

The controversies regarding the role of estrogens in urogynecology

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Abstract: Estrogens are crucial for the proper functioning of genitourinary tract. Hypoestrogenism related to menopause could be linked to numerous disturbances of lower urinary tract. However, the results of most well designed clinical studies do not support use of estrogen or hormone replacement therapy for the treatment of genitourinary symptoms. According to evidence base medicine stress urinary incontinence, overactive bladder syndrome or pelvic organ prolapse are best treated by the surgery or non-hormonal drug therapy.

Key words: Estrogen - Menopause - Lower urinary tract

Urinary and reproductive tracts not only have common embryologic origin but also are linked anatomically and functionally. Both systems require ovarian sex steroids for proper function. The occurrence of surgical or natural menopause is associated with sharp increase of urogenital tract disturbances including stress urinary incontinence, overactive bladder syndrome, recurrent urinary tract infections, pelvic organ prolapse and vaginal atrophy.

On the one hand, sex steroids are widely believed to be useful in the treatment of above mentioned ailments. On the other hand, there is scarcity of high quality data proving the efficacy of sex hormones in these clinical settings. The background for the administration of the hormone replacement therapy (HRT) in the urogynecology is the identification of both type α and type β estrogen receptors (ER) and progesterone receptors in the pelvic floor support structures, vagina, urethra, trigone and central nervous systems neurons controlling micturition reflexes (Table 1).

The influence of sex hormones on lower urinary tract function

Cyclic fluctuations of sex steroids levels affect lower urinary tract function. Urodynamic data showed 6% increase of functional length of urethra in periovulatory when compared to postmenstrual phase [1]. The

instability of detrusor is markedly increased in late secretory phase. This phenomenon may be explained by the procontractory effect of progesterone that is able to antagonise estrogen-dependent relaxation of the detrusor [2].

Abnormal function of hypothalamus-pituitary-ovarian axis is linked to the deficiency of continence mechanism in reproductive age women. Also, dysuric symptoms are attributed to hypoestrogenism, anorexia and polycystic ovarian syndrome [3,4].

Epidemiological data clearly show that rapid increase of all urogynecological disturbances parallels with the occurrence of menopause. The value of maximal urethral closure pressure - the main urodynamic parameter reflecting function of continence mechanism is markedly decreased in the menopausal women. Also, bladder capacity and detrusor pressure during micturition are significantly lowered in elderly population. Urinary incontinence became common condition affecting from 19 to even 70% of investigated subjects [5]. In some analyses nearly half of menopausal women suffer from stress urinary incontinence, while another 20% report urge incontinence [6].

Urogenital atrophy related to the hypoestrogenism

Nearly 75% of women in late menopause experience genital disturbances related to hypoestrogenism (Table 2). Most bothersome are vaginal dryness, thinning of mucosa and loss of elasticity of vaginal wall, atrophy of uterine cervix, atrophy of the vulva and clitoris,

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Table 1. The distribution of the sex steroids receptors within urogenital diaphragm.

	Estrogen receptors	Progesterone receptors	Androgen receptors
Urethra	+		+
Urethral sphincter	+		
Periurethral venous plexuses	+		
Vagina	+	+	+
Trigone	+	+	+
Pelvic floor support			
▪ pubo-cervical muscle	+		
▪ levator muscle	? (+/-)		
▪ cardinal ligament	+	+	
▪ sacrouterine ligament	+ (α , β)	+	
▪ pubourethral fascia	+ (α , β)	-	
▪ perivaginal tissue	+	-	

decrease of pelvic floor muscle tone. Epithelium of vaginal portion of uterine cervix became thin and prone to injury [7].

Hypoestrogenism induced changes of vaginal flora composition increase the risk of lower urinary tract infections. Profound mucosal atrophy leads to dyspareunia that is even made worse by itching and burning of the vulva. Sexually inactive menopausal women experience contraction and gradual obliteration of the vagina.

Consequences of the chronic hypoestrogenism for the lower urinary tract

Menopausal urinary symptoms - improper perception of bladder fullness, dysuria, polyuria, nocturia, overactive bladder syndrome and stress or mixed urinary incontinence at least in part may be linked to the atrophy of trigone, loss of pelvic floor striated muscle tone, improper collagen metabolism leading to the urethral stiffness and finally, the decrease of the activity of α -adrenergic system [8]. Moreover, thinning of urethral mucosa and decrease of urethral blood flow reduce intraurethral pressure and lead to the development of stress urinary incontinence [9] (Table 3).

The influence of estrogens on the pelvic floor connective tissue metabolism

Most data on estrogen regulation of connective tissue metabolism came from animal models. Unfortunately

Table 2. The effects of estrogen deprivation on vagina, pelvic floor and vulva.

The urogenital effects of estrogens deprivation
<p>Vagina</p> <ul style="list-style-type: none"> ▪ dryness ▪ itching ▪ burning ▪ feeling of increased tension ▪ dyspareunia ▪ leukorrhoea ▪ bad odour discharge ▪ vaginal contraction ▪ atrophy of vaults ▪ disappearance of rugae ▪ insufficient blood flow ▪ insufficient lubrication ▪ lack of elasticity ▪ thinning and keratinization of mucosa ▪ increased susceptibility to the injury ▪ mucosal petechia ▪ insufficient postoperative healing ▪ decreased glycogen content in the epithelium ▪ elevated pH ▪ changes in the bacterial flora ▪ infiltration of the mucosal stroma by lymphocytes and plasmatic cells
<p>Pelvic floor</p> <ul style="list-style-type: none"> ▪ descent or prolapse of uterus, vagina, rectum
<p>Vulva</p> <ul style="list-style-type: none"> ▪ dryness and labia adhesions ▪ dermatoses ▪ susceptibility to the injury ▪ erythema ▪ loss of pubic hair

human studies are scarce and their results inconclusive. The influence of estrogens on connective tissue may be dependent on the regulation of collagen metabolism (Table 4). Estrogens not only stimulate biosynthesis of the fibrillar collagens but also increase synthesis, secretion and activity of metalloproteinases. These enzymes are able to degrade numerous connective tissue components including collagens and play crucial role in connective tissue remodelling during wound healing.

Studies on women with stress urinary incontinence showed diminished fibrillar collagen content in skin, vaginal epithelium stroma, pubocervical fascia and round ligaments [10-12]. Estrogen replacement therapy (ERT) increase skin total collagen content by 48%

Table 3. The influence of estrogens on the function of urinary bladder and urethra.

Hypoestrogenism	Estrogen replacement therapy
<ul style="list-style-type: none"> ▪ elevated volume of postvoid residual urine ▪ decreased cystometric capacity of the bladder ▪ decrease of maximal detrusor pressure during micturition ▪ decrease of urine flow during micturition ▪ urethral syndrome ▪ dysuric symptoms ▪ urinary incontinence ▪ urinary tract infections 	<ul style="list-style-type: none"> ▪ Modification of the density of muscarinic receptors in detrusor muscle ▪ decreased influx of calcium ions to bladder muscle cells ▪ decrease of amplitude and frequency of spontaneous bladder contractions ▪ increase of the threshold of micturition reflex ▪ urethral smear – increase of kariopyknotic and maturation indices ▪ increase of urethral closure pressure by 33% ▪ sensitization of α-adrenergic receptors in smooth muscle cells of external urethral sphincter ▪ increase of blood flow in periurethral plexuses ▪ stimulation of collagen biosynthesis

when compared to control menopausal women. Also the rate of skin collagen loss is lower in women on ERT [13]. Jackson *et al.* [11] showed that ERT induce metabolism of vaginal connective tissue only after 6-month use. Simultaneously, the total collagen content decrease mainly due to induction of activity of collagenolytic enzymes. The author concluded that possibly long term ERT is able to increase collagen content in the vaginal wall.

The clinical value of estrogen administration in urogynecology

Profound decrease in estrogen concentration associated with menopause has been considered as a factor responsible for the increasing urinary incontinence prevalence in aging women. As it was mentioned before estrogens have been shown to influence in positive way several parameters responsible for proper functioning of female continence mechanism such as increase in urethral closure pressure [14], increase in urethral blood flow [15], increase of α -adrenergic receptor sensitivity [16], restoration of cellular lining of both the vagina and urethra [17].

Data from these experimental studies and clinical observations from few nonrandomized trials caused inclusion of both systemic and vaginal estrogens to medical management of urinary incontinence in post-

Table 4. The influence of estrogens on collagen metabolism

Hypoestrogenism	Estrogen replacement therapy
<ul style="list-style-type: none"> ▪ decrease of collagen content in urogenital diaphragm and periurethral connective tissue ▪ close correlation between collagen content and urethral closure pressure ▪ hydroxyproline depletion by 40% in women with stress urinary incontinence 	<ul style="list-style-type: none"> ▪ activation of the expression of collagen genes ▪ stimulation of the fibrillar collagens synthesis in pelvic floor fascias ▪ increase of periurethral tissue collagen biosynthesis

menopausal women. This attitude was further supported by the results of review that showed subjective improvement (64-75%) of SUI symptoms after estrogen administration [14]. In 2003 Moehrer *et al.* [18] published study based on Cochrane database compiled from twenty eight trials which included 2926 women. Analyzed trials used varying types of estrogen, dose, duration of treatment and length of follow-up. Sample sizes ranged from 16 to 1525 subjects. In the 15 trials that compared estrogen with placebo, 374 women received estrogen and 344 placebo. Subjective impression of cure was higher amongst those treated with estrogen for all categories of incontinence (36/101, 36% versus 20/96, 21%; RR for cure 1.61, 95% CI: 1.04 to 2.49). When subjective cure and improvement were considered together, higher cure and improvement rates were shown for both urge (35/61, 57% versus 16/58, 28% on placebo) and stress (46/107, 43% versus 29/109, 27%) incontinence. For women with urge incontinence, the chance of cure or improvement was approximately a quarter higher than in women with stress incontinence. Taking all trials together, the data suggested that about 50% of women treated with estrogen were cured or improved compared with about 25% on placebo. The final conclusion was that estrogen treatment can improve or cure incontinence and the evidence suggests that this is more likely with urge incontinence. However, the combined estrogen and progesterone appeared to reduce the likelihood of cure or improvement. Because of lack of data authors were not able to address reliably other aspects of estrogen therapy such as estrogen type, dose and route of administration. Finally authors of this review stated that the risk of endometrial and breast cancer after long-term use suggests that estrogen administration in order to treat incontinence should be used for limited periods, especially in women with an intact uterus. Moreover, Osamu *et al.* [19] clearly demonstrated that there are significant interactions between estrogen and the female lower urinary tract because the combination of estriol (E3) and pelvic floor muscle exercises (PFME) was significantly more effective three months

after the commencement of therapy than was PFME alone. The effect of E3 persisted for as long as 18 months in the mild urinary incontinence groups. The finding that the combined effect of E3 could be detected for up to 12 months is important because it indicates the need to use estrogen with PFME for at least one year in stress incontinence.

On the other hand data from the randomized, double-blinded, placebo-controlled trials clearly show that estrogen should not be used in the prevention or relief of stress and urge incontinence. Indeed, in both the Heart Estrogen and Progestin Replacement Study (HERS) [20] and Women's Health Initiative (WHI) authors demonstrated a statistically significant increase of the risk of developing incontinence or a worsening of incontinence after the initiation of estrogen [21]. Among the 1 525 women who reported incontinence at baseline, daily intake of 0.625 mg conjugated estrogen (CEE) and 2.5 mg of medoxyprogesterone acetate (MPA) caused worsening in urinary incontinence episodes (the odds ratio for worsening incontinence was 1.5 among women who reported incontinence at the baseline). In a follow-up study of women in HERS who were continent at baseline, the odds ratio for developing new stress incontinence was 1.7 and urge incontinence was 1.5. Four years of treatment with hormone therapy caused an excess risk of 12% for weekly urge incontinence and 16% for weekly stress incontinence [22]. Clinical messages from the WHI study were similar. After 1 year, standard doses of estrogen (0.625 mg) with or without MPA increased the incidence of symptoms of stress and urge incontinence. The risk was greatest for stress incontinence (odds ratio for CEE-MPA was 1.8 and for CEE alone was 2.2). CEE-MPA had no significant effect on the development of urge incontinence but CEE alone increased the odds of new urge incontinence by 1.3. Women who reported incontinence at the start of the study had a 1.4 odds of worsening incontinence on CEE-MPA and 1.5 on CEE alone compared to placebo, however there was no significant increase in urinary incontinence in women aged <60 years [21]. Moreover, 12 clinical trials analyzed recently by Waetjen and Dwyer revealed that estrogen given to postmenopausal women had either negative or neutral effect on urinary incontinence symptoms [23]. It is unclear why the results of hormone therapy in terms of various types of female UI are so different and even conflicting. Alpha and beta estrogen receptors have been identified throughout the urogenital tract, including the bladder mucosa, trigone, urethra, and vaginal mucosa [24].

These receptors were also identified in almost all structures responsible for proper support of the pelvic organs [25,26]. This is an indirect evidence that estrogen may have an important role in proper functioning

of female urinary continence mechanism. Taking this into account it was surprising that in number of studies administration of estrogen resulted in a reduction of the total collagen concentration, a decrease in the cross-linking of collagen, and an increase in markers of collagen turnover in the periurethral tissues of incontinent women [27,28]. However, we have to remember that the balance of the two types of ER may change during transition from pre- to post-menopause, with ER- α predominating over ER- β in older group [29]. Moreover, ER- α density varies with estrogen use while ER- β does not, and this finding is of critical importance since ER- β is a dominating type of ER in urogenital tract before menopause, while in late menopause only α subtype is present [30]. Since in HERS study the average age of patients treated was 66 years and also 2/3 of the women from WHI were in late menopause it is not surprising that estrogen could simply not act properly on urogenital tract since the lack of ER-beta which is present in premenopausal women.

In animal studies estrogen administration changed the ratio of collagen to smooth muscle fibers and this was associated with higher bladder contractility and resting tension [31,32]. Other changes seen with estrogen treatment include increased peri-urethral vascularity. In rats and monkeys, estrogen increased the loose, vascular connective tissue component of the urethra, which could increase the coaptation of urethral wall [33,34]. Finally, estrogen has a neuromodulation function, increasing sympathetic nerve density (which physiologically promote urine storage) in the pelvis and regulating neurotrophins but how this may affect continence is unknown [35].

To summarize, it seems that estrogen is not effective and could actually be detrimental in women already presenting symptoms of stress urinary incontinence whereas it appears that estrogen is beneficial for postmenopausal women with urgency and urge urinary incontinence [36,37]. Taking into account messages from the WHI study which found not significant increase in urinary incontinence in women aged <60 years while on hormone treatment it is reasonable to speculate that starting estrogen replacement soon after the menopause may be effective in preventing, or at least delaying the onset of stress incontinence.

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