European Journal of Obstetrics & Gynecology and Reproductive Biology 263 (2021) 67–71

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/euro

Full length article

Intravaginal 6.5 mg prasterone administration in postmenopausal women with overactive bladder syndrome: A pilot study

Maria Grazia Matarazzo *, Giuseppe Sarpietro, Debora Fiorito, Salvatore Di Pasqua, Simona Ingrassano, Marco Marzio Panella, Antonio Cianci, Salvatore Caruso

Department of General Surgery and Medical Surgical Specialties, Gynecological Clinic University of Catania, Via S. Sofia 78, 95124 Catania, Italy

ARTICLE INFO

Article history:
Received 24 November 2020
Revised 25 March 2021
Accepted 9 June 2021

Keywords:
Genitourinary syndrome of menopause
Overactive bladder syndrome
Prasterone
Quality of life
Vulvovaginal atrophy

ABSTRACT

Objective: The aim of this study was to evaluate the impact of vaginally prasterone administration on postmenopausal women with genitourinary syndrome of menopause (GSM) affected by overactive bladder syndrome (OAB).

A secondary aim of this study was to assess the efficacy of prasterone on VVA and quality of life (QoL).

Study design: Thirty-two postmenopausal women with GSM and referred OAB symptoms received treatment with daily intravaginal prasterone 6.5 mg. We assessed urinary symptoms through approved ICIQ-OAB and ICIQ-UI questionnaires on incontinence. Women were also screened by the Vaginal Health Index (VHI) to investigate the vulvovaginal atrophy (VVA). Quality of life (QoL) was assessed by the SF-12 Health Survey. Each questionnaire was administrated at baseline (T0) and after a 12-week treatment (T1).

Results: Incontinence questionnaires showed improvement at T1 (from 7.8 ± 2.7 to 2.7 ± 2.2, $p < 0.001$). Even if women referred an improvement of daily urine although the women reported improvement in daily urine leaks, their urine leak amount did not improve statistically significant [T0 (28.6%) Vs T1 (14.3%), $p < 0.16$]. Prasterone therapy improved significantly the VHI [T1(21 ± 3.7) Vs T0 (10.8 ± 4.1), $p < 0.001$]. Finally, women had a statistically significant improvement both in Mental [T1(49.9 ± 11.2) Vs T0 (42 ± 9.2), $p < 0.009$],) and Physical Health [T1(47.1 ± 9.1) Vs T0 (38.6 ± 8.4), $p < 0.006$], domains of the SF-12 questionnaire. No women referred side effects.

Conclusion: Prasterone is an inactive precursor converted into estrogens and androgens into vaginal tissue. It leads to positive effects on VVA through the activation of the vaginal androgen and estrogen receptors. Empirical evidence in this study suggests that intravaginal 6.5 mg prasterone administration could be an effective treatment for postmenopausal women with GMS affected by OAB.

Introduction

Overactive bladder (OAB) is a symptomatic syndrome characterized by the presence of urinary urgency, frequency, and nocturia, with or without urge urinary incontinence (UUI), in the absence of urinary tract infection or other pathologies.[1] There are about 50–100 million OAB sufferers world-wide and it is more prevalent in postmenopausal women with genitourinary syndrome of menopause (GSM)[2,3]. It is an hypoestrogenic condition characterized by genital, urological, and sexual symptoms; it affects approximately 27% to 84% of postmenopausal women and can significantly impair health and quality of life. [4]

OAB symptoms can occur with (54–58%) or without (42–46%) involuntary detrusorial contractions, which define the condition of detrusor overactivity (DO) on urodynamic exam.[5]

Anticholinergic medications are considered first-line pharmacotherapy for OAB. However, some women are intolerant to these drugs, and often report dry mouth but also blurred vision, constipation, fatigue and urinary retention.[6,7] Others do not have any improvement by their usage. When pharmacological treatment fails, bladder injection of Botulinum toxin-A (BTA) represents a rewarding treatment option. The main limitation of this option is that its effect is temporary (it lasts between 3 and 6 months, then it should be repeated) and it can be complicated by urinary retention, for which patients would need to perform intermittent self-catheterization.[8]

Intravaginal prasterone, a synthetic form of DHEA, was approved in 2018 by the U.S. Food and Drug Administration (FDA) for the treatment of dyspareunia in postmenopausal

* Corresponding author at: Via Basile 10, 95124 Catania, Italy.
E-mail address: mariagraziamatarazzo@gmail.com (M.G. Matarazzo).

https://doi.org/10.1016/j.ejogrb.2021.06.009
2215-1532/

women[9] and then in 2019 by the European Medicines Agency (EMA) for the treatment of moderate to severe vulvovaginal atrophy (VVA) symptoms[10] in women with GSM.

Women with GSM usually complain of OAB syndrome: this is not always related to detrusor overactivity, but it can be the result of thinning of the urogenital mucosa caused by a lack of sexual hormones.

Interestingly, bladder, urethra, pelvic floor musculature and vagina have a great affinity for estrogens and androgens. Estrogen receptors (ER) α and β and androgen receptors (AR) are expressed in the squamous epithelium of proximal and distal urethra, where they (especially ER-α) help to maintain muscle tone. Moreover, AR and ER-α/β are expressed in bladder trigone, where they could improve continence by inducing modifications in muscarinic receptors.[11–13]

Dehydroepiandrosterone (DHEA), predominantly secreted by the adrenal glands but also by ovaries, is the most abundant circulating sex hormone found in women, and its secretion is reduced during postmenopause, contributing to decrease of estrogens and GSM.[14] DHEA acts by "intracrine" mechanism:[15,16] circulating DHEA is converted in androstenedione and then in estradiol or testosterone in peripheral genitourinary tissues, at intracellular levels, where sex hormones bind ER-α/β and AR and contribute to maintaining genitourinary tissues health.[17,18] Since the conversion in estrogen and androgen and their inactivation happen inside the cells, DHEA acts only locally and does not influence serum estradiol and testosterone values, unlike estriol, avoiding the risk of systemic side effects in postmenopausal women.[19–21] DHEA improves collagen levels, trophism, vascularization and innervation of the urogenital tract.[22] Estrogens, produced locally, cause an increase in the number of superficial and intermediate cells and a reduction in the number of parabasal cells in the vaginal mucosa. In addition, a decrease in vaginal pH is observed, which facilitates the growth of normal bacterial flora.[18,23]

Although there is some evidence in the literature supporting the use of intravaginal prasterone for VVA treatment, several authors underlined that further studies are needed to confirm this.[24] Moreover, to the best of our knowledge, this is the first study to investigate the effect of prasterone on OAB has never been investigated.

The aim of this study was to evaluate the impact of vaginally administered prasterone on OAB syndrome in women with GSM.

A secondary aim of this study was to assess the efficacy of prasterone on VVA and quality of life (QoL).

Materials and methods

This pre- and post-treatment open–labeled study was performed at the Urogynaecological Service of the Obstetric and Gynecological Clinic, Department of General Surgery and Medical Surgical Specialties, School of Medicine, University of Catania, Italy. The study protocol was conformed to the ethical guidelines of the 2013 Helsinki Declaration. Written informed consent was obtained from each woman before entering the study, and they did not receive any monetary payment.

Women with GSM who reported OAB symptoms were invited to participate in the study. Each woman underwent general and gynaecological history. The women were selected in our Urogynaecological Service based on last menstrual period (postmenopausal state), reported symptoms and vaginal examination. More specifically, reported one or more of these symptoms: dryness, burning, dyspareunia, urinary symptoms such as urgency, urinary incontinence, recurrent UTI.

Moreover, vaginal clinical examination revealed a thin and pale epithelium and vaginal dryness.

Inclusion criteria are represented by postmenopausal status, urgency with frequency and/or with or without urinary incontinence (OAB syndrome), VHI < 15 with urinary symptoms, menopausal symptoms and signs (genital, sexual and urinary symptoms).

Women using oral anticholinergic agents, β3 agonists or α1-blockers, or affected by neurogenic overactive bladder, or pelvic organ prolapse eligible for surgical treatment, estrogen-dependent tumors, thrombophilia, undiagnosed genital bleeding, liver disease, history of venous thromboembolism or recent arterial thromboembolic events, or on-going oral hormone replacement therapy were excluded from the study.

Eligible women, according to inclusion criteria, received treatment with daily intravaginal prasterone 6.5 mg at baseline (T0) for 12 weeks (T1).

Urinary symptoms were assessed by the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) [25] and the International Consultation on Incontinence Questionnaire Urinary Incontinence (ICIQ-UI).[26] In clinical practice, both the questionnaires can be used to monitor changes in OAB and UI over time or following treatment.

The ICIQ-OAB total score is obtained by four items: day and night urinary frequency, urgency and urge incontinence and it corresponds to mild, moderate, or severe symptoms.

The ICIQ-UI investigates frequency of UI, amount of urine leaked, impact on the everyday life of UI and self-perceived cause of incontinence.

VVA was evaluated by the Vaginal Health Index (VHI). VHI score defines the degree of atrophy in the genitourinary tract according to 5 parameters (vaginal elasticity, vaginal secretions, pH, epithelial integrity, vaginal hydration). When the VHI total score is lower than 15, the vagina is considered atrophic. [27]

QoL was assessed by the SF-12 Health Survey.[28] The questionnaire contains 12 questions in four categories of somatic aspects and mental aspects, with higher scores indicating better functioning.

Each questionnaire was administered at T0 and T1.

Statistical analysis

Paired Student's *t*-test was used to compare the values obtained at T0 with those of the T1 follow-up from the ICIQ- OAB and -UI and VHI and SF-12 scores. The values are presented as means ± SD. The result was statistically significant when $p < 0.05$. Statistical analysis was carried out using the Primer of Biostatistics statistical computer package (Glantz, NY: McGraw-Hill, 1997).

Results

Four women (12.5%) dropped out of the study due to non-adherence to treatment. Twenty-eight women (87.5%) completed the study. Table 1 shows the demographic and clinical characteristics of the study participants.

Table 2 shows the results of the ICIQ-OAB total score and the score of each of its items (T0) and after (T1) treatment. At T1 statistically significant improvement was observed in both total score (from 7.8 ± 2.7 to 2.7 ± 2.2, $p < 0.001$) and each item; in fact, frequency improved from 1.6 ± 1.3 to 0.4 ± 0.6 ($p < 0.006$), urgency from 2.4 ± 0.9 to 2.4 ± 0.9 ($p < 0.001$), nocturia from 1.8 ± 1.1 to 0.6 ± 0.5 ($p < 0.001$) and urge incontinence from 2.0 ± 0.8 to 0.8 ± 0.9 ($p < 0.001$).

Fig. 1 shows differences between T0 (11.7 ± 7.5) and T1(4.6 ± 4.9) ICIQ-UI scores ($p < 0.02$). Even if women referred an improvement in daily urine leaks [T0 (35.7%) Vs T1(21.4%), $p < 0.006$)], their

Table 1
Demographic characteristics.

	Participants n.28
Age range, years	52–75
Age, mean ± SD, years	64.7 ± 8.2
BMI, mean ± SD, kg/m^2	25.2 ± 4.7
Menopause duration, mean ± SD, years	15.4 ± 9.7
OAB with UUI	16 (57.1)
OAB without UUI	12 (42.9)
Predominant urinary symptom n. (%)	
Urgency	18 (64.3)
Frequency	14 (50)
Nocturia	14 (50)
SUI	18 (64.3)
Voiding symptoms	6 (21.4)
Parity, n. (%)	
0	0 (0)
One	0 (0)
Two	14 (50)
Three	6 (21.4)
Four	6 (21.4)
Five	2 (7.1)
Systolic blood pressure, mean ± SD, mmHg	129.5 ± 12
Diastolic blood pressure, mean ± SD, mmHg	69.4 ± 9.7
Heart rate, mean ± SD, beats/min	72.3 ± 8.3

Table 2
ICIQ-OAB items and total score before and after vaginal prasterone treatment.

	Baseline (mean ± SD)	3 months (mean ± SD)	*p* value
Frequency	1.6 ± 1.3	0.4 ± 0.6	<0.006
Urgency	2.4 ± 0.9	0.9 ± 0.8	<0.001
Nocturia	1.8 ± 1.1	0.6 ± 0.5	<0.001
Urge incontinence	2.0 ± 0.8	0.8 ± 0.9	<0.001
ICIQ-OAB total score	7.8 ± 2.7	2.7 ± 2.2	<0.001

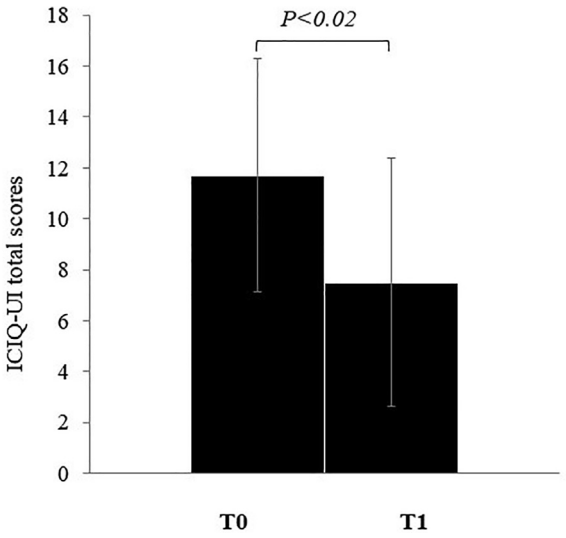

Fig. 1. ICIQ-UI total scores of women before (T0) and after (T1) vaginal prasterone treatment.

amount of urine leaks did not significant statistically improve [T0 (28.6%) Vs T1(14.3%), p < 0.16]. Finally, at T0, 71.4% of women complained of low QoL secondary to urine leaks; at T1, it improved to 28.6% (p < 0.006).

Fig. 2 shows the VHI results. At T0, the total score was 10.8 ± 4.1. At T1, the mean VHI total score was 21 ± 3.7 (p < 0.000).

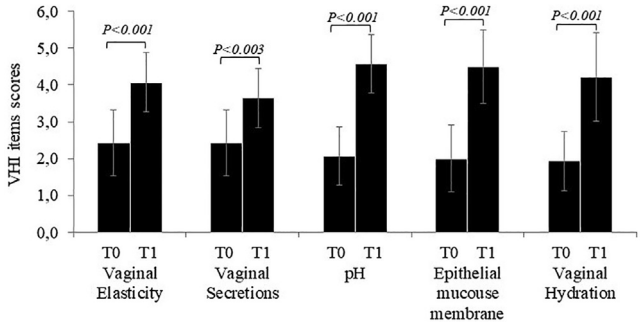

Fig. 2. VHI items scores of women before (T0) and after (T1) vaginal prasterone treatment.

Specifically, at T1, pH < 4.6 and normal mucosa were observed in the 71.4% (p < 0.000) and in the 75% (p < 0.003) of women, respectively. Moreover, the aspect of the vaginal epithelial mucous membrane [T1(4.5 ± 2.3) Vs T0 (2 ± 1.3), p < 0.001], the vaginal elasticity [T1(4.1 ± 2.1) Vs T0 (2.4 ± 1.4), p < 0.001], and the vaginal hydration [T1(4.2 ± 2.7) Vs T0 (1.9 ± 1.2), p < 0.001], assessed by the number of secretions, improved after prasterone therapy (p < 0.000).

Fig. 3 shows differences in SF-12 total scores between T0 and T1. Women had a statistically significant improvement in both the Mental [T1(49.9 ± 11.2) Vs T0 (42 ± 9.2), p < 0.009],) and Physical Health [T1(47.1 ± 9.1) Vs T0 (38.6 ± 8.4), p < 0.006], total scores.

At T1 follow-up, no women reported side effects. Only four women (14.3%) declared treatment was not effective at all and switched to antimuscarinic drugs.

Discussion

To the best of our knowledge, this is was the first study showing the effects of vaginal prasterone administration in postmenopausal women affected by OAB. In this study, we observed an improvement of urgency, UI, nocturia, and frequency after prasterone three months treatment (T1), assessed by ICIQ-UI and ICIQ-OAB questionnaires. Moreover, an improvement of the QoL was observed in women on intravaginal prasterone.

Therapy for GSM is actually based on different hormonal and pharmacological therapeutic options. Vaginal estrogen therapy is the first-line pharmacologic treatment recommended by the North American Menopause Society (NAMS)[29] and the International Menopause Society (IMS).[30]

Previously, authors observed that the use of vaginal estrogen caused an improvement of frequency, urgency, and urge urinary incontinence symptoms in hypoestrogenic postmenopausal women by using vaginal estrogen.[31]

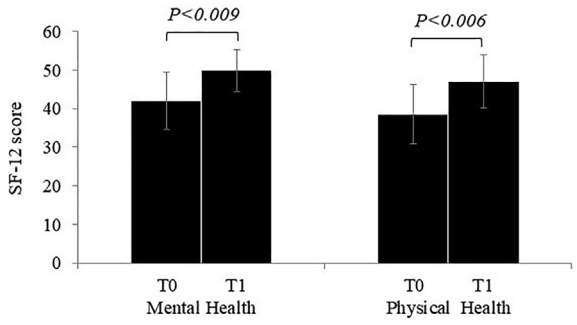

Fig. 3. SF-12 mental and physical health total scores of women before (T0) and after (T1) vaginal prasterone treatment.

Local estriol administration in association with antimuscarinics for treatment of OAB syndrome was more effective than antimuscarinics alone. [32,33]

On GSM, in 2020, Li B published an analysis of 29 randomized controlled trials evaluating 5 different treatment regimens, involving 8311 patients. Laser therapy had an excellent effect on vaginal dryness, dysparunia, urinary incontinence, proportion of parabasal cells, pH, and VHI. Vaginal estrogen also had significant effects on these aspects, although its effect was inferior to that of laser therapy. Ospemifene therapy was superior to laser and vaginal estrogen therapies in ameliorating sexual function however. It presents a high risk of developing adverse events and endometrial hyperplasia. Moisturizer/lubricant was effective on dysparunia, proportion of parabasal cells and, vaginal pH. In conclusion, laser therapy, followed by vaginal estrogen, confers superior clinical outcomes for most aspects associated with GSM. Ospemifene and DHEA treatments on their part significantly improve the sexual function of women with GSM.[34]

Recently, some authors observed that ospemifene improved urinary symptoms in postmenopausal women receiving ospemifene for VVA, markedly reducing their sanitary/incontinence pad requirements to manage leakage. Doppler ultrasound suggests that increased angiogenesis of the vaginal and periurethral tissues may underlie the benefits.[35]

OAB has been associated with menopause and VVA because of urogenital atrophy due to a lack of estrogens on the urogenital epithelium.[36,37] Indeed, the bladder and the urethra epithelium share a common embryologic origin with genital tract epithelium, and they are also sensitive to sex steroid hormones, such as the vulvar vestibule, the upper vagina, and the pelvic floor.[38] These evidence could explain the beneficial effect of DHEA on OAB symptoms highlighted by our study.

Nowadays guidelines indicate a local low dose of estriol as the gold standard to treat postmenopausal women with VVA. For its efficacy ospemifene, a selective estrogen receptor modulator, was approved for the treatment of moderate-severe dyspareunia and vaginal dryness.[39]

Recently, prasterone was recommended as an option for the therapy of VVA in GSM.[40] Moreover, low doses of prasterone have minimal effects on blood levels of estrogens, androgens, and their metabolites with reduced systemic side effects.[41]

Several authors recorded that prasterone 6.5 mg/day improved VVA signs and symptoms. Two prospective, randomized, double-blind, and placebo-controlled phase III clinical trials show that prasterone decreased vaginal pH, decreased the percentage of vaginal parabasal cells, usually predominant in the vaginal smear of postmenopausal women with VVA, while increased superficial cells. Moreover, at a gynecological evaluation, vaginal secretions, epithelial integrity, epithelial surface thickness and color all improved after prasterone 12-week treatment.[20,23 Prasterone is generally well tolerated, with the most common discharge represented by site application. [24,42]

According to the literature, in our study, we observed an improvement in VVA signs and symptoms after prasterone treatment. Specifically, we observed a good vaginal elasticity, moderate-normal amount of fluid secretions, good hydration with reduced mucosa inflammation. A decrease in vaginal pH was observed, which facilitates the growth of normal bacterial flora. Epithelial mucosa appeared less fragile and not bloody.

Two large studies, VVIVA (Vaginal Health: Insights, Views, & Attitudes)[43] and REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) [44], evidenced the negative impact of GSM on women QoL.

Furthermore, several authors demonstrated that intravaginal administration of prasterone has beneficial effects on QoL in women affected by VVA, by analyzing dyspareunia and QoL related to sexual function.[40,45] Our study showed that prasterone can improve the QoL of women with UI, assessed by question number four of the ICIQ-UI questionnaire ("*how much does leaking urine interfere with your everyday life?*"), and also that prasterone can improve generally QoL of women suffering VVA, as assessed by the state of general health and mental health through the SF-12 questionnaire. Finally, women on prasterone did not report on side effects at three months follow-up.

Our study has some limitations. First, small number of participants and short treatment interval; second, the absence of a control group. Its main strength is that this is the first study to investigate the effects of prasterone on OAB syndrome.

Conclusions

Empirical evidence in our pilot study suggests that intravaginal 6.5 mg prasterone administration could be effective in improving subjective urinary symptoms of OAB in women with vulvovaginal atrophy related to GSM. Future studies are needed to validate the present findings, with a placebo-controlled group and a larger number of participants.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, 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.
[2] Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327–36.
[3] Portman DJ, Gass ML. 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. Menopause 2014;21:1063–8.
[4] The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society, Menopause: September 2020 - Volume 27 - Issue 9 - p 976-992
[5] Latthe P, Middleton L, Rachaneni S et al. On behalf of the BUS Collaborative Group. Ultrasound bladder wall thickness and detrusor overactivity: a multicentre test accuracy study. 2017 Royal College of Obstetricians and Gynaecologists.
[6] Akino H, Namiki M, Suzuki K, et al. Factors influencing patient satisfaction with antimuscarinics treatment of overactive bladder syndrome: results of real-life clinical study. Int J Urol 2014;21:389.
[7] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol. 2008 Sep;54(3):543–62. https://doi.org/10.1016/j.eururo.2008.06.047. Epub 2008 Jun 20 PMID: 18599186.
[8] Sahai A, Khan M, Fowler CJ, Dasgupta P. Botulinum toxin for the treatment of lower urinary tract symptoms: a review. Neurourol Urodyn. 2005;24(1):2–12. https://doi.org/10.1002/nau.20090. PMID: 15578628.
[9] Intrarosa, DHEA intravaginal (prasterone, intravaginal) dosing, indi- cations, interactions, adverse effects, and more. Published March 12, 2018.
[10] European Medicines Agency. Intrarosa: summary of product characteristics. 2019.
[11] Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. Urology. 2003;62(4 Suppl 1):45–51. https://doi.org/10.1016/s0090-4295(03)00676-9.
[12] Söderberg MW, Johansson B, Masironi B, Byström B, Falconer C, Sahlin L, et al. Pelvic floor sex steroid hormone receptors, distribu tion and expression in pre- and postmenopausal stress urinary in- continent women. Acta Obstet Gynecol Scand. 2007;86(11):1377–84.
[13] Traish AM, Vignozzi L, Simon JA, et al. Role of Androgens in Female Genitourinary Tissue Structure and Function: Implications in the Genitourinary Syndrome of Menopause. Sex Med Rev. 2018;6(4):558–71.
[14] Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. Maturitas. 2011;70:22–5.
[15] Holton M, Thorne C. Goldstein AT : An overview of dehydroepiandrosterone (EM-760) as a treatment option for genitourinary syndrome of menopause. Expert Opin Pharmacother 2020.

[16] Labrie F, Belanger A, Luu-The V, et al. DHEA and the intracrine formation of androgens and estrogen's in peripheral target tissues: its role during aging. Steroids 1998;63(5–6):322–8.
[17] Labrie F, Luu-The V, Labrie C, Simard J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. Front Neuroendocrinol. 2001;22:185–212.
[18] Labrie F. Intracrinology and menopause: the science describing the cell-specifc intracellular formation of estrogens and androgens from DHEA and their strictly local action and inactivation in peripheral tissues. Menopause. 2019;26 (2):220–4.
[19] Martel C, Labrie F, Archer DF, et al. Serum steroid concentrations remain within normal postmenopausal values in women receiving daily 6.5mg intravaginal prasterone for 12 weeks. J. Steroid Biochem. Mol. Biol. 2016;159:142–53.
[20] Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) onmoderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause. 2016;23(3):243–56.
[21] Archer DF, Labrie F, Montesino M, Martel C. Comparison of Intravaginal 6.5mg (0.50%) Prasterone, 0.3mg Conjugated Estrogens and 10μg Estradiol on Symptoms of Vulvovaginal Atrophy. Steroid Biochem. Mol Biol. 2017 Nov;174:1–8.
[22] Labrie F, Belanger A, Pelletier G, Martel C, Archer DF, Utian WH. Science of intracrinology in postmenopausal women. Menopause. 2017;24(6):702–12.
[23] Labrie F, Archer D, Bouchard C, et al. Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause 2009.
[24] La Rosa VL, Ciebiera M, Lin LT, et al. Treatment of genitourinary syndrome of menopause: the potential effects of intravaginal ultralow-concentration oestriol and intravaginal dehydroepiandrosterone on quality of life and sexual function. Prz Menopauzalny. 2019;18(2):116–22.
[25] Tubaro A, Zattoni F, Prezioso D, Scarpa RM, Pesce F, Rizzi CA, et al. Italian validation of the International Consultation on Incontinence Questionnaires. BJU International 2006;97:101–8.
[26] Timmermans L, Falez F, Mélot C, et al. Validation of use of the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) for impairment rating: A transversal retrospective study of 120 patients. Neurourol. Urodyn. 2013;32:974–9.
[27] Bachmann G. Urogenital ageing: an old problem newly recognized. Maturitas 1995;22:S1–5.
[28] Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. J Clin Epidemiol 1998;51 (11):1171–8.
[29] North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. Menopause. 2007;14(3 Pt 1):355–69.
[30] Baber RJ, Panay N, Fenton A. 2016 IMS recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109–50.
[31] Matarazzo MG, Caruso S, Giunta G, Valenti G, Sarpietro G, Cianci A. Does Vaginal Estriol Make Urodynamic Changes in Women With Overactive Bladder Syndrome and Genitourinary Syndrome of Menopause?. Eur J Obstet Gynecol Reprod Biol. 2018 Mar;222:75–9.
[32] Tseng LH, Wang AC, Chang YL, Soong YK, Lloyd LK, Ko YJ. Randomized comparison of tolterodine with vaginal estrogen cream versus tolterodine alone for the treatment of postmenopausal women with overactive bladder syndrome. Neurourol Urodyn 2009;28:47–51.
[33] Ellington DR, Szychowski JM, Malek JM, Gerten KA, Burgio KL, Richter HE. Combined tolterodine and vaginal estradiol cream for overactive bladder symptoms after randomized single-therapy treatment. Female Pelvic Med Reconstr Surg 2016;22:254–60.
[34] Li B, Duan H, Chang Y, Wang S. Efficacy and safety of current therapies for genitourinary syndrome of menopause: A Bayesian network analysis of 29 randomized trials and 8311 patients..Pharmacol Res. 2021;164:105360. doi: 10.1016/j.phrs.2020.105360. Epub 2020 Dec 8.
[35] Experience with ospemifene in patients with vulvar and vaginal atrophy and urinary incontinence: case studies. Blanco ZE, Lilue M, Palacios S. Drugs Context. 2020 Jul 1;9:2020-3-6. doi: 10.7573/dic.2020-3-6. eCollection 2020.
[36] Constantine GD, Bruyniks N, Princic N, et al. Incidence of genitourinary conditions in women with a diagnosis of vulvar/vaginal atrophy. Curr Med Res Opin 2014;30:143–8.
[37] Robinson D, Cardozo L. The pathophysiology and management of postmenopausal urogenital oestrogen deficiency. J Br Menopause Soc 2001;7:67–73.
[38] Robinson D, Toozs-Hobson P, Cardozo L. The effect of hormones on the lower urinary tract. Menopause Int 2013;19:155–62.
[39] Kagan R, Kellogg-Spadt S, Parish SJ. Practical Treatment Considerations in the Management of Genitourinary Syndrome of Menopause. Drugs Aging 2019;36:897–908.
[40] Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause. 2009;16:923–31.
[41] Labrie F, Cusan L, Gomez JL, et al. Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. J Steroid Biochem Mol Biol 2008;111:178–94.
[42] Heo YA. Prasterone: A Review in Vulvovaginal Atrophy. Drugs Aging. 2019 Aug;36(8):781–8. https://doi.org/10.1007/s40266-019-00693-6.
[43] Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) - results from an international survey. Climacteric. 2012 Feb;15(1):36–44.
[44] Nappi RE, Palacios S, Particco M, Panay N. The REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey in Europe: Country-specific comparisons of postmenopausal women's perceptions, experiences and needs. Maturitas. 2016 Sep;91:81–90.
[45] Labrie F, Archer D, Bouchard C, et al. Lack of influence of dyspareunia on the beneficial effect of intravaginal prasterone (dehydroepiandrosterone, DHEA) on sexual dysfunction in postmenopausal women. J Sex Med 2014;11:1766–85.