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STRESS INCONTINENCE AND PROLAPSE (WS REYNOLDS, SECTION EDITOR)

# Hormone Replacement for Pelvic Floor Disorders

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## Abstract

**Purpose of Review** The purpose of this review article is to summarize the recent literature regarding the effect of hormone replacement therapy on pelvic floor disorders and its role as a preventative or treatment option.

**Recent Findings** The recent evidence describing the effect of hormone replacement therapy on pelvic floor disorders is mainly limited to cohort studies, systematic reviews, and secondary analysis of randomized controlled trials such as the Women's Health Initiative and Nurses' Health Study. There are few quality randomized controlled trials, especially within the last 5 years on this topic. The data that does exist does not show hormone therapy to be beneficial in the treatment or prevention of pelvic floor disorders. In fact, it may worsen urinary and fecal incontinence when given systemically. The exception to this is the local application of vagina estrogen, where it may be of some benefit in the treatment of urinary incontinence. Local application has been shown to be beneficial when treating genitourinary syndrome of menopause and in the prevention of recurrent urinary tract infections.

**Summary** There is a paucity of quality data regarding the secondary effects and use of hormone replacement as a treatment for pelvic floor disorders. Given the lack of studies, limited efficacy, and possible side effects, it should not be offered as first-line or single treatment for pelvic floor disorders such as urinary or fecal incontinence and pelvic organ prolapse. It may be used as a treatment for genitourinary syndrome of menopause and for prevention of urinary tract infections when placed locally in the vagina.

**Keywords** Hormone replacement therapy · Urinary incontinence · Pelvic organ prolapse · Fecal incontinence

## Introduction

Pelvic floor disorders occur when the muscles and connective tissue of the pelvic floor and organs are weakened or injured. There are a wide range of pelvic floor disorders; the most common include urinary incontinence, fecal incontinence, and pelvic organ prolapse. As women age, pelvic floor disorders become more common [1, 2]. While many pelvic floor disorders are caused by trauma during child birth, there are other factors that play a role in their development such as age and genetics [3]. As women age, especially after menopause, there is a decrease in circulating hormones. Often, treatment with hormonal medications may be initiated for symptoms of menopause such as hot flashes, vaginal atrophy, and mood disturbances [4•]. Since many of the pelvic organs (bladder, urethra, vagina, rectum) have hormone receptors, hormone replacement therapy (HRT) for the systemic symptoms of menopause may have an effect on coexisting pelvic floor disorders [5]. Additionally, hormonal therapy may be thought of as a possible option for the prevention or treatment of pelvic floor disorders, aside from the treatment of other symptoms of menopause. There is a lack of high-quality evidence related to the treatment of pelvic floor disorders with hormone therapy, and the available literature suggests that it not only is ineffective but also may worsen many these disorders. The exception to this is the application of local estrogen to the vaginal tissue for the treatment of urinary incontinence (UI), genitourinary

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syndrome of menopause (GSM), and in the prevention of recurrent urinary tract infections (UTI) [4•, 6, 7].

## Forms of hormone therapy and side effects

Vasomotor symptoms are the most common symptom of menopause with a prevalence reported as high as 82% among US women who experience natural menopause [8]. Vaginal atrophy, another common menopausal symptom, is a consequence of the hypoestrogenic state associated with menopause and the North American Menopause Society estimates that 10–40% of menopausal women will experience the symptoms of vaginal atrophy [9]. Management of menopausal symptoms can be treated with a variety of hormone replacement medications. These medications vary in their routes, dosages, and side effect profiles. Vasomotor symptoms are best treated with oral estrogen or combined estrogen and progesterone, while vaginal symptoms may be treated with systemic or local estrogen. Local estrogen is available in the form of a tablet, ring, or cream. Systemic estrogen is available in the form of a pill or patch [4•]. Vasomotor and vaginal symptoms may also be treated with nonhormonal treatment options such as selective serotonin reuptake inhibitors (SSRI), clonidine, gabapentin, ospemifene (estrogen agonist/antagonist), vaginal lubricants, and moisturizers, which are effective alternatives to hormone therapy and should not be avoided or preferred based on a patient's pelvic floor disorders given the lack of data. The major risks of combined systemic HT include thromboembolic disease and breast cancer. Other reported risks include coronary heart disease, and stroke [10–12]. Since there is a variable response to HT, the American College of Obstetrics and Gynecology recommends healthcare professionals individualize care and treat women with the lowest effective dose for the shortest period of time needed to relieve symptoms [4•].

## Urinary Incontinence

Urinary incontinence is defined as the involuntary loss of urine and can be divided most commonly into stress urinary incontinence (SUI), urgency urinary incontinence (UUI), or mixed urinary incontinence. Stress urinary incontinence occurs when there is leakage of urine with an increase in intraabdominal pressure in the absence of a detrusor contraction, while urgency incontinence is incontinence with a strong sense of urgency felt by the patient just prior to or with leakage. UUI is often brought on by an involuntary detrusor muscle contraction (detrusor overactivity) [13]. UUI is more prevalent after menopause, and SUI has a peak prevalence during the perimenopausal years but declines following menopause [14]. Many patients have a combination of SUI and UUI, termed mixed incontinence [13].

The treatments for urinary incontinence vary based on the type. In practice, conservative treatments are often tried prior to more invasive or surgical interventions [15]. These treatments may include the following: pelvic floor physical therapy, timed voiding, fluid restriction, oral medications, continence pessaries, and local hormone therapy [16]. In a study published in Journal of the American Medical Association (JAMA), oral menopausal hormone therapy increased the incidence of all types of urinary incontinence at 1 year among women who were continent at baseline. The risk was highest for stress urinary incontinence and estrogen therapy alone with a relative risk (RR) as high as 2.15 compared to placebo at 1 year. Among women with baseline urinary incontinence, frequency, and the amount of urinary incontinence worsened in both the estrogen alone and combined estrogen and progesterone arms compared to placebo. Additionally, women receiving menopausal hormone therapy were more likely to report that urinary incontinence limited their daily activities and bothered them. This study included a secondary analysis of over 20,000 women from the Women's Health Initiative multicenter double-blind, placebo-controlled, randomized clinical trial [17••]. Another study utilized the Nurses' Health Study cohort of 39,436 postmenopausal women aged between 50 and 75 years who were initially without urinary incontinence. These patients were followed for 4 years to identify the incidence of UI. The yearly incidence of UI was 3% for women who had never taken hormone therapy and 3.8% for women how were current users of HRT. This study determined the age-related relative risk to be 1.54 for users of oral estrogen alone and 1.68 for users of transdermal estrogen. Combined estrogen and progesterone had a RR of 1.34. There was still an additional risk after discontinuation of hormone replacement RR 1.14, but a decreasing risk of incontinence with increasing time since the last hormone use. Ten years after stopping hormones, the risk was back to baseline with those who had never taken HRT, RR 1.02 [18]. The Heart and Estrogen/progestin Replacement Study (HERS), a cardiac prevention trial, had a secondary end point evaluating the effects of HRT on the risk of SUI and UUI. During the 4 years of treatment, a significantly higher proportion of the women randomly assigned to hormone treatment reported weekly incontinence compared to placebo. The higher risk was present at 4 months after initiation of treatment and persisted throughout [19]. A recent Cochrane database systematic review confirmed these findings, with the combined results of six trials of oral estrogen administration resulting in worse incontinence compared to placebo (RR 1.32) [7]. A large portion of the women in this review was part of the Hendrix trial published in JAMA previously mentioned above [17••]. The results for women with an intact uterus using combined estrogen and progesterone also showed a statistically significant worsening of incontinence from baseline (RR 1.11). The reasons for an increased in urinary incontinence with oral HRT are unclear, however it may be due to a decrease in vaginal and

periurethral collagen [20]. This Cochrane review also included studies that used local estrogen. There was some evidence that local estrogen may improve urinary incontinence (RR 0.74). Patients with urgency, frequency, and urgency incontinence had one to two fewer voids in 24 h and decreased urgency. The authors concluded that urinary incontinence may be improved with the use of local estrogen treatment, and conversely, systemic hormone replacement may worsen incontinence. However, there was not enough data to reliably address other aspects of estrogen therapy such as type and dose.

More evidence for the treatment of urinary incontinence with local estrogen therapy comes from a trial which assessed the effects of the combination of pelvic floor rehabilitation and transvaginal estradiol administration on SUI, urogenital atrophy, and recurrent urinary tract infections in postmenopausal women. This prospective randomized controlled trial compared two groups of women; the treatment group received intravaginal estriol ovules and PFPT, while the control group received estriol ovules only. While signs and symptoms of urogenital atrophy significantly improved in both group, 73.5% of the patients in the treatment group vs. 9.7% of the patients in the control group had a subjective improvement in their incontinence. Those who received combination treatment also had significant improvement of colposcopic findings, maximum urethral pressure, and mean urethral closure pressure [21]. Some of the improvement in incontinence was likely due to the PFPT; however, the improvement in symptoms among the control group suggests that the local estrogen alone also had some effect.

## Pelvic Organ Prolapse

Pelvic organ prolapse (POP) is a common condition affecting up to 50% of women [22]. The International Continence Society defines POP as downward descent of the pelvic organs, which results in protrusion of the vagina and/or uterine cervix and does not include rectal prolapse [23]. Symptoms of prolapse include the feeling of a bulge, sitting on a ball, back pain, and vaginal pain from atrophy and rubbing of vaginal epithelium. Local estrogen preparations have been used to improve vaginal atrophy with success, eliminating some of the discomfort from prolapse [24].

A Cochrane review from 2010 including only randomized or "quasi-randomized" controlled trials examining the use of any estrogens or drugs with estrogenic actions for pelvic organ prolapse concluded that the use of local estrogen in conjunction with pelvic floor muscle training before surgery may reduce the incidence of postoperative cystitis within 4 weeks of surgery. Another conclusion drawn was that oral raloxifene (estrogen agonist/antagonist) may reduce the need for pelvic organ prolapse surgery in women older than 60 years; however, this is not an indication for treatment with this medication. Given the lack of data (only two trials and a meta-analysis were included in the review), it was determined that there is was a need for rigorous randomized controlled trials with long-term follow-up to assess estrogen preparation for prevention and management of pelvic organ prolapse. This is especially true as an adjunctive treatment for women using pessaries before and after prolapse surgery [25].

A retrospective observational study involving 1443 postmenopausal women with pelvic floor dysfunction determined that current hormone therapy was significantly associated with sonographically determined descent of the rectal ampulla and clinical genital hiatal distensibility. Past hormone therapy use, duration of HT use, or current vaginal estrogen use was not associated with pelvic organ support. They concluded that hormone therapy may have a negative effect on pelvic organ support; however, it is likely too small to be significant [26].

A 2018 study using the National Health and Nutritional Examination Survey (NHANES) Database evaluated the associations between the type and route of hormone use and POP as well as UI. In premenopausal women, they found that birth control pills, estrogen/progestin pills, and estrogen-only patch use were associated with UI. Additionally, birth control pills were associated with both UI and POP in premenopausal women. In postmenopausal women, estrogen-only pills and estrogen/progestin pill use were associated with UI. Birth control pill use was associated with POP in postmenopausal women [27]. This study is consistent with the HERS and WHI studies listed above with regard to urinary incontinence. Another retrospective study from 2018 compared the former use of estradiol-progesterone in postmenopausal hormone therapy in Finnish women with uterine prolapse surgery (12,072) and control women (33,704). They found that women with uterine prolapse had used hormone therapy more often than control women and the risk for prolapse was higher with longer exposure. The risks were comparable using estradiol and different preparations of progesterone including the levonorgestrel releasing intrauterine device [28].

The effect of local estrogen on the expression of proteins participating in collagen/elastin biogenesis and immune markers in women with POP has also recently been examined [29]. While there is evidence from this study that local estrogen therapy does play an important role in the activation of the immune system within the local vaginal environment limiting extracellular matrix degradation in hypoestrogenic women, the clinical significance of these findings is yet to be fully determined.

## Anal Incontinence

Fecal incontinence (FI) is defined as the recurrent, involuntary loss of solid, or liquid stool from the rectum and anal incontinence includes leakage of gas and/or stool [30]. While low

estrogen levels can contribute to the development of FI after menopause by altering neuromuscular continence mechanisms, studies have produced mixed results on the association between HRT and the risk of FI [31, 32]. The majority of studies in this area are small and retrospective or cross-sectional in design. A recent cohort study evaluating the association between HRT and the risk of FI among 55,828 postmenopausal women in the Nurses' Health Study found that compared to women who never used HRT, past and current users had an increased risk (HR: 1.26 and 1.32, respectively). Fecal incontinence increased with longer duration of HRT and decreased with time since discontinuation. There was an increased risk of FI among women receiving combination HRT compared to estrogen monotherapy [33•].

## Other Pelvic Floor Issues

### Recurrent Urinary Tract Infections

Local vaginal estrogen has been shown to decrease urinary tract infection recurrence in hypoestrogenic women with recurrent UTI. In a randomized double-blind, placebo-controlled trial of 93 postmenopausal women assigned to either topical estriol cream or placebo, UTI incidence in the treatment group decreased significantly over an 8-month period [34]. Another multicenter randomized noncontrolled trial of 108 postmenopausal women with recurrent UTI found that those women randomized to a vaginal estrogen ring decreased UTI occurrences and prolonged the time to next occurrence compared to a control group [35]. A systematic review of vaginal estrogen for the treatment of vulvoaginal atrophy found moderate quality evidence of decreased UTI risk in women with vaginal atrophy using local estrogen therapy [36]. A recent American Urogynecologic Society Best-Practice Statement on Recurrent Urinary Tract Infection in Adult Women endorses the use of vaginal estrogen in the prevention and recurrence of UTI as does the American Urologic Association Guidelines for Recurrent Uncomplicated Urinary Tract Infections in Women [6, 37]. Local estrogen in the vagina helps to prevent urinary tract infections by increasing the amount of lactobacillus present, altering the microbiome making it less inhabitable for UTI causing bacteria such as *Escherichia coli* [38].

### Genitourinary Syndrome of Menopause

Also known as vulvovaginal atrophy, vaginal atrophy, and atrophic vaginitis, genitourinary syndrome of menopause (GSM) is a common, undertreated condition affecting nearly 50% of postmenopausal women [9]. Low-dose vaginal estrogen therapy is the preferred treatment if GSM is unresponsive to nonprescription therapies [39]. It is both more effective and safer than system estrogen for the treatment of GSM. Multiple Food and Drug Administration–approved vaginal estrogen products (as described above) are available and the choice is typically determined by patient preference as all have similar efficacy in treating symptoms. Vaginal capsules have been shown to provide a statistically significant improvement in the symptoms of GSM compared with placebo with minimal systemic absorption [40, 41]. In a prospective randomized study that divided women into two groups: one receiving therapy with a vaginal ovule containing estriol and Lactobacilli acidophili and other containing intravaginal estriol alone showed significant improvement of urogenital atrophy in both groups (76% vs. 41% improvement) [42].

## Special Considerations

### Women with History of Estrogen Receptor–Positive Cancer

Nonhormonal treatment options for vaginal dryness and atrophy in patients with breast cancer include vaginal lubricants and moisturizers [43]. These have been found to be highly effective with small studies showing benefit compared to placebo [44, 45]. The variable rates of estrogen absorption have raised safety concerns in the past for the treatment of vaginal atrophy with topical estrogen in women with breast cancer. The estradiol vaginal ring is frequently used in patients with breast cancer due to its low systemic absorption, but there are no randomized trials assessing its safety. Since there is a lack of data to determine where increases in estradiol are clinically significant, and if the effects of continued exposure to estrogen pose a risk, nonhormonal methods should be considered first-line therapy for vaginal atrophy in women with a history of hormone sensitive breast cancer. It is the authors' opinion that a consultation with a patient's oncologist may be necessary before the initiation of any type of HRT in a woman with a history of breast cancer.

### Phytoestrogens

Phytoestrogens are biochemically similar to estradiol [46]. They are typically found in food such as nuts flax seed oil, soy products, cereals, breads, and legumes [47]. Depending on their concentration and bioavailability, they can act as estrogen agonists or antagonists [48]. There are studies which show phytoestrogens, similar to topical estrogen, increase proliferation of the pubocervical musculoconnective tissue and the responsiveness of the bladder detrusor muscle and urethra [49, 50]. There are small observation and clinical studies which show improvement in nocturia with phytoestrogens [51]. Future studies will need to be completed to assess the role of phytoestrogens on pelvic floor disorders. At this time, no recommendations can be made for or against their use.

## Conclusions

While there is limited quality data on the treatment effects of hormone replacement therapy for pelvic floor disorders, the existing literature suggests that it likely worsens the majority of these conditions. The exceptions are local estrogen for the treatment of urinary incontinence, GSM, and prophylaxis against recurrent urinary tract infection. As local estrogen therapy is also beneficial in the treatment of vagina aging and atrophy, its use may decrease the symptoms of pelvic organ prolapse; however, it will not treat or reverse the prolapse itself. While local estrogen may be a useful adjunct to other conservative or surgical options, the authors cannot endorse its use as a primary treatment or prevention for pelvic floor disorders outside of those listed above. Patients who are placed hormone replacement therapy for the symptoms of menopause should be counseled regarding the possible deleterious effects on the pelvic floor, especially in the development of urinary and fecal incontinence.

### 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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