Volume 4 Issue 1
March 2023

SLJOM The Sri Lanka Journal of Menopause

Review Article

A Review on Hormonal Replacement and Urinary Incontinence following Menopause.

Hewawitharana KG[1], Liyanapatabendi D[2], Bodhinarayana TN[3], Meegoda JV[4]

[1] *Acting Consultant Obstetrician and Gynaecologist, Base Hospital, Maha Oya, Sri Lanka*
[2] *Consultant Obstetrician and Gynaecologist, Base Hospital, Dehiathtakandiya, Sri Lanka*
[3] *Senior Registrar (Obstetrics & Gynaecology), Sunshine Hospital, St. Albans, Victoria Australia*
[4] *Medical Officer, Colombo South Teaching Hospital, Kalubowila, Sri Lanka*

Corresponding Author *– Hewawitharana KG – Email - kavi88fmas@gmail.com*

Abstract

The female lower urinary tract originates from the same embryological precursors as parts of the vagina and genital fascia. Estrogen and progesterone receptors are present on the urethra, vaginal mucosa, pubo urethral and pubo vaginal fasciae, pelvic floor muscle, and supporting ligaments. This shows the possibility of an endocrine impact on the anatomical structure and functional integrity of these. Hormonal deprivation is linked to symptoms of lower urogenital structures. HRT is a promising therapy for symptoms of menopause. However, its impact on urinary incontinence is still unresolved and many questions exist. Emerging RCTs suggest HRT has potential disadvantages over UI discouraging its use over UI. This review reflects on the effects of HRT on UI.

Keywords-Hormonal Replacement Therapy (HRT), Menopause, Urinary Incontinence (UI)

Introduction

Estrogen and progesterone receptors are present on the urethra, vaginal mucosa, pubo urethral and pubo vaginal fasciae, pelvic floor muscle, and supporting ligaments. Female lower genito-urinary structures share the same embryological origin and menopausal hormonal deprivation creates symptoms in these structures[1,2,3].

In urogynaecology, the impact of HRT (Oestrogen) over lower urogenital symptoms such as vaginal dryness-related dyspareunia is well established, and clinicians prescribe local estrogen for such patients with no potential HRT-related malignancy risk. In addition to this vaginal Dehydroepiandrosterone (DEHA) is another promising agent for dyspareunia in menopausal women[4]. However, the efficacy of HRT over UI (urinary incontinence) is still controversial and not conclusive. But theoretically, these lower urinary symptoms should be resolved with estrogen.

According to available small-scale studies and meta-analyses, HRT has been used in post-menopausal women even to address lower urinary problems as well. However, few significant RCTs discourage this practice showing the possibility of HRT-related exaggeration of de novo UI.

Cochrane Reviews and International Consultation on Incontinence Perspective over HRT and UI

In 2003, a Cochrane review on estrogen effects on urinary incontinence using a meta-analysis of 28 clinical studies (total of 2926 women, sample size 16–1525)[5]. In

fifteen clinical studies (with 374 Oestrogen treated and 344 control women), both urge and stress incontinence symptoms improved more in the estrogen group, and the conclusion was reached that estrogen therapy is effective in treating urinary incontinence symptoms, especially urinary urgency.

In 2004, international consultation on incontinence stated that estrogen has no major beneficial effect over stress urinary incontinence. But it was beneficial in addressing overactive bladder (OAB)/Urge incontinence. But in 2012, revision of the same was done with thirty-four trials[6]. These included approximately 19,676 incontinent women of whom 9599 received estrogen therapy (1464 were involved in trials of local vaginal estrogen administration). Sample sizes of the studies ranged from 16 to 16,117 women. The combined result of six trials of systemic administration (of oral systemic estrogens) resulted in worse incontinence than on placebo risk ratio (RR) 1.32, 95% CI 1.17 to 1.48). This result was heavily weighted by a subgroup of women from the Hendrix trial, which had large numbers of participants and a longer follow-up of one year. All of the women had had a hysterectomy and the treatment used was conjugated equine estrogen. The result for women with an intact uterus where estrogen and progestogen were combined also showed a statistically significant worsening of incontinence (RR 1.11, 95% CI 1.04 to 1.18). There was some evidence that estrogens used locally (for example vaginal creams or pessaries) may improve incontinence (RR 0.74, 95% CI 0.64 to 0.86). Overall, there were around one to two fewer voids in 24 hours amongst women treated with local estrogen, and there was less frequency and urgency. No serious adverse events were reported although some women experienced vaginal spotting, breast tenderness, or nausea.

Women who were continent and received systemic estrogen replacement, with or without progestogen, for reasons other than urinary incontinence were more likely to report the development of new urinary incontinence in one large study. One small trial showed that women were more likely to have an improvement in incontinence after pelvic floor muscle training (PFMT) than with local estrogen therapy (RR 2.30, 95% CI 1.50 to 3.52).

The author's conclusion from this meta-analysis was "Urinary incontinence may be improved with the use of local estrogen treatment. However, there was little evidence from the trials on the period after estrogen treatment had finished and no information about the long-term effects of this therapy was given. Conversely, systemic hormone replacement therapy using conjugated equine estrogen may worsen incontinence. There were too little data to reliably address other aspects of estrogen therapy, such as estrogen type and dose, and no direct evidence comparing routes of administration. The risk of endometrial and breast cancer after long-term use of systemic estrogen suggests that treatment should be for limited periods, especially in those women with an intact uterus".

Heart Oestrogen/Progestogen Replacement Study[7]

This study was a blind RCT investigating the effect of conjugated equine estrogen (CEE) 0.625mg and medroxyprogesterone acetate (MPA) 2.5mg daily on the prevention of symptoms of coronary arterial disease in postmenopausal women with coronary arterial disease. In the same

(Table 1): Summary of findings of the study

Table 1 Risks, excess risks and numbers needed to harm urinary incontinence after 4 years of hormone therapy according to the Heart Estrogen progesterone Replacement Study

	Cumulative risk (%)			
	Placebo	Hormone therapy	Excess risk (%)	No. needed to harm
Total	49	64	15	6.9 (5.0–11.1)
Urge	36	48	12	8.6 (5.8–16.6)
Stress	38	54	16	6.2 (4.6–9.4)

study, there was a sub-group of 1208 women with lower urinary symptoms. The HRT arm consisted of 597 women (49%) in comparison with 611 in the control (51%). UI was diagnosed using a questionnaire and it was based on symptoms in the previous week, 4 months, and 4 years after enrolment. At 4 months, symptoms were significantly more frequent in the HT group and remained so at 4 years. The odds ratio for the HT compared to the control group was 1.5 for urge incontinence and 1.7 for stress incontinence giving an excess frequency of these symptoms of 12% and 16%, respectively, in the fourth year.

These figures indicate that HRT causes urge incontinence in one out of eight individuals treated and stress incontinence in one out of six. No significant effects of age, years after menopause, race, parity, complications, or body mass index, were found. When the analysis was limited to individuals under 60 years of age, there was no significant difference between the two groups, although more urinary incontinence was found in the HT group (HT vs. control, 59: 48% for total UI; 40: 32% for urge incontinence and 48: 37% for stress incontinence).

Women's Health Initiative Study[8]

This was designed to investigate the effect of HRT on the prevention of coronary disease and femoral bone fracture in postmenopausal women. The Oestrogen + Progesterone arm was stopped at 5.6 years because of increased adverse effects. Oestrogen alone was terminated at 7.1 years as enough data had been accrued to indicate an increased risk of stroke and no benefit in the prevention of coronary disease.

In the WHI subgroup analysis of UI, the effects of Oestrogen + Progesterone or Oestrogen alone on stress, urge and mixed UI were investigated in postmenopausal healthy women after one year of treatment.

Table 2: Summary of Results

Table 2 Relative risks of urinary incontinence of hormone therapy according to the Women's Health Initiative

Incidence	E+P	E alone
Stress	1.87 (1.61–2.18)	2.15 (1.77–2.62)
Urge	1.15 (0.99–1.34)	1.32 (1.10–1.58)
Mixed	1.49 (1.10–2.01)	1.79 (1.26–2.53)
Symptoms		
Frequency	1.38 (1.28–1.49)	1.47 (1.35–1.61)
Amount	1.20 (1.06–1.36)	1.59 (1.39–1.82)
Decrease in activity	1.18 (1.06–1.32)	1.29 (1.15–1.45)
Decrease in quality of life	1.22 (1.13–1.32)	1.50 (1.37–1.65)

Data were obtained from 27347 postmenopausal women aged 50 to 79, registered between 1993 and 1998. There

were 8506 women in the Oestrogen + Progesterone group and 8102 controls while the Oestrogen alone group contained 5310 women and 4429 controls.

There was an increase in all types of UI in those who had not had any symptoms before. The relative risk (RR) is the highest for stress incontinence (E+P: RR 2.15, E alone: RR 1.49), followed by mixed incontinence (E+P: RR 1.49, E alone: RR 1.79). For urge incontinence, there was no significant difference in the E+P group (E+P: RR 1.15, E alone: RR 1.32). In the E+P group, the risk increased in women more than 15 years after menopause and the effect continued for 3 years after stopping HRT.

Women who experienced urinary incontinence at the start of the WHI trial mentioned that HRT increased the amount and frequency of incontinence, giving a decreased quality of life. Based on these findings, the authors concluded that HRT should not be used either to prevent or as therapy for urinary incontinence.

What could be the Mechanism for this HRT-related UI?

1. Collagen has an important role in supporting the function of the lower urinary tract. Structural changes in collagen and related proteoglycans have been detected in incontinent women[9]. Decreased collagen and increased collagen degradation have been reported after treatment with oestrogen[10,11,12,13].
2. In animal studies, estrogen caused blood vessel proliferation in the tissues surrounding the urethra, which was initially thought to be desirable but may result in a decrease of collagen in the supporting tissue[12].

Controversies and Important Observations.

Though increased urinary incontinence was evident with Oestrogen alone in the WHI trial, progesterone must play an important role because symptoms tend to occur during the luteal phase[13]. In pre-menopausal women, HRT sometimes improves UI, especially urge symptoms, indicating that HRT itself is not necessarily bad for urinary function. It should be noted that the large trials discussed above deal only with postmenopausal women. Above mentioned trials are not primarily designed for evaluation of the relationship between HRT and UI, this is an important limitation.

The WHI trial showed a significant decrease in quality of life (QOL) in the HRT group, the difference was not significant when the analysis was limited to younger women (less than 50 years old). Because QOL can be influenced by many factors, it may not be appropriate to attribute decreased QOL to UI only, especially in elderly women.

The health effects of endogenous estrogens can not be ignored as even in post-menopausal women still there is an intact supply of natural estrogen with peripheral androgen conversion. This is more in obese women.

What are Current Recommendations in Clinical Practice?

The American College of Obstetrics and Gynaecology announced that female hormone therapy is beneficial in the treatment of urogenital symptoms related to menopause[14]. But, in 2006 as well as 2019 last updated format of NICE guideline advice was **"Do not offer systemic hormone replacement therapy to treat**

urinary incontinence" and **"Offer intra-vaginal estrogens to treat overactive bladder symptoms in postmenopausal women with vaginal atrophy".**

Conclusion

Until new data is available with large-scale RCT, only local estrogen should be offered in women with OAB when it coexists with vaginal atrophy. Under no circumstances HRT alone or in combinations should not prescribe for the prevention or treatment of any form of urinary incontinence.

Disclosure of interests-No conflicts of interest

References

1. Gebhardt J, Richard D, Barrett T. Expression of estrogen receptor isoforms alpha and beta messenger RNA in vaginal tissue of premenopausal and post-menopausal women. Am. J. Obstet. Gynecol. 2001; 185: 1325–30.
2. Copas P, Bukovsky A, Asbury B, et al. Estrogen, progesterone, and androgen receptor expression in levator ani muscle and fascia. J. Women's Health Gend. Based Med. 2001; 10: 785–95.
3. Smith P, Heimer G, Norgren A, et al. Steroid hormone receptors in pelvic muscles and ligaments in women. Gynecol Obstet Invest 1990; 30: 27–30
4. Androgen Therapy in Women, The Journal of Women'sHealth, 2018, https://doi.org/10.1089/jwh.2018.7494
5. Moehrer B, Hextall A, Jackson S. Oestrogen for urinary incontinence in women. Cochrane Database Syst. Rev. 2003; 2: CD001405.
6. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogens for urinary incontinence in women. Cochrane Database Syst.Rev.2012: CD001405
7. Steinauer JE, Waetjen LE, Vittinghoff E, et al. Postmenopausal hormone therapy: Does it cause incontinence? Obstet. Gynecol. 2005; 106: 940–5.
8. Hendrix SL, Cochrane BB, Nygaard LE, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005; 293:935–48
9. Falconer C, Blomgren B, Johansson O, et al. Different organization of collagen fibrils in stress incontinence women of fertile age. Acta Obstet. Gynecol. Scand. 1998; 77: 87–94
10. Rud T. The effects of estrogens and gestagens on the urethral pressure profile in urinary continent and stress incontinent women. Acta Obstet. Gynecol. Scand. 1980; 59: 265–70.
11. Falconer C, Ekman-Ordeberg G, Malmstrom A, et al. Clinical outcome and changes in connective tissue metabolism after intravaginal slingplasty in stress incontinence women. Int. Urogynecol. J. Pelvic Floor Dysfunct. 1996; 7: 133–7.
12. Falconer C, Ekman-Ordeberg G, Blomgren B, et al. Paraurethral connective tissue in stress-incontinence women after menopause. Acta Obstet. Gynecol. Scand. 1998; 77: 95–100.
13. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. Br. J. Obstet. Gynecol. 2002; 109: 339–44
14. Endo RM, Girao MJ, Sartori MG, et al. Effect of estrogen-progestogen hormonal replacement therapy on periurethral and bladder vessels. Int. Urogynecol. J. Pelvic Floor Dysfunct. 2000; 11: 120–23

15. Hextall A, Bidmead J, Cardozo L et al. The impact of the menstrual cycle on urinary symptoms and the results of the urodynamic investigation. Br. J. Obstet. Gynecol. 2001; 108: 1193–96.
16. Response to the women's health initiative results by the American College of Obstetricians and Gynecologists. Jun 3, 2003.
17. Urinary-incontinence-and-pelvic-organ-prolapse-in-women management. NICE,24 June 2019. https://www.nice.org.uk/guidance/ng123/resources/