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SYSTEMATIC REVIEW OPEN ACCESS

The Role of Vaginal Oestrogen Therapy in Postmenopausal Women With Pelvic Organ Prolapse: Does It Have Any Impact on Perioperative Outcomes? A Systematic Review of Randomised Controlled Trials

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ABSTRACT

Background: Pelvic organ prolapse (POP) affects up to 50% of postmenopausal women, negatively impacting sexual function and quality of life. While surgery remains the primary treatment, increasing attention has been given to perioperative vaginal oestrogen therapy and its potential impact on surgical outcomes.

Objectives: This systematic review aims to evaluate the latest evidence on the role of vaginal oestrogen therapy in perioperative management and its impact on surgical outcomes in postmenopausal women with POP.

Search Strategy: A systematic literature search was performed across PubMed, MEDLINE, ClinicalTrials.gov and Embase from inception to December 31, 2024. No geographic restrictions were imposed and only peer-reviewed English-language studies were included.

Selection Criteria: Only prospective, randomised controlled trials (RCT) examining perioperative vaginal oestrogen therapy in postmenopausal women undergoing POP surgery were included.

Data Collection and Analysis: Study identification and data extraction were independently performed by two and three authors, respectively. The Cochrane Collaboration's tool was used to assess bias, with disagreements resolved by a fourth reviewer.

Main Results: Ten studies involving 709 patients were analysed. Vaginal oestrogen therapy showed a positive effect on Vaginal Maturation Index (VMI), vaginal thickness and surgeon's perception of tissue quality. It also appeared to reduce postoperative urinary tract infections (UTIs) and antibiotic use. However, no significant impact on sexual function, surgical ease, rates of surgical failure or POP recurrence was observed.

Conclusions: Despite potential benefits in enhancing vaginal tissue quality and reducing UTIs and antibiotic use, current evidence is limited. Further standardised trials are needed for more definitive conclusions.

1 | Introduction

Pelvic organ prolapse (POP) is a major healthcare issue characterised by the descent of one or more of the female pelvic organs (bladder, uterus, rectum, vaginal walls or vaginal cuff), affecting up to 50% of postmenopausal women [1–3]. Frequently, it can be associated with symptoms such as pelvic pressure or discomfort, urinary incontinence or difficulties in urinating, bowel dysfunctions and discomfort during sexual intercourse, having a detrimental impact on sexual function and overall quality of life [4–11]. The descent of the pelvic organs is often inextricably bound up with a very common comorbid condition: the genitourinary syndrome of menopause (GSM), comprising vulvovaginal atrophy (VVA) that also plays a crucial role [12–14]. This pathologic condition is strongly connected to weakening or damage of pelvic floor muscles and connective tissues, often occurring during postmenopause along with declining oestrogen levels, with incidence rising with age [15, 16]. Although separating menopause effects from general ageing is arduous, the oestrogen-responsiveness of pelvic organs and surrounding epithelium, connective and muscular tissues is well-established. The decline of endogenous oestrogen levels gradually leads to thinning of the vaginal wall, causing dryness, soreness and irritation: factors all contributing to a vicious cycle, worsening POP severity [17, 18]. For all these reasons, despite surgical repair remaining the mainstay treatment for symptomatic prolapse, considerable attention has been paid to perioperative vaginal oestrogen as a potential aid in maximising surgical outcomes. Many trials have been conducted on this issue, using different molecules, compounds, treatment schemes and follow-up protocols [19]. Nevertheless, to date, the real effects and impact of adjuvant vaginal oestrogen therapy on perioperative outcomes in postmenopausal women with POP remain vague.

To clarify the state of evidence, we conducted a systematic review of randomised controlled trials (RCT) available in the literature up to December 31, 2024 on the topic, intending to shed light on the ongoing long-standing issue: does perioperative vaginal therapy with oestrogen have any impact on the perioperative outcomes of postmenopausal women with POP who undergo vaginal surgical repair?

2 | Methods

2.1 | Eligibility Criteria, Information Sources, Search Strategy

The protocol was structured a priori. It outlined strategies for screening the literature, including examining articles, as well as data extraction and analysis. Therefore, it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024620629). A systematic literature review was conducted, searching for eligible trials in four electronic databases (PubMed, MEDLINE, ClinicalTrials.gov and Embase) from their inception to December 31, 2024 (Appendix S1, Table 1). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed [20]. Specific search terms used for study development were the following text words and Medical Subject Headings (MeSH): ('hormonal treatment' or 'oestrogen' or 'hormonal therapy') and ('pelvic organ prolapse' or 'POP') and ('surgery' or 'surgical management' or 'repair') and 'postmenopausal women'. Furthermore, the reference lists of all eligible papers were extensively screened and manually checked, searching for potential studies not initially comprehended by the electronic search.

Concerning the study design, the selection was strictly limited to prospective RCTs. Neither language nor geographic location limitations were adopted, but only English-language articles were included in the final analysis.

The focus of the present review was specific to RCTs examining the perioperative outcomes of vaginal oestrogen treatment (compared to placebo or no treatment) in postmenopausal women (at least 1 year after spontaneous or surgical menopause) with any grade or type of POP eligible for surgical repair. We considered both preoperative and postoperative outcomes, any compound containing natural or synthetic oestrogen in any route of vaginal administration (cream, gel, ring and pessary) or dose, with no restriction to the treatment length of time. We included, in the final analysis, all the studies in which a vaginal surgery for POP repair was scheduled, with no limitations in the vaginal surgical technique (e.g., vaginal hysterectomy, native tissue reconstructive techniques and reconstructive procedures using mesh). All the studies that did not meet the inclusion criteria were excluded.

2.2 | Study Selection

The electronic search and the eligibility of selected studies were performed independently by two authors (G.S. and S.G.V.). To deal with discrepancies, any dispute regarding study inclusion was resolved by consulting a third reviewer (S.A.). The first step was excluding duplicate studies according to the title, authors, year of publication and journal. Afterwards, studies were selected according to the title and abstracts. A thorough perusal of the full text of the eligible studies then followed.

2.3 | Data Extraction

Data extraction was carried out by three authors (G.S., S.G.V. and S.S.), sifting information about the study design, participants' baseline characteristics, intervention protocol scheme and analysed outcomes for each study.

2.4 | Assessment of Risk of Bias

To assess the risk of bias, Cochrane Collaboration's tool was independently applied by three reviewers (G.S., S.G.V. and M.N.D.) [21]. Disagreement was resolved by discussion with a fourth reviewer (S.A.). The results of the risk of bias assessment are listed in Table S1.

2.5 | Data Synthesis

The synthesis of the findings from the included studies was structured around the target population characteristics, the type of intervention (compounds and route of vaginal administration,

TABLE 1 | Study characteristics of eligible trials.

Authors	Years	Study design	Patients	Intervention(s)	Surgery	Timing
Felding et al.	1992	Double-centre, randomised double-blind controlled trial	Total 48 TG: $N=22$ (2 drop-outs) 63.5 (95% CI: 44–82) years PG: $N=23$ (1 drop-out) 64 (95% CI: 50–77) years	TG: vaginal pessaries containing 25 μg micronized oestradiol, daily for 3 weeks prior to surgery CG: same vaginal pessaries containing placebo	VH, or anterior/posterior colporrhaphy, or Manchester-Fothergill operation, or a combination of these	T0: Baseline T1: At surgery (after 3 weeks of treatment) T2: 4 weeks after surgery
Karp et al.	2012	Single-centre, randomised partially blinded controlled trial[a]	Total 72 (65 randomised) TG: $N=19$ (3 drop-outs) 65 (7.4) years PG: $N=18$ (3 drop-outs) 66 (7.9) years CG: $N=22$ (0 drop-outs) 65 (7.8) years	TG: low dose oestradiol-releasing vaginal ring (7.5 μg per day) for 12 weeks immediately after vaginal reconstructive surgery PG: placebo vaginal ring CG: no vaginal ring	VH, or Native tissue RS or 'kit' RS, +/− concomitant anti-incontinence surgery with sling	T0: Baseline (right before surgery) T1: 6 weeks after surgery T2: 12 weeks after surgery
Marschalek et al.	Jun. 2021	Double-centre, randomised double-blind, placebo-controlled study	Total 120 (randomised) TG: $N=51$ (9 drop-outs) 64.3 ± 9.7 years PG: $N=52$ (8 drop-outs) 61.2 ± 10.1 years	TG: 1 g vaginal oestradiol cream at 0.01% once daily for 1 week, every 48 h for the following week and then twice weekly for the remaining 4 weeks (total treatment duration: 6 weeks), before surgery PG: 1 g placebo cream containing the same ingredients apart from oestradiol, for the same duration of treatment	29 uterus preservation with SSL hysteropexy +/− anterior/posterior colporrhaphy 55 VH with McCall culdoplasty +/− anterior/posterior colporrhaphy 19 RS (of which 1 Neugebauer Le-Fort colpocleisis)	T0: baseline T1: after 6 weeks of treatment, before planned surgery
Marschalek et al.	Sep. 2021	Double-centre, randomised double-blind, placebo-controlled study	Total 120 (randomised) TG: $N=51$ (9 drop-outs) 64.3 ± 9.7 years PG: $N=52$ (8 drop-outs) 61.2 ± 10.1 years	TG: 1 g vaginal oestradiol cream at 0.01% once daily for 1 week, every 48 h for the following week and then twice weekly for the remaining 4 weeks (total treatment duration: 6 weeks), before surgery PG: 1 g placebo cream containing the same ingredients apart from oestradiol, for the same duration of treatment	29 uterus preservation with SSL hysteropexy +/− anterior/posterior colporrhaphy 55 VH with McCall culdoplasty +/− anterior/posterior colporrhaphy 19 RS (of which 1 Neugebauer Le-Fort colpocleisis)	T0: baseline T1: after 6 weeks of treatment, before planned surgery

(Continues)

TABLE 1 | (Continued)

Authors	Years	Study design	Patients	Intervention(s)	Surgery	Timing
Rahn et al.	2014	Double-centre, randomised double-blind controlled trial	Total 30 (randomised) TG: $N=8$ (7 drop-outs) 55.1 ± 5.4 years PG: $N=$(3 drop-outs) 58.9 ± 5.1 years	TG: 1 g of vaginal conjugated oestrogen cream (0.0625%) via applicator nightly for 2 weeks and then twice weekly until surgery. A minimum of 4 and a maximum of 8 weeks of treatment was required before surgery PG: 1 g of vaginal placebo cream with the same regimen	VH or Total Abdominal Hysterectomy (not further specified)	T0: Baseline T1: After treatment (before surgery)
Rahn et al.	Aug. 2023	Multi-centre, randomised double-blind superiority controlled trial	Total 199 (randomised) TG: $N=93$ (9 drop-outs) 64.9 (6.1) years PG: $N=93$ (4 drop-outs) 65.2 (7.3) years	TG: 1 g of vaginal conjugated oestrogen cream (0,0625%) via applicator nightly for 2 weeks and then twice weekly until surgery, for a minimum of 5 total weeks before the surgical procedure and then continued twice weekly for 12 months after surgery PG: 1 g of vaginal placebo cream with the same regimen	VH +/− anterior colporrhaphy/ posterior colporrhaphy/ midurethral sling+ apical suspension (USL/SSL)	T0: Baseline T1: At surgery T2: 1 month after surgery T3: 6 months after surgery T4: 12 months after surgery
Rahn et al.	Sep. 2023	Planned ancillary analysis of a multi-centre, randomised double-blind superiority controlled trial	Total 199 (randomised) Patients with preoperative data 191 Among patients who underwent surgery TG: $N=93$ (9 drop-outs) 64.9 (6.1) years PG: $N=93$ (4 drop-outs) 65.2 (7.3) years	TG: 1 g of vaginal conjugated oestrogen cream (0.0625%) via applicator nightly for 2 weeks and then twice weekly until surgery, for a minimum of 5 total weeks before the surgical procedure and then continued twice weekly for 12 months after surgery PG: 1 g of vaginal placebo cream with the same regimen	VH +/− anterior colporrhaphy/ posterior colporrhaphy/ midurethral sling+ apical suspension (USL/SSL)	T0: Baseline T1: Before surgery (approximately after 7 weeks of treatment)
Rahn et al.	2024	Planned 3-year follow-up ancillary analysis of a 3-center, randomised double-blind superiority controlled trial	Total 186 1st TG: $N=82$ (11 drop-outs) 1st PG: $N=78$ (15 drop-outs) 2nd TG: $N=87$ (40/82 + 47/78) 2nd PG: $N=73$ (42/82 + 31/78) 40/160: Oestrogen cream before and after surgery 42/160: Oestrogen before, placebo after surgery 47/160: Placebo before surgery, oestrogen after 31/160: Placebo before and after	TG: 1 g of conjugated oestrogen cream, 0.625 mg/g (Premarin) inserted vaginally nightly twice weekly for 12 months after surgery and continued according to participants' will as necessary to address symptoms of genitourinary syndrome of menopause up to 36 months after surgery. PG: 1 g of vaginal placebo cream with the same regimen	VH +/− anterior colporrhaphy/ posterior colporrhaphy/ midurethral sling+ apical suspension (USL/SSL)	T0: Baseline T1: At surgery T2: 1 month after surgery T3: 6 months after surgery T4: 12 months after surgery T5: 36 month after surgery

(Continues)

TABLE 1 | (Continued)

Authors	Years	Study design	Patients	Intervention(s)	Surgery	Timing
Sun et al.	2016	Single-centre, randomised partially blinded controlled non-inferiority trial	Total 186 (randomised) TG: $N = 86$ (7 drop-outs) 66 (50–75) years CG: $N = 87$ (6 drop-outs) 65 (51–74) years	TG: 0.5 g of promestriene vaginal cream, twice a week for 6 6 weeks before surgery CG: no treatment	Pelvic RS with mesh	T0: baseline T1: 2 months after surgery T2: 6 months after surgery T3: 12 months after surgery
Vaccaro et al.	2013	Single-centre, randomised single-blinded controlled trial	Total 54 (randomised) TG: $N = 22$ (9 drop-outs) 66.3 (10.2) years CG: $N = 20$ (3 drop-outs) 64.3 (10) years	TG: 1 g conjugated oestrogen vaginal cream daily from 2 to 12 weeks before surgery CG: No treatment	Posthysterectomy RS	T0: baseline T1: at surgery (2 to 12 weeks after surgery)

Abbreviations: CG, control group; PG, placebo group; RS, reconstructive surgery; SSL, sacrospinous ligament; TG, treatment group; USL, uterosacral ligament; VH, vaginal hysterectomy.
[a]Blinding of examiners to ring versus no ring was impossible, but examiners remained blinded to active versus placebo ring.

lengths of treatment and follow-up) and the type of perioperative outcome considered.

3 | Results

3.1 | Study Selection and Study Characteristics

A total of 469 records were originally identified through database search and citation checking. Details of the selection processes are shown in Figure S1. Seventy-five trials were removed as duplicated records. After title and abstract screening, 382 trials were removed as out-of-topic, as studies having a design different from RCTs or as ongoing studies with still no publication available. After screening the full text, 10 trials were assessed to meet the eligible criteria and included in the final analysis, representing 709 total patients. The results of the included studies are detailed in Table 2.

3.2 | Risk of Bias of Included Studies

The results of the risk-of-bias assessment are shown in Figure S2 and Figure S3.

The details of support for each judgement are shown in Table S1.

3.3 | Synthesis of Results

3.3.1 | Compounds and Route of Vaginal Administration

Among the included trials, eight used vaginal cream as a treatment compound [22–29]. Only in one study was a vaginal pessary used [30]. Lastly, in another trial, a low-dose oestradiol-releasing vaginal ring was administered [31]. The detailed compounds and routes of administration have been summarised in Table S2.

3.3.2 | Treatment and Follow-Up Lengths

The majority of included studies assessed the effect of vaginal treatment with oestrogen administered before surgery [22–24, 28–30]. Only one study focused on the effect of postoperative local treatment [31]. To a population of 199 randomised women, the treatment was administered both before and after surgery and the results obtained were the subject of three different studies with different outcomes and follow-up lengths [25–27]. The shortest treatment length was 3 weeks before surgery with vaginal pessaries, the longest was 12 months after surgery with 1 g of conjugated oestrogen cream, 0.625 mg/g, with the longest follow-up lasting 36 months [27, 30].

3.3.3 | Perioperative Outcomes

3.3.3.1 | Cytological and Histological Changes of Vaginal Tissue. Among the 10 enrolled studies, 3 assessed cytological changes on the vaginal epithelium after local oestrogen

TABLE 2 | Results of the included trials.

Authors	Years	Variable	Treatment group	Control group		Between-group difference (95% CI) or *p*
Felding et al.	1992	MI	MO	MO		—
		EI	54.97 (53.00–57.00)	53 (51.00–56.00)		NG
		ET (at T1) (mm)	0.271 (0.220–0.312)	0.233 (0.169–0.288)		0.017
		Subjective atrophy assessment (%)	22.7 (5/22)	17.3 (4/23)		NG
		Sufficient cleavage	MO	MO		—
		Estimated blood loss	MO	MO		—
		Postoperatively Cystitis at T2 (%)	9.0 (2/22)	43.4 (10/23)		0.02
Karp et al.	2012			PG	CG	
		MI (at T2)	61.1 (12.3)	36.7 (15.8)	39.9 (13.8)	< 0.01
		Subjective signs of atrophy (4-point scale)	1 (0–5)	1 (0–10)	2 (0–6)	> 0.05
		Objective signs of atrophy (score)	1 (0–7)	6 (4–9)	7 (1–8)	< 0.01
		Vaginal pH	5.3 (0.87)	6.61 (0.71)	5.97 (0.67)	0.014
		Granulation tissue (at T2) (%)	15.7 (3/19)	66.6 (12/18)	18.1 (4/22)	< 0.01
		Major healing abnormalities	—	—		—
		Satisfaction rate with the ring (%)*	NG	NG	NG	0.42*
Marschalek et al.	Jun. 2021	Intraoperative Surgeon's Assessment				
		Adequate tissue perfusion	2.12 ± 1.03	2.19 ± 0.99		0.219
		Atrophy or poor tissue perfusion	0.55 ± 0.95	0.54 ± 0.96		0.863
		Tissue consistency	0.16 ± 0.42	0.15 ± 0.36		0.435
		Easy dissection of surgical plans	1.67 ± 1.16	1.88 ± 1.15		0.225
		Easy vesico-vaginal dissection				0.518
		No	8 (16)	9 (17)		
		Yes	43 (84)	43 (82)		
		Easy recto-vaginal dissection				0.486
		No	9 (18)	10 (19)		

(Continues)

TABLE 2 | (Continued)

Authors	Years	Variable	Treatment group	Control group	Between-group difference (95% CI) or *p*
		Yes	42 (82)	41 (79)	
		Douglas not opened	0 (0)	1 (2)	
		Regular pelvic anatomy			0.597
		No	7 (14)	7 (14)	
		Yes	44 (86)	45 (87)	
		Guessing presurgical oestrogen			0.034
		No	12 (24)	22 (42)	
		Yes	39 (77)	30 (58)	
		Operative time	88.73 ± 30.3	78.46 ± 32.2	> 0.05
		Total length of stay	4.5 ± 1.2	4.6 ± 1.2	> 0.05
		Significant blood loss (> 500 mL)	1 (2)	1 (2)	> 0.05
		Use of analgesics	51 (100)	52 (100)	> 0.05
		Use of antibiotics	3 (6)	15 (29)	0.003
		Readmission	3 (6)	2 (4)	> 0.05
		Postsurgical complications	11 (22)	15 (29)	0.045
		POUR	6/11 (55)	4/15 (27)	
		UTIs	3/11 (27)	6 (40)	
		Postoperative haemorrhage	1/11 (9)	2 (13)	
		Surgical site infection	1/11 (9)	3 (20)	
Marschalek et al.	Sep. 2021	Prolapse domain score	4.4 ± 0.19	4.6 ± 0.19	0.445
		Bladder domain score	2.7 ± 1.1	2.6 ± 1.1	0.868
		Bowel domain score	1.8 ± 0.09	1.8 ± 0.09	0.765
		Sexual domain score	1.3 ± 0.14	1.5 ± 0.14	0.265
		Global pelvic floor score	6.9 ± 0.22	7.0 ± 0.22	0.838

(Continues)

TABLE 2 | (Continued)

Authors	Years	Variable	Treatment group	Control group	Between-group difference (95% CI) or *p*
Rahn et al.	2014	Thickness of the vaginal mucosa (μm)	+1.8-fold	MO	0.002
		Thickness of the vaginal muscularis (μm)	+2.7-fold	MO	0.088
		Collagen 1α1	+6.8-fold	MO	< 0.05
		Collagen 1α2	+1.8-fold	MO	0.037
		Collagen 3	+2.5-fold	MO	0.059
		MMP-12 (RU/mg protein)	5.8 ± 1.5	MO	0.011
		Matrix metalloprotease-9 (RU/mg prot.)	+6.0 fold (mucosa)	MO	0.02
		Serum E1 at T1 (pg/mL)	27.7 ± 4.2	249 ± 6.5	0.76
		Serum E2 at T1 (pg/mL)	9.3 ± 1.6	11.6 ± 2.7	0.56
Rahn et al.	Aug. 2023	12-month surgery failure incidence (%)	19 (*N* = 20)	9 (*N* = 10)	1.97 [0.92–4.22] (aHR)
		Median POP-Q			
		Ba	−2 (−2 to −1)	−2 (−2 to −1)	0 (0 to 1)
		Bp	2 (−3 to −2)	2 (−3 to −2)	0 (−0.5 to 0.5)
		C	−7 (−8 to −6)	−7 (−8 to −6)	0 (−0.5 to 0.5)
		Total vaginal length	9 (7.5 to 9)	8 (7.25 to 9)	−1 (−1 to 0)
		Genital hiatus	3 (2.5 to 4)	3 (2.5 to 3.5)	0 (0 to 0)
		PFDI-20	23.1 (14.1 to 32.2)	23.1 (13.9 to 32.2)	−7.1 (−28.8 to 14.6)
		PFIQ-7	8.9 (0.1 to 17.8)	9.5 (0.5 to 18.5)	−8.3 (−30.8 to 14.2)
		PGII scale (%)	98	97	0.62
		PISQ-IR	3.55 (3.35 to 3.75)	3.70 (3.50 to 3.90)	0.10
		Operative time (min)	170 (61)	170 (60)	−0.3 (−17.7 to 17.2)
		Estimated blood loss (mL)	189 (139)	175 (110)	14.1 (−22.2 to 50.4)
		Transfusion at time of surgery (%)	0	0	
		VASQ	−2.14 (−2.64 to −1.64)	−1.27 (−1.78 to −0.77)	0.003
		VAAT	9.2 (2.2)	8.3 (2.0)	0.01
		Surgeon's rated tissue quality at vag. apex	3.6 (0.8)	3.3 (0.9)	0.02
		Granulation tissue at T3	16/90 (18)	7/87 (8)	0.048
		Postop. UTIs (or pyelonephritis) at T4	18 (19)	23 (25)	−5.4 (−17.3 to 6.5)

(Continues)

TABLE 2 | (Continued)

Authors	Years	Variable	Treatment group	Control group	Between-group difference (95% CI) or *p*
Rahn et al.	Sep. 2023	UDI-6	−0.6 (−4.6 to 3.5)	−0.8 (−5.0 to 3.4)	0.94
		PISQ-IR	−0.02 (−0.19 to 0.15)	- 0.10 (−0.27 to 0.06)	0.47
		Dyspareunia at T1 (%)	37 (42)	44 (48)	0.49
		VASQ	−0.61 (−0.95 to 0.27)	−0.28 (−0.64 to 0.08)	0.19
		VAAT	1.54 (1.11 to 1.97)	0.69 (0.24 to 1.13)	0.01
Rahn et al.	2024	36-month surgery failure incidence (%)**	38.4 (33/86)	28.2 (22/78)	9.1 (−4.8 to 23.0) (aHR)
		Median POP-Q			
		Ba	−1.3 (−1.7 to −0.8)	−1.6 (−2.0 to −1.1)	0.76
		Bp	−2.2 (−2.7 to −1.7)	−2.3 (−2.8 to −1.8)	0.50
		C	−6.2 (−6.7 to −5.5)	−6.5 (−7.3 to −5.8)	0.53
		Total vaginal length	8.2 (7.9 to 8.4)	8.0 (7.9 to 8.3)	0.88
		Genital hiatus	3.3 (3.1 to 3.6)	3.1 (2.9 to 3.4)	0.71
		POP-Q Max	−1.1 (−1.6 to −0.7)	−1.4 (−1.8 to −0.9)	0.85
		PGIS	1.1 (1.0 to 1.3)	1.1 (0.9 to 1.2)	0.80
		PFDI-20	MO	MO	> 0.05
		PFIQ-7	MO	MO	—
		PGII scale (%)	MO	MO	—
		POPDI-6	6.8 (2.7 to 11.0)	6.1 (1.9 to 10.3)	0.51
		POPIQ-7	1.8 (−2.9 to 6.4)	1.8 (−3.0 to 6.5)	0.73

(Continues)

TABLE 2 | (Continued)

Authors	Years	Variable	Treatment group	Control group	Between-group difference (95% CI) or *p*
Sun et al.	2016	Mesh exposure			
		Rate (%)	16.1	12.9	0.02 (non-inferiority p)
		Area	$0.32 \pm 0.14\,cm^2$	$0.34 \pm 0.13\,cm^2$	0.74
		Time to exposure	MO	MO	> 0.05
		Need for removal	0	0	—
		Anatomic success (POP-Q < 2) (%)	100	98.9	1.0
		PGC-I (%)	97.8	97.8	0.61
		PFIQ-7 (≥ 70%)	97.8	95.7	0.67
		PISQ-12 (improvement ≥ 5 points)	15.8	14.3	0.75
Vaccaro et al.	2013	VMI (increase %)	+15.5	−1.5	0.025
		VHCS	14.3 (3.8)	12.9 (2.6)	0.44
		VET (epithelium) (μm)	339	302	> 0.05

Abbreviations: aHR, adjusted hazard ratio; E1, Estrone; E2, 17 β-oestradiol; EI, oestrogen index; ET, endometrial thickness; MI, maturation index; MMP, human macrophage elastase; MO, missing outcome; NG, not given; PDS, prolapse domain score (of the Comprehensive German pelvic floor questionnaire); PFDI, pelvic floor distress inventory; PFIQ, pelvic floor impact questionnaire; PGC-I, patient global impression of change; PGII, patient global impression of improvement; PGIS, patient global impression of severity; PISQ, POP/urinary incontinence sexual questionnaire; POPDI, pelvic organ prolapse distress inventory; POPIQ, pelvic organ prolapse impact questionnaire; POUR, postoperative urinary retention; QoL, quality of life; UDI, Urogenital Distress Inventory; UTIs, urinary tract infection; VAAT, vaginal atrophy assessment tool; VASQ, vaginal atrophy symptoms questionnaire; VET, vaginal epithelial thickness; VHCS, vaginal health composite score; VHI, vaginal health index; VMI, vaginal maturation index.

*Satisfaction rate (global impression of 'cure' or 'greatly satisfied') was 72.3% (47/65) and did not differ among the groups ($p = 0.42$).

**Adherence rates to the study cream using the per-protocol definition (i.e., at least 50% of anticipated study cream preoperatively and for 12 months postoperatively, per participant medication diary) were 77% for oestrogen users and 74% for placebo users. Using this per-protocol definition for adherence, the adjusted HR of failure for vaginal oestrogen compared with placebo was 1.52 (95% CI, 0.83–2.76; $p = 0.17$).

treatment [28, 30, 31]. The first trial ever published on this topic aimed to evaluate the changes in the Vaginal Maturation Index (VMI) and the Estrogenic Index (EI) by assessing the proportional representation of superficial, intermediate and parabasal cells. After 3 weeks with vaginal pessaries containing 25 μg of micronized oestradiol, a significant improvement in EI was found immediately before surgery and the histological analysis demonstrated an improvement in vaginal epithelium thickness in the treatment group ($p < 0.001$ and $p = 0.017$, respectively) [30]. Two trials evaluated perioperative VMI modification [28, 31]. One single-blinded RCT evaluated presurgical treatment with 1 g of conjugated oestrogen vaginal cream daily from 2 to 12 weeks before surgery and showed a significant improvement of vaginal tissue maturation compared to placebo ($p < 0.001$) [28]. This occurred in spite of the total vaginal thickness not showing significant differences between the groups at the end of the treatment [28]. In 2012, Karp et al. [31] evaluated the effects of postoperative local treatment with oestrogen on VMI, finding that the administration of 7.5 μg of oestradiol per day through a vaginal ring for 12 weeks after vaginal reconstructive surgery significantly improved VMI compared to placebo or no treatment ($p < 0.01$).

Regarding histological analysis, three trials assessed modifications in vaginal epithelium thickness with perioperative vaginal oestrogen treatment [24, 28, 30]. Felding et al. [30] showed that preoperative treatment with vaginal pessaries containing 25 μg of micronized oestradiol succeeded in an improvement of vaginal mucosa thickness ($p = 0.017$). In 2014, Rahn et al. [24] showed that preoperative treatment with vaginal conjugated oestrogen cream for 4–8 weeks significantly improved vaginal mucosa thickness, but not muscularis thickness ($p = 0.002$ and $p = 0.088$, respectively), compared to placebo. On the other hand, Vaccaro et al. [28] found no significant improvement in vaginal thickness after preoperative treatment ($p > 0.05$).

Among the trials, two investigated the presence of granulation tissue and microscopic inflammation in vaginal smears of patients treated with vaginal oestrogen. Karp et al. found a significantly lower granulation tissue presence after 12 weeks of postoperative treatment in women treated with oestradiol-releasing vaginal ring compared to placebo vaginal ring and controls without vaginal ring ($p < 0.01$). Conversely, Rahn et al. [25, 31] reported a significantly higher occurrence of granulation tissue in the oestrogen group compared to placebo at 6 months post-surgery ($p = 0.048$).

One trial assessed the changes in vaginal pH with perioperative local oestrogen treatment, assessing that postoperative treatment provided an improvement (decreasing) in vaginal pH in women who received postsurgical treatment compared to placebo or no treatment ($p = 0.014$) [31].

3.3.3.2 | Objective Improvement of Atrophy and Clinical Changes. Rahn et al. [25, 26] through the Vaginal Atrophy Assessment Tool (VAAT), reported a significant difference in the objective improvement of atrophy at the blinded preoperative assessment after treatment with oestrogen ($p = 0.01$). Similarly, Karp et al. [31] found an improvement in objective atrophy after postoperative treatment at 12 weeks ($p < 0.01$). In contrast, no differences were reported in two other trials [22, 28]. No significant differences were found after presurgical treatment in POP-Q measurement [24, 25].

3.3.3.3 | Subjective Improvement of POP-Related Discomfort. Two studies investigated outcomes related to subjective improvement in POP-associated discomfort [25, 29]. Rahn et al. [25] reported data on the Pelvic Floor Impact Questionnaire-7 (PFIQ-7) and the Pelvic Floor Distress Inventory-20 (PFDI-20), assessed after 12 months of perioperative oestrogen treatment, showing improvement in both treatment and placebo groups, though without a statistically significant difference. Similarly, Sun et al. [29] presented PFIQ-7 results at 12 months following surgery, after a 6-week preoperative course of vaginal oestrogen. Despite improvements in both groups, these changes were not statistically significant in either the intention-to-treat or per-protocol analyses.

3.3.3.4 | Quality of Life. No trial among the included ones assessed this outcome.

3.3.3.5 | Sexual Function. Three trials assessed this outcome [23, 25, 26]. Rahn et al. in 2023, through the POP/urinary incontinence sexual questionnaire (PISQ), found no significant difference in sexual function after perioperative vaginal oestrogen treatment both at the preoperative assessment and at 12 months after surgery [25, 26]. Nevertheless, sexual function improved in both groups at 12 months after surgery, with a PISQ-IR score increased by 0.36 points (95% CI, 0.16–0.56) in the vaginal oestrogen group and by 0.42 points (95% CI, 0.23–0.61) in the placebo group, showing a minimal, although not statistically significant difference (−0.06 points; 95% CI, −0.37 to 0.24, $p = 0.10$) [25]. Moreover, in another study by the same authors, dyspareunia rates before surgery did not differ between treatment and placebo groups ($p = 0.49$) [26]. Similarly, Marschalek et al. [23] found no significant difference at surgery time in the sexual domain score with or without presurgical treatment for 6 weeks with vaginal oestradiol cream.

3.3.3.6 | Intraoperative Outcomes. Of the ten included studies, one carried out on 120 randomised women assessed differences in intraoperative outcomes after presurgical vaginal treatment with oestrogen. After 6 weeks of presurgical treatment with vaginal oestrogen, no significant differences were found with placebo regarding operative time, total length of stay and intraoperative blood loss > 500 mL rate (all $p > 0.05$) [22]. Likewise, Rahn et al. reported no significant differences in the operative time, intraoperative estimated blood loss and need for transfusion [25]. However, the intraoperative surgeon's perception of tissue quality at vaginal apex on a scale ranging from 1 (thin, attenuated and poor) to 5 from (thick, healthy and robust) was significantly greater in the oestrogen group ($p = 0.02$) [25].

3.3.3.7 | Postoperative Outcomes. *Use of analgesics, antibiotics and readmission rate*: Marschalek et al. found no significant difference in the postoperative use of analgesics or readmission rate between the two groups (both $p > 0.05$). However, they noted a significant difference in the need for antibiotics after surgery, with a higher recurrence in the group that did not receive presurgical treatment (6% vs. 29%, $p = 0.003$) [22]. *Postsurgical Complications*: Two studies outlined a significant difference regarding the incidence of postoperative Urinary

Tract Infection (UTI), with a lower incidence in the treated group [22, 30]. A lower incidence of UTIs in the oestrogen group within 1 year after surgery, though not statistically significant, was reported in two other studies ($p = 0.12$ and $p = 0.419$) [25, 29]. One study reported Postoperative Urinary Retention (POUR) incidence, showing a higher rate in the oestrogen group (55% vs. 27%, $p = 0.045$) [22]. Notably, this was the only postsurgical complication statistically more prevalent in the oestrogen group, unlike UTIs, postoperative haemorrhage and surgical site infection [22]. No differences were found in the mesh exposure rate or surgical failure at 12 and 36 months in the other three included trials [25, 27, 29]. Nevertheless, Rahn et al. observed, though not significant, a worse incidence of surgery failure at 12 and at 36 months in oestrogen-treated patients [25, 27]. However, a per-protocol analysis showed a significant difference in failure probability at 12 months, with the oestrogen group having a higher risk (HR 2.44 [95% CI, 1.01–5.89]) [25].

4 | Discussion

4.1 | Main Findings

Among the outcomes assessed in the included trials, cytological and histological changes of the vaginal tissue after oestrogen treatment are the most frequently investigated (7 out of 10 studies), with the majority evidencing a favourable impact of oestrogen therapy on VMI and vaginal thickness at surgery [24, 28, 30, 31]. Nevertheless, results regarding the presence of granulation tissue after local oestrogen treatment were inconclusive [25, 31]. Indeed, Karp et al. reported a lower degree of inflammation and granulation tissue in the oestrogen-releasing vaginal ring group, but these findings were based on comparisons with both a control group that did not receive any vaginal ring postoperatively and a placebo vaginal ring group. As such, it is difficult to disregard the potential confounding effect of a non-active vaginal ring, which not only lacks hormone-releasing properties but also functions as a foreign body in direct contact with a recent surgical wound, potentially influencing inflammation and granulation tissue formation. Furthermore, in trials assessing vaginal tissue quality at surgery after preoperative treatment, the intraoperative surgeon's assessment is often lacking and the impact on the easiness of surgical technique, effortless surgical plans dissection, operative time and intraoperative blood loss is poorly investigated. Only Rahn et al. [25] reported data regarding both histological characteristics of the vaginal tissue and surgeon's intraoperative assessment, along with intraoperative outcomes details. Nevertheless, they did not focus on VMI, EI or vaginal wall thickness, but only on the presence of granulation tissue. Moreover, this analysis was not actually conducted at surgery time, but 6 months after surgery. Although the correlation between improved tissue quality (based on cytological and histological improvements) after vaginal oestrogen and surgical performance remains unclear, the surgeon's intraoperative perception of vaginal apex tissue quality, rated 1–5, showed significantly better thickness, health and robustness in patients receiving vaginal oestrogen [25]. Perioperative treatment with vaginal oestrogens seems to have a positive impact on lowering postsurgical complications (surgical site infection, postoperative haemorrhage and postoperative infection). However, the number of trials assessing these outcomes is low. The most apparent result is the decreased incidence of postoperative UTIs, which may be associated with the lower recourse to antibiotics in patients treated with perioperative oestrogens [22, 25, 29, 30]. In 2023, Taithongchai et al. drew aligned conclusions: from their results it emerged that topical vaginal oestrogen combined with surgery was associated with a reduced occurrence of postoperative UTIs, compared with surgery alone [19]. However, they concluded that these results should be interpreted with caution, due to the extreme heterogeneity of assessed outcomes, tools and time points in the analysed studies.

4.2 | Interpretation

The lower susceptibility and frequency of urogenital infections could be linked to the improvement of vaginal pH (which appears to be lower after local oestrogen treatment) noted by certain authors [31]. Indeed, it is well-known that an oestrogen-related improvement in both VMI and vaginal pH could promote the proliferation of vaginal lactobacilli, which are poorly represented in women with GSM [32–36]. Nevertheless, no trial has been found assessing the modification of vaginal microbiota before and after local oestrogen treatment in postmenopausal women focusing on the impact of such a change on perioperative outcomes when surgical repair is performed. In light of this, further data are needed to draw more weighted conclusions.

From the results of this review, sexual activity quality does not seem to improve with perioperative local oestrogen therapy: instead, sexual function appears to be improved in both oestrogen-treated group and placebo group or patients who received no therapy at all [25, 26]. A 2017 subanalysis of an RCT by Caruso et al. showed that sexual function, evaluated with PISQ-12 score, significantly improved at 13th week after surgery in patients who received both preoperative and postoperative vaginal oestrogens, compared to those who only received preoperative therapy. Furthermore, the improvement of sexual function in those who did not receive oestrogen was significantly lower than in those who received both therapies, but similar to the patients who received only presurgical treatment [37]. This suggests that surgery may play a crucial role in the improvement, regardless of perioperative treatment, but the use of local oestrogen before and after surgery may maximise its beneficial effect. Available data on this outcome are too few and further research is needed to draw more thoughtful conclusions.

The female genital tract is highly responsive to oestrogen. After menopause, decreased oestrogen levels can lead to vaginal atrophy, dryness and a weakening of both the vaginal epithelium and the pelvic-supporting structures [15–18]. Local oestrogen therapy can counteract these effects by stimulating cell proliferation, improving blood flow and enhancing tissue strength and elasticity. These changes may not only play a key role in reducing the risk of trauma during surgery but also promote better surgical outcomes by restoring vaginal tissue integrity and enhancing collagen synthesis. A recent systematic review and meta-analysis investigating the effect of vaginal oestrogen therapy on vaginal wound healing after vaginal surgery, both in animals and in humans, showed that local oestrogen therapy improves neovascularisation, accelerates microscopic wound closure and enhances collagen synthesis in pelvic tissues [38].

Furthermore, oestrogen appears to mitigate the inflammatory response, reducing excessive inflammation that could impair healing and contribute to postoperative complications [38]. By improving tissue health and facilitating optimal wound healing, vaginal oestrogen therapy may accelerate recovery and promote short- and long-term surgical success.

4.3 | Strengths and Limitations

This systematic review has several limitations in terms of the heterogeneity of the included studies. Besides the lack of standardisation of the assessed outcomes, surgical techniques for POP repair and length of follow-up periods, one of the most constraining aspects is the non-uniformity of treatments, oestrogen molecules and administration methods. While most authors used vaginal oestrogen cream, dosages and durations varied. Additionally, one study adopted vaginal rings as hormone-releasing method, which release oestrogen systemically, not just locally [31]. Furthermore, some trials focused on preoperative treatment, while only one focused on exclusive postoperative treatment and others on both preoperative and postoperative treatment. Collectively, due to the lack of homogeneity in the data of the included studies, there was insufficient scope to conduct a meta-analysis. These aspects may affect the accuracy of the conclusions and strength of evidence of the review. Further trials on the topic with the same design and methodology could facilitate more weighed conclusions and ensure more trustworthy scientific evidence.

5 | Conclusion

Data concerning the impact of perioperative vaginal oestrogen therapy in postmenopausal women undergoing surgery for POP are limited. To date, the preponderance of evidence supports the use of vaginal oestrogens before surgical interventions for POP, based on objective improvements in tissue quality at surgery and likely decreased frequency of early postoperative infections (including UTIs). Nevertheless, ongoing postoperative use of local oestrogen for preventing recurrent prolapse is not supported by the literature and current evidence is too weak to draw any solid conclusion. So far, no clear impact on sexual function, quality of life, surgical ease or POP recurrence seems to stand out. Further research should better address the role of vaginal oestrogen treatment in postmenopausal women before and after vaginal surgical repair for POP, with more trials following standardised protocols (uniformizing compounds, posology, therapy lengths, surgical techniques and time points of measurement), with the aim to provide more accurate scientific evidence on the impact on perioperative outcomes and possible benefits or harms of vaginal oestrogen therapy in this category of patients.

Author Contributions

Gilda Sicilia: conceptualization, data curation, investigation, methodology, validation, writing – original draft, writing – review and editing. **Salvatore Giovanni Vitale:** conceptualization, data curation, investigation, methodology, validation, writing – review and editing. **Maurizio Nicola D'Alterio:** data curation, investigation, methodology, validation, writing – review and editing. **Stefania Saponara:** data curation, methodology, validation, writing – original draft, writing – review and editing. **Francesco Scicchitano:** methodology, validation, writing – original draft, writing – review and editing. **Anna Maria Fulghesu:** supervision, validation, writing – review and editing. **Rossella E. Nappi:** supervision, validation, writing – review and editing. **Stefano Angioni:** conceptualization, formal analysis, methodology, supervision, validation, writing – review and editing. All authors approved this final version to be published.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.