Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 2, pp. 140-144
DOI: 10.1097/GME.0000000000001173

Postmenopausal hormone therapy is accompanied by elevated risk for uterine prolapse

Päivi Rahkola-Soisalo, MD, PhD,[1] Hanna Savolainen-Peltonen, MD, PhD,[1,2] Mika Gissler, PhD,[3,4] Fabian Hoti, PhD,[5] Pia Vattulainen, MSc,[5] Olavi Ylikorkala, MD, PhD,[1] and Tomi S. Mikkola, MD, PhD[1,2]

Abstract

Objective: Receptors for estrogen and progesterone are present in the pelvic floor, and therefore, postmenopausal hormone therapy may affect its function. We compared the former use of estradiol-progestogen postmenopausal hormone therapy in nonhysterectomized women with a uterine prolapse surgery ($N = 12,072$) and control women ($N = 33,704$).

Methods: The women with a history of uterine prolapse operation were identified from the Finnish National Hospital Discharge Register, and the control women from the Finnish Central Population Register. The use of hormone therapy was traced from the national drug reimbursement register, and the odd ratios with 95% CIs for prolapse were calculated by using the conditional logistic regression analysis.

Results: The women with uterine prolapse had used hormone therapy more often than control women ($N = 4,127$; 34.2% vs $N = 9,189$; 27.3%; $P < 0.005$). The use of hormone therapy was accompanied by significant (23%-53%) elevations in the risk for prolapse, being higher with longer exposure. The risk elevations (33%-23%) were comparable between sole norethisteroneacetate-estradiol and sole medroxyprogesteroneacetate-estradiol therapy. The use of estradiol in combination with a levonorgestrel releasing intrauterine device was accompanied by a 52% elevation.

Conclusions: The postmenopausal use of estradiol in combination with various progestogen regimens may weaken the pelvic floor, resulting in uterine prolapse. This data should be incorporated into the information given to the users of estradiol-progestogen hormone therapy.

Key Words: Estradiol – Hormone therapy – Menopause – Pelvic organ prolapse – Progestin – Uterus.

It is currently understood that pelvic organ prolapse develops as a result of uniform failure of pelvic floor support. The key risk factors for pelvic floor insufficiency are pregnancy, child birth, advancing age, obesity, and genetic predisposition.[1,2] Some bulging of vaginal walls in parous women is a physiological phenomenon that does not cause any symptoms or require any treatment. In contrast, the descending uterus, with or without vaginal wall prolapse, may cause a number of troublesome symptoms (eg, bulging, bladder, bowel, and sexual dysfunction), and in Finland approximately 12% of women face a life-time risk for prolapse-related vaginal hysterectomy, with or without vaginal wall repair.[3]

Receptors for estrogen (ER) and progesterone (PR) are present in the pelvic floor (eg, musculature, pubocervical fascia, and uterosacral ligaments). These receptors mediate the effects of estrogen and progesterone on collagens, elastin, smooth muscle cells, and fibroblasts that are crucial for pelvic floor support.[4-9] The possible molecular mechanisms are complex, but they are likely linked to extracellular regulators, such as transforming growth factor-β (TGF-β) and tropoelastin which estradiol modulates.[9] Estradiol may also affect the structure of extracellular matrix.[8] The impact of sex steroids on the pelvic floor can be seen, for example, during pregnancy, when high circulating levels of estrogens and progesterone, alone or in combination with relaxin, soften the pelvic floor to facilitate the forthcoming delivery.[10] Sensitivity for steroid hormones in the pelvic floor gains additional support from the rapid development of pelvic organ prolapse in women using some new selective estrogen receptor modulators in initial/phase III clinical studies.[11,12]

Received May 2, 2018; revised and accepted June 7, 2018.

From the [1]Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [2]Folk-Folkhälsan Research Center, Biomedicum, Helsinki, Finland; [3]National Institute for Health and Welfare, Helsinki, Finland; [4]Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Division of Family Medicine, Stockholm, Sweden; and [5]EPID Research Oy, Espoo, Finland.

Funding/support: None reported.

Financial disclosure/conflicts of interest: PR-S has received funding for congress trips from Johnson & Johnson and Astellas Pharma. HS-P has been a speaker for Mylan and received funding for congress trips from Mylan and MSD. TM has been a speaker and/or received consulting fees from Mylan and Astellas Pharma. MG and OY have nothing to disclose. FH and PV work for EPID Research. EPID Research is a company that performs financially supported studies to several pharmaceutical companies.

Address correspondence to: Tomi S. Mikkola, MD, PhD, Helsinki University Hospital, Department of Obstetrics and Gynecology, Haartmaninkatu 2, Box 140, FIN-00029 HUS, Helsinki, Finland.
E-mail: tomi.mikkola@hus.fi

The use of postmenopausal systemic hormone therapy also stimulates steroid hormone receptors in the pelvic floor.[4-8] Based on the Cochrane analysis, the impact of postmenopausal hormone therapy on the pelvic floor support is, however, still unclear.[13] In the majority of these studies, conjugated equine estrogens (CEE), rather than estradiol, have been used. Estradiol, however, differs in many biological effects from CEE,[14] and thus, the impact of estradiol containing hormone therapy on pelvic organ prolapse needs to be assessed separately. Progestogens, of which noretisterone acetate (NETA) and medroxyprogesterone acetate (MPA) are the most popular, at least in Finland,[15] also differ in many biological effects,[16] but their possible differences in the regulation of the pelvic floor are not known. Likewise, no data exist for the levonorgestrel releasing intrauterine device (Levo-IUD) or tibolone in possible connection with pelvic organ prolapse. Thus, in the present study, we evaluated the impact of various systemic postmenopausal combined hormone therapy regimens (EPT) containing estradiol and progestogen and that of tibolone on the risk of uterine prolapse (UP) in Finnish women.

PARTICIPANTS AND METHODS

Cases

We collected from the Nationwide Hospital Discharge Register 12,072 women who had undergone vaginal hysterectomy for UP from 1998 to 2012. Although the uterus was the dominant prolapsing organ, hysterectomy could have been accompanied by vaginal repair, but these additional surgeries were not recorded into our data registry. The cases had not undergone any previous vaginal operation, and the index operations had been performed in 19 hospital districts located evenly throughout Finland

Control women

For each woman with UP three control women without a history of hysterectomy or any prolapse operation were collected from the Finnish National Population Register. The control women ($N = 36{,}216$) were matched in regards to age (± 1 mo), number of deliveries, and hospital district. A number of selected women ($N = 2{,}512$) failing to fulfill inclusion criteria were excluded. Thus, the control group consisted of 33,704 women (Table 1).

TABLE 1. *Characteristics of the women with uterine prolapse and control women*

	Cases *N* (%) 12,072	Controls *N* (%) 33,704
Parity		
No births	86 (0.7)	235 (0.7)
1 to 3 births	9,604 (80.1)	26,562 (79.4)
>3 births	2,382 (19.9)	6,907 (20.6)
Age at start of hormone therapy		
<55 y	3,693 (89.5)	8,212 (89.4)
≥55 y	434 (10.5)	977 (10.6)

The use of postmenopausal hormone therapy

Because all the cases had uterus in situ, their postmenopausal hormone therapy had been exclusively EPT, the use of which was assessed from the National Drug Reimbursement Register for the cases and the controls. In Finland, various EPT regimens, available only with a physician's prescription, contain only estradiol as an estrogenic component. A 3-month use of EPT can be purchased at each pharmacy visit, and therefore, repeat visits and EPT purchases entered into the drug reimbursement register confirmed continuous use of the regimen. The register was opened in 1994, and thus a woman buying EPT regimens at the opening year 1994 ($N = 5{,}826$, 43.8%) was considered to have started the use of EPT at the age of 52 years, the mean starting EPT age in this population,[17] and the duration of preregister EPT use was approximated accordingly. From 1995 onward to the end of 2011, the initiation date of EPT use was accurately known ($N = 7{,}490$, 56.2%).

Among the whole study population 13,316 (29.1%) women had used EPT. Of various progestogens, sole NETA-EPT was used by 2,923 women (21.9%) and sole MPA-EPT by 2,299 women (17.3%). The rest of the EPT users who had switched from one regimen to another and were exposed to NETA, MPA, dydrogesterone, megestrol acetate, lynestrenol, drospirenone, or trimegestone were categorized into mixed-EPT ($N = 7{,}622$, 57.2%). The EPT regimen could have been sequential or continuous and given orally or transdermally, but all EPT users were considered as one group. Altogether 317 women (2.4%) had used a Levo-IUD (Mirena) in addition to systemic use of estradiol, and 155 women (1.2%) had used tibolone. The use of local vaginal estrogen, alone or in addition to EPT was not recorded.

Statistical analyses

The various background factors between the cases and controls were tested with test of Equal or Given Proportions. The odds ratio of UP (OR; 95% CI) was assessed with a conditional logistic regression analysis. Subgroup analyses were carried out in women with NETA, MPA, Levo-IUD, mixed progestogen, and tibolone. Separate subanalyses were done for women who had started the use of EPT at and under or over 55 years of age. Moreover, to analyze the possible impact of EPT exposure duration subgroup analyses were done for exposures lasting under 3 years, 3 to 5 years, and over 5 years.

Permissions

The appropriate permissions for the study were obtained from the National Institute of Health and Welfare (THL/1370/5.05.00/2010), the Finnish National Population Register (901/410/14), and Social Insurance Institution of Finland (KELA 40/522/2010).

RESULTS

At the time of UP operation 36.2% of the cases had been under 60 years, 31.5% between 60 and 69 years, and 32.3%

TABLE 2. *The prevalence (N, %) of use of various hormone regimens, durations of hormone exposures and time periods from the initiation of hormone therapy to the study closure (years, mean ± SD) in women with uterine prolapse and control women*

Therapy	Cases			Controls		
	N (%)	Exposure	Time-period	*N* (%)	Exposure	Time-period
No EPT use	7,945 (65.8)			24,515 (72.7)		
Systemic						
Any progestogen-EPT	4,127 (34.2)[a]	6.4 ± 4.9	8.8 ± 4.6	9,189 (27.3)[a]	6.2 ± 4.9	9.0 ± 4.5
Other/mixed-EPT	2,482 (20.6)[a]	4.6 ± 4.0	7.4 ± 4.4	5,140 (15.3)[a]	4.7 ± 4.4	7.7 ± 4.5
NETA-EPT	870 (7.2)	5.5 ± 4.7	7.8 ± 4.6	2,053 (6.1)	5.4 ± 4.8	8.0 ± 4.5
MPA-EPT	657 (5.4)[a]	6.9 ± 5.6	8.8 ± 4.7	1,642 (4.9)[a]	6.3 ± 5.2	9.0 ± 4.6
Estradiol + Levo-IUD	103 (0.9)	3.0 ± 2.1	5.5 ± 3.3	214 (0.6)	2.7 ± 1.9	5.6 ± 3.6
Tibolone	15 (0.1)[a]	2.5 ± 2.3	4.8 ± 3.1	140 (0.4)[a]	2.2 ± 1.7	5.4 ± 3.2

[a] $P < 0.005$.

EPT, estrogen- progestogen hormone therapy; Levo-IUD, levonorgestrel releasing intrauterine device; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate.

were 70 years or older. The matching succeeded in age, parity and hospital district. The groups were also comparable with regard to age at the initiation of EPT regimens (Table 1).

The cases had used EPT more often than the controls (34.2% vs 27.3%; $P < 0.005$). The use of MPA-EPT was also more common among cases, whereas the distribution of NETA-EPT and estradiol with Levo-IUD showed no difference between the groups (Table 2). Instead, tibolone had been used less frequently ($P < 0.005$) by the cases than the controls. The EPT exposure durations and follow-up times did not differ between the cases and controls. (Table 2)

The use of any EPT was associated with a 41% elevation in the risk for UP (Table 3). The risk increase did not differ between the sole NETA-EPT and the sole MPA-EPT users (Table 3). Furthermore, the use of estradiol with the Levo-IUD was associated with a risk increase (52%), but in contrast, the use of tibolone was accompanied with a risk decrease of 70% (Table 3).

The elevations in UP risk were independent of the EPT initiation age (Table 4). The rise in the UP risk was seen already with an EPT use shorter than 3 years, but it increased further with longer exposures (Table 4).

DISCUSSION

The present data indicate that estradiol, if given in combination with systemic or intrauterine progestogen, is accompanied with an elevated risk of UP in postmenopausal women. Because EPT users became exposed to both estradiol and various progestogens, it is not possible to distinguish whether estradiol or progestogen or their combination accounted for risk increase in the development of UP. The Cochrane meta-analysis of four studies could not draw any definite conclusions on the role of estrogen (mostly CEE) on pelvic organ prolapse.[13] This could be in part due to diagnostic difficulties because the diagnosis of pelvic organ prolapse has been based on subjective questionnaires in many previous studies.[13,18] Questionnaires have often been used for recording the use of hormone therapy, although such a method is prone to recall biases. We focused solely on UP because the uterus is the leading prolapsing pelvic organ. Moreover, UP should have been severe enough to require hysterectomy, and thus, the UP diagnosis was accurate. We also benefited from using hormone register data which allowed us to accurately trace the use of EPT in our study women. Our data imply that the use of EPT may decrease the pelvic floor support to the extent that UP ensues. On the whole, our finding is in line with data from the WHI trial that hysterectomy with retained ovaries is accompanied with a higher prolapse risk than hysterectomy with bilateral oophorectomy.[19] Thus, the common use of EPT, particularly some decades ago, may have contributed to the elevation in the incidence of pelvic floor failures during the last few decades, at least in our country.[3]

TABLE 3. *The odd ratios (OR) and 95% CI for uterine prolapse in women using various hormone therapies in relation to women without any hormone use*

Therapy	Cases *N*	Controls *N*	OR (95% CI)	
No user	7,945	24,515	1 (reference)	*P*
Systemic therapy				
Any progestogen-EPT	4,127	9,189	1.41 (1.34-1.48)	<0.005
Other/mixed-EPT	2,482	5,140	1.53 (1.44-1.63)	<0.005
NETA-EPT	870	2,053	1.33 (1.22-1.45)	<0.005
MPA-EPT	657	1,642	1.23 (1.12-1.36)	<0.005
Estradiol + Levo-IUD	103	214	1.52 (1.19-1.94)	<0.005
Tibolone	15	140	0.30 (0.18-0.52)	<0.005

EPT, estrogen-progestogen hormone therapy; Levo-IUD, levonorgestrel releasing intrauterine device; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate.

TABLE 4. *Odd ratios (OR) and 95% CI for uterine prolapse among women using hormone therapy according to the starting age and exposure time*

	Cases *N*	Controls *N*	OR (95% CI)	*P*
Starting age				
Under or 55 y	3,677	8,186	1.41 (1.34-1.49)	<0.005
≥55 y	391	865	1.42 (1.23-1.63)	<0.005
Exposure to EPT				
0-3 y	1,215	3,032	1.24 (1.15-1.34)	<0.005
3-5 y	779	1,671	1.45 (1.32-1.59)	<0.005
>5 y	2,133	4,486	1.52 (1.42-1.62)	<0.005

EPT, estrogen-progestogen hormone therapy.

Although we conducted our large epidemiological study in a case-controlled manner, it can only show associations between preceding use of EPT and UP but no definite cause and effect relationship. In view of the presence of estrogen and progesterone receptors in the pelvic floor,[4-8] it is, however, possible that EPT-derived estradiol and/or various progestogens could have had a role in the development of prolapse in our cases. Although the exact mechanisms are not known, they could resemble those in pregnancy, when high circulating levels of both estrogens and progesterone alone or together with relaxin, soften the pelvic floor. Pelvic organ prolapses are associated with degradative changes in collagen, metalloproteins, elastin, smooth muscle cells, and fibroblasts in the pelvic floor[2,8,20,21] which, if developed for any reason, can perhaps be exaggerated by EPT. The fact that estradiol in combination with the Levo-IUD-EPT also carried UP risk increase suggests that estradiol rather than progestogens is the key factor for UP because the circulating levels of levonorgestrel are very low.[22] This could be supported by the findings that estradiol affects extracellular matrix mediators, such as TGF-β and tropoelastin,[9] and postmenopausal use of estradiol may also cause the structure of the extracellular matrix to be more vulnerable.[8] Progestogens may, however, oppose or potentiate the effects of estradiol in many tissues,[23] and such a phenomenon may also exist in the pelvic floor. Our data, however, imply that the two leading progestogens, MPA and NETA, in combination with estradiol, show no differences for pelvic floor support.

Tibolone is metabolized to estrogenic, progestogenic, and androgenic derivatives in a tissue-specific manner; for example, in breast, endometrium, bone, and blood vessel walls.[24] This may also hold true for the pelvic floor because the androgenic metabolites of tibolone occur in higher levels, for instance, in the myometrium and vagina than in circulating blood.[25] Androgenic metabolites may stimulate the growth of pelvic floor muscles,[26] and thus, this could at least in part explain the decreased UP risk detected in our study, even if the number of women with tibolone was small. This finding, if confirmed in future larger studies, may favor the use of tibolone in women being at high risk of UP.

Our study has limitations. First, we did not have a placebo group, and therefore an EPT prescription bias should be considered. This is, however, unlikely because in Finland severe hot flushes and other subjective menopausal symptoms, but not pelvic organ prolapse, are primary indications for the initiation of hormone therapy, and no data link these symptoms with subsequent UP. Second, the indications for UP operations are to some extent relative, and one can argue that women seeking a better quality of life from the use of EPT were also more likely to have surgery due to milder forms of UP than similar women without EPT history. This argument is unlikely because UP surgery is done only with nationally approved uniform indications. Moreover, in Finland no socioeconomic differences are observed between EPT users and nonusers,[27] and UP surgery is basically free of charge. Third, it is possible that women with UP may have started using EPT before the UP operation, wishing to relieve prolapse symptoms, but such a possible prolapse-induced bias in EPT prescription would have been against the uniform national guidelines for optimal use of EPT and most likely concerned local vaginal regimens that were excluded from our study. Moreover, the fully comparable EPT exposure times between cases and controls also speak against this bias. Fourth, we acknowledge as a weakness the small number of cases with estradiol + Levo-IUD and with tibolone, and thus, all conclusions for these therapies must be drawn with caution. Fifth, our patient series, although a large national one, was nevertheless too small to analyze the relationship between various modes of administration and doses of systemic EPT. Furthermore, we were unable to study the possible association between the degree of prolapse and doses of EPT. And finally, obesity is a risk factor for UP,[28] but we had no data on body weight. However, it is unlikely that EPT users would have been more obese than the controls.

The strengths of our study include first a large number of cases and controls. Second, the UP diagnosis was accurate, because all UP patients had been operated on using nationally scrutinized indications. Third, the history of EPT use was also accurate because it is unlikely that a woman would have repeatedly bought, but not used EPT. And finally, we were able to compare MPA and NETA from a new point of view and to produce novel data for Levo-IUD and tibolone.

CONCLUSIONS

Women with UP had used systemic estradiol-EPT regimens and estradiol with Levo-IUD more often than women without UP. This may have weakened the pelvic floor, resulting in uterine prolapse. Therefore, our data must be incorporated into information for the present and future users of EPT.

REFERENCES

1. Tinelli A, Malvasi A, Rahimi S, et al. Age-related pelvic floor modifications and prolapse risk factors in postmenopausal women. *Menopause* 2010;17:204-212.
2. Chen B, Yeh J. Alterations in connective tissue metabolism in stress incontinence and prolapse. *J Urol* 2011;186:1768-1772.
3. Kurkijarvi K, Aaltonen R, Gissler M, Makinen J. Pelvic organ prolapse surgery in Finland from 1987 to 2009: a national register based study. *Eur J Obstet Gynecol Reprod Biol* 2017;214:71-77.
4. Skala CE, Petry IB, Albrich S, Puhl A, Naumann G, Koelbl H. The effect of genital and lower urinary tract symptoms on steroid receptor expression in women with genital prolapse. *Int Urogynecol J* 2011;22:705-712.
5. Skala CE, Petry IB, Albrich SB, Puhl A, Naumann G, Koelbl H. The effect of hormonal status on the expression of estrogen and progesterone receptor in vaginal wall and periurethral tissue in urogynecological patients. *Eur J Obstet Gynecol Reprod Biol* 2010;153:99-103.
6. Fuermetz A, Schoenfeld M, Ennemoser S, Muetzel E, Jeschke U, Jundt K. Change of steroid receptor expression in the posterior vaginal wall after local estrogen therapy. *Eur J Obstet Gynecol Reprod Biol* 2015;187:45-50.
7. Gebhart JB, Rickard DJ, Barrett TJ, et al. Expression of estrogen receptor isoforms alpha and beta messenger RNA in vaginal tissue of premenopausal and postmenopausal women. *Am J Obstet Gynecol* 2001;185:1325-1330.
8. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. *BJOG* 2002;109:339-344.
9. Chakhtoura N, Zhang Y, Candiotti K, Medina CA, Takacs P. Estrogen inhibits vaginal tropoelastin and TGF-beta1 production. *Int Urogynecol J* 2012;23:1791-1795.
10. Rahn DD, Ruff MD, Brown SA, Tibbals HF, Word RA. Biomechanical properties of the vaginal wall: effect of pregnancy, elastic fiber deficiency, and pelvic organ prolapse. *Am J Obstet Gynecol* 2008;198:590.e1-590.e6.
11. Goldstein SR, Nanavati N. Adverse events that are associated with the selective estrogen receptor modulator levormeloxifene in an aborted phase III osteoporosis treatment study. *Am J Obstet Gynecol* 2002;187:521-527.
12. Albertazzi P, Sharma S. Urogenital effects of selective estrogen receptor modulators: a systematic review. *Climacteric* 2005;8:214-220.
13. Ismail SI, Bain C, Hagen S. Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women. *Cochrane Database Syst Rev* 2010;CD007063.
14. Bhavnani BR, Stanczyk FZ. Pharmacology of conjugated equine estrogens: efficacy, safety and mechanism of action. *J Steroid Biochem Mol Biol* 2014;142:16-29.
15. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. *Obstet Gynecol* 2009;113:65-73.
16. Binkowska M, Woron J. Progestogens in menopausal hormone therapy. *Prz Menopauzalny* 2015;14:134-143.
17. Savolainen-Peltonen H, Tuomikoski P, Korhonen P, et al. Cardiac Death Risk in Relation to the Age at Initiation or the Progestin Component of Hormone Therapies. *J Clin Endocrinol Metab* 2016;23:1199-1203.
18. Cardenas-Trowers OO, Borgstrom M, Addis I. Associations between type and route of hormone use on urinary incontinence and pelvic organ prolapse in premenopausal and postmenopausal women. *Female Pelvic Med Reconstr Surg* 2017;24:100-104.
19. Shveiky D, Kudish BI, Iglesia CB, et al. Effects of bilateral salpingo-oophorectomy at the time of hysterectomy on pelvic organ prolapse: results from the Women's Health Initiative trial. *Menopause* 2015;22:483-488.
20. Kerkhof MH, Ruiz-Zapata AM, Bril H, et al. Changes in tissue composition of the vaginal wall of premenopausal women with prolapse. *Am J Obstet Gynecol* 2014;210:168.e1-168.e9.
21. Ruiz-Zapata AM, Kerkhof MH, Ghazanfari S, et al. Vaginal fibroblastic cells from women with pelvic organ prolapse produce matrices with increased stiffness and collagen content. *Sci Rep* 2016;6:22971.
22. Nilsson CG, Lahteenmaki P, Luukkainen T. Levonorgestrel plasma concentrations and hormone profiles after insertion and after one year of treatment with a levonorgestrel-IUD. *Contraception* 1980;21:225-233.
23. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. *Climacteric* 2005;8 (Suppl. 3):4-12.
24. Formoso G, Perrone E, Maltoni S, et al. Short-term and long-term effects of tibolone in postmenopausal women. *Cochrane Database Syst Rev* 2016;10:CD008536.
25. Verheul HA, Blok LJ, Burger CW, Hanifi-Moghaddam P, Kloosterboer HJ. Levels of tibolone and estradiol and their nonsulfated and sulfated metabolites in serum, myometrium, and vagina of postmenopausal women following treatment for 21 days with tibolone, estradiol, or estradiol plus medroxyprogestrone acetate. *Reprod Sci* 2007;14:160-168.
26. Ho MH, Bhatia NN, Bhasin S. Anabolic effects of androgens on muscles of female pelvic floor and lower urinary tract. *Curr Opin Obstet Gynecol* 2004;16:405-409.
27. Topo P, Luoto R, Hemminki E, Uutela A. Declining socioeconomic differences in the use of menopausal and postmenopausal hormone therapy in Finland. *Maturitas* 1999;32:141-145.
28. Lee UJ, Kerkhof MH, van Leijsen SA, Heesakkers JP. Obesity and pelvic organ prolapse. *Curr Opin Urol* 2017;27:428-434.

