Women Health Bull. 2018 April; 5(2):e14390. doi: 10.5812/whb.14390.

Published online 2017 December 10. **Review Article**

Changes of Bladder Function Related to the Effects of Menopause

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Received 2017 April 10; **Revised** 2017 May 31; **Accepted** 2017 August 08.

Abstract

Female sex hormones are thought to be important in the histological and functional maintenance of the genitourinary tract. Estrogen deficiency after menopause may be related to urinary symptoms. Postmenopausal atrophic changes cause genital and urinary deterioration and reduce sexual health, resulting in an overactive bladder. Ovariectomized virgin rats appear to be an optimal postmenopausal animal model, as they are free of the confounding effects of delivery and advancing age. Although the exact mechanisms of postmenopausal bladder dysfunction are undetermined, decreased vascularity has been introduced as the primary event resulting in atrophy, with possible underlying mechanisms, which can explain bladder dysfunction. Local administration of estrogen seems to be effective in the management of urinary symptoms in postmenopausal women, and this route of administration has the advantage of alleviating the adverse side effects of systemic replacement.

Keywords: Menopause, Overactive Badder, Ovariectomy, Estrogen

1. Postmenopausal Bladder Function

The female urinary tract shares the same origin as the genital tract in the urogenital sinus. Menopause can change the histological and physiological characteristics of the urinary tract, as well as the genital organs. Female sex hormones are thought to be important in the histological and functional maintenance of the genitourinary tract.

Moreover, estrogen deficiency after menopause may be related to urinary symptoms (1). Bladder function is known to become overactive after menopause (2, 3). However, researchers have reported no correlations between menopause and overactive bladder (OAB) (4-7). The difficulty in determining the effects of menopause on OAB stems partly from the aging of the postmenopausal population, as age is an important factor in OAB.

OAB is a symptom complex of urinary urgency, which is usually accompanied by urinary frequency and nocturia, with or without incontinence in the absence of metabolic, infectious, or local pathologic conditions (8). The overall prevalence of OAB in a large population study was 11.8% (9), while in an epidemiological study in North America, the prevalence was estimated at 16.9% among women (10). Moreover, in a European study, the prevalence was 16.6% in women aged over 40 years, whereas a more recent population-based study reported a prevalence of 7.8% in women aged 45 - 60 years (11).

The variations in the prevalence rates may be related to the characteristics of the studied populations, such as age, race, and ethnicity, or differences in the evaluation tools. Among OAB symptoms, urinary frequency is the most common (85%), followed by urinary urgency (54%) and incontinence (36%) (12). Overall, OAB is not a life-threatening condition, but its impact on quality of life is substantial and deteriorates patients' social, psychological, emotional, physical, and sexual functioning (13, 14).

Menopause also influences the prevalence of OAB. It refers to a transition to non-reproductive years due to decreased production of sex hormones in the ovaries (15). After menopause, urogenital atrophy, besides a variety of sexual and lower urinary tract symptoms, can develop or worsen (16, 17). A number of studies have reported associations between menopausal symptoms and OAB, although the causative relationship is not clear (18, 19). Postmenopausal atrophy leads to both genital and urinary deterioration and reduces sexual health, resulting in the development of OAB.

Recently, the concept of genitourinary syndrome of menopause (GSM) has been introduced to properly define the symptoms and signs of menopause (20). The urinary tract undergoes the same atrophic changes as the vagina. Decreased amount of collagen in periurethral tissues, besides urethral mucosal atrophy, causes the so-called "atrophic urethritis". These changes are known to lead to urinary frequency, nocturia, urinary incontinence, and increased risk of urinary tract infection.

Similar to atrophic vaginitis, atrophic urethritis itself is not an infective condition. If combined with stenosis, it can cause bladder pathology and functional impairment, similar to bladder outlet obstruction in male patients. It is unclear if atrophic urethritis changes the bladder function or the bladder undergoes similar atrophic changes, resulting in functional impairment. One recent animal study reported explainable bladder changes in terms of weight similar to the uterus and modulatory proteins (21).

It seems that various factors affect bladder function related to menopause. Menopause is also associated with obesity (22), diabetes (23), cardiac diseases (24), and psychological stress, and these conditions are in turn associated with OAB (10, 25, 26). Besides age, a variety of other factors are associated with OAB, causing problems in the epidemiological assessment of menopause and OAB.

2. Ovariectomized Animals in an Experimental Menopause Model

Bladder function may be affected by many factors, including age and menopausal status, which can distort interpretation of the results. In experimental animal models, the possibility of bias can be overcome in early iatrogenic menopause via ovariectomy. Ovariectomized virgin rats have been established as optimal models for studying the menopausal effects, as they are free of the confounding effects of delivery and advancing age (27).

Prior to ovariectomy, the rats need time to adjust to the environment. The optimal age for ovariectomy in virgin rats is approximately 10 weeks before they reach menopause. After the rats are anesthetized, their ovaries are typically exposed using a lateral flank approach rather than making midline incisions, as the ovaries are located in the flank area (21). A few weeks later, bladder function in ovariectomized rats can be evaluated with cystometry or observation of voiding patterns in the metabolic cage.

Rat cystometry has been well-described in many articles (28). The infusion rate of filling saline should be sufficiently low to avoid artifacts, and the frequency of bladder contractions can take a range of cut-off values. Breyer et al. considered more than 4 contractions in 10 minutes to be indicative of detrusor overactivity at an infusion rate of 0.1 ml/min (29).

Ovariectomy in rats increases their body weight; additionally, their uterus shrinks, and the bladder appears to become thinner. Ovariectomized rats also have OAB (30), and unlike rats with obstructed bladder outlets, which is another OAB rat model, the bladder wall does not thicken in ovariectomized rats, at least not in the early period after ovariectomy. Ovariectomy in rats also attenuates their bladder muscles and causes fibrotic changes due to decreased vascularity, whereas rats with obstructed bladder outlets develop bladder hypertrophy. Therefore, the bladder of ovariectomized animals may appear overactive with low contractility (31).

3. Possible Mechanisms of OAB After Menopause

Decreased concentrations of female sex hormones after menopause appear to make the bladder overactive (31, 32), although the exact mechanisms remain unknown. Decreased vascularity can be described as the starting point of a cascade of events, which lead to bladder dysfunction (33). Muscarinic receptors play a central role in OAB, and blocking these receptors is a common treatment for OAB; therefore, they can be important in postmenopausal OAB.

In ovariectomized animals, increased levels of muscarinic receptors have been reported as a possible cause of OAB (34), whereas other studies have found contradictory results (35). In this regard, a recent study reported no increase in muscarinic receptors in ovariectomized rats (21). Muscarinic receptors may be functionally potentiated without changes in receptor density; this can be accomplished by gap junction proteins. These proteins are responsible for coordination of cell-to-cell communication and major simultaneous contractions of bladder smooth muscle cells, which occur when these cells are coupled (36).

Connexin-43 is the main gap junction protein in rat detrusor cells (37); it can be found in the suburothelium, besides the detrusor (38, 39). The level of connexin-43 has been reported to increase in the detrusor cells of patients with overactive neurogenic bladder (40), as well as the rat bladder after ovariectomy. In a previous study, hormone replacement after ovariectomy was followed by decreased connexin-43 level, reflected as improved bladder function (41).

Other possible mechanisms of OAB induced by ovariectomy may involve gap junction proteins, vanilloid receptors, Rho-kinase receptors (42), neurokinin receptors (43), or purinergic receptors (44). Although changes in bladder function after menopause begin with decreased levels of sex hormones and atrophy in the urogenital tract, the eventual manifestations and mechanisms of postmenopausal OAB may be the same as other types of OAB. If important stages in postmenopausal changes of the bladder are identified, they can be extrapolated to all types of OAB.

4. Can Hormone Replacement Reverse OAB?

Contrary to the previous notion of the beneficial effects of estrogen on urinary symptoms in postmenopausal women (45), recent studies of systemic estrogen administration have revealed no improvement or deterioration in urinary incontinence, compared with the placebo. In the Heart and Estrogen/progestin Replacement Study (HERS, a large prospective randomized study), patients treated with conjugated estrogen plus progesterone showed a 21% improvement in incontinence versus a 26% improvement in the placebo group. Incontinence deteriorated in 39% of patients treated with hormones versus 27% of patients in the control group (46). Meanwhile, the Women's Health Initiative (WHI) reported similar results. Postmenopausal women were treated with either conjugated estrogen alone or conjugated estrogen plus progesterone, and hormone treatment worsened urgency and stress incontinence (47).

The negative effects of systemic hormone replacement on urinary symptoms were found in another large-scale study on postmenopausal women (48). In this longitudinal study, all 4 methods of hormone administration (oral estrogen, transdermal estrogen, oral estrogen with progestin, and transdermal estrogen with progestin) increased the risk of incontinence, compared with women who had never received hormones. On the other hand, discontinuation of hormones decreased the risk of incontinence over time. Ten years after the end of hormone therapy, these women had the same risk as women who had never used hormones.

Although the primary focus of the mentioned studies was cardiac diseases or osteoporosis, and some studies (49) have expressed concerns about the misinterpretation of WHI results, analysis of previous studies about urinary symptoms as additional endpoints seems clear. However, local administration of estrogen appears to be effective in the management of urinary symptoms in postmenopausal women, and local administration has the advantage of alleviating the adverse side effects of systemic replacement. There are concerns about protection of the endometrium in breast cancer after hormone replacement, especially with systemic administration (50). One study reported vaginal bleeding and hysterectomy in some patients due to complications after estradiol implants for OAB (51); based on the findings, systemic administration should not be applied in the postmenopausal management of OAB.

Low-dose, vaginally administered estrogen was reported to be beneficial against the adverse symptoms of urinary urgency, frequency, and incontinence (52). However, this effect was thought to result from the reversal of urogenital atrophy rather than any direct activities in the lower urinary tract. A meta-analysis regarding the role of estrogen therapy in the management of OAB examined 11 randomized trials, including 430 patients (53). Overall, estrogen was associated with all outcome parameters. Diurnal and nocturnal frequency, urgency, number of incontinence episodes, and bladder capacity improved, whereas local administration was superior to systemic administration.

Moreover, Simunic et al. reported urodynamic changes after local estrogen therapy in postmenopausal OAB patients. The subjective symptoms, maximal cystometric capacity, strong desire to void, and uninhibited bladder contractions improved with local administration of 25 μg of micronized 17 beta-estradiol (54). In another study, a locally administered estradiol-releasing ring was compared with oral 5-mg oxybutynin, and the efficacy results were comparable (55). Moreover, local estrogen therapy, combined with oral anticholinergic drugs, has been applied. However, the synergistic effects of combination therapy were not consistent, and more data are needed (56-58).

Acknowledgments

None.

Footnote

Conflicts of Interest: None.

References

1. Robinson D, Toozs-Hobson P, Cardozo L. The effect of hormones on the lower urinary tract. *Menopause Int*. 2013;**19**(4):155–62. doi: 10.1177/1754045313511398. [PubMed: 24336244].
2. Thomas TM, Plymat KR, Blannin J, Meade TW. Prevalence of urinary incontinence. *Br Med J*. 1980;**281**(6250):1243–5. [PubMed: 7427654].
3. Quinn SD, Domoney C. The effects of hormones on urinary incontinence in postmenopausal women. *Climacteric*. 2009;**12**(2):106–13. doi: 10.1080/13697130802630083. [PubMed: 19259853].
4. Waetjen LE, Johnson WO, Xing G, Feng WY, Greendale GA, Gold EB, et al. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. *Menopause*. 2011;**18**(12):1283–90. doi: 10.1097/gme.0b013e31821f5d25. [PubMed: 21785372].
5. Gopal M, Sammel MD, Arya LA, Freeman EW, Lin H, Gracia C. Association of change in estradiol to lower urinary tract symptoms during the menopausal transition. *Obstet Gynecol*. 2008;**112**(5):1045–52. doi: 10.1097/AOG.0b013e31818b4cad. [PubMed: 18978104].
6. Teleman PM, Persson J, Mattiasson A, Samsioe G. The relation between urinary incontinence and steroid hormone levels in perimenopausal women. A report from the Women's Health in the Lund Area (WHILA) study. *Acta Obstet Gynecol Scand*. 2009;**88**(8):927–32. doi: 10.1080/00016340903117986. [PubMed: 19579140].
7. Legendre G, Ringa V, Fauconnier A, Fritel X. Menopause, hormone treatment and urinary incontinence at midlife. *Maturitas*. 2013;**74**(1):26–30. doi: 10.1016/j.maturitas.2012.10.005. [PubMed: 23141079].

8. 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**(1):5–26. doi: 10.1007/s00192-009-0976-9. [PubMed: 19937315].
9. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol*. 2006;**50**(6):1306–14. discussion 1314-5. doi: 10.1016/j.eururo.2006.09.019. [PubMed: 17049716].
10. 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**(6):327–36. doi: 10.1007/s00345-002-0301-4. [PubMed: 12811491].
11. Juliato CR, Baccaro LF, Pedro AO, Costa-Paiva L, Lui-Filho J, Pinto-Neto AM. Subjective urinary urgency in middle age women: A population-based study. *Maturitas*. 2016;**85**:82–7. doi: 10.1016/j.maturitas.2015.12.009. [PubMed: 26857885].
12. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;**87**(9):760–6. [PubMed: 11412210].
13. Bartoli S, Aguzzi G, Tarricone R. Impact on quality of life of urinary incontinence and overactive bladder: a systematic literature review. *Urology*. 2010;**75**(3):491–500. doi: 10.1016/j.urology.2009.07.1325. [PubMed: 19962738].
14. Chiaffarino F, Parazzini F, Lavezzari M, Giambanco V. Impact of urinary incontinence and overactive bladder on quality of life. *Europ Urol*. 2003;**43**(5):535–8.
15. Speroff L. The perimenopause: definitions, demography, and physiology. *Obstet Gynecol Clinic North America*. 2002;**29**(3):397–410.
16. Fantl JA. The lower urinary tract in women—effect of aging and menopause on continence. *Experiment Gerontol*. 1994;**29**(3):417–22.
17. Sturdee DW, Panay N, International Menopause Society Writing G. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric*. 2010;**13**(6):509–22. doi: 10.3109/13697137.2010.522875. [PubMed: 20883118].
18. Chen Y, Yu W, Yang Y, Duan J, Xiao Y, Zhang X, et al. Association between overactive bladder and peri-menopause syndrome: a cross-sectional study of female physicians in China. *Int Urol Nephrol*. 2015;**47**(5):743–9. doi: 10.1007/s11255-015-0948-6. [PubMed: 25838031].
19. Zhu L, Cheng X, Sun J, Lv S, Mei S, Chen X, et al. Association between Menopausal Symptoms and Overactive Bladder: A Cross-Sectional Questionnaire Survey in China. *PLoS One*. 2015;**10**(10). e0139599. doi: 10.1371/journal.pone.0139599. [PubMed: 26448626].
20. Vieira-Baptista P, Marchitelli C, Haefner HK, Donders G, Perez-Lopez F. Deconstructing the genitourinary syndrome of menopause. *Int Urogynecol J*. 2017;**28**(5):675–9. doi: 10.1007/s00192-017-3295-6. [PubMed: 28293790].
21. Lee KC. Changes of muscarinic receptors and connexin-43 expression as a mechanism of overactive bladder in ovariectomized rats. *World J Urol*. 2015;**33**(11):1875–9. doi: 10.1007/s00345-015-1496-5. [PubMed: 25647175].
22. Matthews KA, Abrams B, Crawford S, Miles T, Neer R, Powell LH, et al. Body mass index in mid-life women: relative influence of menopause, hormone use, and ethnicity. *Int J Obes Relat Metab Disord*. 2001;**25**(6):863–73. doi: 10.1038/sj.ijo.0801618. [PubMed: 11439301].
23. McGrother CW, Donaldson MM, Hayward T, Matthews R, Dallosso HM, Hyde C, et al. Urinary storage symptoms and comorbidities: a prospective population cohort study in middle-aged and older women. *Age Ageing*. 2006;**35**(1):16–24. doi: 10.1093/ageing/afi205. [PubMed: 16234314].
24. Trémollières FA, Pouilles JM, Cauneille C, Ribot C. Coronary heart disease risk factors and menopause: a study in 1684 French women. *Atheroscl*. 1999;**142**(2):415–23.
25. Lai H, Gardner V, Vetter J, Andriole GL. Correlation between psychological stress levels and the severity of overactive bladder symptoms. *BMC Urol*. 2015;**15**:14. doi: 10.1186/s12894-015-0009-6. [PubMed: 25887525].
26. Liu RT, Chung MS, Lee WC, Chang SW, Huang ST, Yang KD, et al. Prevalence of overactive bladder and associated risk factors in 1359 patients with type 2 diabetes. *Urology*. 2011;**78**(5):1040–5. doi: 10.1016/j.urology.2011.05.017. [PubMed: 21958505].
27. Diep N, Constantinou CE. Age dependent response to exogenous estrogen on micturition, contractility and cholinergic receptors of the rat bladder. *Life Scie*. 1999;**64**(23):PL279–89.
28. Lee KS, Na YG, Dean-McKinney T, Klausner AP, Tuttle JB, Steers WD. Alterations in voiding frequency and cystometry in the clomipramine induced model of endogenous depression and reversal with fluoxetine. *J Urol*. 2003;**170**(5):2067–71. doi: 10.1097/01.ju.0000080648.01911.9a. [PubMed: 14532855].
29. Breyer BN, Wang G, Lin G, Shindel AW, Yang R, Lin CS, et al. The effect of long-term hormonal treatment on voiding patterns during filling cystometry and on urethral histology in a postpartum, ovariectomized female rat. *BJU Int*. 2010;**106**(11):1775–81. doi: 10.1111/j.1464-410X.2010.09268.x. [PubMed: 20201831].
30. Patra PB, Thorneloe KS, Laping NJ. Effect of estrogen and progesterone on urodynamics in the conscious rat. *Urology*. 2009;**74**(2):463–6. doi: 10.1016/j.urology.2008.12.046. [PubMed: 19573897].
31. Bujok J, Wincewicz E, Czerski A, Zawadzki W. Influence of ovariohysterectomy and deslorelin acetate on the spontaneous activity of the rabbit urinary bladder in vitro. *Theriogenology*. 2016;**85**(3):441–6. doi: 10.1016/j.theriogenology.2015.09.018. [PubMed: 26474688].
32. Liang W, Afshar K, Stothers L, Laher I. The influence of ovariectomy and estrogen replacement on voiding patterns and detrusor muscarinic receptor affinity in the rat. *Life Sci*. 2002;**71**(3):351–62.
33. Long CY, Liu CM, Hsu SC, Chen YH, Wu CH, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the lower urinary tract of hysterectomized postmenopausal women. *Fertil Steril*. 2006;**85**(1):155–60. doi: 10.1016/j.fertnstert.2005.06.042. [PubMed: 16412747].
34. Juan YS, Chuang SM, Long CY, Chen CH, Levin RM, Liu KM, et al. Neuroprotection of green tea catechins on surgical menopause-induced overactive bladder in a rat model. *Menopause*. 2012;**19**(3):346–54. doi: 10.1097/gme.0b013e31822d652d. [PubMed: 22042325].
35. Long CY, Hsu CS, Shao PL, Liu CM, Su JH, Tsai EM. Effect of ovariectomy on the gene expression of detrusor muscarinic receptors in female rats. *Fertil Steril*. 2009;**92**(3):1147–9. doi: 10.1016/j.fertnstert.2009.01.161. [PubMed: 19328480].
36. Neuhaus J, Weimann A, Stolzenburg JU, Wolburg H, Horn LC, Dorschner W. Smooth muscle cells from human urinary bladder express connexin 43 in vivo and in vitro. *World J Urol*. 2002;**20**(4):250–4. doi: 10.1007/s00345-002-0289-9. [PubMed: 12215856].
37. Haefliger JA, Tissieres P, Tawadros T, Formenton A, Beny JL, Nicod P, et al. Connexins 43 and 26 are differentially increased after rat bladder outlet obstruction. *Exp Cell Res*. 2002;**274**(2):216–25. doi: 10.1006/excr.2001.5465. [PubMed: 11900482].
38. Sui GP, Rothery S, Dupont E, Fry CH, Severs NJ. Gap junctions and connexin expression in human suburothelial interstitial cells. *BJU Int*. 2002;**90**(1):118–29. [PubMed: 12081783].
39. Ikeda Y, Fry C, Hayashi F, Stolz D, Griffiths D, Kanai A. Role of gap junctions in spontaneous activity of the rat bladder. *Am J Physiol Renal Physiol*. 2007;**293**(4):F1018–25. doi: 10.1152/ajprenal.00183.2007. [PubMed: 17581924].
40. Haferkamp A, Mundhenk J, Bastian PJ, Reitz A, Dorsam J, Pannek J, et al. Increased expression of connexin 43 in the overactive neurogenic detrusor. *Eur Urol*. 2004;**46**(6):799–805. doi: 10.1016/j.eururo.2004.08.020. [PubMed: 15548450].
41. Okada S, Kojima Y, Hamamoto S, Mizuno K, Sasaki S, Kohri K. Dietary soy isoflavone replacement improves detrusor overactivity of ovariectomized rats with altered connexin-43 expression in the uri-

nary bladder. *BJU Int*. 2009;**103**(10):1429–35. [PubMed: 19462485].
42. Hong SK, Yang JH, Kim TB, Kim SW, Paick JS. Effects of ovariectomy and oestrogen replacement on the function and expression of Rho-kinase in rat bladder smooth muscle. *BJU Int*. 2006;**98**(5):1114–7. doi: 10.1111/j.1464-410X.2006.06486.x. [PubMed: 17034613].
43. Ouslander JG. Management of overactive bladder. *N Engl J Med*. 2004;**350**(8):786–99. doi: 10.1056/NEJMra032662. [PubMed: 14973214].
44. Carley ME, Cliby WA, Spelsberg TC. P2X(3) receptor subunit messenger RNA expression in the female mouse bladder after oophorectomy with or without estrogen replacement. *Am J Obstet Gynecol*. 2002;**187**(1):103–6. [PubMed: 12114896].
45. Samsioe G, Jansson I, Mellström D, Svanborg A. Occurrence, nature and treatment of urinary incontinence in a 70-year-old female population. *Maturit*. 1985;**7**(4):335–42.
46. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmenopausal hormones and incontinence: the heart and estrogen/progestin replacement study. *Obstet Gynecol*. 2001;**97**(1):116–20.
47. Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005;**293**(8):935–48. doi: 10.1001/jama.293.8.935. [PubMed: 15728164].
48. Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. *Obstet Gynecol*. 2004;**103**(2):254–60. doi: 10.1097/01.AOG.0000107290.33034.6f. [PubMed: 14754692].
49. Shapiro S, de Villiers TJ, Pines A, Sturdee DW, Baber RJ, Panay N, et al. Risks and benefits of hormone therapy: has medical dogma now been overturned?. *Climacteric*. 2014;**17**(3):215–22. doi: 10.3109/13697137.2014.905529. [PubMed: 24654673].
50. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA*. 2002;**288**(7):872–81. [PubMed: 12186605].
51. Rufford J, Hextall A, Cardozo L, Khullar V. A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. *Int Urogynecol J Pelvic Floor Dysfunct*. 2003;**14**(2):78–83. doi: 10.1007/s00192-003-1054-3. [PubMed: 12851747].
52. Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. *Urol*. 2003;**62**(4):45–51.
53. Cardozo L, Lose G, McClish D, Versi E. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand*. 2004;**83**(10):892–7. doi: 10.1111/j.0001-6349.2004.00581.x. [PubMed: 15453881].
54. Šimunić V, Banović I, Ciglar S, Jeren L, Pavičić Baldani D, Šprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynecol Obstet*. 2003;**82**(2):187–97.
55. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DJ. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. *Menopause*. 2011;**18**(9):962–6. doi: 10.1097/gme.0b013e3182104977. [PubMed: 21532512].
56. 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**(1):47–51. doi: 10.1002/nau.20583. [PubMed: 19089890].
57. Serati M, Salvatore S, Uccella S, Cardozo L, Bolis P. Is there a synergistic effect of topical oestrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity?. *Eur Urol*. 2009;**55**(3):713–9. doi: 10.1016/j.eururo.2008.06.051. [PubMed: 18584946].
58. Chughtai B, Forde JC, Buck J, Asfaw T, Lee R, Te AE, et al. The concomitant use of fesoterodine and topical vaginal estrogen in the management of overactive bladder and sexual dysfunction in postmenopausal women. *Post Reprod Health*. 2016;**22**(1):34–40. doi: 10.1177/2053369116633017. [PubMed: 26883688].