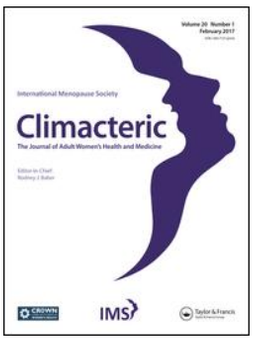

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REVIEW

The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review

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ABSTRACT

Objectives: To evaluate the efficacy and safety of estriol for the treatment of vulvovaginal atrophy in postmenopausal women.

Methods: A systematic literature review was performed. We searched the following electronic databases: Medline, Cochrane, Embase, Lilacs, CINHAL and Google Scholar. The studies selected included controlled clinical trials and quasi-experimental studies. Selections were made in pairs and independently, first by title and abstract and then complete texts.

Results: We identified 188 studies, 22 of which met the inclusion criteria; 13 were controlled clinical trials and nine were quasi-experimental, and 1217 women were included. These studies confirmed the efficacy of local estrogens to treat symptoms of vulvovaginal atrophy with few adverse effects reported. Following treatment, serum estriol levels rose, peaking at 1 h. At the 6-month follow-up, there was no increase in serum estriol in treated women.

Conclusions: The available evidence (of low and moderate quality) shows that, when administered vaginally, estriol preparations appear to be safe for women who have risk factors related to systemic estrogen therapy.

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KEYWORDS
Estriol; vulvovaginal atrophy; systematic literature review

Introduction

Vulvovaginal atrophy (VVA) is part of a collection of symptoms, including those of the urinary tract, now known as the genitourinary syndrome of menopause[1]. With increased life expectancy, many women will spend more than one-third of their lives after their last menstrual period. It is important to recognize the signs and symptoms of VVA which present commonly after the menopause and to provide adequate treatment to improve quality of life[2,3].

Up to 45% of postmenopausal women present with symptoms associated with VVA. It affects the quality of life of over 80% of patients. VVA symptoms are a problem in postmenopausal women who have a history of breast cancer and are thus unable to use systemic estrogen therapy. Of women undergoing chemo- and radiotherapy, 64% experience decreased libido and 42% dyspareunia[4–7].

Topical VVA treatments are divided into two types: non-hormonal lubricants and moisturizing creams, which may alter pH but do not alter the vaginal maturation index[4]. Topical hormonal treatments have been shown to restore vaginal pH and increase epithelium thickness and revascularization, thereby increasing vaginal lubrication. Ten to 15% of women receiving systemic menopausal hormone therapy (MHT) will also require topical estrogen therapy for VVA. Because of possible systemic effects, several guidelines have recommended avoiding the use of topical vaginal estrogens in patients with a history of breast cancer[4].

Treatment efficacy has been reported for 80–90% of women using topical estrogen preparations, by measuring the maturation index, changes in vaginal pH and improvement of symptoms[8]. Topical estrogen preparations include vaginal rings, pessaries and creams containing conjugated estrogens, estradiol and estriol. A 2006 Cochrane systematic review found them to be equally effective for improving symptoms[9].

Materials and methods

A balanced search strategy was performed to identify relevant references. The search strategy was created with the PubMed platform and was adapted for the rest of the databases consulted: Medline, Cochrane, Embase, Lilacs, CINHAL and Google Scholar. The subject search and text word search were done separately in all databases and then combined. DeCS terms included estriol and vulvovaginal atrophy.

To minimize reporting and selection biases, we used a robust and sensitive search strategy which included electronic and manual searches, reviews of gray literature and conference abstracts, records from clinical trials and researchers working in the areas of menopause and hormone supplements.

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Studies selected included controlled clinical trials and quasi-experimental studies comparing vaginal estriol with placebo, with different formulations or with other types of vaginal estrogens for the treatment of VVA in postmenopausal women; the studies had to be written in English, Spanish or Portuguese. The exclusion criteria were studies that did not include the outcomes of interest to the systematic review and for which the complete text could not be obtained.

Selections were made in pairs and independently, first by title and abstract and then complete texts of the studies that met the eligibility criteria. If disagreements arose between the pair of evaluators, a third participated in order to resolve the differences in criteria. For the extraction of data and synthesis of evidence, we followed the methodology in the Cochrane Manual for Systematic Reviews of Interventions and we independently evaluated the risk of bias using the Cochrane risk of bias assessment tool[10]. Each study was evaluated according to the six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Additional, the GRADE instrument was used to synthesize the evidence and calculate its global score. The criteria proposed by the GRADE group include: the limitations of the study, risk of bias, coherent effect, inaccuracy, indirectness and reporting bias. For each outcome, we explained and documented our assessments of the quality of the evidence (high, moderate or low)[10,11].

For the dichotomous data, we used the number of events in the control and intervention groups in each study. The odds ratio (OR), relative risk (RR) and difference in means reported by the primary studies were entered along with their 95% confidence intervals (CI) for all of the results. The characteristics of the studies included in this review were evaluated to determine whether the participants, interventions and results were similar enough to perform a meta-analysis. These were found to be inadequate, the statistical value over 50% indicating substantial heterogeneity[10].

Results

We identified 176 bibliographical references through the electronic database search and 12 references through the manual search based on consultation with experts. Forty references were excluded because they were duplicate references ($n = 2$) or were not available in English, Spanish or Portuguese ($n = 38$). After screening by title and abstract, the full texts of 32 studies were obtained for analysis, ten of which did not include the outcome of interest to the systematic review ($n = 7$) or the interventions established by the researchers ($n = 3$). The final selection included 22 studies: 13 controlled clinical trials and nine quasi-experimental studies (Figure 1).

Our included studies were published between 1980 and 2012. The studies ranged in size from three to 251

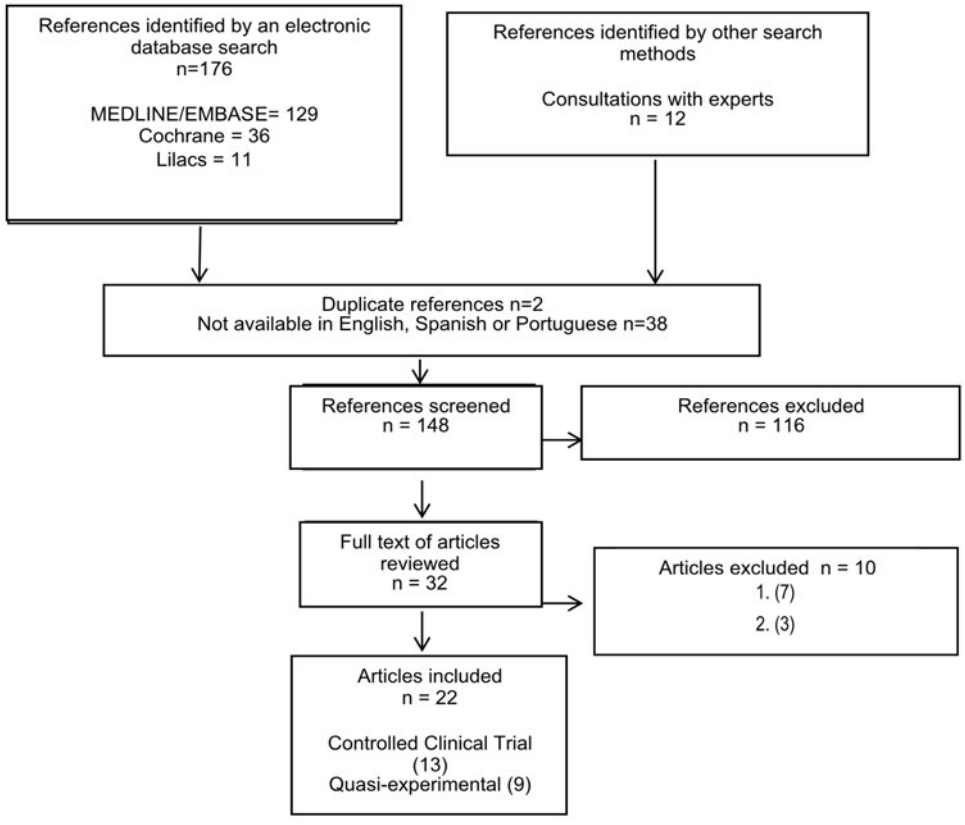

Figure 1. Flow diagram of the selection and assessment of the studies.

participants, with a total number of 1234 postmenopausal women with VVA. The study participants ranged in age from 44 to 87 years[12–33]. To be included, each study was required to include an estriol arm (Table 1).

Risk of bias

The risk of bias in the studies was that information available about treatment groups and their randomization was poor. Studies which could not blind patients to the type of intervention were classified as an unclear risk of bias. Most studies did not specify how the evaluators were blinded to the intervention and, therefore, these were also classified as unclear risk. Last, measurement bias is present since there was no standardization for the evaluation of the results in the studies reviewed. Figure 2 presents the assessment of the global risk of bias.

Genitourinary symptoms

Twelve studies provided data for genitourinary symptoms[12–23]. The follow-up period ranged from 56 days to 12 months (Table 2). Not all studies included a placebo group.

Studies assessing improvement in urinary symptoms between estriol pessaries and the estradiol vaginal ring found the two interventions to be equal in alleviating urinary urgency (51% vs. 56%), urgency incontinence (58% vs. 58%), stress incontinence (53% vs. 59%) and nocturia (51% vs. 54%). Differences in urinary frequency and dysuria were not statistically significant[12]. A study that compared vaginal estriol plus rehabilitation of the pelvic floor versus rehabilitation of the pelvic floor alone, and another, which assessed estriol versus placebo, reported a subjective improvement in urgency incontinence and stress incontinence in the estriol-treated group (73.49% vs. 9.71%, $p < 0.01$) and a decrease in bacteriuria after 6 months (43.75% vs. 19.23%, $p < 0.001$)[13,14]. A further study, which compared estriol cream versus placebo, found the annual mean incidence of urinary tract infections was significantly less for the estriol group (0.5 vs. 5.9 episodes per patient year, $p < 0.001$)[15].

For patients treated with estriol compared with no adjunctive medical treatment after placement of tension-free vaginal tape (TVT), improvement in stress incontinence was the same for both groups. Urinary frequency was more persistent in the control group but did not achieve statistical significance. The only symptom that improved during the 6-month follow-up period was the incidence of urgency, which was found in 4% (1/28 patients) of the intervention group and 29% (8/28 patients) of the control group ($p = 0.01$)[16].

VVA effects

Studies comparing vaginal estriol pessaries with the estradiol vaginal ring or vaginal estriol tablets found no difference in response of vaginal pH or subjective improvement in symptoms. Vaginal maturation index improvement was greater with the estradiol ring[17–19].

Studies comparing estriol with placebo found a significant improvement in vaginal atrophy, dryness and dyspareunia in the treatment group compared to the control group. An increase in lactobacillus colonization from 0 to 58% with a concurrent decrease in Enterobacter colonization was also reported[15]. Significant improvement was also found on colposcopy, with a reduction of the portio epithelium thickness in the treatment group from 100% to 30% as well as increases in vaginal pH and karyopyknotic index of urethral epithelium[13]. A quasi-experimental study that assessed treatment with suppositories containing estriol 1 mg and progesterone 30 mg found significant improvements in vaginal dryness, vaginal pH and maturation index as well as menopausal quality of life[21].

A study that compared 0.5 mg estriol cream versus pessaries and another study that compared 0.5 mg versus 1 mg estriol vaginal cream did not find differences between the two treatment groups in terms of clinical evaluation, cervical mucus, the vaginal maturation index or colposcopy results[22,23].

Estriol levels in plasma

Eleven studies contributed data on plasma estriol levels using radioimmunoassay techniques[20–30]. The follow-up period in these studies ranged from 30 min to 6 months (Table 3). Most but not all of these studies found a short-term increase in serum estriol levels following treatment with vaginal estriol preparations. Mattsson and Cullberg[22] found levels of estriol remained below detection for 20 h following treatment with 0.5 mg estriol cream or pessaries. There were no changes in sex hormone binding globulin or estrone levels.

Four studies[23–26] found serum estriol levels peaked 1 h after administration of 1 mg vaginal estriol cream or pessaries, thereafter tapering over 21 days. One study of 0.5 mg estriol administered vaginally found an increase in serum estriol which peaked on day 21 and thereafter declined[20].

Another study found that estriol (0.5 mg/day vaginally) reached its maximum incremental peak 12 h after administering the medication, rising from 21 pmol/l to 70 pmol/l[27]. The studies reported a range of times at which the maximum incremental peak occurred, which may in part reflect dosing differences and different pharmacokinetics for estriol, conjugated estrogens and estradiol administered vaginally but may also reflect inaccuracy of radioimmunoassay at low hormone levels[30]. Considerable differences also existed among individuals, resulting in different blood concentrations while using the same estriol treatment[28,29].

Although most studies assessed short-term blood levels, one study of 1 mg estriol with progesterone pessaries reported that the serum estriol level continued to rise for 3 months and plateaued for up to 6 months[21].

Effects at the endometrial level

Four studies, with follow-up from 1 day to 12 months, contributed to data on endometrial effects[27,31–33] (Table 4). The administration of 0.5 mg estriol led to an increase in the

Table 1. Characteristics of the studies included.

Author; country	Study design	Study period	Sample size	Age group (years)	Types of intervention	Duration of intervention	Outcome	Risk of bias
Lose[12]; Denmark	CCT	September 1994 and April 1996	251	47–87	Estradiol ring 7.5 mg vs. 0.5 mg estriol pessaries	24 weeks	Urinary tract symptoms	RSG: LR; AC: LR; BPP: UR; BER: UR; IOD: UR; SOR: LR
Capobianco[13]; Italy	CCT	May 2005 to April 2010	206	55–70	Estriol pessaries 1 mg daily plus rehabilitation of the pelvic floor muscles and electrical stimulation vs. only estriol	6 months	Genitourinary symptomatology, urinary cultures, colposcopy findings	RSG: LR; AC: LR; BPP: UR; BER: UR; IOD: LR; SOR: LR
Zullo[16]; Italy	CCT	September 2000 to December 2003	56	Mean 56.4 and 55.9	Estrogens after placement of TVT vs. not treatment	6 months	Not losing urine during the stress and urodynamic testing	RSG: UR; AC: UR; BPP: UR; BER: LR; IOD: LR; SOR: LR
Dessole[14]; Italy	CCT	May 1999 to April 2002	88	56–58 ± 5	Estriol pessaries 1 mg vs. placebo pessaries	6 months	Genitourinary symptoms, urinary cultures, colposcopy findings, urinary cytology findings	RSG: LR; AC: LR; BPP: LR; BER: UR; IOD: LR; SOR: LR
Van Haaften[27]; Netherlands	CCT	No information	20	49–82	No treatment vs. vaginal estriol 0.5 mg and estradiol 0.05	12 hours	Levels of estrogen in blood, uterine and vaginal tissue in women after hysterectomy	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: UR
Mattsson[22]; Sweden	CCT	No information	27	50–72	Estriol cream 0.5 mg vs. estriol pessary 0.5 mg	8 weeks	Endometrial biopsies and levels of unconjugated and conjugated estriol, FSH, LH, prolactin and SHBG	RSG: UR; AC: UR; BPP: UR; BER: UR;IOD: UR; SOR: UR
Mattsson[29]; Sweden	CCT	No information	8	54–63	0.5 mg vaginal estriol cream or pessary	14 days	Conjugated and unconjugated estriol, FSH and LH	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: UR
Kicovic[23]	CCT	No information	53	44–82	Estriol cream 1 mg for 3 weeks vs. 0.5 mg for 3 weeks vs. 0.5 mg for 2 weeks	16 weeks	Vaginal cytology and colposcopic findings. Effect on plasma levels (estriol, estradiol, FSH, LH, prolactin and SHBG)	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: LR
Raz[15]; Israel	CCT	No information	93	51–81	Estriol cream 0.5 mg vs. placebo	8 months	Urinary tract infection, use of antibiotics and vaginal pH and lactobacillus	RSG: LR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: LR
Punnonen[28]; Finland	CCT	No information	10	5071	Conjugated estrogens 2.4 mg vs. micronized estradiol 2 mg vs. estriol pessaries 0.5 mg	24 hours	Total blood levels of estrone, estriol and estradiol	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: LR
Van Haaften[33]; Netherlands	QE	No information	20	49–81	Estriol 0.5 mg and estradiol 0.05 mg vs. control group	3 weeks	Influence of estriol and estradiol on the concentration of estrogen and progesterone receptors after hysterectomy	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: UR
Chollet[21]; Israel	QE	No information	19	51–70	Estriol pessary 1 mg and progesterone 30 mg	6 months	Vaginal pH, maturation index, uroanalysis, subjective improvement of symptoms, blood levels and endometrial biopsies	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: LR; SOR: UR
Englund[31]; Sweden	QE	No information	5	50–74	Estriol pessaries 0.5 mg	16 days	Histopathologic evaluation of the endometrial structure	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Batra[24]; Sweden	QE	No information	17	44–73	Estriol pessaries 1 mg in women who underwent surgery for uterine prolapse	14 h pre-operative and 1 h post	Estriol levels in plasma, progesterone receptors in vagina and myometrium	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Henriksson[17]; Finland & Denmark	CCT	No information	165	46–80	Micronized estradiol ring 2 mg vs. pessary 0.5 mg	12 weeks	Genitourinary symptoms, appearance of vaginal mucosa evaluated by physical exam and laboratory	RSG: UR; AC: UR; BPP: HR; BER: HR; IOD: UR; SOR: LR
Keller[25]; Switzerland	QE	No information	3	62–72	Estriol pessary daily 0.5 mg	10 days	Peak of estriol in plasma, FSH, LH and prolactin levels	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Dugal[18]; Norway	CCT	No information	96	Mean 58.2	Estradiol tablets 25 μg vs. estriol pessaries 0.5 mg	24 weeks	Cytology results and genitourinary symptoms	RSG: UR; AC: UR; BPP: LR; BER: UR; IOD: UR; SOR: LR

(*continued*)

Table 1. Continued

Author; country	Study design	Study period	Sample size	Age group (years)	Types of intervention	Duration of intervention	Outcome	Risk of bias
Gerbaldo[32]; Italy	QE	No information	23	64.0 ± 9.2	Estriol cream 0.5 mg	12 months	Endometrial structure by hysteroscopy and histological examination before and after treatment	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Haspels[20]; Italy	QE	No information	11	54–70	Estriol cream 0.5 mg	56 days	Degree of maturation, blood levels of FSH and LH	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Heimer[26]; Sweden	QE	No information	6	53–62	Estriol pessary 1 mg	21 days	Estriol levels in plasma	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Heimer[30]; Sweden	QE	No information	9	53–62	Estriol pessary 0.5 mg	21 days	Estriol levels in plasma	RSG: HR; AC: HR; BPP: HR; BER: HR; IOD: LR; SOR: LR
Iosif[19]; Sweden	CCT	1980–1989	48	57–65	Estriol pessary 0.5 mg	10 years	Histological examination of the endometrium	RSG: UR; AC: UR; BPP: UR; BER: UR; IOD: UR; SOR: LR

CCT, controlled clinical trial; QE, quasi-experimental; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; RSG, random sequence generation; AC, allocation concealment; BPP, blinding of participants and personnel; BER, blinding of evaluators to the result; IOD, incomplete outcome data; SOR, selective outcome reporting; LR, low risk; UR, unclear risk; HR, high risk; TVT, tension-free vaginal tape.

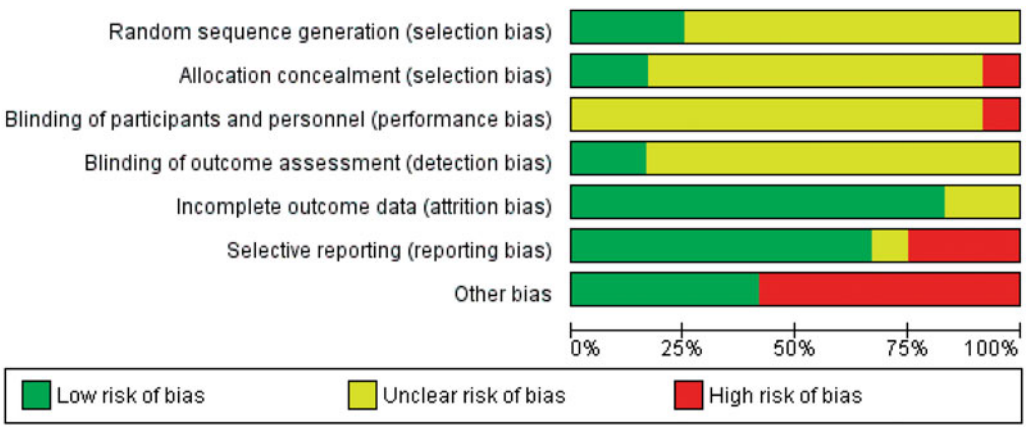

Figure 2. Assessment of global risk of bias.

Table 2. Vulvovaginal atrophy symptoms.

Author; country	Study design	Sample size	Symptoms	Intervention group		Control group		p-Value
				Before treatment	After treatment	Before treatment	After treatment	
Lose[12]; Denmark	CCT	251		*Estradiol-releasing vaginal ring* ($n = 134$)		*Estriol pessary* ($n = 117$)		
			Urgency	84%	51%	91%	56%	
			Frequency	75%	61%	73%	58%	
			Urge incontinence	66%	58%	64%	58%	
			Stress incontinence	67%	59%	58%	59%	
			Nocturia	60%	54%	66%	54%	
			Dysuria	25%	63%	23%	63%	
Capobianco[13]; Italy	CCT	206		*Vaginal estriol + rehabilitation of the pelvic floor* ($n = 103$)		*Rehabilitation of the pelvic floor alone* ($n = 103$)		
			Urinary incontinence	83/103 (80.58%)	22/103 (21.36%)	103/103 (100%)	93/103 (90.29%)	$<0.01^a$
			Significant bacteriuria	52/103 (50.48%)	10/103 (9.71%)	48/103 (46.60%)	21/103 (20.39%)	$<0.001^a$
			Vaginal dryness	103/103 (100%)	32/103 (31.07%)	103/103 (100%)	82/103 (79.61%)	$<0.01^a$
			Dyspareunia	75/103 (72.81%)	15/103 (14.56%)	65/103 (63.11%)	57/103 (55.34%)	$<0.001^a$
			Urogenital atrophy	103/103 (100%)	25/103 (24.27%)	103/103 (100%)	37/103 (35.92%)	$<0.01^a$
			Vaginal pH	5.53 ± 0.86	4.34 ± 0.76	5.36 ± 0.74	4.62 ± 0.81	$<0.05^b$
			Portio epithelium thickness reduction	103/103 (100%)	31/103 (30.10%)	103/103 (100%)	35/103 (33.98%)	$<0.01^a$
Dessole[14]; Italy	CCT	88		*Intravaginal estriol ovules* ($n = 44$)		*Placebo* ($n = 44$)		
			Urinary incontinence	44/44 (100%)	14/44 (31.8%)	44/44 (100%)	37/44 (84.09%)	$<0.01^a$
			Significant bacteriuria	17/44 (38.6%)	6/44 (13.63%)	16/44 (36.36%)	20/44 (45.45%)	$<0.001^a$
Raz[15]; Israel	CCT	93		*Intravaginal estriol* ($n = 50$)		*Placebo* ($n = 43$)		
			Episodes of infection		0.5		5.9	<0.001
			Vaginal pH	5.5 ± 0.7	3.6 ± 1.0	5.8 ± 1.2	6.1 ± 2.0	<0.001
			Lactobacilli	0	21 (58%)	0	0	<0.001
			Enterobacteriaceae	24 (67%)	10 (28%)	16 (67%)	17 (71%)	<0.005
Zullo[16]; Italy	CCT	56		*Intravaginal estriol ovules + TVT* ($n = 28$)		*TVT* ($n = 28$)		
			Frequency	2 (7)	2 (7)	1 (4)	5 (18)	ns
			Urgency	2 (7)	1 (4)	2 (7)	8 (29)	0.01
			Nocturia	0	0	1 (4)	1 (4)	ns
Henriksson[17]; Finland & Denmark	CCT	165		*Estradiol vaginal ring* ($n = 112$)		*Estriol pessary* ($n = 53$)		
			Vaginal dryness	89%		71%		ns
			Atrophy	82%		67%		ns
Dugal[18]; Norway	CCT	96		*Estradiol vaginal tablets* ($n = 48$)		*Estriol ovules* ($n = 48$)		
			Symptoms	75%	44%	75%	54%	<0.0001
Iosif[19]; Sweden	CCT	48		*Estriol pessary 0.5 mg* ($n = 48$)				
			Symptoms	100%	79–98%			
Haspels[20]; Italy	QE	11		*Estriol vaginal cream* ($n = 11$)				
			Maturation value	39.4 ± 3.8	72 ± 3.9			
Chollet[21]; Israel	QE	19		*Estriol pessary 1 mg and progesterone 30 mg* ($n = 19$)				
			VMI	R: 0–55 (M: 40)	R: -5–65 (M: 15)			<0.001
			Vaginal pH	R: 5–7.5 (M: 6)	R: 4–7.0 (M: 4.5)			<0.001
			Vaginal dryness	R: 6–10 (M: 9)	R: -10– -3 (M: -7)			<0.001
Mattsson[29]; Sweden	CCT	27		*Estriol cream 0.5 mg* ($n = 14$)		*Estriol vaginal suppository* ($n = 13$)		
			Cervical mucus	0	2.5	0	1.5	<0.001
			Vaginal cytology: KI	0.5	43.4	0.5	16.5	<0.01
Kicovic[23]	CCT	53		*Estriol vaginal cream 1 mg* ($n = 23$)		*Estriol vaginal cream 0.5 mg* ($n = 30$)		
			Cervical mucus	0	1.4	0		
			Maturation value	40	70	40	68	

CCT, controlled clinical trial; QE, quasi-experimental; TVT, tension-free vaginal tape; VMI, vaginal maturation index; R, range; M, median; ns, not significant; KI, karyopyknotic index.
[a], χ^2 test; [b], one-way ANOVA.

Table 3. Levels in plasma.

Author; country	Study design	Sample size	Symptoms	Intervention group: Before treatment	Intervention group: After treatment	Control group: Before treatment	Control group: After treatment	p-Value
Haspels[20]; Italy	QE	11		*Estriol vaginal cream* ($n = 11$)				
			Estriol levels	Undetectable[a]	Day 21: 86.8 ± 8.1			
					Day 35: 68.2 ± 6.3			
					Day 56: 60.4 ± 10.1			
			FSH, LH		Slight suppression			
			E1, E2, PRL, SHBG, TSH, GH, TRH, CBG, TBG		No changes			
Chollet[21]; Israel	QE	19		*Estriol pessary 1 mg and progesterone 30* mg ($n = 19$)				
			Estriol levels	0.1 ng/ml	2 weeks: 0.16 ng/ml			0.04
					3 months: 0.33 ng/ml			<0.001
					6 months: 0.35 ng/ml			<0.001
Mattsson[29]; Sweden	CCT	27		*Estriol cream 0.5 mg* ($n = 14$)		*Estriol vaginal suppository* ($n = 13$)		
			Unconjugated estriol	Not detectable	0.23 ± 0.08 nmol/l	Not detectable	0.11 ± 0.02 nmol/l	<0.001
			Conjugated estriol	0.28 ± 0.01 nmol/l	0.13 ± 0.01 nmol/l	0.33 ± 0.05 nmol/l	1.57 ± 0.2 nmol/l	<0.001
Kicovic[23]	CCT	53		*Estriol vaginal cream 1 mg* ($n = 23$)		*Estriol vaginal cream 0.5 mg* ($n = 30$)		
			Estriol levels	<12 pg/ml	1 h: 123.6 pg/ml	<12 pg/ml	1 h: 110.8 pg/ml	
					5 h: 70 pg/ml		5 h: 70 pg/ml	
			E1, E2, FSH, LH, PRL, SHBG		No changes		No change	
Batra[24]; Sweden	QE	17		*Estriol pessaries 1 mg + uterine prolapse* ($n = 10$)		*No treatment* ($n = 7$)		
			Estriol levels	10 pg/ml	1 h: 50 mg/ml			
Keller[25]; Switzerland	QE	3		*Estriol pessary 0.5 mg*				
			Estriol levels	R: 35–70 (M: 40) pg/ml	1 h: R: 500–1950 (M: 1290) pg/ml			
					2 days: R: 105–143 (M: 123) pg/ml			
					10 days: R: 125–495 (M: 293) pg/ml			
			E1, E2, FSH, LH		No changes			
Heimer[26]; Sweden	QE	6		*Estriol pessary 1 mg* ($n = 6$)				
			Estriol levels	Day 1: 9133 (AUC)	Day 21: 6743 (AUC)			0.05
					Decrease: 32.1%			
Van Haaften[27]; Netherlands	CCT	20		*Vaginal estriol 0.5 mg*		*No treatment*		
			Estriol levels	21 pmol/l	12 h: 70 pmol/l		No changes	
			E1, E2, FSH, LH, SHBG		No changes		No changes	
Punnonen[28]; Finland	CCT	10		*Estriol pessaries 0.5 mg* ($n = 5$)				
			Estriol levels	0.15 nmol/l	2 h: 0.4 nmol/l			0.05
					8 h: < 0.10 nmol/l			
					12 h: 0.09 nmol/l			
					24 h: < 0.05 nmol/l			
			E1, E2		No changes			

(*continued*)

Table 3. Continued

Author; country	Study design	Sample size	Symptoms	Intervention group		Control group		p-Value
				Before treatment	After treatment	Before treatment	After treatment	
Mattsson[22]; Sweden	CCT	8		*Estriol vaginal cream 0.5 mg*		*Estriol vaginal pessary 0.5 mg*		
			Unconjugated estriol	0	30 min: 0.3 nmol/l	0	30 min: 0.3 nmol/l	0.05
					2 h: 0.61 ± 0.11 nmol/l		1 h: 0.51 ± 0.24 nmol/l	0.01
					24 h: baseline levels		24 h: baseline levels	
			Conjugated estriol	0.3 nmol/l	4 h: 1.33 ± 0.17 nmol/l	0.29 nmol/l	8 h: 1.43 ± 0.33 nmol/l	<0.01
					48 h: baseline levels		48 h: baseline levels	
Heimer[30]; Sweden	QS	9		*Estriol pessary 0.5 mg*				
			AUC: 0–12 h		Morning: 5943			ns
					Evening: 4713.5			ns
			AUC: 0–24 h		Morning: 9941			ns
					Evening: 8722.5			ns

CCT, controlled clinical trial; QE, quasi-experimental; E1, estrone; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; SHBG, sex hormone binding globulin; TSH, thyrotropin; GH, growth hormone; CBG, corticosteroid binding globulin; TBG, thyroxine binding globulin; R, range; M, mean; AUC, plasma concentration curves; ns, not significant.
[a], < 35 pmol/l.

number of ciliated cells in the endometrium, together with some atypical protrusions consistent with an estrogenic response in the surface endometrium[31]. However, a study using 0.5 mg estriol vaginally twice weekly, with follow-up at 6 and 12 months by hysteroscopy and histology, found no endometrial estrogenic effects, with only atrophy seen and reported on histology[32].

Other studies have found administration of vaginal estriol 0.5 mg led to increased levels of estriol in the endometrium compared to the myometrium or vagina and no significant difference in uptake or retention of estriol between vagina and uterus. Serum estriol levels were increased 12 h after administration, whilst serum estradiol and estrone levels were unaffected[27,33].

Adverse events

The majority of the adverse events reported include local reactions such as discomfort (irritation, burning sensation, itching) and vaginal leukorrhea[12–15,18,19,22]. Reasons for discontinuing treatment included reports of fever and an asthmatic crisis, although the use of local estrogens was not considered to be a direct cause[17]. Some studies reported mastalgia, which was present in two patients treated with estradiol versus three patients treated with estriol[12]. No adverse events were reported in three studies[13–15].

One study evaluated systemic estriol levels plus endometrial histology and concluded that estriol is an effective therapy and does not pose a risk of endometrial hyperplasia or mastodynia[23]. Only one study reported a biopsy with endometrial hyperplasia following 6 months of vaginal estriol therapy. Overall, the incidence of adverse effects was low[21].

Discussion

This systematic review demonstrates the efficacy of using local estriol preparations to treat vulvovaginal atrophy in postmenopausal women. The use of estriol preparations, when compared to placebo, led to an increase in the subjective reporting of reduced vaginal dryness and the objective assessment of improvement based on maturation indices and pH measurements. Vaginal estriol passes into the circulatory system with a peak concentration 1 h after administration, which decreases over a short time. It is noteworthy that the study with a maintenance dosage and a longer follow-up time of 6 months did not show evidence of elevated serum levels of estriol during follow-up[21] and did not demonstrate systemic effects on the breast or estrogenic changes in endometrial histology. Consistent with this, a Finnish register-based study which evaluated data on 18 314 women using vaginal estrogenic preparations found that none of the estrogens studied resulted in a significant increase in the risk of breast cancer[34].

Earlier studies on the use of local estrogens reported an improvement in genitourinary symptoms of 80–90%. This is consistent with the findings of this systematic review on the use of estriol, which evaluated the efficacy of treatments based on the maturation index, changes in pH and

Table 4. Effects at the endometrial level.

				Intervention group		Control group		
Author; country	*Study design*	*Sample size*	*Symptoms*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*	*p-Value*
Van Haaften[27]; Netherlands	CCT	20		*Vaginal estriol 0.5 mg*		*No treatment*		
			Estriol levels					
			Myometrium		132 fmol/g			<0.001
			Endometrium		1047 fmol/g			<0.001
			Vagina		157 fmol/g			<0.001
Englund[31]; Sweden	QE	5		*Estriol pessaries 0.5 mg* ($n = 5$)				
			Endometrial biopsies		More numerous and longer microvilli and several non-ciliated cells			
Gerbaldo[32]; Italy	QE	23		*Estriol cream 0.5 mg*				
			Endometrial biopsies		Atrophy, none had focal proliferations or proliferative changes, and the glandular structures were trophic due to fibrotic stroma			
Van Haaften[33]; Netherlands	QE	20		*Estriol 0.5 mg*				
			Estrogen receptor concentration					
			Myometrium	161 fmol/mg	300 fmol/mg			
			Endometrium	424 fmol/mg	800 fmol/mg			
			Vagina	43 fmol/mg	30 fmol/mg			

CCT, controlled clinical trial; QE, quasi-experimental.

improvement in symptoms[1,8]. The forms of administering estriol included vaginal creams and pessaries. Whilst previous studies had associated vaginal estriol cream with more adverse effects, this review found the frequencies among the different formulations of estriol to be similar[12–15,18,19,22].

The present systematic review included 13 controlled clinical trials and nine quasi-experimental studies, none of which explicitly described the assignment of the intervention or the blinding of the participants and evaluators. The results demonstrate the effectiveness of local estriol to treat genitourinary symptoms based on poor quality of evidence. Nevertheless, although evidence was found that both the quality and the design of the studies have improved over time, new studies of effectiveness and safety still need to be performed, with a better design and with adequate random assignment and blinding of the intervention in order to decrease possible bias.

It is important to note that, in the analysis of the efficacy of local estriol to treat genitourinary symptoms in postmenopausal women and the review of adverse effects, the results from the majority of studies (which contained both low-quality and higher-quality evidence) pointed in a similar direction, indicating certainty in the subjective and objective improvements in vulvovaginal atrophy as well as in the safety of the medication.

This publication has a risk of reporting bias because it was not possible to obtain the full text of all of the studies found in the initial database search, and various studies with the same objective used different measuring or assessment elements as well as different units of measurement. A more in-depth search of systemic effects is also recommended, particularly with respect to mammary tissue since this was not the main objective of any of the primary or secondary studies.

A meta-analysis could not be performed because of substantial differences among the patients, interventions and results in the different studies analyzed. That analysis would have resulted in a heterogeneity value over 50%. The heterogeneity can be explained by the qualitative measurement of outcomes, since the perception of quality of life and symptoms can vary depending on the measurement strategies used.

Conclusions

The evidence from this systematic review suggests that estriol is an effective and safe medication for the treatment of vulvovaginal atrophy in postmenopausal women. Available evidence (low and moderate quality) shows that, when applied vaginally, the blood levels of estriol increase 1 h after application and then progressively return to baseline. In addition, the low potency of this molecule at the systemic level appears to make it safe for women who have risk factors related to estrogen therapy. Use of local estrogens in breast cancer survivors using adjuvant estrogen therapy requires careful counseling and discussion with both patient and her oncology team[35].

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