Menopause, hormone treatment and urinary incontinence at midlife.

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Title

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Abstract

Whether there is any association between urinary incontinence and menopause is the subject of debate, partly due to the fact it is difficult to tell the difference between the effects of menopause and those of ageing. For some time it was hoped that hormonal treatment for menopause would be beneficial for urinary incontinence because there are hormonal receptors in the urinary tract. The goal of this survey of current knowledge on the subject is to explore thoroughly the relationship between menopause and urinary incontinence .

Our study is based on a review of the literature dealing with the epidemiology of urinary incontinence in women aged between 45 and 60, and the effects of hormonal treatment with respect to the symptoms of involuntary loss of urine.

Analysis of the epidemiological data drawn from large cohorts shows that on the one hand, the menopause has little if any impact on the risk of urinary incontinence, and on the other hand that the effects of œstrogen medication on urinary incontinence vary according to how it is administered and the type of incontinence. The effect of oral hormone treatments for menopause is rather negative with respect to stress incontinence. Vaginal treatment appears to be beneficial for overactive bladder symptoms.

Key-words: *Urinary Incontinence, Stress Urinary Incontinence, Urge Incontinence, Overactive bladder, Menopause, Hormone therapy,* Œ*strogen, Epidemiology.*

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1. Introduction

The menopause is a universal physiological event related with the drop in ovarian hormone secretions (œstrogens and progestin) that occurs as the stock of ovarian follicules is depleted. Menopause is diagnosed when menstruation has stopped for 12 successive months, and the average age at which it occurs is between 47 and 51 [1,2]. Its clinical expression varies very considerably between socio-cultural groups and individuals [3]. These variations depend on many factors, such as women's social status, their nutrition, life style (smoking) and weight, not forgetting genetic factors [3]. It is difficult to draw the distinction between the effects of menopause and those of ageing. In addition to the menopausal "syndrome" itself, which mainly comprises vasomotor symptoms and vaginal dryness, urinary symptoms including incontinence (UI) have been attributed to menopause. The hormonal dependence of the genital tract tissues has been evoked in order to explain the appearance of these female low urinary tract symptoms (FLUTS) at the menopause. Œstrogen receptors have been found not only in the pelvic floor muscles but also in the uro-genital ligaments and detrusor muscle cells along with the connective tissues and all the fascias that maintain a stable relationship between the various organs [2].

Urinary incontinence can be defined as "the complaint of any involuntary leakage of urine" [4]. The standard classification gives three main types of UI: Stress Urinary Incontinence (SUI), Urge Urinary Incontinence (UUI) and Mixed Urinary Incontinence (MUI). Stress urinary incontinence is characterised by involuntary loss of urine without any previous feeling of a need to void, which takes place on the occasion of a physical stress (cough, lifting something heavy, or any other physical activity). Urge urinary incontinence (or urgent need to void) is characterised by involuntary loss of urine preceded by an urgent and irresistible need to void resulting in uncontrollable leakage of urine. Mixed urinary incontinence is the association in variable proportions of SUI and UUI.

UI may be experienced simply as a nuisance or as a real handicap [5,6]. Women frequently present the symptoms of UI, but the estimates for its prevalence in the general population vary widely, from 8 to 30 %. This variability is due not only to the very heterogeneous nature of the populations studied but also to the varying definitions of UI used in the studies.

Many different factors are associated with an increased risk of UI [7]. The main of these are ageing, pregnancy, childbirth, past history of pelvic and perineal surgery, obesity, and chronic pathologies (diabetes, cognitive problems, etc.). There is more debate about the roles of menopause and hormone replacement therapy (HRT) [8,9]. As mentioned above, it is difficult

to differentiate between the role of ageing and that of the menopause, and equally to differentiate the true role of menopause from that of treatments instigated at the time of menopause, such as HRT.

The relationship postulated between UI and hormone deficiencies induced by menopause is based mainly on "physiological" data, i.e. the existence of (œstrogen and progestin) hormonal receptors in the epithelial tissues of bladder, urethra and trigone and also in the vagina, uterosacral ligaments, levator ani and puborectal muscles [10]. The other argument supporting this relation is clinical observation of an increase in the prevalence of overactive bladder (OAB) syndrome after the menopause. The lack of œstrogens could contribute in various ways to other urinary symptoms that arise: œstrogens play a role in (i) the increase in epithelial cellular trophicity in the vagina, urethra and bladder (ii) the increase in peri-urethral vascularisation (an important factor for regulation of closing pressure), (iii) the increase in maximum closing pressure and (iv) the increase in concentration and sensitivity of α-adrenergic receptors with modification of the α-adrenergic receptors/β-adrenergic receptor ratio in favour of the α-adrenergic receptors [11-13]. Progestin receptors are also to be found in the entire female genital tract, although in less constant fashion than œstrogen receptors. Progestin appears to have a detrimental effect on continence, by reducing muscle tone of bladder and urethra [10].

The aim of our review is to analyse the data in the literature with respect to the relationship between menopause and UI. We present the main epidemiological data dealing with the relationship between prevalence, incidence and remission of UI, and the menopause. We then try to supply answers to the two main questions raised by this relationship: What consequences do hormonal changes at the menopause have on UI symptoms? What consequences do hormonal treatments have on continence?

2. **Methods:**

A review of the literature was carried out by consulting the *Medline* database entries between January 2000 and June 2012. Articles were selected by cross-referencing the following keywords: "*urinary incontinence, stress urinary incontinence, urge incontinence, overactive bladder, menopause, œstrogen therapy"*. In this selection priority was given to meta-analyses, literature reviews, randomised controlled trials and cohort studies. The level of evidence (LE)

scale proposed by the *Oxford Centre for Evidence-Based Medicine (www.cebm.net)* was used to class the articles selected.

The terminology used complies with *International Continence Society* (ICS) and *International UroGynecological Association* (IUGA) recommendations.

3. **Results**

3.1. Study selection

Among the 488 articles initially selected during the *Medline* search, 29 articles were finally retained, including 3 meta-analyses, 4 literature reviews, 5 randomised controlled trials and 12 cohort studies. Figure 1 gives details on this selection of articles.

3.2. Prevalence or incidence of UI according to age

The prevalence of urinary incontinence is proportional to age. The distribution of the various types of UI changes with age.Several articles report a peak in the prevalence of SUI at midlife (LE3). The majority of cases before the age of 50 are SUI, but after that age it represents a minority [14]. After 60 it is mixed UI that predominates. The prevalence of UI at the time of menopause varies from 8 to 27 % depending on the population studied and the definition used for UI [14-17] (LE2).

Only a few cohort studies specifically address the menopause period (45-60 years). Mac Grother *et al.* report an annual incidence of UI of 8% in a population of 108 women aged between 40 and 59 in the general population [16] (LE3). Two other cohorts of women under the age of 60 found annual incidence rates at 4 and 5 % [15, 17] (LE3). In another cohort of 2860 femmes between 40 and 60, the authors report an annual incidence rate of 6% [18] (LE3). A longitudinal study of a cohort of nurses aged 36 to 55 by Townsend *et al.* found an annual incidence of 7% [19] (LE3).

There is considerable disparity between the cohort studies concerning the annual rate of remission. On the one hand Hagglund [17], Samuelsson [20], and Townsend [19] report annual remission rates for UI of 4, 6, and 7% respectively (LE3). On another hand other authors report higher annual remission rates, at 25 to 29% [16, 18] (LE3). These results can be explained in part by the definition of remission of UI depending on the studies: complete disappearance or lessening of the severity of UI symptoms.

3.3. Prevalence or incidence of UI according to menopausal status

The American prospective cohort *Study of Women's Health Across the Nation (SWAN)* followed 1529 women, without any UI symptoms at inclusion, annually for 6 years. The women were classed according to their hormonal status at the end of the study as follows: pre-menopause, early peri-menopause (irregular menses), late peri-menopause (3 to 11 months amenorrhoea), and post-menopause (over 12 months amenorrhoea). The peri-menopause period is associated with an increased risk of UI for all types of UI together (OR= 1.52 [95% CI: 1.12–2.05] in late peri-menopause) but this association disappears post-menopause (0.88 [0.63-1.23]). Analysis by the type of UI shows that this association with the peri-menopause above all concerns UUI (2.12 [1.26-3.56] in late peri-menopause) while the association is non significant for SUI (1.24 [0.75-2.05] in late peri-menopause). Analysis of frequent UI alone (at least one episode of UI a week) does not show any association with early peri-menopause (0.99 [0.60-1.63]), late peri-menopause (1.14 [0.51-2.54]), or post-menopause (1.10 [0.46-2.64]) (LE2) [21]. In another study covering 2415 women from the SWAN cohort who were incontinent (at least one episode of UI per month) at inclusion, Waetjen reports that the worsening of UI symptoms observed after the menopause is not attributable to the menopause itself [22] but to an increase in weight. The menopause appears to be associated with an increase in weight and this would explain the increase in the prevalence of UI (LE2).

The study by Sherburn *et al.* of the Australian cohort of 1897 femmes, *The Melbourne Women's Midlife Health Project,* addressed the impact of the menopause on UI symptoms. Simultaneous cross-sectional and longitudinal analysis of the data did not reveal any statistical relationship between UI and menopause (LE3). In the longitudinal analysis of 438 women from the same cohort who were followed for 7 years the menopause was not associated with any increase in the incidence of UI as a whole (LE3) [15].

The results obtained by another longitudianl study, the *National Survey of Health and Development (NSHD)* concerning 1211 women between 48 and 54 years of age did not find any association between menopause and UUI (LE3). SUI alone was associated with the hormonal status, since in this study the peri-menopause was associated with an increased prevalence of urine leakage symptoms due to stress, as compared with the group of post-menopausal women (OR= 1, 39 [1, 4-1, 7]) (LE3). This study, in which it is not possible to distinguish clearly between the effects of age and those of menopause because there is no comparison of the incidence rates between the different groups, nevertheless appears to reveal

an effect of ageing independent of that of the menopause with respect to the occurrence of UUI or SUI (LE3) [23].

A large Chinese cross-sectional study of nearly 20 000 women aged 20 to 99 shows an association between SUI and menopause (OR= 1, 26 [1, 04-1, 52]), even when age is taken into account as a risk factor (LE4) [24].

3.4. Prevalence or incidence of UI according to hormone levels

A recent cohort study looked at the effect of changes in œstrogen concentrations on urinary symptoms during the transition to menopause. A big drop in œstrogen levels is associated in significant fashion with an improvement in UI symptoms (LE2) [25]. Moreover, analysis of the annual fluctuation in endogenous œstrogen levels during the menopausal period using the data from *SWAN* did not find any association with the onset of UI or worsening of UI symptoms (LE2) [26]. A Swedish cohort study of 6917 women aged between 50 and 59 even found a positive association between a high œstradiol level and UI (LE2) [27].

3.5. Prevalence or incidence of UI depending on menopause hormonal treatment

3.5.1. Data obtained from random studies of women treated for urinary symptoms

A meta-analysis based on eleven randomised studies of the effects of œstrogen (versus placebo) on overactive bladder symptoms found a significant association between œstrogen treatments and an improvement in the urinary symptoms: less pollakiuria and nocturia, fewer episodes of UUI and urine leaks, improvement in the latence of the first urge to void and increase in bladder capacity (LE1) [28]. However the effects vary according to the mode of administration of the œstrogens. Local application (vaginal or intravesical) is associated in significant fashion with an improvement in all the urinary symptoms (pollakiuria, nocturia, UUI, bladder capacity). Systemic administration results in only partial improvement of these symptoms, and statistically is associated only with a drop in the number of episodes of incontinence and later perception of the first urge to void.

A review of the literature covering several randomised trials (comparisons between different protocols for œstrogen treatment or versus placebo) confirms the advantage of vaginal treatments in case of post-menopausal lower urinary tract symptoms, especially in the presence of vaginal atrophy (LE2) [11]. The findings of recent studies of the effect of

œstrogens in association with anti-muscarini agents did not agree. A controlled study of 229 femmes presenting an overactive detrusor did not show any benefit for topical vaginal œstrogen therapy associated with tolterodine versus tolterodine alone for overactive bladder symptoms (LE2) [29]. Another randomised controlled trial in 80 women with overactive bladder syndrome, also comparing the effect of topical vaginal œstrogen therapy associated with tolterodine with that of tolterodine alone, found a significant improvement of objective parameters and quality of life when œstrogens were associated with tolterodine (LE2) [30]. Finally, a recent randomised trial comparing the efficiency of topical vaginal œstrogen therapy with that of oxybutynin for the treatment of overactive bladder syndrome found that the two products were similar in terms of efficiency (LE2) [31].

A review of the literature covering eight controlled studies and 14 prospective non-controlled studies concluded that œstrogen treatment is not efficient for SUI (LE2) [32].

3.5.2. Data resulting from secondary analyses of randomised trials in the general population

Among the post-menopausal women enrolled in the *Womens' Health Initiative study* (WHI), HRT significantly increased the incident risk at one year of all types of UI (SUI, UUI, MUI) in women who were continent at the time they were included (LE2). This effect of HRT is particularly distinct for SUI and less so if at all for UUI [33]. In women taking oral œstrogens and progestin, the relative risk of *de novo* UI is 1.87 [1.61-2.18] for SUI, 1.15 [0.99-1.34] for UUI and 1.49 [1.10-2.01] for MUI. The results are similar for women taking œstrogen alone: 2.15 [1.77-2.62], 1.32 [1.10-1.58], and 1.79 [1.26-2.53] respectively. In women who were incontinent when included, HRT slightly increased the quantity lost (1.20 [1.06-1.36] when treated using œstrogen and progestin and 1.59 [1.9-1.82] when treated with œstrogen alone), and the frequency of leaks (1.36 [1.28-1.49] and 1.47 [1.35-1.61] respectively) [33].

Steineauer *et al.* carried out a subsidiary analysis of the *Heart Estrogen/Progestin Replacement Study* (a double-blind randomised study assessing the effect of HRT for prevention of cardiovascular risks) concerning patients with no UI at inclusion [34]. A significant relationship between HRT and the onset of both UUI and SUI was found during the first four months of treatment. This detrimental effect of HRT persisted throughout the 4 years of the study, with a cumulated additional risk of 12% and 16 % respectively for UUI and SUI compared with treatment by placebo (LE2).

The results of these studies were included and confirmed in the Cochrane Database [35] meta-analysis which covered a total of 19 313 incontinent women among whom 9417 were treated by œstrogens, in 33 studies (16 of which addressed specifically SUI). There was no analysis by type of UI. A worsening of UI symptoms was found when HRT was taken systemically (RR= 1.32 [1.17-1.42]) (LE1). However, topical vaginal œstrogen therapy contributed towards remission of UI by improving both the episodes of urge urinary incontinence (0.74 [0.64-086]) and pollakiuria (LE1).

3.5.3. Data obtained from cohort studies

The data of the *Nurses' Health Study* addressing the impact of HRT on UI in a cohort of nurses aged between 30 and 55 at the time of inclusion were analysed by Grodstein *et al.* [36]. The occurrence of incident UI was associated in significant fashion with systemic hormone therapy whatever the type of HRT and mode of administration: oral œstrogen (RR= 1.54 [1.44-1.65]), transdermal œstrogen (1.68 [1.41-2.00]), oral œstrogen and progestin (1.34 [1.24-1.44]) and transdermal œstrogen and progestin therapies (1.46 [1.16-1.84]) (LE3). The overall risk of UI remained low however, with an annual incidence of 1.6%, and the effects of HRT disappeared when treatment ceased.

A recent cohort study of post-menopausal women found an association between UI symptoms and duration of œstrogen treatment. Prolonged oral œstrogen therapy (5 years or more) is associated with a worsening of leakage symptoms (OR= 3.99 [1.21-13.1]) and also an increase in the frequency of handicapping UI (3.97 [1.02-15.4]) [37] (LE3).

3.5.4. Data obtained from studies concerning intermediate markers

Certain older studies report that the use of oral œstrogens appears to increase the urethral closing pressure and could thus improve SUI symptoms in 65 to 70% of women [38] (LE5). Two randomised controlled trials concerning the oral route versus placebo to treat UI and including 83 and 67 post-menopausal women were unable to demonstrate any effect of œstrogens with respect to urodynamic parameters or urinary symptoms, whether in terms of objective measurements (pad-test, cystometrography, prolifometry) or in terms of subjective measurements (assessed by approved quality of life questionnaires) [39] (LE2).

3.5.5. Influence of hormonal treatment after surgery for SUI

Certain studies looked at the impact of œstrogen therapy when surgery is used for SUI. A prospective randomised study comparing the effects of adjuvant topical vaginal œstradiol or not for six months immediately after surgical correction of SUI using a sub-urethral tape (TVT-O) in 183 post-menopausal patient, found that pollakiuria (2 vs. 11 %, p=0.02) and urge urinary incontinence (3 vs. 12 %, p= 0.01) alone were improved by hormone therapy (LE2) [40]. The objective parameters of the urodynamic tests remained unchanged in both groups (LE2). In a randomised controlled trial Zullo *et al.* found exactly the same results with urge urinary incontinence alone being improved by topical vaginal œstrogen therapy (LE2) [41]. No study of the long-term advantages of œstrogen after installation of a sub-urethral tape was found.

4. Discussion

The results of our review concerning the link between menopause and UI do not all agree, but this overview shows that the menopause has little if any impact on the risk of UI in general, when confounding factors such as age or changes in weight are taken into account. It appears that SUI decreases after the menopause while UUI or mixed UI increase at this time. Oral HRT has a rather detrimental effect on stress urinary incontinence, by doubling the risk of *de novo* SUI. Concerning UUI, HRT has less of an effect, which is variable according to the population in question and the type of treatment. Topical vaginal œstrogen therapy is the only treatment that seems to have a really beneficial effect on urge urinary incontinence or overactive bladder symptoms.

Most of these results are drawn from longitudinal analyses of large cohorts enabling a distinction to be drawn between the effect of age and that of the menopause. Longitudinal studies are the only way to examine the timing, and consequently any cause and effect relationship between events. Cross-sectional studies cannot assess time-dependent variables such as age, weight and menopausal status. Nevertheless, the large cohort studies included in this review present several problems. For example, the definition of UI is not identical in all the studies because follow-up of the cohorts often started prior to the harmonisation of the terminologies proposed by ICS and IUGA. The frequency of UI as a "functional complaint" depends on the tools used. Moreover, few of the studies draw a distinction between the various types of UI (SUI, UUI, MUI), their frequency or their severity. Finally in this type of

cohort, the lack of any overall assessment of incontinence risk factors (because the studies were not designed initially to study this problem specifically) can result in confounding biases.

Part of the results of this review is based on secondary analyses of randomised trials in which the main objective was not to study UI but instead the cardiovascular morbidity of HRT. So the level of evidence contributed by these secondary analyses is lower.

Certain pathophysiological data would tend to indicate a worsening of UI due to lack of œstrogen. However, in contradiction with this postulate, the epidemiological data obtained with the cohorts shows that the menopause has little if any effect on urinary symptoms. The results of several large randomised trials in the general population reveal an aggravation of UI in case of systemic HRT. This detrimental effect of HRT needs to be seen in the light of what is observed during pregnancy, when an increase in the prevalence of UI is observed [42]. This greater prevalence of UI during pregnancy could be explained by the increase in œstrogen concentrations.

Topical vaginal œstrogen therapy alone appears to have a beneficial effect on overactive bladder symptoms. This effect could be explained by the improvement in terms of vaginal dryness and a drop in recurrent urinary infections [8,11]. The learned societies do not recommend the use of œstrogens (whether or not associated with progesterone) for the treatment of UI. However, in case of overactive bladder symptoms in a post-menopausal woman, topical vaginal treatment may be proposed [43,44].

5. Conclusion

Female urinary incontinence is a complex and dynamic phenomenon, related with age and a many other factors that can change with time. In order to gain greater insight, longitudinal studies are necessary, with several years or even decades of follow-up in order to clarify its evolution and risk factors.

The onset and/or worsening of UI at the menopause that is expected on the basis of physiological observations is not confirmed by the results of most of the epidemiological studies that mostly cover a large number of women followed up over many years. Moreover, correction of the lack of œstrogen by HRT gives rise to paradoxical results that depend on the type of UI and mode of administration. Systemic œstrogen therapy results in an increase in UI

symptoms and SUI in particular. Topical vaginal administration appears to be the most beneficial by improving overactive bladder symptoms.

6. References

[1]. Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. Hum Reprod Update 2005;11:495-512.

[2]. Nelson HD. Menopause. Lancet 2008;371:760-70.

[3]. Delanoe D, Hajri S, Bachelot A, Mahfoudh Draoui D, Hassoun D, Marsicano E, et al. Class, gender and culture in the experience of menopause. A comparative survey in Tunisia and France. Soc Sci Med; 2012;75:401-9.

[4]. 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. Neurourol Urodyn 2010;29:4-20.

[5]. Bartoli S, Aguzzi G, Tarricone R. Impact on quality of life of urinary incontinence and overactive bladder: a systematic literature review. Urology 2010;75:491-500.

[6]. Saadoun K, Ringa V, Fritel X, Varnoux N, Zins M, Breart, G. Negative impact of urinary incontinence on quality of life, a cross-sectional study among women aged 49-61 years enrolled in the GAZEL cohort. Neurourol Urodyn 2006;25:696-702.

[7]. Menezes M, Pereira M, Hextall A. Predictors of female urinary incontinence at midlife and beyond. Maturitas 2009;65:167-71.

[8]. Robinson D, Cardozo L. Estrogens and the lower urinary tract. Neurourol Urodyn 2011;30:754-7.

[9]. Berecki-Gisolf, J, Begum, N, and Dobson, AJ, Symptoms reported by women in midlife: menopausal transition or aging? Menopause 2009;16:1021-9.

[10]. Quinn SD, Domoney C. The effects of hormones on urinary incontinence in postmenopausal women. Climacteric 2009;12:106-13.

[11]. Ewies AA, Alfhaily F. Topical vaginal estrogen therapy in managing postmenopausal urinary symptoms: a reality or a gimmick? Climacteric 2010;13:405-18.

[12]. Kobata SA, Girao MJ, Baracat EC, Kajikawa M, Di Bella V, Sartori MG, et al. Estrogen therapy influence on periurethral vessels in postmenopausal incontinent women using Dopplervelocimetry analysis. Maturitas 2008;61:243-7.

[13]. Jarmy-Di Bella ZI, Girao MJ, Di Bella V, Sartori MG, Szejnfeld J, Baracat EC, et al. Hormonal influence on periurethral vessels in postmenopausal incontinent women using Doppler velocimetry analysis. Maturitas 2007;56:297-302.

[14]. Hannestad YS, Rortveit G, Sandvik,H, Hunskaar S. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. J Clin Epidemiol 2000;53:1150-7.

[15]. Sherburn M, Guthrie JR, Dudley EC, O'Connell HE, Dennerstein L. Is incontinence associated with menopause? Obstet Gynecol 2001;98:628-33.

[16]. McGrother CW, Donaldson MM, Shaw C, Matthews RJ, Hayward TA, Dallosso HM, et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int 2004;93:763-9.

[17]. Hagglund D, Walker-Engstrom ML, Larsson G, Leppert J. Changes in urinary incontinence and quality of life after four years. A population-based study of women aged 22-50 years. Scand J Prim Health Care 2004;22:112-7.

[18]. Moller LA, Lose G, Jorgensen T. Incidence and remission rates of lower urinary tract symptoms at one year in women aged 40-60: longitudinal study. BMJ 2000;320:1429-32.

[19]. Townsend MK, Danforth KN, Lifford KL, Rosner B, Curhan GC, Resnick NM, et al. Incidence and remission of urinary incontinence in middle-aged women. Am J Obstet Gynecol 2007;197:167e1-5.

[20]. Samuelsson EC, Victor FT, Svardsudd KF. Five-year incidence and remission rates of female urinary incontinence in a Swedish population less than 65 years old. Am J Obstet Gynecol 2000;183:568-74.

[21]. Waetjen LE, Ye J, Feng WY, Johnson WO, Greendale GA, Sampselle CM, et al. Association between menopausal transition stages and developing urinary incontinence. Obstet Gynecol 2009;114:989-98.

[22]. Waetjen LE, Feng WY, Ye J, Johnson WO, Greendale GA, Sampselle CM, et al. Factors associated with worsening and improving urinary incontinence across the menopausal transition.Obstet Gynecol 2008;111:667-77.

[23]. Mishra GD, Cardozo L, Kuh D. Menopausal transition and the risk of urinary incontinence: results from a British prospective cohort. BJU Int 2010;106:1170-5.
[24]. Zhu L, Lang J, Liu C, Han S, Huang J, Li X. The epidemiological study of women with urinary incontinence and risk factors for stress urinary incontinence in China. Menopause 2009;16:831-6.
[25]. 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;112:1045-52.
[26]. Waetjen LE, Johnson WO, Xing G, Feng WY, Greendale GA, and Gold EB. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. Menopause 2011; 8:1283-90.
[27]. 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;88:927-32.
[28]. 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;83:892-7.
[29]. Serati, M Salvatore S, Uccella S, Cardozo L, and Bolis P. Is there a synergistic effect of topical œstrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity? Eur Urol 2009;55:713-9.
[30]. 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.
[31]. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. Menopause 2011;18:962-6.
[32]. Sultana CJ, Walters MD. Estrogen and urinary incontinence in women. Maturitas 1994;20:129-38.
[33]. 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;293:935-48.
[34]. Steinauer JE, Waetjen LE, Vittinghoff E, Subak LL, Hulley SB, Grady D, et al. Postmenopausal hormone therapy: does it cause incontinence? Obstet Gynecol 2005;106:940-5.
[35]. Cody JD, Richardson K, Moehrer B, Hextall A, Glazener CM. Œstrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev 2009:CD001405.
[36]. Grodstein F, Lifford K, Resnick NM, Curhan GC. Postmenopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol 2004;103:254-60.
[37]. Northington GM, de Vries HF, Bogner HR. Self-reported estrogen use and newly incident urinary incontinence among postmenopausal community-dwelling women. Menopause 2012;19:290-5.
[38]. Rud T. Urethral pressure profile in continent women from childhood to old age. Acta Obstet Gynecol Scand 1980;59:331-5.
[39]. Jackson S, Shepherd A, Brookes S, Abrams P. The effect of œstrogen supplementation on post-menopausal urinary stress incontinence: a double-blind placebo-controlled trial. Br J Obstet Gynaecol 1999;106:711-8.
[40]. Liapis A, Bakas P, Georgantopoulou C, Creatsas G. The use of œstradiol therapy in postmenopausal women after TVT-O anti-incontinence surgery. Maturitas 2010;66:101-6.
[41]. Zullo MA, Plotti F, Calcagno M, Palaia I, Muzii L, Manci N, et al. Vaginal estrogen therapy and overactive bladder symptoms in postmenopausal patients after a tension-free vaginal tape procedure: a randomized clinical trial. Menopause 2005;12:421-7.
[42]. Fritel X, Ringa V, Quiboeuf E, Fauconnier A. Female urinary incontinence, from pregnancy to menopause, a review of epidemiologic and pathophysiologic findings. Acta Obstet Gynecol Scand 2012;91:901-10
[43]. Fritel X, Fauconnier A, Bader G, Cosson M, Debodinance P, Deffieux X, et al. Diagnosis and management of adult female stress urinary incontinence: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol 2010;151:14-9.
[44]. Thuroff JW, Abrams P, Andersson KE, Artibani W, Chapple CR, Drake MJ, et al. EAU guidelines on urinary incontinence. Eur Urol 2011;59:387-400.