

Ultralow 0.03 mg vaginal estriol in postmenopausal women who underwent surgical treatment for stress urinary incontinence: effects on quality of life and sexual function

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Abstract

Objective: To evaluate the efficacy of low-dose, intravaginal estriol ovules in postmenopausal women with stress urinary incontinence (SUI) before and after transobturator tape (TOT) placement, assessing vaginal health, quality of life (QoL), and sexual function.

Methods: Ninety-six postmenopausal women affected by SUI and scheduled for TOT placement were enrolled. Women were randomized and divided into two groups through 1:1 at baseline (T0): study group (group A, n = 48) and control group (group B, n = 48). Group A was treated daily for 16 weeks with an intravaginal ovule containing 0.03 mg estriol. Vaginal epithelium maturation, QoL, and sexual function were investigated by using the Vaginal Maturation Index (VMI), Short Form-36 (SF-36) questionnaire, and Female Sexual Function Index (FSFI) questionnaire at baseline (T0), before surgery (T1), and 8 weeks after surgery (T2), respectively.

Results: Thirty-six women from group A and 44 women from group B completed the study. The VMI improved in group A at T1 (T1 [43.1] vs T0 [38.1]; $P = 0.04$) and T2 (T2 [47.8] vs T0 [38.1]; $P = 0.001$). The physical index score of the QoL improved only after surgery in group A (T2 [49.4] vs T0 [39.7]; $P = 0.001$). On the contrary, the mental index score improved at T1 [T1 (41.9) vs T0 (37.9), ($P = 0.02$)] and at T2 [T2 (49.6) vs T0 (37.9), $P = 0.001$]. Group B had improvement of the physical (45.6 vs 39.4; $P = 0.001$) and mental (43.6 vs 38.9; $P = 0.002$) index scores at T2. Sexual function improved in group A at T1 (13.9 vs 18.6; $P = 0.001$) and at T2 (13.9 vs 25.2; $P = 0.001$), and in group B at T2 (14 vs 17.2; $P = 0.001$). Moreover, it improved after TOT placement more in group A than in group B ($P = 0.001$).

Conclusions: Ultralow-dose topical vaginal ovules containing 0.03 mg estriol administered before and after TOT placement could improve the vaginal epithelium maturation of postmenopausal women affected by SUI. Moreover, vaginal estriol ovules also improved the surgical outcome investigated by SF-36 and FSFI.

Key Words: Estriol – Female Sexual Function Index – Quality of Life – Stress urinary incontinence – Transobturator tape – Vaginal Maturation Index.

Urinary incontinence (UI) is a common physical condition negatively affecting QoL. UI is defined by the International Continence Society and International Urogynecological Association as any involuntary leakage of urine. It can affect women with a prevalence of 15% to 55%.¹

Due to a progressively ageing population, in the future, a sharp increase in the incidence rate of UI is expected, and also in the surgical treatments of UI, especially for SUI—the most common form of UI in perimenopausal women.^{2,3}

The TOT sling procedure is an effective treatment of SUI with low morbidity: generally improving health-related QoL.⁴ Menopausal women undergoing a vaginal surgical treatment for SUI usually have dystrophic lesions caused by physiological

hypoestrogenism. This condition can impair the success of the therapy and may interfere with a woman's sexual function and QoL. It is well-known that the urogenital system is particularly sensitive to a decline in estrogens: almost half of postmenopausal women refer with symptoms related to urogenital atrophy.⁵

Indeed, women with vaginal atrophy can report dyspareunia, which, in turn, might induce sexual dysfunctions and consequent loss of sexual desire, reduced sexual arousal, and satisfaction and anorgasmia.⁶

Hypoestrogenism also acts on the transitional epithelium of the bladder and the proximal part of the urethra with similar vaginal alterations: thinning of tissues and exposure of the neurosensorial components to the irritative action of urine; reduction of urethral pressure; and increase in the involuntary loss of urine.⁵

The North American Menopause Society has introduced the term genitourinary syndrome of menopause (GSM), to include both “vulvovaginal atrophy” and “bladder epithelium atrophy.”⁷ This syndrome presents with a variety of signs and symptoms linked to hypoestrogenism and atrophy, among

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which are the following: vaginal dryness, burning, dyspareunia, SUI, nocturia, and pollakiuria. Epidemiological data show a prevalence of GSM of 45% to 63% in the postmenopausal population.⁸ Topical estrogenic hormonal therapy has strong beneficial effects by reducing the symptomatology due to atrophy.⁹ Lowest local dose of estrogen is used to treat women having symptoms today compared with the past.^{10,11}

Postmenopausal women undergoing vaginal surgery for pelvic floor disorders usually have altered tissue due to hypoestrogenism. Furthermore, hypoestrogenism could influence the effectiveness of the surgery and therefore the functional anatomical recovery. The efficacy of topical estriol was demonstrated as preoperative therapy before vaginal surgery for pelvic organ prolapse, but its effects are not known postoperatively.¹²

The aim of this randomized study was to evaluate the vaginal epithelium, QoL, and sexual function in postmenopausal women affected by SUI, treated with an ultralow dose of vaginal estriol ovules before and after TOT placement.

METHODS

This study was performed at the Obstetrical Gynecological Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania, Italy. The study was approved by the institutional ethics committee of the department. Written informed consent was provided to all the participants before entering the study, which was conducted in accordance with the Declaration of Helsinki. The study was not advertised and no remuneration was offered.

Ninety-six postmenopausal women ranging in age from 47 to 73 years (mean age 57.5 ± 6.8), affected by SUI requiring surgical treatment, were eligible for this study.

Women were enrolled by a single operator (M.G.M.) who performed both the clinical examination and urodynamic test to make the diagnosis of urodynamic SUI. Women with a body mass index (BMI) $\geq 35 \text{ kg/m}^2$; with endometrial thickness equal to or greater than 4 mm, measured by transvaginal ultrasound before study initiation and/or abnormal uterine bleeding; hormone-dependent malignancies; history of thromboembolic disease; liver disease; and/or using systemic or local hormone therapy for less than 3 months; who had received phytoestrogens; were using nonhormonal lubricants or moisturizers within 30 days before the start of the study; without any sexual activity for more than a month; having a partner with a sexual disorder; were excluded from the study.

After the baseline evaluation (T0), the sample was 1:1 randomly divided into two groups: the study group (group A) and the control group (group B). Each woman in group A was prescribed a 0.03 mg daily estriol vaginal ovule to use for 8 weeks before and 8 weeks after TOT surgical placement.

Instruments

To evaluate the effect of the estriol ovule on the vaginal epithelium, the VMI was used. To calculate the VMI, a vaginal smear was taken by scraping the upper third of the vaginal wall with a spatula. The sample was fixed, stored, and

stained using the Papanicolaou technique, followed by analysis. All samples were evaluated by the same clinician (M.P.) who was blind to the origin of the specimens (women of group A or B). The index quantifies parabasal, intermediate, and superficial cells by using the following formula: $VMI = (1 [\% \text{ superficial cells}] + 0.6 [\% \text{ intermediate cells}] + 0.2 [\% \text{ parabasal cells}])$.¹³ Values from 20 to 49, 50 to 64, and 65 to 100 indicate a low, moderate, or high estrogenic stimulation of the vaginal epithelium, respectively.

The Short Form-36 (SF-36) questionnaire was used to assess QoL.¹⁴ The questionnaire contains 36 questions grouped in four categories: somatic aspects (physical activity [10 items]; physical role [4 items]; bodily pain [2 items]; general health [6 items]); and four in mental aspects (vitality [4 items], social activity [2 items], emotional role [3 items], and mental health [5 items]). The women had to place a mark on a 0 to 100 scale for each item that best corresponded to their feelings, from the lowest to the highest score of a given category of the questionnaire. Thereafter, the sum of all items of each category was made. Mean values were calculated based on individual items within a given category. Consequently, eight scale scores were obtained, with higher scores indicating better functioning.

To study the effects on sexual function a short form of the FSFI validated in the Italian gynecological population was used.¹⁵ The FSFI consists of six domains: desire (two items)—arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and pain (three items)—answered on a five-point Likert scale (0, no sexual activity; 1, never/very low; 5, always/very high). A score is calculated for each of the six domains, and the total score is obtained by summing all of the items. The total score ranges from 2 to 36. A cut-off score of 26.55 or lower is usually accepted for diagnosing sexual dysfunction in women within a wide age range. The women were instructed to answer both questionnaires by the same clinician (S.C.).

The same team of surgeons (M.G.M., A.C., and G.S.) performed all surgical procedures. These procedures were performed in a short-stay unit under spinal anesthesia and under antibiotic coverage with one night of hospitalization. The woman was placed in the dorsal lithotomy position with hyperabducted thighs. A 16-Ch balloon catheter was inserted into the bladder and the balloon filled with 10 mL of water. Hydrodissection between the anterior vaginal wall and the urethra was carried out. Specially designed fine atraumatic needles were introduced from outside in. The tape was attached to the needle and the tape was passed from inside out. The catheter was removed 12 hours after surgery.

The VMI, QoL, and sexual function were investigated at baseline (T0), presurgery (T1), and postsurgery (T2) TOT placement.

Statistical analysis

Assuming a standard deviation (SD) of 2.5 and a mean difference of 1.5 between before and after treatment with

a $P=0.05$, the sample size calculation indicated that 35 participants for each group would be the minimum number required for the study to have 95% power. Considering a usual dropout of 10% to 20%, 48 women were enrolled in each group.

The VMI, SF-36, and FSFI total scores obtained at T0 were compared with T1 and T2 scores through paired Student's t test. The P value of each intragroup FSFI item was determined by the nonparametric Wilcoxon's rank-sum test. The P value of each intergroup FSFI item was determined by the Mann-Whitney U test. Clinical data were compared with the intergroup demographic via a two-sided t test for independent samples by analysis of variance. Scores are presented as means \pm SDs, and results are considered statistically significant when $P < 0.05$. A clinician of the team (S.C.) performed the statistical analysis using Primer of Biostatistics statistical computer package (Glantz SA, New York, NY: McGraw-Hill, Inc., 1997).

RESULTS

Ninety-six women were enrolled; Fig. 1 shows the flowchart of the study. Each group (group A and group B) included 48 women. Table 1 shows the demographic characteristics of both groups. However, after the baseline evaluation and randomization, six (12.7%) women from group A withdrew from the study refusing estriol ovule treatment, and six (12.7%) women reported adverse events consisting of vaginal burning occurring during the first week of the vaginal estriol

TABLE 1. Baseline demographic characteristics

Characteristics	Study group (group A) (n = 48)	Control group (group B) (n = 48)	P
Age range, y	51 to 73	53 to 64	1
Age, mean \pm SD, y	62.3 \pm 3.7	57.5 \pm 4.2	0.39
BMI, mean \pm SD, kg/m ²	24.8 \pm 4.6	27.7 \pm 5.4	0.45
Age at menopause, y	49.5 \pm 2.1	50.1 \pm 2.6	0.27
Type of menopause, natural, n. (%)	36 (100)	44 (100)	1
Parity, n (%)			
One	3 (7.9)	2 (5.4)	0.4
Two or more children	35 (92.1)	35 (94.6)	1
Cigarette smoking			
Nonsmoker, n (%)	28 (76.3)	30 (72.9)	0.8
Current smoker, n (%)	8 (23.7)	14 (27.1)	0.2
Daily cigarettes, mean \pm SD	10.6 \pm 6.8	9.9 \pm 7.1	0.66
SBP, mean \pm SD, mm Hg	131.7 \pm 11.8	129.3 \pm 14.8	0.47
DBP, mean \pm SD, mm Hg	81.4 \pm 8.3	85.2 \pm 7.6	0.3
Heart rate, mean \pm SD, beats/ min	66.7 \pm 11.2	65.9 \pm 10.1	0.74

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

administration. Therefore they also dropped out of the study. Among the women from group B, four dropped out after TOT surgical placement. Consequently, 36 and 44 women from group A and group B, respectively, completed the study.

Intraoperatively, vaginal detachment from the urethral and paraurethral tissues was easier and faster in group A than in group B, which had a pale and fragile mucosa. The postoperative results were not influenced by the technique or by

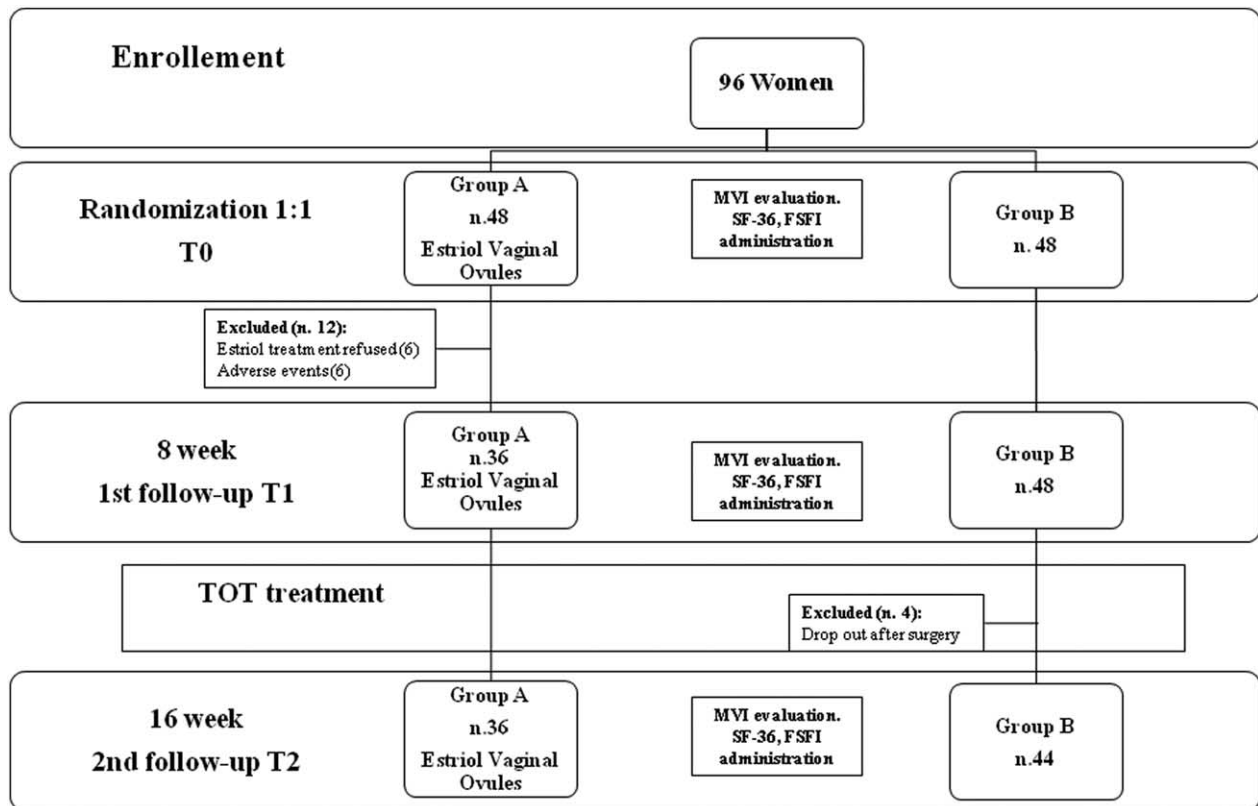


FIG. 1. Flowchart.

anesthesia, because the operators and the anesthesia protocols were the same for each woman. The bladder catheter was removed 18 hours after surgery; the same type of mid-urethral sling was used for each participant. The early complications that occurred were hesitancy in starting urination and slight pain in the thigh root; however, they resolved spontaneously before T2 follow-up. There was no statistically significant difference between the two groups ($P = NS$). Surgery solved the SUI of all participants in both groups.

Figure 2A shows the intragroup VMI analyses. At T1, the vaginal epithelium of group A underwent moderate estrogenic stimulation (T1 [43.1] vs T0 [38.1]; $P = 0.04$). At T2, group A maintained moderate estrogenic stimulation, having VMI of 47.8 ($P = 0.001$). On the contrary, the VMI score of group B did not change at T1 (T1 [37.8] vs T0 [37.1]; $P = 0.77$), worsening at T2 (T2 [30.6] vs T0 [37.1]; $P = 0.003$). Figure 2B shows the intergroup VMI analyses. At T0 group A and group B had similar low estrogenic VMI values (AT0

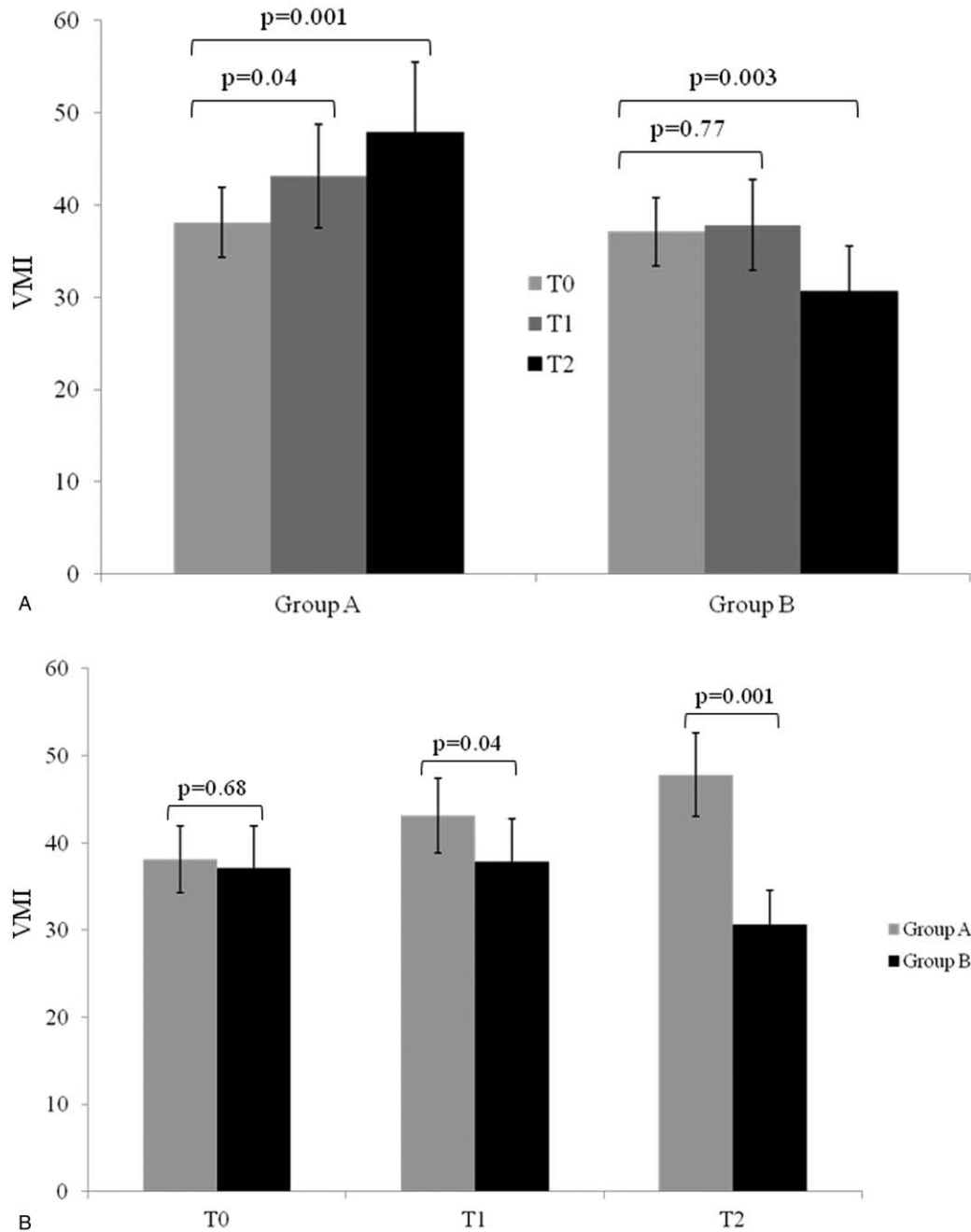


FIG. 2. (A) Intragroup VMI analyses at baseline (T0), and at presurgical week 8 (T1) and postsurgical week 8 (T2) TOT values of women on (group A) and not on (group B) estriol vaginal ovules. (B) Intergroup VMI analysis between baseline (T0), and at presurgical week 8 (T1) and postsurgical week 8 (T2) TOT values among women on (group A) and not on (group B) estriol vaginal ovules. TOT, transobturator tape; VMI, Vaginal Maturation Index.

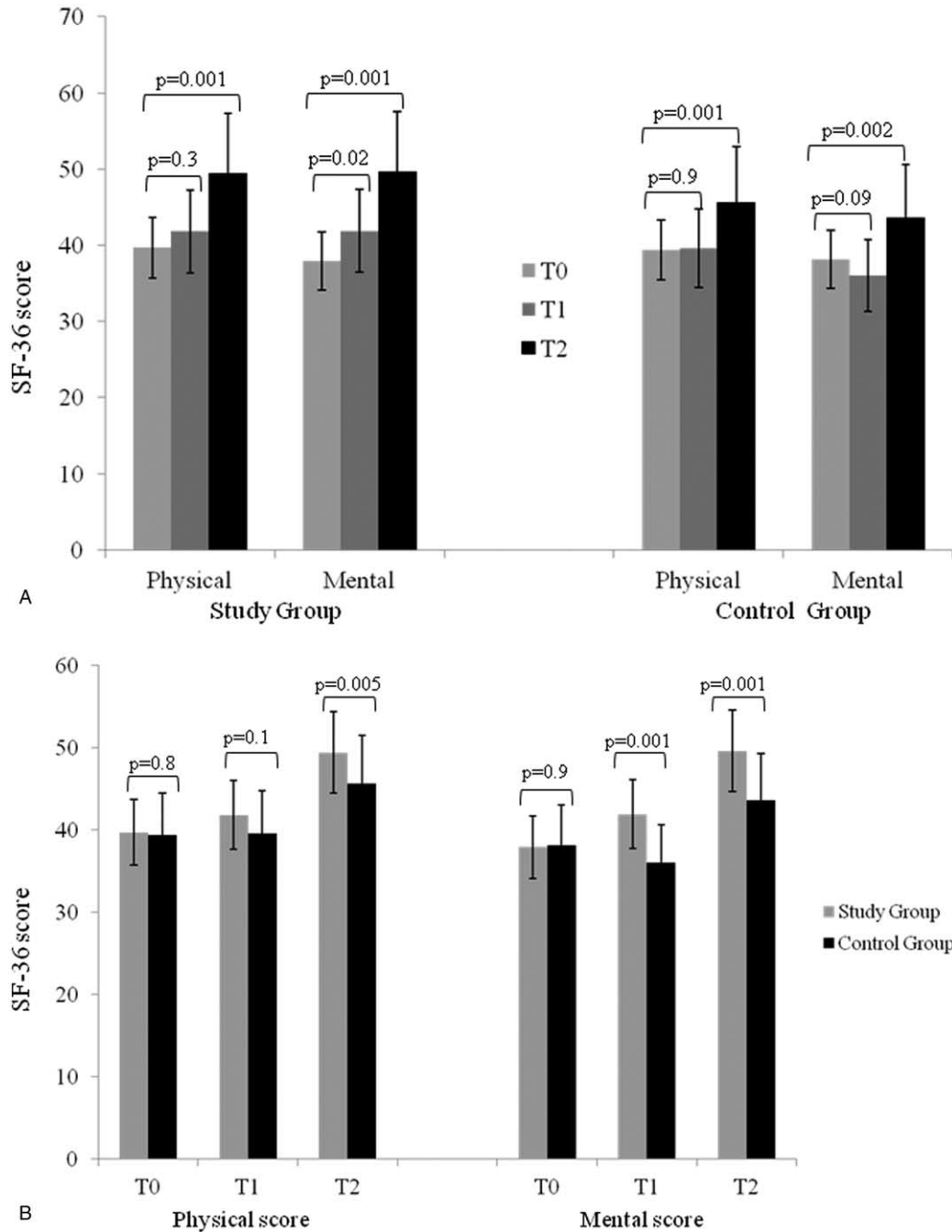


FIG. 3. (A) Intragroup Short Form-36 (SF-36) analyses at baseline (T0), and at presurgical week 8 (T1) and postsurgical week 8 (T2) TOT values of women on (group A) and not on (group B) estriol vaginal ovules. (B) Intergroup SF-36 analysis between baseline (T0), and at presurgical week 8 (T1) and postsurgical week 8 (T2) TOT values among women on (group A) and not on (group B) estriol vaginal ovules. TOT, transobturator tape.

[38.1] vs BT0 [37.1]; $P=0.68$). At T1 (AT1 [43.1] vs BT1 [37.8]; $P=0.04$) and T2 (AT2 [47.8] vs BT2 [30.6]; $P=0.001$) group A had better VMI values than those of group B.

Figure 3A shows the intragroup SF-36 QoL scores. At T1, group A reported no change of the physical index score (T1 [41.9] vs T0 [39.7]; $P=0.3$), and an improvement at T2 (T2 [49.4] vs T0 [39.7]; $P=0.001$). On the contrary, the mental index score improved at T1 (T1 [41.9] vs T0 [37.9]; $P=0.02$)

and at T2 (T2 [49.6] vs T0 [37.9]; $P=0.001$). At T1, group B did not have any change in the physical (T1 [39.6] vs T0 [39.4]; $P=0.9$) and mental (T1 [36.1] vs T0 [38.9]; $P=0.09$) index scores. At T2, both the physical (T2 [45.6] vs T0 [39.4]; $P=0.001$) and mental (T2 [43.6] vs T0 [38.9]; $P=0.002$) index scores improved. Figure 3B shows the intergroup SF-36 QoL scores. The physical score of both the groups was similar at T0 (AT0 [39.7] vs BT0 [39.4]; $P=0.8$) and at T1 (AT1 [41.8] vs BT1 [39.6]; $P=0.1$); at T2, it improved more in

TABLE 2. FSFI item and total score intragroup statistical comparison analysis at baseline, and at presurgical 8 week (T1) and postsurgical 8 week (T2) TOT values of women on (group A) and not on (group B) estriol vaginal ovules

FSFI items	Group A						Group B					
	Baseline T0	T1	<i>P</i> ^a	Baseline	T2	<i>P</i> ^a	Baseline T0	T1	<i>P</i> ^a	Baseline T0	T2	<i>P</i> ^a
Desire	1.9 ± 1.1	2.6 ± 1.1	0.005	1.9 ± 1.1	4.1 ± 0.9	0.001	2.7 ± 1.2	2.5 ± 1.2	1	2.7 ± 1.2	2.8 ± 1.1	0.7
Arousal	2.1 ± 1.3	2.6 ± 1.1	0.06	2.1 ± 1.3	3.5 ± 1.1	0.001	2.5 ± 1.2	2.4 ± 1.1	0.4	2.5 ± 1.2	2.7 ± 1.1	0.4
Lubrication	2.6 ± 1.8	3.5 ± 1.5	0.01	2.6 ± 1.8	4.5 ± 1	0.001	2.5 ± 1.3	2.5 ± 1.3	0.05	2.5 ± 1.3	3 ± 1.2	0.06
Orgasm	1.8 ± 1.3	2.4 ± 1.2	0.15	1.8 ± 1.3	3.3 ± 1	0.001	1.6 ± 1.1	1.5 ± 1.1	0.4	1.6 ± 1.1	2.4 ± 1.3	0.002
Satisfaction	2.9 ± 1.3	3.6 ± 1.2	0.005	2.9 ± 1.3	4.6 ± 0.7	0.001	2.6 ± 1.1	2.5 ± 1.1	0.01	2.6 ± 1.1	3.1 ± 1.1	0.03
Pain	2.6 ± 1.5	3.9 ± 1.5	0.001	2.6 ± 1.5	5.2 ± 0.5	0.001	2.1 ± 1.3	2.1 ± 1.2	0.4	2.1 ± 1.3	3.2 ± 1.2	0.001
	<i>P</i> ^b			<i>P</i> ^b			<i>P</i> ^b			<i>P</i> ^b		
FSFI total score	13.9 ± 1.2	18.6 ± 1.3	0.001	13.9 ± 1.2	25.2 ± 1.5	0.001	14 ± 1.3	13.5 ± 1.2	0.053	14 ± 1.3	17.2 ± 1.3	0.001

Values are means ± SD.

FSFI, Female Sexual Function Index; TOT, transobturator tape.

^a*P* determined by nonparametric Wilcoxon's rank-sum test.

^bPaired Student's *t* test.

group A (49.4) than in group B (45.6) (*P* = 0.005). Regarding the mental score, at T0, it was similar between the groups (AT0 [37.9] vs BT0 [38.1]; *P* = 0.9), but at T1 (AT1 [41.9] vs BT1 [36]) and at T2 (AT2 [49.6] vs BT2 [43.6]), it was better in group A than in group B (*P* = 0.001).

Women of group A and group B had 1 ± 2 and 1.1 ± 1 sexual activity, respectively, during the month before the start of the study (*P* = 1). At T1, the frequency of sexual activity of group A was similar to that at T0 (1 ± 5 vs 1 ± 2; *P* = 1). At T2, it was 2.4 ± 1 (T2 vs T0; *P* < 0.001). Group B did not have any change in frequency of sexual activity at T1 (T1 [1 ± 3] vs T0 [1.1 ± 1]; *P* = 1). At T2, it was 1.7 ± 1 (vs T0 [1.1 ± 1]; *P* = 0.008). At T1, both groups had similar frequency (AT1 [1 ± 5] vs BT1 [1 ± 3]; *P* = 1). At T2, the intergroup analyses showed a better improvement of frequency of the sexual activity in group A than in group B (AT2 [2.4 ± 1] vs BT2 [1.7 ± 1]; *P* = 0.003).

Table 2 shows the intragroup FSFI items and total scores. At T1, group A reported an improvement of the total score with respect to T0 (*P* = 0.001), mainly due to desire, lubrication, satisfaction, and pain item scores. At T2, the improvement of the total score was due to all the FSFI items (*P* = 0.001). On the contrary, the total score of group B did not change at T1 (*P* = 0.053), whereas there was an

improvement at T2, mainly due to orgasm, satisfaction, and pain item scores (*P* = 0.001).

Table 3 shows the intergroup FSFI item and total scores. At T0 both groups A and B had similar FSFI total scores, 13.9 ± 1.2 and 14 ± 1.3, respectively (*P* = 0.76). At T1, the score improved in group A with respect to that of group B (18.6 ± 1.3 vs 13.5 ± 1.2; *P* = 0.001), mainly due to lubrication, orgasm, satisfaction, and pain improvement scores. At T2, group A had a further improvement of FSFI total score with respect to that of group B (25.2 ± 1.5 vs 17.2 ± 1.3; *P* = 0.001), due to an improvement of all items.

DISCUSSION

The study evaluated the effects of a topical formulation of ultralow 0.03 mg intravaginal estriol ovules in postmenopausal women affected by SUI eligible for TOT placement, comparing the results with those of women who underwent TOT surgical placement alone.

Firstly, an increase of VMI was observed in women on estriol with respect to that of women on no drug. In fact, a decrease in the parabasal cells with a corresponding increase in the intermediate and superficial cells, reflecting a status of estrogenism, was detected by cytology in women on the estriol. On the contrary, a decrease of the VMI in the control

TABLE 3. FSFI item and total scores intergroup statistical comparison analysis between baseline, and at presurgical 8 week (T1) and postsurgical 8 week (T2) TOT values among women on (group A) and not on (group B) estriol vaginal ovules

FSFI items	Baseline T0		<i>P</i> ^a	T1		<i>P</i> ^a	T2		<i>P</i> ^a
	Group A	Group B		Group A	Group B		Group A	Group B	
Desire	1.9 ± 1.1	2.7 ± 1.2	0.55	2.6 ± 1.1	2.5 ± 1.2	0.53	4.1 ± 0.9	2.8 ± 1.1	0.001
Arousal	2.1 ± 1.3	2.5 ± 1.2	0.69	2.6 ± 1.1	2.4 ± 1.1	0.29	3.5 ± 1.1	2.7 ± 1.1	0.006
Lubrication	2.6 ± 1.8	2.5 ± 1.3	0.68	3.5 ± 1.5	2.5 ± 1.3	0.001	4.5 ± 1	3 ± 1.2	0.001
Orgasm	1.8 ± 1.3	1.6 ± 1.1	0.71	2.4 ± 1.2	1.5 ± 1.1	0.01	3.3 ± 1	2.4 ± 1.3	0.002
Satisfaction	2.9 ± 1.3	2.6 ± 1.1	0.57	3.6 ± 1.2	2.5 ± 1.1	0.001	4.6 ± 0.7	3.1 ± 1.1	0.001
Pain	2.6 ± 1.5	2.1 ± 1.3	0.61	3.9 ± 1.5	2.1 ± 1.2	0.001	5.2 ± 0.5	3.2 ± 1.2	0.001
	<i>P</i> ^b			<i>P</i> ^b			<i>P</i> ^b		
FSFI total score	13.9 ± 1.2	14 ± 1.3	0.76	18.6 ± 1.3	13.5 ± 1.2	0.001	25.2 ± 1.5	17.2 ± 1.3	0.001

Values are means ± SD.

FSFI, Female Sexual Function Index; TOT, transobturator tape.

^a*P* determined by Mann-Whitney *U* test.

^bNonpaired Student's *t* test.

group reflected a hypoestrogenic condition. Secondly, a general improvement in the psychophysical conditions of the women after both surgical and topical estriol treatment was observed. Interestingly, a considerable improvement in the health status of the women on both treatments was observed before and after TOT placement. Women with surgery alone underwent improvement after TOT placement. Similarly, sexual function improved more in women on topical estriol before and after TOT placement than in women who underwent TOT placement alone. Thus, after the vaginal estriol and/or surgical treatment, on average, women did not report sexual dysfunction. Moreover, the positive effect on QoL and sexual function appeared before TOT placement, but the difference between women on estriol and the control group was statistically evident only after surgery.

Currently, TOT surgical placement represents the gold standard for treatment of SUI, having a 90% success rate.¹⁶ This procedure does not usually cause denervation of the urethral sphincter; this was evaluated by an electromyographic test.^{17,18} It does not alter clitoral area vascularization, preserving clitoral sensitivity.¹⁸ Consequently, the clitoral biological role of sexual response is preserved.

In the literature, there are few data on presurgical treatment for SUI with vaginal formulations of estrogens. Presurgical administration of promestriene might favor tropism and vascularization of either muscular or fascial support of the pelvic floor.¹⁹ Moreover, vaginal estrogen usage after a mid-urethral sling could decrease the development of urinary urgency and frequency.²⁰

Interestingly, the efficacy of estrogen administration on lower urinary tract dysfunction could be explained by the effect of exogenous estrogen on collagen remodeling.²¹ Some authors have observed that the preoperative application of conjugated estrogen vaginal cream may increase both the synthesis of mature collagen and the thickness of the vaginal wall. It also decreases degradative enzyme activity.²⁰ These biological effects suggest that presurgery vaginal estriol treatment could improve surgical repair and maintenance of the connective tissue integrity of the pelvic floor.²⁰

There are data in the literature about the evaluation of sexual function and QoL in women treated with TOT surgical placement for SUI: our results showed a high rate of continence without any major complications. There was also a significant improvement of sexual function investigated by FSFI.^{22,23} Surgical treatment alone in postmenopausal women affected by SUI could resolve the continence, but not the GSM events. It is well-known that GSM is characterized by disorders of sexual function, affecting QoL, mainly due to both the genital and urological biological disorders.¹¹ Consequently, it is not uncommon for women to continue to suffer from a sexual condition, consisting of coital pain that promotes reduction in sexual function and decrease in sexual desire.²⁴ During physiological sexual function, lubrication depends on the sexual steroid effect on the neurovascular and epithelial patterns (objective-genital arousal). Of course, the psychological dimension (subjective arousal) is able

to modify, positively or negatively, genital arousal. In our study, women on estriol were receiving positive effects on the biological pattern of the genital “arousal.” This was better perceived by the women on estriol, not at T1 (in fact the level of arousal and desire were similar to the T0 values), but at T2. Desire, arousal, and lubrication remained low in the women in group B. Interestingly, the frequency of the sexual activity did not change before TOT placement in both groups. Estriol therapy alone was not sufficient in improving frequency. On the contrary, women on estriol and TOT placement had more improvement in sexual activity than women on TOT placement alone. These results support the clinical evidence that urinary disorders negatively affect sexual function.²⁴ Estriol vaginal therapy may be adopted to treat urogenital atrophy in an effective and safe manner. In this way, it is possible to control vaginal symptoms and urinary alterations.²⁵ Estrogen deficiency, in fact, could cause irritative urinary symptoms because of the increased contact of sensitive nerve endings with urine due to the thinning of the bladder.^{26,27}

Estrogen therapy usually results not only in the maturation of vaginal epithelium but also in improved blood flow; moreover, it maintains the low pH of the vagina, fostering lactobacilli proliferation.¹⁰ We did not investigate the vaginal microbiota before or after estriol treatment. However, other authors showed that a small quantity of lactobacilli is associated with GSM.²⁸ Investigations studying the effects of vaginal estradiol showed the re-establishment of the vaginal microflora and an improvement of epithelial differentiation and integrity in the urogenital tract.²⁹ Similar effects have been obtained by using ultralow-dose estriol and vaginal lactobacilli tablets.³⁰ Premenopausal vaginal lactobacilli, converting epithelial glycogen into lactic acid, usually maintain the vaginal pH between 3.5 and 4.5.^{31,32}

Interestingly, one of the main aspects of the current study was to observe if the ultralow dose of 0.03 mg local estriol might be effective. In fact, the results of the study showed that the lower dose of estriol was able to improve the objective parameters, namely VMI, and the subjective aspects, namely QoL and sexual function, similar to previous studies using slightly higher—0.05 mg—estriol doses.^{11,12} This evidence will lead us to design a future study, adopting a methodology similar to that of the current investigation, by which to compare groups of women on different doses of vaginal estriol and evaluate effectiveness and differences. These data could have an important clinical impact because we could choose a lower dosage rather than a higher one. Intraoperatively, vaginal detachment from the urethral and para-urethral tissues was easier and faster in women on estriol than in women of the control group who had a pale and fragile mucosa. The postoperative results were not influenced by the technique or by anesthesia, because the operator and the anesthesia protocols were the same for each woman. Early complications were hesitancy in starting urination and slight pain in the thigh root; however, they resolved spontaneously

before the T2 follow-up. There was no statistically significant difference between the two groups.

Among the limitations of our study, apart from those mentioned above, was the lack of a placebo group. Therefore, in future studies, both a placebo group and a larger sample will be needed. Finally, it will be necessary to observe the long-term efficacy of the vaginal estriol treatment and verify its extended benefits.

CONCLUSIONS

The data from this study suggest that treatment with 0.03 mg estriol intravaginal ovules could improve the vaginal health and related symptoms in women with SUI before surgical treatment. It is also expected to enhance surgical outcome. Furthermore, this treatment should be continued after surgery to maintain vaginal epithelium tropism and manage signs and symptoms of GSM. Our results also suggest that QoL and sexual functioning improved in postmenopausal women with SUI as a consequence of topical estriol therapy and surgical treatment.

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REFERENCES

- Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* 2010;21:5-26.
- Luber KM. The definition, prevalence and risk factors for stress urinary incontinence. *Rev Urol* 2004;6 (Suppl 3):S3-S9.
- Hunskar S, Lose G, Sykes D, Voss S. The prevalence of urinary incontinence in women in four European countries. *BJU Int* 2004;93:324-330.
- Magon N, Chopra SV. Transobturator tape in treatment of stress urinary incontinence: it is time for a new gold standard. *Am J Med Sci* 2012;4:226-230.
- Calleja-Agius J, Brincat MP. Urogenital atrophy. *Climacteric* 2009;12:279-285.
- Caruso S, Rapisarda AM, Cianci S. Sexuality in menopausal women. *Curr Opin Psychiatry* 2016;29:323-330.
- Portman DJ, Gass ML. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Maturitas* 2014;79:349-354.
- Kim HK, Kang SY, Chung YJ, Kim JH, Kim MR. The recent review of the genitourinary syndrome of menopause. *J Menopausal Med* 2015;21:65-71.
- Rahn DD, Carberry C, Sanses TV, et al; Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen for genitourinary syndrome of menopause. A systematic review. *Obstet Gynecol* 2014;124:1147-1156.
- Lindahl SH. Reviewing the options for local estrogen treatment of vaginal atrophy. *Int J Womens Health* 2014;6:307-312.
- Caruso S, Cianci S, Amore FF, et al. Quality of life and sexual function of naturally post-menopausal women on an ultralow-concentration estriol vaginal gel. *Menopause* 2016;23:47-54.
- Caruso S, Cianci S, Vitale SG, Matarazzo MG, Amore FF, Cianci A. Effects of ultra-low topic estriol on vaginal health and quality of life in postmenopausal women who underwent surgical treatment for pelvic organ prolapse. *Menopause* 2017;24:900-907.
- Hustin J, Van den Eynde JP. Cytologic evaluation of the effect of various estrogens given in postmenopause. *Acta Cytol* 1977;21:225-228.
- Ware JE, Kosinski M, Gandek B, et al. The factor structure of the SF-36 Health Survey in 10 countries: results from the International Quality of Life Assessment (IQOLA) project. *J Clin Epidemiol* 1998;51:1159-1165.
- Filocamo MT, Serati M, Li Marzi V, et al. The Female Sexual Function Index (FSFI): linguistic validation of the Italian version. *J Sex Med* 2014;11:447-453.
- Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? *Nat Rev Urol* 2013;10:78-89.
- Caruso S, Panella MM, Cianci S, et al. TOT does not affect the urethral sphincter innervation: a pilot study. *Int Urogynecol J* 2011;22:739-742.
- Matarazzo MG, Cianci S, Rampello L, Presti LL, Caruso S. Urethral sphincter innervation and clitoral blood flow after the transobturator (TOT) approach. *Int Urogynecol J* 2013;24:621-625.
- Tinelli A, Malvasi A, D'Anna L, Tinelli R, Perrone A, Tinelli FG. Presurgical promestriene therapy in postmenopausal women with stress urinary incontinence. *Gynecol Endocrinol* 2007;23:445-450.
- Rahn DD, Ward RM, Sanses TV, et al; Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines. *Int Urogynecol J* 2015;26:3-13.
- Hanna-Mitchell AT, Robinson D, Cardozo L, Everaert K, Petkov GV. Do we need to know more about the effects of hormones on lower urinary tract dysfunction? *Neurourol Urodyn* 2016;35:299-303.
- Simsek A, Ozgor F, Yuksel B, et al. Female sexual function after transobturator tape in women with urodynamic stress urinary incontinence. *Springerplus* 2014;3:570.
- Soliman T, Sherif H, Fathi A, Kandeel W, Abdelwahab O. Impact of transobturator vaginal tape on female stress urinary incontinence and sexual function. *Arab J Urol* 2017;15:380-386.
- Caruso S, Brescia R, Matarazzo MG, Giunta G, Rapisarda AM, Cianci A. Effects of urinary incontinence subtypes on women's sexual function and quality of life. *Urology* 2017;108:59-64.
- Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. *Menopause* 2019;26:431-453.
- Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. *Urology* 2003;62 (4 Suppl 1):45-51.
- Stamm WE, Raz R. Factors contributing to susceptibility of postmenopausal women to recurrent urinary tract infections. *Clin Infect Dis* 1999;28:723-772.
- Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric* 2016;19:151-161.
- Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92 (4 Pt 2):722-727.
- Donders G, Bellen G, Neven P, et al. Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors. *Eur J Clin Microbiol Infect Dis* 2015;34:2023-2028.
- Vaccaro CM, Mutema GK, Fellner AN, et al. Histologic and cytologic effects of vaginal estrogen in women with pelvic organ prolapse: a randomized controlled trial. *Female Pelvic Med Reconstr Surg* 2013;19:34-39.
- Rahn DD, Good MM, Roshanravan SM, et al. Effects of preoperative local estrogen in postmenopausal women with prolapse: a randomized trial. *J Clin Endocrinol Metab* 2014;99:3728-3736.