.30 ± 0.75	<0.05 <sup>b</sup>

SUI, stress urinary incontinence.

<sup>a</sup>χ<sup>2</sup> test

<sup>b</sup>Anova one-way

**TABLE 3.** Colposcopic and cytologic findings before and after 6 months of treatment

Colposcopic and cytologic findings	Treatment group (n = 44)		Control group (n = 44)		P
	Before treatment	After treatment	Before treatment	After treatment	
Portio epithelium thickness reduction	44/44	12/44	44/44	42/44	<0.001 <sup>a</sup>
Positivity at Schiller's test	0/44	40/44	1/44	6/44	<0.001 <sup>a</sup>
Petechiae	22/44	3/44	23/44	25/44	<0.001 <sup>a</sup>
KPI of vaginal epithelium	9.27 ± 1.43	29.75 ± 7.72	9.52 ± 1.84	10.17 ± 1.82	<0.001 <sup>b</sup>
KPI of urethral epithelium	5.50 ± 0.68	15.07 ± 4.04	5.15 ± 0.73	7.12 ± 1.26	<0.01 <sup>b</sup>

KPI, karyopyknotic index.

<sup>a</sup>χ<sup>2</sup> test.

<sup>b</sup>Anova one-way.

**TABLE 4.** Urodynamic variables (urethral pressure profile) before and after 6 months of treatment

Urodynamic variables	Treatment group (n = 44)		Control group (n = 44)		P <sup>a</sup>
	Before treatment	After treatment	Before treatment	After treatment	
MUP (cm H <sub>2</sub> O)	50.82 ± 6.15	62.15 ± 8.64	52.35 ± 6.30	49.40 ± 6.54	<0.05
MCUP (cm H <sub>2</sub> O)	45.25 ± 7.20	56.87 ± 9.23	44.77 ± 6.86	43.32 ± 6.32	<0.05
FUL (mm)	26.30 ± 2.40	27.95 ± 3.13	26.32 ± 2.22	26.55 ± 2.48	NS
PTR (%)	72.52 ± 10.31	88.85 ± 9.66	70.75 ± 9.08	70.77 ± 9.04	<0.05

Data expressed as mean ± SD. MUP, maximum urethral pressure; MCUP, maximum urethral closure pressure; FUL, functional urethral length; PTR, pressure transmission ratio.

<sup>a</sup>Anova one-way.

The urethra and distal vagina, which have a common embryonic origin from the urogenital sinus, are both responsive to estrogen hormonal stimulation. Furthermore, there is the same concentration of estrogen receptors in both organs.<sup>6</sup> A recent meta-analysis on 77 studies<sup>3</sup> has shown estrogens (administered orally or vaginally, and in all dosage regimens) to be efficacious in the treatment of urogenital atrophy. In particular, the local low-dose estrogen therapy (using both estradiol and estriol) is as effective as systemic estrogen therapy (ET) in the treatment of urogenital atrophy in postmenopausal women. Notable pharmacokinetic advantages derive from intravaginal administration of estriol: by this route estriol bypasses the first hepatic inactiva-

tion, its absorption is fast and efficacious, is not modified by the time of administration or by consumption of food, and more stable circulating levels are achieved compared with the oral route.<sup>40,41</sup> The effectiveness of estriol on the vaginal epithelium and urethra is well documented.<sup>16,19</sup>

Our results show that intravaginal estriol therapy was effective in the treatment of symptoms and signs of urogenital aging. The amelioration of urogenital atrophy assessed by urethral and vaginal smears was due to the positive effect of estrogens on growth and maturation of squamous epithelium of urethral and vaginal mucosa. This is an important finding because the mucosa serves as a "packing" in the urethral valve.<sup>29</sup>

TABLE 5. Urodynamic variables (urethrocystometry) before and after 6 months of treatment

Urodynamic variables	Treatment group (n = 44)		Control group (n = 44)		P <sup>a</sup>
	Before treatment	After treatment	Before treatment	After treatment	
First stimulus (mL)	149.61 ± 19.20	160.25 ± 23.38	154.07 ± 16.49	151.64 ± 15.13	NS
Normal urinary stimulus (mL)	172.81 ± 19.59	185.91 ± 21.96	169.73 ± 16.99	172.26 ± 16.57	NS
Urinary stimulus that cannot be postponed (mL)	346.12 ± 21.30	355.71 ± 23.34	343.79 ± 24.75	346.25 ± 23.00	NS
Bladder capacity (mL)	437.33 ± 40.95	452.46 ± 47.41	424.48 ± 42.10	429.00 ± 43.23	NS
Bladder compliance (mL/cm H <sub>2</sub> O)	45.28 ± 14.80	41.12 ± 13.45	45.61 ± 15.37	43.43 ± 13.89	NS
MBP (cm H <sub>2</sub> O)	12.12 ± 2.63	10.61 ± 2.37	12.61 ± 3.36	11.69 ± 3.07	NS

MBP, maximum bladder pressure; NS, not significant.

<sup>a</sup>Anova one-way.

Recurrent urinary tract infections represent a serious complaint for many postmenopausal women.<sup>42</sup> During menopause, the reduction of lactobacillus colonization, vaginal pH reduction, and atrophy of the vaginal mucosa are involved in the higher frequency of urinary tract infections. In our study, the use of intravaginal estriol for 6 months resulted in a significant reduction in the number of cases of bacteriuria and a decrease of vaginal pH.

Several investigators, addressing mainly the problem of stress incontinence, have studied the efficacy of estrogen as a treatment modality for urinary incontinence in postmenopausal women. The available literature is difficult to interpret because of methodological heterogeneity and the paucity of randomized controlled study.<sup>34</sup> Thus, the effectiveness of estrogen treatment of lower urinary tract symptoms is still a controversial issue. In 1991, a metaanalysis, including seven prospective trials, showed a beneficial effect of estrogen in treating stress urinary incontinence (SUI).<sup>43</sup> However, that same year a larger placebo-controlled, randomized trial, with 109 participants, did not demonstrate a benefit of ET in women with subjectively documented SUI.<sup>18</sup> The metaanalysis conducted in 1994 by the Hormones and Urogenital Therapy Committee<sup>13</sup> found an overall significant effect of ET on subjective improvement for all participants and for participants with GSI alone. However, the randomized, controlled trial published in 1996 by Fantl et al<sup>44</sup> showed that 3 months of cyclic HT affect neither clinical nor quality-of-life variables of incontinent, hypoestrogenic women, and the long-term effect is unlikely to be substantially different.

The effectiveness of local estriol administration for the treatment of urogenital symptoms has been well documented by several authors. Schmidbauer<sup>31</sup> showed a resolution of the subjective symptoms of stress and urgent urinary incontinence, dryness of the vagina and dyspareunia, cytologic and colposcopic,

thus pointing out an improvement of quality of life. Schar and coworkers<sup>32</sup> suggested local therapy with estriol as an effective mode of primary treatment in postmenopausal women with urinary incontinence.

In a recent multicenter study of 251 postmenopausal women, Lose et al<sup>34</sup> showed that the vaginal administration of low-dose estradiol and estriol are equally efficacious in alleviating lower urinary tract symptoms that appear after menopause. Sacco et al<sup>30</sup> reported that, in 17% of treated women, incontinence was cured and, in 41%, it subjectively improved. These women also showed improvement of urodynamic parameters. Iosif and colleagues,<sup>28</sup> in a longitudinal study, reported that 75% of the women reported significant subjective improvement of stress incontinence, and a significant increase in pressure transmission ratio to the proximal urethra was noted after vaginal medication with estriol.

In our study, 75% of the treated women registered, on clinical examination, an improvement of their incontinence after local estrogenic therapy. Statistically significant increases were noted in urodynamic parameters such as MUP, MUCP, and PTR in comparison with the control participants.

According to several authors, ET relieves the symptoms of stress incontinence by causing proliferation and growth of the urethral mucosa and blood vessel engorgement, which in turn constitutes the "urethral softness factor."<sup>17,45</sup>

According to Bathia,<sup>45</sup> the significant increase of abdominal pressure transmission to the proximal third of the urethra is to be considered a positive clinical response. This crucial effect is probably due to extraurethral factors such as improved functioning of the pelvic floor muscles.<sup>46</sup> In summary, increased tissue tension and urethral pressure, along with improved pressure transmission to the proximal urethra, play an important role in the alleviation of GSI.

The contrasting results of the present study compared with those reported by Fantl and coworkers<sup>44</sup>

may be explained by the following characteristics. First, the women enrolled in the study of Fantl et al<sup>44</sup> had a longer duration of menopause (on average 18 years past menopause), and it is reasonable to assume that the earlier the therapy, the lower the effect of hypoestrogenism, thus reducing the incidence and severity of conditions such as urinary incontinence and genital prolapse. The second characteristic is the use of concomitant progestin therapy because there is some evidence that progesterone may have the opposite effect of estrogen in the lower urinary tract.<sup>47</sup>

The modifications evaluated by the urethral pressure profile produced, in our study, more significant results than those observed by urethrocystometry. However, the latter displayed enhanced bladder compliance in the treated participants.

The women enrolled in the study presented GSI. This type of incontinence occurs as a result of urethral rather than bladder dysfunction, the latter being responsible for urinary incontinence due to detrusor overactivity or urge incontinence.

With regard to the risks of local ET, estriol is considered to be free from potential adverse reactions of systemic estrogenic therapy.<sup>14</sup> Several authors have definitively demonstrated that intravaginal estriol does not stimulate the proliferation of endometrium.<sup>15,16</sup> Iosif et al<sup>17</sup> recovered endometrial biopsies from 48 women after 8 to 10 years of therapy with estriol suppositories, and 7 showed weak proliferative changes, thus demonstrating that the risk of adverse reactions to estriol is insignificant.

Indeed, there are no long-term data on incidence of breast cancer in users of low-dose estrogen treatment. Nevertheless, in a recent study performed on 53 postmenopausal women treated with oral estriol, ultrasound assessment of the breasts, after 12 months of treatment, found tumors in none of the women.<sup>48</sup>

Women's acceptance of long-term local therapy is still debatable. According to Iosif et al,<sup>17</sup> most older women find vaginal therapy difficult or unacceptable and prefer oral treatment, and Takahashi et al<sup>48</sup> state that long-term therapy using the intravaginal route for estriol administration has not received acceptance by women in Japan. However, according to Cardozo et al,<sup>3</sup> many postmenopausal women prefer local estrogenic therapy because they do not want a return of withdrawal bleeding and are concerned about the possible increased risk of breast cancer associated with long-term estrogen use. In our study, the compliance of tested women was high, and almost all completed the study. We did not observe adverse drug systemic effects, and collateral effects were limited to localized

pruritus or burning. The sole disadvantage of local estrogenic therapy is that the beneficial effects of systemic therapy (eg, prevention of osteoporosis) is lost. However, Melis et al<sup>27</sup> reported a slight protective effect of intravaginal estriol on bone mineral loss. Thus, this finding indicates that estriol may also exert systemic effects.

## CONCLUSION

Low-dose estrogenic therapy was highly efficacious in reducing the urogenital atrophy and frequency of urinary tract infections, as well as the symptoms and signs of SUI. Furthermore, this treatment was seen to be safe and well tolerated by the participating women. Thus, we believe that the intravaginal administration of estriol may represent a good therapeutic choice for those postmenopausal women who have contraindications or who refuse the standard HT.

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