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POST-PROSTATECTOMY AND ACQUIRED VOIDING DYSFUNCTION (V TSE, SECTION EDITOR)

The Role of Estrogen Status in the Causation of Female Lower Urinary Tract and Pelvic Floor Dysfunction

Sum Sum Lo[1] · Ee Jean Lim[1] · Lay Guat Ng[1] · Tricia Li Chuen Kuo[1,2]

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Abstract

Purpose of Review In this review, we aim to examine current literature focused on the effects of estrogen in causing conditions such as urinary incontinence, overactive bladder, recurrent urinary tract infections, pelvic organ prolapse, and anorectal dysfunction.

Recent Findings Small studies have confirmed the role of local estrogen therapy in the treatment of overactive bladder and recurrent urinary tract infection.

Summary Although well recognized that the female lower urinary tract and pelvic floor are estrogen responsive, there is paucity in the role of estrogen status in causing such conditions.

Keywords Estrogen · Female lower urinary tract · Pelvic floor dysfunction · Urinary incontinence · Overactive bladder · Anorectal dysfunction · Sexual dysfunction

Introduction

Dysfunction of the female pelvic floor encompasses a broad spectrum of interrelated conditions, including urinary incontinence (UI), overactive bladder (OAB), recurrent urinary tract infections (rUTIs), pelvic organ prolapse (POP), and anorectal dysfunction. Epidemiological studies have demonstrated that menopause is a major risk factor for the development of pelvic floor disorders [1••]. Currently, up to 16% of women experience urinary incontinence, with 9% experiencing fecal incontinence and 3% with pelvic organ prolapse [2]. It is projected that over the next three decades, the growth in demand for services for female pelvic floor disorders will increase double the rate of growth of the same population [3].

It is well recognized that the lower urinary tract, surrounding pelvic organs and urogenital tissue, is estrogen sensitive [4–6]. Current literature tends to focus on the outcomes of hormone replacement therapy (HRT). However, the role of estrogen status in the causation of such female pelvic floor dysfunction remains to be elucidated. This article aims to provide a review of recent literature regarding the role of estrogen status in association with the dysfunction of the female lower urinary tract and pelvic floor.

Pathophysiology: Role of Estrogen in Female Lower Urinary Tract

Estrogen plays an important role in the function of the lower urinary tract all throughout adult life. Estrogen receptors (ER) are expressed in the lower urinary tract and expressed in the squamous epithelium of the urethra, vagina, and trigone of the bladder [7]. The musculature of the pelvic floor, pubococcygeus,

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✉ Tricia Li Chuen Kuo
tricia.kuo.l.c@singhealth.com.sg

Sum Sum Lo
losumsum@gmail.com

Ee Jean Lim
Eejean.lim@mohh.com.sg

Lay Guat Ng
ng.lay.guat@singhealth.com.sg

[1] Department of Urology, Singapore General Hospital, 20 College Road, Academia Level 5, Bukit Merah, 169856, Singapore

[2] Department of Urology, Sengkang General Hospital, Sengkang, Singapore

and uterosacral ligaments have also been shown to be estrogen sensitive, although with decreased expression of ER receptors in postmenopausal women [8, 9].

Estrogen plays an important role in maintaining urinary continence as the bladder and urethral function deteriorates with age. Continence is preserved when the urethral pressure remains greater than the intravesical pressure at rest; ERs in the urethra and bladder are activated resulting in increased urethral resistance and sensory threshold of the bladder and urethral smooth muscle [10, 11]. Estrogen also directly affects detrusor function through the regulation of muscarinic receptors and inhibition of movement extracellular calcium ions into the cells, reducing the amplitude and frequency of detrusor contractions [12].

Urogenital atrophic changes in women are also manifested with decreased estrogen effects on systemic collagenase activity. The reduced thickness of the squamous epithelial layer and vaginal and periurethral collagen result in generalized atrophic change and risk for urogenital prolapse [13].

By contrast, estrogen influences the expression and action of alpha adrenergic and beta-adrenergic receptors. After menopause, there are more alpha adrenergic receptors than beta-adrenergic receptors. This change in the ratio between these receptor subtypes contributes to stress urinary incontinence [14•]. There is also an animal model which suggests exogenous estrogen increases the collagen to smooth muscle ratio, which may lead to increase OAB symptoms by reducing bladder compliance [15].

Aside from local effects, ERs are present in structures of the central nervous system, including the cerebral cortex, limbic system, and hippocampus, which indirectly influences the central neurologic control of micturition through the regulation of the density of nerve fibers and associated neurotrophins [16].

Role of Estrogen Status in Lower Urinary Tract Pathology

Urinary Incontinence

The prevalence and severity of urinary incontinence increase with age. In the USA, more women over the age of 80 have significant urinary incontinence compared with women aged 40–59 (31.7% vs 17.2%) [17]. When women were asked regarding the onset of urinary incontinence, 70% of them associated the event to their final menstrual period.

In a Cochrane Systematic review conducted in 2012, 34 trials involving more than 19,000 women, of whom over 9000 received local estrogen therapy, reported improvement in their urinary incontinence. To date, there is no evidence to show whether this benefit continues to be observed after the treatment is stopped [18]. A review paper published in 2015 by Rahn et al. confirmed that for postmenopausal women with stress urinary incontinence (SUI) without intrinsic sphincter deficiency (ISD) treated with local estrogen therapy showed improvement in leakage although evidence was of very low quality [19].

Estrogen enhances urethral resistance by increasing the number of periurethral vessels that account for a third of urethral pressure in maintaining continence [14•]. However, systemic hormone replacement therapy has been shown to increase the risk of developing UI. Three trials found that women who had UI at baseline not only complained that their symptoms worsened after systemic estrogen therapy but their quality of life also deteriorated [17].

From recent studies, women with lower estradiol levels during menopause have significantly lower incontinence rates. However, both storage and voiding symptoms were not influenced by the changes in estradiol levels [17]. Estrogen increases the risk of stress urinary incontinence by altering the collagen remodeling process [19]. Estrogen reduces the total collagen concentration which reduces the collagen cross-linking. Consequently, there is an increase in the levels of collagen turnover [20]. After taking oral systemic estrogen therapy for six months, women with SUI have shown a reduction in total collagen and an increase in the level of collagen degradation products [14•]. This translates to a change in the structure and composition of the connective tissue affecting periurethral tissue and increases urethral mobility.

Overactive Bladder (OAB)

The prevalence of OAB increases with age, and it has been reported at 11.8–16% [14•]. Evidence is encouraging for postmenopausal women with OAB symptoms. It is difficult to distinguish if the subjective improvement of OAB symptoms is due to a direct effect of estrogen on LUT function or an indirect effect of improvement in vaginal atrophy. There is definite evidence showing significant improvements in objective and subjective outcomes which include diurnal, nocturnal frequency, and urgency, number of incontinence episodes, first sensation to void, and bladder capacity [14•].

On the contrary, in a study involving 229 postmenopausal women with detrusor overactivity (DO), there was no synergistic effect for vaginal estrogen and anticholinergic drug [14•]. This was also observed in the addition of local estrogen to tolterodine (immediate- or extended-release forms) that did not confer an advantage over tolterodine alone. One of the studies nevertheless reported a lower frequency of voiding and greater voided volume in the combination therapy group. With the higher rate of side effects of oral anticholinergics, there was poorer treatment compliance compared with vaginal estrogen therapy reported in the same study [19]. We have yet to see evidence showing beta agonist being superior to vaginal estrogen alone or in combination [19].

Recurrent Urinary Tract Infections (UTI)

There is clinical data attributing low estrogen state to the pathogenesis of UTI [21•]. This is supported by the increased incidence of rUTI in postmenopausal women. The three factors described by Petral et al. are the change in structural and chemical composition in the urogenital tract, high post void residual volume, and changes in the vaginal microflora [21•]. Improving the local estrogen status by local therapy substantiate the integrity of the urogenital tract by forming a tighter intercellular connection and to prevent the intrusion of bacteria and restoration of lactobacilli-dominated vaginal microflora [21•]. Other well-known risk factors in this age group include sexual activity, diabetes mellitus, urinary incontinence, cystocele, and prior urinary tract infection. Five to 15% of women aged 60 and above report having UTIs. A Cochrane Review in 2008 concluded that local vaginal estrogen reduced the number of UTI in women as compared with placebo. In contrast, 4 studies showed that oral systemic estrogen did not reduce the occurrence of UTIs [21•]. Local estrogen reduces the number of UTI episodes but has not shown to replace antibiotic therapy for an actual infection.

Role of Estrogen Status in Pelvic Floor Dysfunction

Pelvic Organ Prolapse

The annual incidences of anterior, central, and posterior compartment prolapse have been estimated at 9.3, 1.5, and 5.7 cases per 100 women-years. Thirty-two percent of postmenopausal women have clinically significant pelvic organ prolapse. Length of menopause was found to be an independent predictor of pelvic organ support and pelvic floor muscle function [22••].

Other well-known risk factors for POP are vaginal childbirth, age, and obesity. Estrogen receptors have been found in uterosacral ligaments, pubocervical fascia, and pelvic floor musculature. Furthermore, these receptors play a role in the supportive mechanism of the pelvis by influencing the synthesis and breakdown of collagen. Whether the collagen metabolism is directly related to pelvic organ prolapse is still not well understood. It is postulated that estrogen reverses the collagen metabolism back to a premenopausal state. Estrogen deficiency is known to cause atrophic changes, and POP progression may be influenced by the weakening and thinning of supportive genital tract tissues as well as the supporting ligaments of the pelvic organs.

However, evidence regarding the effectiveness of local estrogen in the treatment of POP is lacking. Trutnovsky et al. [23] study reported that past or present HRT use or local estrogen for more than 3 months showed no association with pelvic organ support and levator ani function.

In 2010, a Cochrane Review conducted to determine the effects of estrogen (or drugs with estrogenic effects) on the prevention or management of POP concluded that the evidence was extremely limited [24••]. A 16-women study in 1999 compared local estrogen therapy plus duloxetine and Kegel exercises with anterior repair for stage 1 cystocele concluded that no progression of cystocele in the former [25].

Sexual Dysfunction

Vaginal atrophy affects half of all postmenopausal women [24••]. Local estrogen therapy has been shown to be more effective with 80–90% of patients reporting a favorable response compared with 75% in the systemic therapy group. In the 2006 Cochrane Review, 19 trials reported similar efficacy in local estrogen therapy across all products [26]. A further review in 2010 showed a similar conclusion [27].

Local estrogen therapy improves blood flow to the urogenital region. This increases vaginal lubrication and oxygen level. Consequently, this may improve sexual desire, arousal, and orgasmic function. Aging women are often living with symptoms of pelvic organ prolapse, urinary incontinence, and chronic constipation. These symptoms affect women's sexual function due to dyspareunia or chronic pelvic pain. An altered body image associated with the change in the appearance of the genitalia or to the loss of urine, flatus, or feces associated with attempted coital activity could also cause significant distress to the patient.

Anorectal Dysfunction

The anorectal component as part of a range of pelvic floor dysfunction is sometimes forgotten by the Urologist and Urogynecologist. It encompasses a spectrum of conditions and is a cause of significant discomfort and embarrassment in women. The primary functions of the rectum of pelvic floor musculature are to allow defecation and prevent fecal incontinence. In anorectal dysfunction, these primary mechanisms are affected, and the patient may complain of symptoms ranging from constipation to fecal incontinence and organ prolapse. Anorectal dysfunction has a multifactorial etiology with proposed causes such as vaginal delivery for pregnancy, obesity, prior pelvic surgery, excessive straining, and defective collagen. There is no current convincing literature demonstrating evidence that the role of estrogen loss in menopause is a direct contributing factor causing anorectal dysfunction. Current epidemiological studies

are unable to differentiate the significance of various confounding factors as the women age.

There is no direct correlation of estrogen deficiency causing anorectal dysfunction. Current evidence is circumstantial at best. The prevalence of chronic constipation in the aging population seems to be more common in elderly women with a ratio of 1.5 to 1 as compared with men [22••]. However, these seem to be more of a functional problem due to the aging process rather than due to the estrogen-deficient state. A study on a group of 334 women with obstructed defecation showed that the occurrence of rectocele, mucosal prolapse and grade III enterocele or sigmoidocele increase with age [22••]. On the contrary, women younger than 50 with obstructed defecation are most likely caused by paradoxical contraction or lack of relaxation of the pelvic floor muscles.

Local Estrogen Therapy in the Perioperative Setting

A rather indirect means of assessing the role of estrogen is looking at its efficacy when used as a perioperative treatment modality. Since many of the treatments for pelvic floor dysfunction are surgical, local estrogen therapy in the perioperative setting has shown to be beneficial.

In the setting of post-op estrogen use after mid-urethral sling placement, local estrogen therapy has shown to reduce urinary frequency and urgency. In a double-blinded randomized controlled trial (RCT) in 1995, local estrogen therapy was reported to reduce the frequency of bacteriuria up to 1 month following vaginal surgery but failed to improve symptomatic cystitis [14•]. In 2014, Rahn et al. also found that local estrogen therapy in combination with pelvic floor muscle exercise reduces the incidence of cystitis up to 4 weeks post op [19].

Risks and Benefits of Estrogen Therapy

Lastly, concerns with safety and potential adverse events associated with estrogen therapy should not be underestimated. Up to 41% of women have expressed long term safety concerns [19]. Thirty percent are particularly bothered by the risk of breast cancer associated with estrogen therapy. Hence, 9% of menopausal women receiving a local estrogen therapy prescription never fill it and those who do fill prescriptions for estrogen creams typically discontinue therapy after just 3 months [19]. This suggests that either this treatment has minimal clinical effectiveness or that its utility might be underappreciated.

Besides breast cancer, systemic estrogen therapy in the form of oral hormone replacement therapy increases the risk of venous thromboembolism. There is evidence to show hormone replacement therapy (HRT) increases the risk of stroke in postmenopausal women. However, there is no convincing evidence that HRT increases the risk of cardiovascular disease in women under the age of 65. There is weak evidence that HRT improves muscle mass and strength as well as reduces the risk of fragility fracture associated with osteoporosis.

Fortunately, the systemic absorption and effect of local estrogen therapy are limited providing it a more favorable risk profile. Perhaps the greatest absorption is at the beginning of therapy due to the thin, atrophic vaginal mucosa. Despite its low levels of absorption giving rise to potential circulating estrogen, there is still concern regarding their potential to induce endometrial hyperplasia. Therefore, in patients with higher risks of adverse events, it is wise to assess the risk-benefit ratio.

Conclusion

Our review found evidence in support of the notion that local estrogen therapy can improve urge urinary incontinence and overactive bladder symptoms and reduces the incidence of recurrent urinary tract infection especially during the perioperative period up to 4 weeks. There is more robust evidence in how local estrogen supplementation improves vaginal atrophy and subsequently sexual dysfunction. Despite known associations between estrogen status and pelvic floor musculature, local estrogen supplementation has consistently been shown not to prevent the occurrence or recurrence of pelvic organ prolapse. There is also no evidence regarding any direct correction of estrogen on anorectal dysfunction.

In summary, our review illustrated that most of the evidence regarding estrogen as the causation for LUTs as well as pelvic floor dysfunction is mainly epidemiological and not from rigorous randomized prospective trials. The paucity of data reflects the challenging nature of conducting prospective randomized trials in this heterogenous group of patients and many questions remain unanswered. The responsibility therefore lies with the physician working in tandem with the patient to moderate goals and expectations to achieve satisfactory treatment outcomes. Importantly, additional research is needed with longer patient follow-up to fully assess the role of estrogen in the causation of LUTs and pelvic floor dysfunction.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest..

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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