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REVIEW ARTICLE

Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines

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Abstract
Introduction and hypothesis Risk of pelvic floor disorders increases after menopause and may be linked to estrogen deficiency. We aimed to systematically and critically assess the literature on vaginal estrogen in the management of pelvic floor disorders in postmenopausal women and provide evidence-based clinical practice guidelines.
Methods MEDLINE and Cochrane databases were searched from inception to July 2014 for randomized controlled trials of commercially available vaginal estrogen products compared with placebo, no treatment, or any medication for overactive bladder or urinary incontinence. We double-screened 1,805 abstracts and identified 12 eligible papers. Studies were extracted for participant information, intervention, comparator, efficacy outcomes, and adverse events, and they were individually and collectively assessed for methodological quality and strength of evidence.
Results Evidence was generally of poor to moderate quality. Vaginal estrogen application before pelvic organ prolapse surgery improved the vaginal maturation index and increased vaginal epithelial thickness. Postoperative vaginal estrogen use after a midurethral sling resulted in decreased urinary frequency and urgency. Vaginal estrogen and immediate-release oxybutynin were similar in improvement of urinary urgency, frequency, and urgency urinary incontinence in women with overactive bladder, but oxybutynin had higher rates of side effects and discontinuation. Conversely, the addition of vaginal estrogen to immediate or extended-release

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tolterodine did not improve urinary symptoms more than tolterodine alone. One study reported an improvement in stress urinary incontinence with use of vaginal estrogen.
Conclusion Vaginal estrogen application may play a useful role as an adjunct in the management of common pelvic floor disorders in postmenopausal women.

Keywords Incontinence · Overactive bladder · Menopause · Pelvic organ prolapse · Vaginal estrogen

Introduction

Aging is a well-known factor affecting pelvic floor and lower urinary tract anatomy and function. With increasing age, pelvic floor disorders increase in frequency, including pelvic organ prolapse (POP), overactive bladder (OAB), stress urinary incontinence (SUI), and sexual dysfunction. A number of factors, including an aging population, forecast a marked increase in demand for health care and therapies for these pelvic floor disorders in coming decades [1, 2]. Although it is difficult to separate the effects of declining estrogen levels in menopause from aging in general, it is clear that the pelvic organs and their surrounding muscular and connective tissue support are estrogen-responsive, epidemiological studies indicate that the menopause is a major risk factor for the development of pelvic floor disorders, and the symptoms and severity of these disorders increase significantly after the menopause [3, 4].

Despite innovations in surgical technique, recurrence of POP after surgery is common [5], and up to 17 % of patients who have surgery need a repeat operation within 10 years [6]. First-line medications for the treatment of OAB are also disappointing; anticholinergic medications have only a modest treatment effect with common side effects and high discontinuation rates [7]. Systemic estrogen replacement does not treat [8], and may aggravate stress [9] and urgency [10] urinary incontinence in postmenopausal women, but the impact of vaginal estrogen replacement on urinary incontinence is not clear. Similarly, perioperative use of vaginal estrogen replacement in postmenopausal women may have an impact upon postoperative outcomes.

Patients are wary of estrogen treatment. Forty-one percent of women have long-term safety concerns; 30 % are particularly apprehensive about breast cancer [11]. Nine percent of menopausal women receiving a vaginal estrogen prescription never fill it, and those who do fill prescriptions for estrogen creams typically discontinue therapy after just 3 months [11, 12]. This clear reluctance of patients to continue vaginal estrogens (or physician disinclination to recommend therapy) suggests either that vaginal estrogen might have minimal effectiveness in the management of pelvic floor disorders or that its utility might be underappreciated. In either case, a need exists for a comprehensive, systematic review of the efficacy and safety of vaginal estrogens and their alternatives in the management of pelvic floor disorders in postmenopausal women. The Society of Gynecologic Surgeons (SGS) Systematic Group Review (SRG) aimed to systematically and critically assess the efficacy and safety of vaginal estrogens in the management of pelvic floor disorders, with the balance of these benefits and harms used to generate evidence-based clinical practice guidelines.

Materials and methods

We performed a search to identify randomized controlled trials comparing vaginal estrogen application with other interventions following standard systematic review methodology [13]. The overall search focused on two populations: women with a general genitourinary syndrome of menopause (i.e., vulvovaginal atrophy), who are covered in a separate review [14], and a smaller population presenting specifically with urogynecological complaints. We searched MEDLINE and Cochrane Central Register of Controlled Trials from their inception through 15 July 2014. The search included numerous terms for estrogen products, pelvic organ prolapse, pelvic reconstructive surgery, overactive bladder, urinary incontinence, and was limited to English-language comparative studies in humans (see Appendix A for complete search details). Reference lists of selected articles and review papers were screened for additional eligible references. We did not attempt to identify unpublished articles or abstracts, and we did not contact study authors.

Participants of interest were postmenopausal women for whom vaginal estrogen was considered preoperatively before planned repair of POP or after pelvic reconstructive surgery, or presenting with urogynecological complaints such as OAB, urgency urinary incontinence, or SUI. All commercially available vaginal estrogen creams, tablets, suppositories, and rings intended for local (not systemic) absorption/therapy were allowed as interventions and comparators, including estriol products not FDA-approved but commonly used outside the USA. Placebo, no intervention, and oral agents (not oral estrogens) used for urinary incontinence and OAB treatment were also permitted as comparators. The main outcomes of interest were patient-reported subjective changes in urinary symptoms including urinary frequency, urgency, nocturia, urgency, and stress urinary incontinence, and UTI frequency. Relevant to studies of perioperative use of vaginal estrogen were measures of objective tissue atrophy and inflammation:

vaginal pH, vaginal maturation index, histological thickness of the vaginal epithelium and muscularis, and the presence of granulation tissue. Endometrial biopsy results, serum estradiol levels, and urodynamic measures were extracted, including maximum bladder capacity, detrusor overactivity, volume associated with strong urge to void, maximum flow rate, postvoid residual, and maximum urethral closure pressure. Adverse events and discontinuation rates and reasons were also collected.

The titles, abstracts, and full texts (when necessary) were double-screened for eligibility by nine reviewers, with discrepancies adjudicated by a third reviewer. Individual reviewers recused themselves from the evaluation, data extraction, and quality grading of any study they in which they were involved or for which they had co-authorship. Abstract screening was conducted using Abstrackr (http://abstrackr.cebm.brown.edu/) [15]. Data extraction was then completed in duplicate by the same nine independent reviewers, all with experience in the systematic review process [16, 17]. Data were extracted into customized forms in the Systematic Review Data Repository (SRDR) and can be accessed at http://srdr.ahrq.gov. The following data were collected: study characteristics (year, design, number enrolled/analyzed, length of follow-up); patient age; intervention (type of estrogen, medication details [dose, frequency, duration], length of follow-up, and comparator); outcome descriptions and results.

We assessed the methodological quality of each study using predefined criteria from a three-category system modified from the AHRQ [18]. Studies were graded as being of good (A), fair (B), or poor (C) quality based on scientific merit, the likelihood of biases, and the completeness of reporting. The quality of individual outcomes was separately graded within each study. Studies were grouped by sub-population, i.e., preoperative use of vaginal estrogen before prolapse repair, postoperative use after pelvic reconstructive surgery, and use for OAB and SUI. For each grouping, we generated an "evidence profile" by grading the quality of evidence for each outcome across studies. This process considered the methodological quality, consistency of results across studies, directness of evidence, and other factors such as imprecision or sparseness of evidence to determine an overall quality of evidence in accordance with the Grades for Recommendation, Assessment, Development and Evaluation (GRADE) system [19]. This system categorizes based on four quality ratings: high, moderate, low, and very low.

Guideline statements were then developed by incorporating the balance between benefits and harms of the compared interventions and the overall quality of evidence across all outcomes of interest. Each guideline received a "grade" in two parts: the strength of recommendation (1=strong, "we recommend" or 2=weak, "we suggest"), and the overall quality of evidence (high [A] to very low [D]). This strength of recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The wording and its implications for patients, physicians, and policy makers are detailed further in the Discussion. The review and guidelines were presented for public comment at the 40th SGS Annual Scientific Meeting in March 2014 and posted on the SGS website, after which comments were solicited for 4 weeks. A flow diagram of the study search and systematic review is shown in Fig. 1.

Results

The search identified 1,805 citations. After title and abstract screening, 96 full-text articles were evaluated in detail. Thirty-seven of these were rejected primarily because of ineligible interventions, comparators or study design. Among the remaining studies, 44 (47 articles) reported women presenting with genitourinary syndrome of menopause and are the topic of a second review [14]. The remaining 12 studies involved a urogynecological population (Tables 1, 2 and 3) and assessed the utility of vaginal estrogen given before (4 studies) [20–23] or after (3 studies) [24–26] pelvic reconstructive surgery or as a treatment for OAB or SUI (5 studies) [27–31] and are the subject of this review. Overall study quality was deemed to be good in 4 studies, fair in 7 studies, and poor in 1 study. Downgrades in quality were commonly due to small sample size, lack of blinding, unclear or inappropriate randomization technique, and poor clarity of results reporting. Study arm sample sizes ranged from 12 to 129. Perioperative estrogen trials had study durations that varied from 12 weeks of preoperative medication use up to 3 years of postoperative surveillance. Vaginal estrogen use in the OAB and SUI subpopulation was up to 12 weeks.

Preoperative vaginal estrogen before prolapse repair

Among women with POP planning surgical repair, 3 studies (in 4 papers) compared preoperative vaginal estrogen by various methods with placebo (or no treatment) with 111 total participants (Table 1) [20–23]. No vaginal estrogen was given following surgery. Overall quality of evidence was poor, largely because of the sparseness of evidence and outcomes such as epithelial and subepithelial thickness serving as surrogate outcomes for tissue quality, postoperative wound healing, and long-term integrity of surgical repair. The interventions were provided for 2 to 12 weeks preoperatively with patient surveillance continuing from the time of surgery [20, 22, 23] until 4 weeks [20] to 3 years [21] postoperatively.

It is uncertain whether preoperative vaginal estrogen was beneficial. Use of vaginal estrogen improved the vaginal maturation index at the time of surgery (high-quality evidence) [20, 22] and increased vaginal epithelial thickness (low quality) [20, 22, 23], but this did not translate to increased vaginal subepithelial/muscularis thickness (low

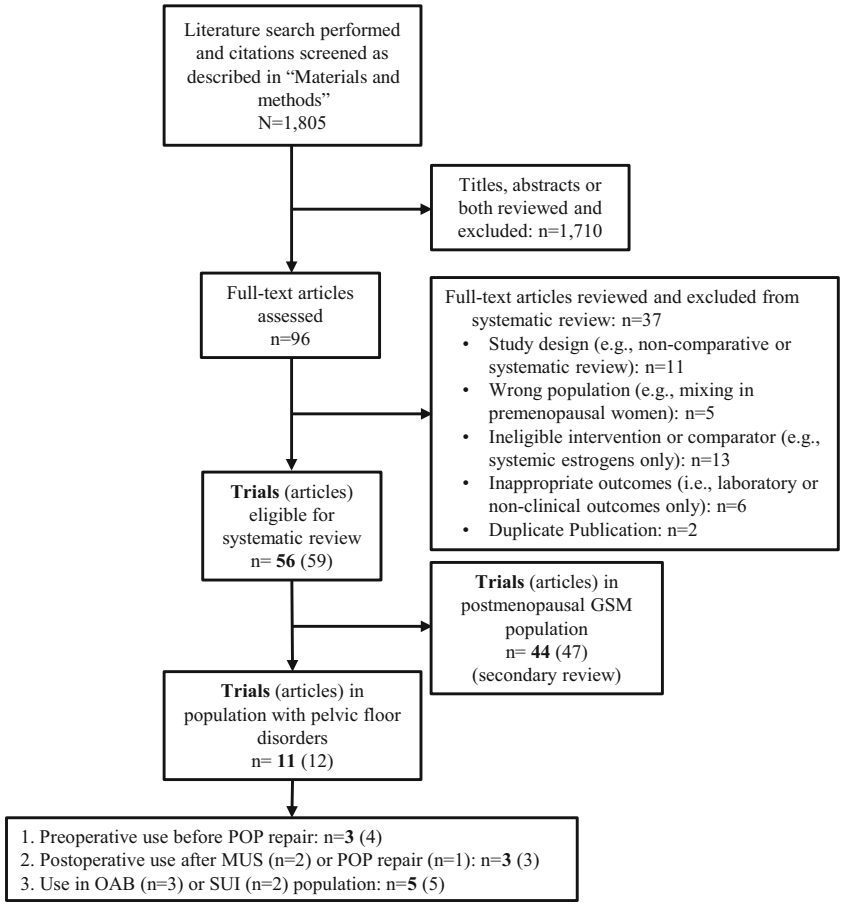

Fig. 1 Flow diagram of study search and systematic review. *GSM* genitourinary syndrome of menopause, *POP* pelvic organ prolapse, *MUS* midurethral sling, *OAB* overactive bladder, *SUI* stress urinary incontinence

quality) [22, 23]. Using vaginal estrogen preoperatively decreased the frequency of bacteriuria in the first postoperative month (low quality), but no difference was seen for symptomatic cystitis (very low quality) [21]. Data were insufficient to compare subjective measures of other urinary complaints, vulvovaginal atrophy, or the integrity of prolapse repair or wound healing. Regarding safety, 2 out of 22 participants (9 %) receiving 3 weeks of daily preoperative 25 μg vaginal estradiol tablets (Vagifem®) had simple endometrial hyperplasia without atypia on curettage at the time of surgery [20], while none of the 12 women receiving 1 g conjugated estrogens cream (Premarin® 0.625 mg/g cream) twice-weekly for 6–8 weeks preoperatively had any notable endometrial pathology at hysterectomy (i.e., proliferative, secretory, or hyperplastic endometrium) [23]. Serum estradiol levels did not increase above postmenopausal norms (moderate quality) with preoperative vaginal estrogen application [20, 23].

Postoperative vaginal estrogen use after pelvic reconstructive surgery

Three studies evaluated the use of vaginal estrogen after pelvic reconstructive surgery with 297 combined participants; overall quality of evidence was poor (Table 2) [24–26]. Liapis et al. and Zullo et al. gave vaginal estradiol tablets (25 μg) and estriol ovules respectively, or no treatment for 6 months after placement of a midurethral sling [24, 26]. Karp et al. evaluated a vaginal estradiol ring (Estring®) or placebo ring for 12 weeks following transvaginal repair of POP [25].

There were net benefits to estrogen application after surgery, with decreased prevalence or severity of urinary frequency and urgency (moderate quality) [24, 26] and less common granulation tissue (compared with placebo vaginal ring, low quality) [25] and other objective signs of atrophy (very low to low quality) [25]. The impact of local estrogen upon prolapse recurrence, nocturia, urgency urinary incontinence, urodynamic measures, or postoperative UTI was uncertain. No studies were powered to determine the effect of postoperative vaginal estrogen on surgical complications such as mesh erosion, and none assessed for impact on the endometrium or serum estradiol levels. There were no significant adverse events attributable to the vaginal estrogen treatment.

Vaginal estrogen use in postmenopausal women with OAB or SUI

Five studies with 441 total participants evaluated vaginal estrogen against other agents in postmenopausal women

Table 1 Preoperative vaginal estrogen use before pelvic organ prolapse repair surgery

Reference	Country	Study quality	Intervention (*n*)	Comparator (*n*)	Study duration	Summary of findings							
						Objective atrophy measures				UTI frequency, within 4weeks postoperatively	UTI frequency, beyond immediate postoperative period	Serum estradiol	Endometrial pathology
						Vaginal maturation indices	Epithelial thickness	Subepithelial thickness	Investigator scales of atrophy				
Felding et al. [20]	Denmark	B	Vaginal estradiol tablet 25 μg. Daily 3 weeks, then surgery (22)	Placebo tablet. Same frequency (23)	3 weeks preoperatively; observation 4 weeks postoperatively	I	I			I	NS	NS	NS[b]
Mikkelsen et al. [21][a]	Denmark	C	Vaginal estradiol tablet 25 μg. Daily 3 weeks, then surgery (21)	Placebo tablet. Same frequency (19)	3 years postoperatively						NS		
Vaccaro et al. [22]	USA	A	Conjugated estrogens cream (0.625 mg/g) 1 g nightly (22)	No treatment (20)	2–12 weeks preoperatively, then observation at surgery	I	NS	NS	NS				
Rahn et al. [23]	USA	B	Conjugated estrogens cream (0.625 mg/g) 1 g. Nightly 2 weeks, then 2x/week (12)	Placebo cream. Same frequency (12)	6–8 weeks preoperatively, then observation at surgery		I	NS				NS	NS[c]

I outcome more favorable in intervention, *NS*,no significant difference between intervention and comparator, *UTI* urinary tract infection

[a] This is the 3-year extension of Felding et al. [20]

[b] Two cases of simple hyperplasia without atypia in estrogen-treated participants

[c] All patients underwent hysterectomy with 0 cases of secretory, proliferative, or hyperplastic endometrium

Table 2 Postoperative vaginal estrogen use after pelvic reconstructive surgery

Reference	Country	Study quality	Intervention (*n*)	Comparator (*n*)	Study duration	Summary of findings				
						Objective atrophy measures				Urinary complaints
						Vaginal maturation indices	Vaginal pH	Granulation tissue	Investigator scales of atrophy	Urinary urgency
Liapis et al. [24]	Greece	B	Vaginal estradiol tablet 25 μg. Daily 2 weeks, then 2x/week (92)	No treatment (91)	6 months after TVT-O					I
Zullo et al. [26]	Italy	A	Estriol ovule 1 mg. Daily 1 month, then 2 mg/week (28)	No treatment (28)	6 months after TVT					I
Karp et al. [25][a]	USA	B	Vaginal estradiol ring. Placed once (22)	Placebo ring. Placed once (21) or no treatment[a] (22)	12 weeks after vaginal POP repair	I	I	I	I	

Reference	Summary of findings								
	Urinary complaints			Urodynamic study measures					UTI frequency
	Urinary frequency	Nocturia	Urgency urinary incontinence	Max urethral closure pressure	Maximum flow rate	Maximum bladder capacity	Postvoid residual	Proportion with detrusor overactivity	
Liapis et al. [24]	I	NS	NS	NS	NS	NS	NS		NS
Zullo et al. [26]	NS	NS		NS	NS	NS	NS	NS	
Karp et al. [25][a]									

I outcome more favorable in intervention, *NS* no significant difference between intervention and comparator, *TVT-O* trans-obturator tape mid-urethral sling, *TVT* tension-free vaginal tape mid-urethral sling, *POP* pelvic organ prolapse

[a] A third study arm with no treatment was performed (results not shown here)

Table 3 Vaginal estrogen use in postmenopausal women with overactive bladder and stress urinary incontinence

Reference	Country	Study quality	Intervention (*n*)	Comparator (*n*)	Study duration (weeks)	Summary of findings			
						Objective atrophy measures			Urinary complaints
						Vaginal maturation indices	Vaginal pH	Investigator scales of atrophy	Urinary urgency
Overactive bladder sub-population									
Nelken et al. [29]	USA	B	Vaginal estradiol ring. Placed once (28)	Oxybutynin 5 mg po bid (31)	12	I	I		NS
Serati et al. [30]	Italy	A	Tolterodine ER 4 mg po daily +daily estriol cream (102)	Tolterodine ER 4 mg po daily (129)	12				NS
Tseng et al. [31]	Taiwan	A	Tolterodine 2 mg po bid+ conjugated estrogens cream (0.625 mg/g) 1 g 2x/week (40)	Tolterodine 2 mg po bid (40)	12				NS
Stress urinary incontinence sub-population									
Beisland et al. [27][a] SUI with ISD[b]	Norway	B	Estriol 1 mg suppositories daily (20)	PPA 50 mg po bid (20) or combined treatment[a] (20)	4	I			
Kobata et al. [28][c] SUI without ISD	Brazil	B	Conjugated estrogens cream (0.625 mg/g) 1 g daily (17)	Estriol 1 mg cream daily (16) or promestriene 10 mg cream daily[c] (18)	12				

Reference	Summary of findings							
	Urinary complaints			Maximum urethral closure pressure	Adverse events			
	Frequency/nocturia	Urgency urinary incontinence	SUI, improvement or cure		Dry mouth	Constipation	Blurry vision	Vaginal discharge
Overactive bladder sub-population								
Nelken et al. [29]	NS	NS			I	I	I	C
Serati et al. [30]	NS	NS						
Tseng et al. [31]	I	NS						
Stress urinary incontinence sub-population								
Beisland et al. [27][a] SUI with ISD[b]			C	NS				
Kobata et al. [28][c] SUI without ISD			I					

I outcome more favorable in Intervention, *C* outcome more favorable in Comparator, *NS* no significant difference between Intervention and Comparator, *SUI* stress urinary incontinence, *ISD* intrinsic sphincteric deficiency, *ER* estradiol, *PPA* phenylpropanolamine

[a] A third study arm with combined estriol+PPA was performed – results not shown here

[b] ISD parameters not strictly defined by authors

[c] A third study arm with promestriene 10 mg cream daily was also performed (results not shown here)

presenting with OAB or SUI (Table 3) [27–31]. Overall quality of evidence was poor. Outcomes were evaluated following 4 [27] to 12 weeks [28–31] of therapy.

For women with OAB, both the vaginal estradiol ring and an immediate-release oral anticholinergic (oxybutynin 5 mg by mouth twice daily) similarly improved urinary urgency, frequency, or urgency urinary incontinence (low quality evidence), although the oral anticholinergic demonstrated a higher rate of side effects (constipation, dry mouth, blurry vision) and discontinuation compared with vaginal estrogen [29]. The addition of local estrogen (various methods) to tolterodine (immediate or extended-release forms) did not offer an advantage over tolterodine alone in urinary urgency, nocturia, or urgency urinary incontinence (moderate quality evidence) [30, 31], but one of the studies did demonstrate significantly fewer voids per day and greater voided volumes in the tolterodine plus estrogen arm [31].

For postmenopausal women with SUI without intrinsic sphincteric deficiency treated daily with 1 g of conjugated estrogen cream (0.625 mg/g) or estriol 1 mg cream, improvement in leakage was observed for both therapies (very low quality evidence) [28]. Beisland et al. examined postmenopausal women with SUI with intrinsic sphincteric deficiency (not specifically defined) and compared vaginal estriol 1 mg suppositories with an alpha agonist (phenylpropanolamine (PPA), no longer FDA approved) to combined estriol plus PPA. Greater cure or improvement in leakage was observed in combined estrogen plus PPA therapy compared with either estrogen or PPA alone (very low quality evidence); data were insufficient to comment on the potential harms of PPA or estrogen therapy [27].

In all these studies from this patient subpopulation, data were insufficient to assess impact on the endometrium or serum estradiol levels.

Discussion

Using this comprehensive systematic review of randomized controlled trials comparing vaginal estrogen with placebo, no treatment, and anticholinergic agents, the SGS-SRG has developed evidence-based clinical practice guidelines describing the utility of vaginal estrogen in the management of postmenopausal women presenting with various urogynecological complaints (Table 4). Most of these recommendations are 2C, meaning low quality of evidence supporting a suggestion that the majority of patients would want to follow, but many would not. Physicians must still judge each patient independently and arrive at a management decision consistent with the individual's preferences. From a policymaking standpoint, there is still much room for debate and need for additional evidence.

Table 4 Clinical practice guidelines for vaginal estrogen use in postmenopausal women with urogynecological complaints

Presuming no contraindication to vaginal estrogen, in postmenopausal women...			Grade
undergoing pelvic reconstructive surgery with a midurethral sling[a]	we suggest	postoperative application of vaginal estrogen (agents studied: vaginal estradiol tablet, ring, and estriol ovules) to prevent or treat urinary urgency and frequency	2C
presenting with symptoms of OAB (urinary urgency, frequency, and urgency urinary incontinence) considering immediate-release oral anticholinergic	we suggest	either immediate-release oral anticholinergics (agent studied: oxybutynin 5 mg po twice a day) or application of vaginal estrogen (agent studied: vaginal estradiol ring); oral anticholinergics had a greater occurrence of side effects	2C
presenting with symptoms of SUI (without intrinsic sphincteric deficiency)	we suggest	application of vaginal estrogen (agents studied: conjugated estrogens and estriol creams)	2D

"Grade" provides a level of strength (1 "strong" or 2 "weak") to the guideline, combining quality of the supporting evidence (A high to D very low) with the size of the net medical benefit. See Discussion

OAB overactive bladder, *SUI* stress urinary incontinence

[a] Postoperative use of vaginal estrogens did not demonstrate an improvement over no treatment in addressing symptoms of nocturia (moderate-quality evidence), urgency urinary incontinence (very low-quality evidence), or UTI frequency (very low-quality evidence) in this population

A Cochrane review by Ismail et al. designed 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, but that oral raloxifene may reduce the need for POP surgery in women older than 60 years [32]. While our review adds two additional studies to those identified by the Cochrane review [22, 23], the evidence was still too sparse to support a guideline for the preoperative use of vaginal estrogen before POP repair. Nonetheless, the increase in vaginal epithelial thickness observed in those participants complying with vaginal estrogen [20, 23] may provide a benefit for wound healing. This hypothesis gains some support from Karp et al., where participants receiving the postoperative vaginal estradiol ring demonstrated less granulation tissue compared with those using a placebo vaginal ring [25]. The foreign body placebo ring likely contributed to this inflammatory reaction. An improvement in wound healing may translate to a reduction in erosion of mesh materials utilized in transvaginal repairs and sacral colpopexies, although none of the studies identified in this review were sufficiently large to address this question. Using a Markov state transition model to simulate the probability of 2-year outcomes of mesh erosion, visceral injury, and reoperation after vaginal mesh prolapse surgery or minimally invasive sacral colpopexy, with or without vaginal estrogen, Weidner and colleagues suggest that the required sample size for such a trial might be prohibitively large, ranging from 448 to 1,620 participants depending on the power and the possible efficacy of vaginal estrogen [33].

Estrogen's utility in the management of urinary incontinence has also been reviewed by Cody et al. [34]. They included studies of both systemic and vaginal estrogen and came to the important conclusion that the route of therapy has very different effects: oral systemic estrogen worsened incontinence (RR 1.11, 95 % CI 1.04–1.18), while vaginal estrogen (creams or pessaries) improved incontinence (RR 0.74, 95 % CI 0.64–0.86). Of note, this Cochrane review included many participants receiving estrogen for reasons other than urinary incontinence. Our review collected the few studies of postmenopausal women presenting specifically with a complaint of OAB or SUI and receiving vaginal estrogen as an intervention. We also concluded that vaginal estrogen appears to have utility in the treatment of both conditions and may even provide similar improvements to short-acting oxybutynin in OAB [29]. However, adding estrogen to tolterodine did not significantly reduce urgency, nocturia, or urgency urinary incontinence beyond those improvements seen with tolterodine alone [30, 31]. It is unknown whether other anticholinergic drugs or newer beta agonist medications will also be superior to vaginal estrogens alone in the management of OAB. However, this review underscores that there remains a role for vaginal estrogen as a treatment or adjunct in the treatment of OAB and SUI.

The strengths of this review are its robust methodology and the transparent means of evidence-based clinical practice guideline development. There are, however, several limitations. Foremost, we are limited by the quality of the studies included. Clinical practice guidelines are primarily based on poor to moderate overall quality of evidence. Patient blinding to intervention was not possible for many of these studies that allowed either no treatment as the comparator [22, 24–26] or an oral agent with no vaginal placebo [27, 29–31]. In those studies of vaginal estrogen for the treatment of OAB or SUI, therapy only lasted up to 12 weeks; thus, one cannot comment on the long-term efficacy or safety. While application of vaginal estrogen for a short duration is presumed to have few consequences, safety data were extremely limited in all of these trials, with only two of the preoperative vaginal estrogen studies including data on serum estradiol concentrations and endometrial pathology. Given the estrogens included and the available comparators in the literature, we cannot comment on the relative efficacy or safety of compounded vaginal estrogen products, non-hormonal moisturizers, or ospemifene (i.e., the oral selective estrogen receptor modulator approved for the treatment of moderate to severe dyspareunia).

This review reveals areas for improvement in subsequent trials of vaginal estrogens for the management of POP. No study providing vaginal estrogen preoperatively has attempted to objectively track prolapse recurrence for a meaningful postoperative duration. Mikkelsen et al., who described the 3-year postoperative outcomes after preoperative treatment with vaginal estradiol or placebo tablets before POP repair, did include a questionnaire of patient satisfaction, but no standardized or validated metric of prolapse symptoms [21]. Further, if vaginal estrogen does, in fact, improve the substrate for suture (or mesh) placement at the time of surgery, the therapy may need to be continued postoperatively until the time of complete scar maturation [23]. There is no study currently that provides this combination of pre- and postoperative vaginal estrogen. Finally, as noted above, studies of vaginal estrogen application need more consistent assessment of discontinuation rates and the reasons for discontinuation, and of safety with evaluation of the endometrium—if still with a uterus—in addition to sensitive measurements for changes in serum estradiol [35].

Conclusion

In conclusion, this systematic review of randomized trials confirms that vaginal estrogen can play an important role as an adjunct in the management of common pelvic floor disorders in postmenopausal women. Preoperative use before POP repair may decrease the likelihood of early postoperative UTI and could provide a better substrate for suture or mesh

placement. Further, postoperative use after midurethral sling could decrease the development of urinary urgency and frequency. Postmenopausal women presenting with OAB or SUI who are amenable to a trial of vaginal estrogen may see improvement in symptoms without the common side effects of alternative medications and interventions. Importantly, additional research is needed with longer patient follow-up and consistent assessment of changes in the endometrium and in serum estradiol.

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Conflicts of interest None.

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