Iran J Public Health, Vol. 51, No.8, Aug 2022, pp.1728-1740

Review Article

Local Estrogen Therapy for Pelvic Organ Prolapse in Postmenopausal Women: A Systematic Review and Meta-Analysis

Xia Yu [1], Li He [2], Yanjun Wang [2], Li Wang [2], *Zhenglin Yang [3], *Yonghong Lin [2]

1. *Chengdu Women's and Children's Central Hospital, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*
2. *Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China*
3. *Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China*

***Corresponding Authors:** Emails: zhenglin.yang@hsc.utah.ed; linyh.2007@aliyun.com

(Received 09 Jan 2022; accepted 17 Mar 2022)

Abstract

Background: The prevalence of pelvic organ prolapse (POP) is expected to increase in the next few decades, imposing a substantial medical burden. The effect of local estrogen therapy (LET) on POP in postmenopausal women is still controversial; therefore, we aimed to provide reliable evidence to address this issue from the perspective of vaginal health and quality of life (QoL).

Methods: We searched in the PubMed, the Web of Science, Embase and the Cochrane Library databases for eligible RCTs from beginning to Apr 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in our study.

Results: Seven RCTs(n=570) were included. No significant improvement of the epithelial thickness (SMD=1.38, 95%CI -0.54 to 3.31, *P*=0.16) or vaginal pH (SMD=-0.98, 95%CI -2.65 to 0.69, *P*=0.25) after LET compared with the control. A slight increase was observed in the VMI (MD=16.58, 95%CI 1.14 to 32.02, *P*=0.04). Regarding QoL, no significant differences between the estrogen group and the control group in PFIQ-7 (6m: MD=3.60, 95%CI –3.13 to 10.33, *P*=0.29; 12m: MD=3.53, 95%CI -3.35 to 10.41, *P*=0.31), PISQ-12(6m: MD=0.62, 95%CI –0.73 to 1.98, *P*=0.37; 12m: MD=0.36, 95%CI –1.06 to 1.77, *P*=0.62), or PGI-I (6m: RR=0.99, 95%CI 0.92 to 1.07, *P*=0.88; 12m: RR=1.01, 95%CI 0.95 to 1.07, *P*=0.72) score. Moreover, no more specific adverse events (AEs) (RR=1.11, 95%CI 0.84 to 1.48, *P*=0.46) were observed in the interventional group.

Conclusion: Not find LET caused either a significant improvement in vaginal health and QoL or more AEs.

Keywords: Estrogen; Pelvic organ prolapse; Postmenopausal women; Vaginal health; Quality of life

Introduction

Pelvic organ prolapse (POP) is a common disease in adult women. The clinical definition comprises two inseparable, related components: anatomical prolapse, in which at least part of the vaginal wall drops to or beyond the vaginal hymenal ring with maximal Valsalva effort, and bothersome symptoms due to prolapse, including vaginal bulge, urinary retention, and severe vaginal trauma (1).

POP is not associated with significant mortality but can lead to a decrease in body image, an impaired sense of wellbeing, anxiety and depression (2). Such adverse effects may have other effects on a patient's quality of life (QoL) and potentially cause disability. Approximately one-third of women reported that POP affected at least one component of physical, social or sexual activities (3), which could lead to reduced productivity and negative economic impacts. Uterine prolapse accounted for a loss of 217.0 disability-adjusted life years (DALYs) per 1000 women at age 50 yr and 324.8 DALYs per 1000 women at age 60 yr (4).

Although POP is accompanied by bothersome symptoms, the health-seeking behaviour of women with POP may be affected by their perception of POP, body image, lifestyle, sense of wellbeing and financial situation (5). Many women believe that prolapse is the inevitable result of ageing and childbirth and cannot be treated (23%-38%) or will resolve with time (6). Therefore, health-seeking behavior among women afflicted with POP is inadequate, and it is difficult to obtain accurate predictions. Because of the lack of consensus on how to measure POP in epidemiological studies, the reported prevalence of POP varies widely (1%–65%) based on whether it is diagnosed according to symptoms (1%–31%), pelvic examination (10%–50%), or both (20%–65%) (7). In view of the increasing ageing population in countries with sufficient global resources, the prevalence of POP is expected to increase in the coming decades. 9.2 million women will be affected by POP by 2050 in the United States (8). Moreover, data show that the demand for services for the treatment of POP is increasing. The number of visits for POP health care may increase by 35% in the next 10 years (7).

The first-line treatment of POP includes conservative therapies, such as pelvic floor physiotherapy and pessaries. When conservative treatments fail or are not accepted by individual patients, POP can be corrected by surgical treatment. The main indicator of the successful treatment of POP is that there is no feeling of a "vaginal bulge" after treatment. Therefore, among all POP symptoms, vaginal bulging is the most frequent symptom corrected by surgery. The lifetime incidence rate of POP surgery is between 12.6% and 19% (9). Subjective assessment may be a more meaningful assessment tool than traditional objective examination indicators (10). The health-related QoL questionnaire for POP is an important tool for assessing postoperative outcomes, and several tools now have Level 1 evidence and a Grade A recommendation (5).

The etiology of POP is multifactorial. Risk factors include vaginal delivery, parity, ageing, obesity, connective tissue abnormalities, menopausal status, and chronically elevated intra-abdominal pressure (11). Among them, the correlation of age and menopause with the prevalence of POP suggests that hypestrogenemia is a cause of POP (12), because estrogen has a profound impact on the synthesis and metabolism of interstitial collagen, elastin and fibroblasts, which are components of pelvic connective tissue (13). Postmenopausal women usually experience genitourinary syndrome of menopause and vaginal atrophy (VA) (14, 15); consequently, the vaginal wall thins, which can make the surgical correction of POP more difficult. Therefore, assessment of vaginal health is important in the treatment of POP.

Based on position statements and guidelines from the North American Menopause Society (2020), low-dose vaginal estrogen is considered a first-line treatment for moderate to severe VA due to its safer risk profile than systemic estrogen therapy (16). However, understanding of the role of exogenous estrogen, especially local estrogen therapy (LET), in the prevention and treatment of POP in postmenopausal women is still limited and controversial. Therefore, it is necessary to conduct a study on the role of LET in POP.

To provide reliable evidence to address this issue, we conducted a meta-analysis to review systematically the data of all recent randomized controlled trials (RCTs) of topical estrogen treatment and the effects on vaginal health and QoL in postmenopausal women with POP.

Methods

Search strategy

We used the search terms "prolapse" together with "prolapses" or "estrogen" or "estrogen" or "hormone" and "randomized" or "randomly" or "random" in several online databases, including PubMed, the Web of Science, EMBASE and the Cochrane Library, from inception to Apr 2021, without language restrictions. Only RCTs were eligible for inclusion. Additionally, to identify trials that were ongoing or unpublished, we also searched ClinicalTrials.gov.

Inclusion and exclusion criteria

We included eligible studies according to the following criteria:

1. Population: Women with POP symptoms who were postmenopausal for at least 1 year due to either a natural or surgical reason were included. The women had not received hormone therapy before the experiment. All participants signed informed consent documents after reading them.
2. Interventions: The participants in the experimental group were treated with vaginal estrogen before or after POP repair surgery.
3. Control group: The participants in the control group were given a placebo or no treatment.
4. Outcome: The trials reported at least one of the following results: epithelial thickness, vaginal maturation index (VMI), vaginal pH, Pelvic Floor Impact Questionnaire – Short Form 7 (PFIQ-7) score, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire – Short Form 12 (PISQ-12) score or Patient Global Impression of Improvement (PGI-I) score.
5. Study type: Only RCTs were included.

We excluded duplicate studies, reviews, conference abstracts, animal studies, irrelevant articles and non-RCTs. Studies that did not have complete data were excluded.

Study selection procedure

After removing duplications, two authors independently reviewed the titles and abstracts of the remaining studies to exclude any unqualified studies. Then, full texts were reviewed independently by two authors. If there was a discrepancy between the two authors, a third author reviewed the controversial information, and the disagreement was resolved by discussion.

Assessment of risk of bias

To evaluate the methodological quality of the eligible studies, two authors independently used the Cochrane Risk-of-Bias tool to assess the risk of bias for the included RCTs, and the risk was assessed as low, high or unclear. Disagreements were discussed and resolved in cooperation with the third author. To ensure the objectivity of the research risk assessment, we concealed the journal titles from the investigators.

Data extraction

Two authors independently scanned the full texts of all included RCTs and recorded the necessary information for each trial, including article details (first author name, publication year, country), study data (study location, number and baseline information of participants), intervention details (dose, frequency, and duration of treatment), and outcome information (measurement tools and raw data). The number of adverse events (AEs) was also recorded. To ensure the accuracy of the information, the third reviewer subsequently verified the extracted data and resolved any disagreements through discussion. To evaluate the effect of LET on VA and QoL, we calculated the differences between baseline values and the values at the last follow-up after treatment (17).

Statistical analysis

We performed the meta-analysis using Review Manager ver. 5.3 (Cochrane Collaboration, Oxford). All outcomes, except for the PGI-I score and AEs, which were regarded as dichotomous variables, were considered continuous variables. The VMI-I, PFIQ-7 score and PISQ-12 score were evaluated on the same scale in different studies and were thus analyzed by mean differences (MDs). Epithelial thickness and vaginal pH were measured on different scales and thus analyzed by standardized mean differences (SMDs). For the pooled estimates, the 95% confidence

interval (CI) was calculated. $P<0.05$ was considered to indicate statistical significance. The I^2 statistic was used to assess the statistical heterogeneity, with $I^2 > 50\%$ indicating significant heterogeneity. Taking the heterogeneity among different studies into account, a random-effects model was used instead of a fixed-effect model. To find the source of heterogeneity and ensure the robustness of the results, sensitivity and subgroup analyses were performed to exclude each study in turn. Subgroup analysis was performed according to follow-up time (6 months and 12 months). Publication bias was evaluated by Funnel plots.

Results

Eligible studies and their characteristics

A flow diagram of the inclusion of studies is shown in Fig. 1. Our initial search yielded 481 records, and 196 duplicate records were excluded.

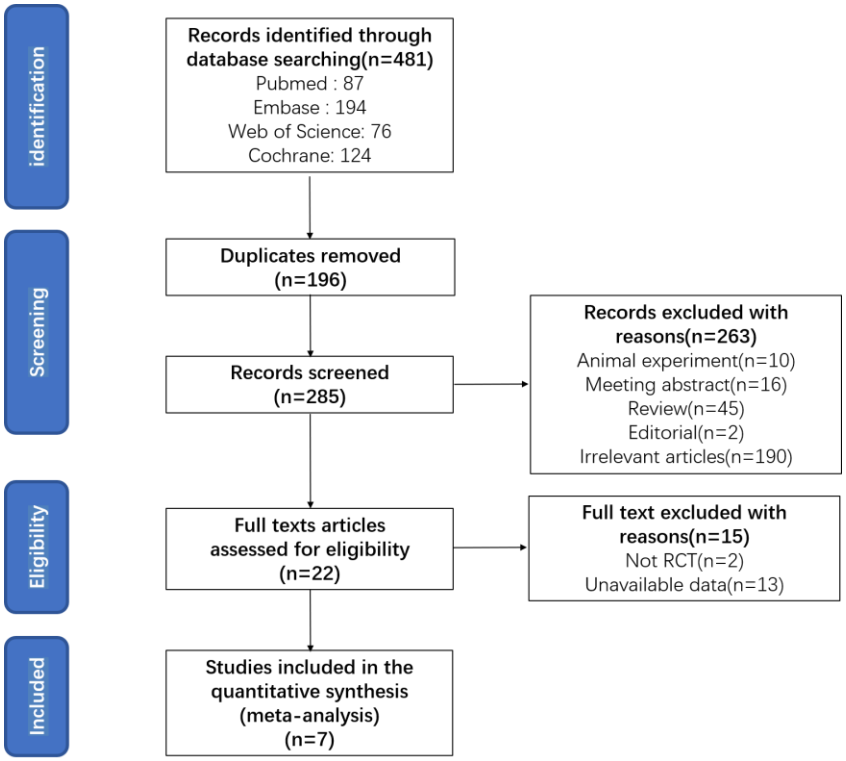

Fig.1: Flowchart of study selection

Through title and abstract screening, we excluded 263 articles according to the exclusion criteria. For the 22 remaining studies, we downloaded the full texts and checked the information carefully, and 2 non-RCTs and 13 studies without available data were additionally excluded. Finally, we included 7 studies in the meta-analysis (Table 1) (18-24). There were 486 participants (244 in the estrogen group and 242 in the control group). The average ages of the participants ranged from 49 to 77 yr old, the body mass index (BMI) ranged from 18.93 kg/m^2 to 35.80 kg/m^2, and all participants were defined as postmenopausal. Vaginal estrogen was used in every trial, with different intervention periods and different treatment doses (10 μg-1 g) and durations (3 wk-24 wk).

Table 1: The main characteristics of the randomized controlled trials

Reference	*Number of participants*		*Average age means (SD), y*		*Intervention*		*Duration of treatment*	*Outcomes*
	E	Control	E	Control	E	Control		
Verghese 2020 (14)	50	50	65.7±8.2	65.9±8.2	Estrogen pessaries	No treatment	Preoperation, 6w Postoperation, 20w	PFIQ-7; PISQ-12; PGI-I
Tontivuthikul 2016 (12)	20	20	66.67±8.05	66.13±6.78	Estrogen cream, Pessary	Pessary	No operation, 24w	Epithelial thickness; Vaginal pH; VMI
Sun 2016 (11)	93	93	66±6.25	65±5.75	Estrogen cream, Mesh	Mesh	Preoperation, 6w	PFIQ-7; PISQ-12; PGI-I
Rahn 2014 (10)	15	15	55.1±5.4	58.9±5.1	Estrogen cream,	Placebo cream	Preoperation, 6w	Epithelial thickness
Vaccaro 2013 (13)	22	20	66.3±10.2	64.3±10	Estrogen cream,	No treatment	Preoperation, 2w-12w	VMI
Karp 2012 (9)	22	21	65±7.4	66±7.9	Estradiol-releasing vaginal ring,	Placebo vaginal ring	Postoperation, 12w	Vaginal pH; VMI
Felding 1992 (8)	22	23	63.5±9.5	64±6.75	Estrogen pessaries,	Placebo pessaries	Preoperation, 3w	Epithelial thickness

E, estrogen treatment group; BMI, body mass index; PFIQ, Pelvic Floor Impact Questionnaire; PISQ, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; PGI-I, Patient Global Impression of Improvement; VMI, vaginal maturation index

Risk of bias in the included studies

All eligible studies performed random assignment, but two of seven RCTs were assessed as having an unclear risk of bias in terms of the mode of generating random sequences because of the lack of a clear explanation of the method of randomization. The remaining studies were identified as having low risk, with random sequences generated by computers. In addition, four trials were conducted with allocation concealment. Because of the nature of the intervention, it was not possible to blind the clinicians or participants in all studies, but to avoid performance bias and detection bias, three trials still reported the use of the double-blind method. With regard to the outcome, only three studies were identified as having a low risk of bias (Fig. 2).

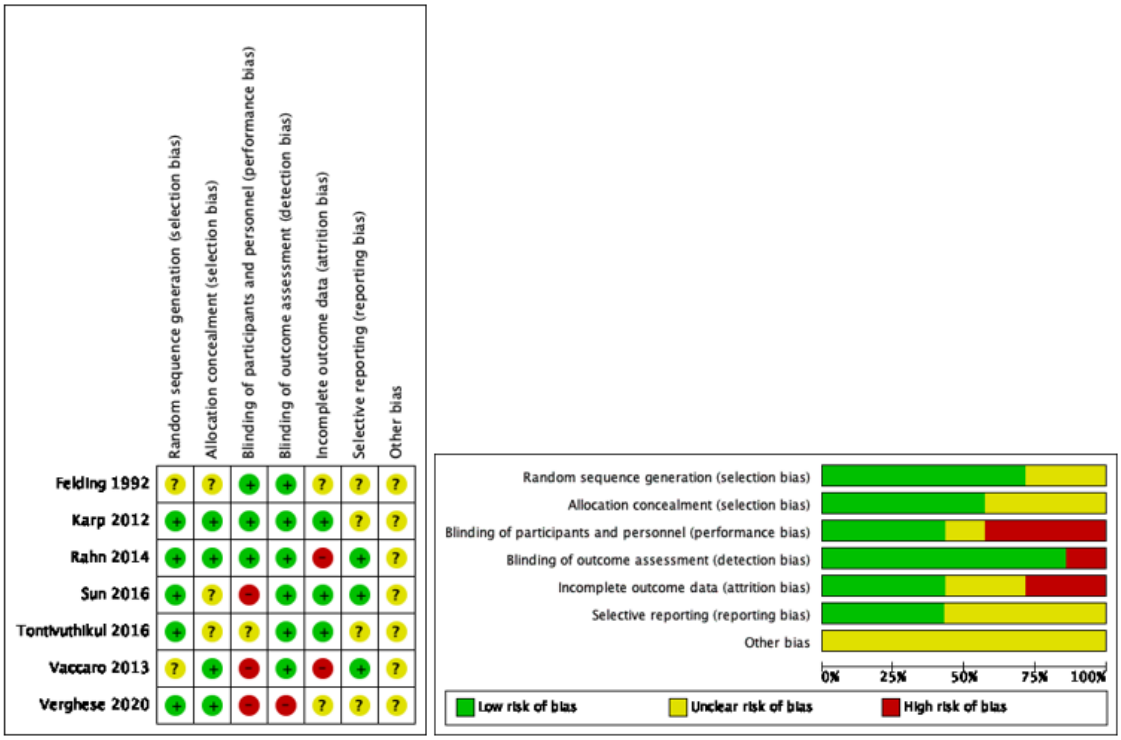

Fig.2: A summary of the results of risk of bias in including RCTs

Effect of treatment on vaginal health

The three vaginal health parameters included in this study demonstrated significant statistical heterogeneity (Table 2). The sensitivity analysis provided in Table 3 revealed no significant change in the heterogeneity or overall effect after excluding studies one by one. The number of trials evaluating vaginal health was too small to perform a subgroup analysis. The funnel plot showed no significant publication bias (Fig. 3). SMDs were used in this analysis to account for the different measurement methods for epithelial thickness and vaginal pH, and the VMI was measured by the MD. The VMI in the estrogen group was slightly higher than that in the control group (95% CI: 1.14-32.02, *P*=0.04); however, no significant differences were observed in the other 2 parameters of epithelial thickness and vaginal pH (95% CI: -0.54-3.31, *P*=0.16; 95% CI: -2.65-0.69, *P*=0.25).

Table 2: Effectiveness of treatment for vaginal health

Variable	*Number of Participations (E: Control)*	*SMD or MD*	*95%CI*	*Overall effect P-Value*	*I²*	*P-Value*
Epithelial thickness	46:50	1.38	[-0.54,3.31]	0.16	93%	<0.0001
VMI	86:84	16.64	[1.15,32.13]	0.04	96%	<0.0001
pH	42:42	-0.98	[-2.65,0.69]	0.25	92%	0.0004

E, estrogen treatment group; SMD, standardized mean difference; MD, mean difference; CI, confidence interval; VMI, vaginal maturation index

Table 3: Results of the sensitivity analysis

Reference	***Epithelial thickness***		***Vaginal maturation index***		***Adverse events***	
	Heterogeneity I^2	Overall effect *P-Value*	Heterogeneity I^2	Overall effect *P-Value*	Heterogeneity I^2	Overall effect *P-Value*
Felding 1992 (8)	95%	0.26	/	/	/	/
Rahn 2014 (10)	64%	0.91	/	/	17%	0.70
Tontivuthikul 2016 (12)	96%	0.41	40%	<0.00001	34%	0.38
Karp 2012 (9)	/	/	97%	0.42	10%	0.23
Vaccaro 2013 (13)	/	/	96%	0.14	/	/
Verghese 2020 (14)	/	/	/	/	25%	0.31
Sun 2016 (11)	/	/	/	/	5%	0.52

The overall effect is significant when the *P-Value* for it is less than 0.05

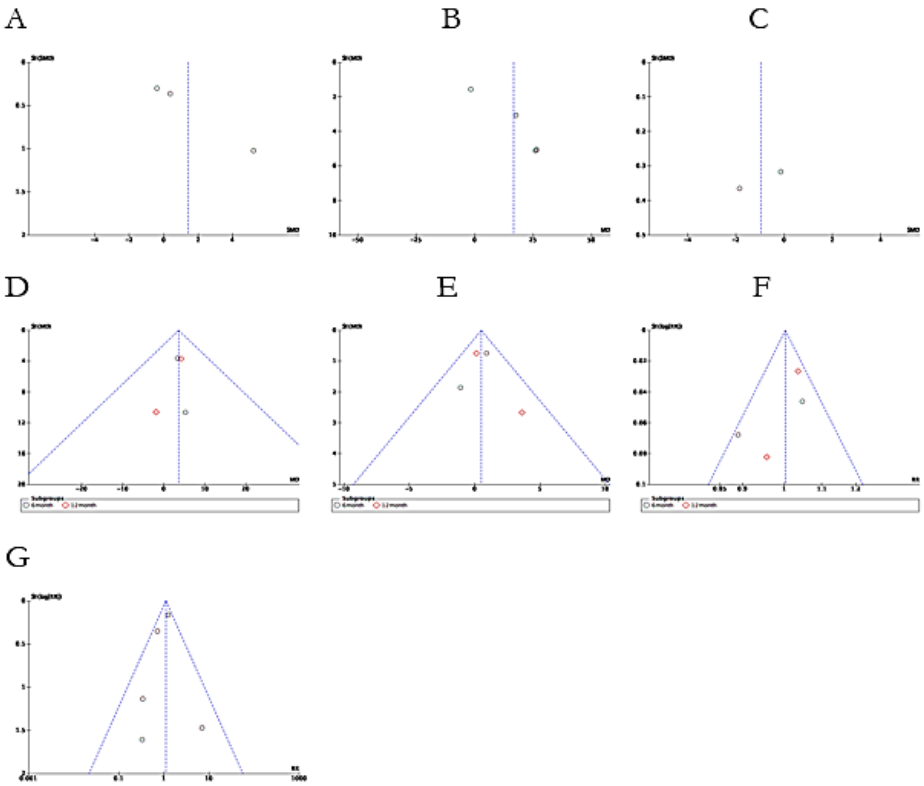

Fig.3: The funnel plots of all parameters. Note: the outcome index is as follows: A. epithelial thickness; B. vaginal maturation index; C. pH; D. PFIQ-7; E. PISQ-12; F. PGI-I; G. adverse events

Effectiveness of treatment for QoL

The analysis of QoL included two studies in which the evaluation indicators included the PFIQ-7, PISQ-12 and PGI-I scores. Table 4 shows that only Sun's study and Verghese's study were included in the analysis of QoL, and their studies were conducted at 6 and 12 months, respectively (21),(24). There was no significant beneficial effect of estrogen compared with the control on the QoL parameters. The homogeneity of the indicators, except the PGI-I score at 6 months (I^2=75%, *P*=0.05), in the two studies was acceptable (I^2<50%, *P*>0.05). However, there were only two studies in this analysis, so subgroup analysis could not be performed. No obvious asymmetry was found in the funnel plot of the PFIQ-7, PISQ-12 or PGI-I scores (Fig. 3).

Table 4: Effectiveness of treatment for QoL

Variable	*Month*	*Number of Participations (E: Control)*	*MD or RR*	*95%CI*	*Overall effect P-Value*	*I^2*	*P-Value*
PFIQ-7	6	131:134	3.60	[-3.13,10.33]	0.29	0%	*0.87*
	12	129:135	3.53	[-3.35,10.41]	0.31	0%	*0.59*
PISQ-12	6	104:107	0.62	[-0.73,1.98]	0.37	0%	*0.32*
	12	104:103	0.36	[-0.16,1.77]	0.62	37%	*0.21*
PIG-I	6	110:118	0.99	[0.92,1.07]	0.88	75%	0.05
	12	113:121	1.01	[0.95,1.07]	0.72	21%	*0.26*

E, estrogen treatment group; MD, mean difference; RR, relative risk; CI, confidence interval; PFIQ, Pelvic Floor Impact Questionnaire; PISQ, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; PGI-I, Patient Global Impression of Improvement

AEs

Fig. 4 shows that five trials were included in the analysis of AEs. Although five of the seven RCTs included in this meta-analysis reported AEs, the analysis showed no significant difference in AEs between the estrogen group and the control group (95% CI: 0.84-1.48, *P*=0.46). Additionally, there was no significant heterogeneity in these two studies (I^2<50%, *P*=0.28), suggesting that compared with the control, the topical use of estrogen in the treatment of POP did not increase the risk of ocular AEs in postmenopausal women. A sensitivity analysis of AEs showed that neither the heterogeneity nor the overall effect changed significantly after excluding studies one by one (Table 4). The funnel plot of AEs did not indicate substantial asymmetry (Fig. 3).

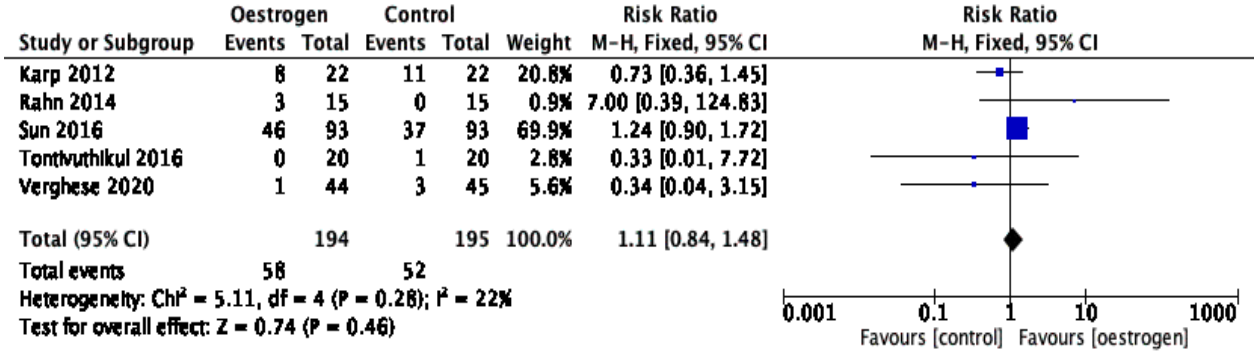

Fig.4: The forest plot of adverse events

Discussion

We analyzed seven RCTs to evaluate the impact of LET on vaginal health and QoL in postmenopausal women with POP. To the best of our knowledge, this is the first systematic review and meta-analysis, which includes the most recent RCTs, of the effects of LET on vaginal health and QoL in postmenopausal women with POP.

Currently, the effect of LET on POP in postmenopausal women is controversial. In contrast with many studies assessed the effect of LET on POP repair-related complications (25, 26), this study focused on vaginal health and QoL and indicated that LET slightly improved the VMI in postmenopausal women with POP but did not lead to a remarkable change in epithelial thickness; vaginal pH; or PFIQ-7, PISQ-12 or PGI-I scores.

Epithelial thickness is a well-established clinical indicator used to reflect vaginal epithelial quality. Vaginal pH was determined in a standardized manner. Since vaginal pH was a dichotomous variable in Coelho's study (27), it could not be compared with the results of other continuous variables, and we could not include the results of this study. A change in epithelial thickness and a change in vaginal pH are regarded as two main indicators for the diagnosis of poor vaginal health in postmenopausal women (28). Our results showed that locally applied estrogen did not significantly improve epithelial thickness, suggesting that locally applied estrogen did not improve the tissue quality. In accordance with the epithelial thickness results, the vaginal pH results indicated that vaginal health was not significantly improved in postmenopausal women with POP after LET. Two of the three included studies reported consistent trends (18), (21). One potential explanation is that the drug concentration of local estrogen was too low to prevent side effects, including stoke and breast and endometrial cancers (29), so even if a highly sensitive analysis was performed to detect E1 and E2 in serum, there would be no significant differences between the groups (20). In addition, the vaginal epithelium of postmenopausal women showed downregulation of steroid hormone receptor expression, resulting in no response to LET (30). Changes in the expression of postmenopausal hormone receptors are also controversial (31). A significant change was found in epithelial thickness after 6 wk of LET compared with a placebo in postmenopausal women with POP (20); A statistically significant decrease was reported at 12 wk after LET (19). These contradictory results may be due to the method of results reporting, as the reports did not provide baseline values; therefore, the results compared were the last values obtained. In addition, the limited sample size could have contributed to the contradictory results, highlighting the importance of recording baseline data and achieving an adequate sample size in this controversial field.

The VMI can be used to quantify basal, intermediate and superficial epithelial cells as objective indicators for the evaluation of vaginal epithelial quality (32). In general, a lower VMI value indicates a higher degree of atrophy. The VMI was higher in the treatment group than in the control group, indicating that LET was able to improve the degree of vaginal atrophy. Interestingly, this result contradicts that found for vaginal pH and epithelial thickness, which are objective, effective and inexpensive indicators that can be used for analysis of vaginal health. The most likely explanation for this discrepancy is that the sample size in the current study was too small, and the heterogeneity between studies was too large. LET significantly improved vaginal health in postmenopausal women with VA (33), but in our analysis, there was almost no difference between the treatment and control groups. The difference in the results may be due to inconsistencies in the methods used. Patients usually choose a cream or tablet for LET, but for nonsevere POP, doctors generally advise insertion of a uterine pessary as the primary treatment (34), so patients are more likely to choose a vaginal ring or cream with a pessary for LET. These therapeutic options may inhibit the therapeutic effect of local estrogen on vaginal health. Notably, the number of studies included in this analysis was limited, which lim-

ited the results to some extent. However, if LET can improve vaginal health in patients with POP, it will be a convenient treatment option for doctors, who can apply the treatment during the operation, thus reducing the occurrence of postoperative complications. However, if the symptoms of VA cannot be improved, treatment with topical estrogen is not recommended because it will increase the discomfort of patients and the cost of treatment. Additionally, though clinical trials and observational studies have found that the risks associated with systemic estrogenic therapy are low, the product label for low-dose vaginal estrogenic therapy still indicates risks associated with systemic estrogenic therapy, and the psychological burden of patients may increase because they are worried about side effects.

The PFIQ and PISQ were developed in 2001, and they are now among the most commonly used instruments for measuring QoL in those affected by POP (35, 36). Because they are sensitive to changes, they are suitable for epidemiological studies and for the evaluation of treatment results. These two questionnaires have been used in numerous studies, and their shorter versions, the PFIQ-7 and PISQ-12, have also been validated (37, 38). The PFIQ-7 covers the impact of POP on daily life, and the PISQ-12 covers sexual function in heterosexual, sexually active women with POP. The results of the present study showed that the PFIQ-7 and PISQ-12 scores of postmenopausal POP patients were not significantly improved at 6 or 12 months after LET. However, this result is contrast with one of the included studies, which concluded that the topical use of estrogen improved the PISQ-12 score at 12 months (24). The reason for this conflicting conclusion may be that only two eligible trials were included. Moreover, the PISQ-12 covers only women who are sexually active in a heterosexual relationship, which led to a small number of studies being included, so the credibility of the findings is also questionable. Regarding PFIQ-7 scores, consistent with our results, the included studies showed no statistically significant difference between the experimental and control groups (21, 24). This is mainly because most of the participants in both groups underwent surgery for prolapse, and the improvement in the symptoms of most patients was related to surgery, largely obscuring the possible benefits of estrogen. Consistent with the results of this study, LET did not significantly improve endothelial thickness or vaginal pH, suggesting that this intervention neither improved the sutured tissue during repair nor maintained the integrity of the pelvic floor tissue, so there may have been no significant effect on QoL. However, our analysis included only two experimental results; therefore, LET might be effective in improving PFIQ-7 and PISQ-12 scores.

As a global index for the evaluation of the efficacy of genitourinary prolapse surgery, the PGI-I is also used to assess QoL (39). Unlike the PFIQ-7 and PISQ-12, which are relatively long and require the calculation of scores, the PGI-I only requires patients to rate their response to interventions such as POP surgery, making the PGI-I easier to use and the results easier to interpret (40). According to our results, the PGI-I score did not significantly improve after treatment with local estrogen, suggesting that vaginal estrogen treatment did not improve the QoL of postmenopausal women with POP, consistent with the conclusion drawn above regarding the lack of improvement in the PFIQ-7 and PISQ-12 scores after LET. The lack of improvement in the PGI-I score may also be due to the lack of improvement in vaginal health after LET. Furthermore, the average time of surgical failure requiring repeat POP repair was within 2 yr after the first operation (41); the follow-up period in the included studies was only one year, which was insufficient and may have affected our results. Moreover, our results are still controversial due to the small number of RCTs included; thus, more RCTs should be performed in the future.

Our study revealed no difference in the rate of AEs between the LET and control groups, but AE-related dropouts were reported in the included studies. Among the patients, the primary reason for dropping out was discomfort caused by the pessary. Patients treated with a pessary had granulation tissue, and it is likely that placing a

foreign object on the thin, recently damaged vaginal epithelium may have led to additional tissue inflammation and vaginal discomfort or pain, consistent with a foreign object reaction. To determine the AEs related to the vaginal estrogen intervention, future research in this field should assess more AEs in those receiving LET without a pessary and those in the control group, and more studies on side effects, especially the long-term monitoring of systemic effects in the course of treatment and in postmenopausal women with severe POP symptoms, should be conducted.

Several potential limitations in our study should be considered. First, because the number of studies included was small, sensitivity and subgroup analyses could not be conducted to identify the source of heterogeneity among the trials, although the random-effects model and SMDs were used to address this problem. Second, because of the short follow-up time, we could not determine the long-term effects of topical estrogen use. Third, although only RCTs were included in our analysis, the number of included trials was limited, which led to the low reliability of the results. Therefore, more large-scale, high quality, randomized, double blind, placebo-controlled trials are needed in the future to obtain a higher level of evidence in this research field.

Conclusion

LET increased the VMI in postmenopausal women with POP but did not significantly improve epithelial thickness or vaginal pH, which are other indicators of vaginal health. Therefore, the efficacy of vaginal estrogen in the treatment of vaginal injury remains a controversial topic, and more RCTs are needed to explore the effect of vaginal estrogen on vaginal health in postmenopausal women with POP symptoms.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

We thank AJE Academic Services (https://www.aje.cn) for English-language editing and review services. This study was funded by the Committee of Health and Family Planning in Sichuan Province (grant number 18PJ057) and the Chengdu science and technology bureau (grant number 2020-YF05-00200-SN). The sponsors did not participate in the study.

Conflict of interests

The authors declare that there is no conflict of interest.

References

1. Collins SA, O'Shea M, Dykes N, Ramm O, Edenfield A, Shek KL, van Delft K, Beestrum M, Kenton K (2021). International Urogynecological Consultation: clinical definition of pelvic organ prolapse. *Int Urogynecol J,* 32:2011-2019.
2. Drage KJ, Aghera M, MacKellar P, et al (2022). The relationship between symptom severity, bother and psychological factors in women with pelvic organ prolapse: A cross-sectional observational study. *Neurourol Urodyn,* 41:423-431.
3. Rortveit G, Brown JS, Thom DH, et al (2007). Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. *Obstet Gynecol,* 109:1396-403.
4. Svihrova V, Svihra J, Luptak J, Swift S, Digesu GA (2014). Disability-adjusted life years (DALYs) in general population with pelvic organ prolapse: a study based on the prolapse quality-of-life questionnaire (P-QOL). *Eur J Obstet Gynecol Reprod Biol,* 182:22-6.
5. Robinson D, Prodigalidad LT, Chan S, et al (2022). International Urogynaecology Consultation chapter 1 committee 4: patients'

perception of disease burden of pelvic organ prolapse. *Int Urogynecol J,* 33:189-210.
6. Davidson ERW, Myers EM, De La Cruz JF, Connolly A (2019). Baseline Understanding of Urinary Incontinence and Prolapse in New Urogynecology Patients. *Female Pelvic Med Reconstr Surg,* 25:67-71.
7. Brown HW, Hegde A, Huebner M, et al (2022). International urogynecology consultation chapter 1 committee 2: Epidemiology of pelvic organ prolapse: prevalence, incidence, natural history, and service needs. *Int Urogynecol J,* 33:173-187.
8. Wu JM, Hundley AF, Fulton RG, Myers ER (2009). Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050. *Obstet Gynecol,* 114:1278-1283.
9. Geoffrion R, Larouche M (2021). Guideline No. 413: Surgical Management of Apical Pelvic Organ Prolapse in Women. *J Obstet Gynaecol Can,* 43:511-523.e1.
10. Srikrishna S, Robinson D, Cardozo L (2010). A longitudinal study of patient and surgeon goal achievement 2 years after surgery following pelvic floor dysfunction surgery. *BJOG,* 117:1504-11.
11. Al-Badr A, Saleem Z, Kaddour O, et al (2022). Prevalence of pelvic floor dysfunction: a Saudi national survey. *BMC Womens Health,* 22:27.
12. Reddy RA, Cortessis V, Dancz C, Klutke J, Stanczyk FZ (2020). Role of sex steroid hormones in pelvic organ prolapse. *Menopause,* 27:941-951.
13. Deng ZM, Dai FF, Yuan MQ, et al (2021). Advances in molecular mechanisms of pelvic organ prolapse (Review). *Exp Ther Med,* 22:1009.
14. Yi M, Wang S, Wu T, et al (2021). Effects of exogenous melatonin on sleep quality and menopausal symptoms in menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Menopause*, 28:717-725.
15. Lien YS, Chen GD, Ng SC (2012). Prevalence of and risk factors for pelvic organ prolapse and lower urinary tract symptoms among women in rural Nepal. *Int J Gynaecol Obstet,* 119:185-8.
16. The NAMS 2020 GSM Position Statement Editorial Panel (2020). The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause,* 27:976-992.
17. Higgins JPT, Thomas J, Chandler J, et al (2021). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). https://training.cochrane.org/handbook
18. Felding C, Mikkelsen AL, Clausen HV, et al (1992). Preoperative treatment with oestradiol in women scheduled for vaginal operation for genital prolapse. A randomised, double-blind trial. *Maturitas,* 15:241-9.
19. Karp DR, Jean-Michel M, Johnston Y, et al (2012). A randomized clinical trial of the impact of local estrogen on postoperative tissue quality after vaginal reconstructive surgery. *Female Pelvic Med Reconstr Surg,* 18:211-5.
20. Rahn DD, Good MM, Roshanravan SM, et al (2014). Effects of preoperative local estrogen in postmenopausal women with prolapse: a randomized trial. *J Clin Endocrinol Metab,* 99:3728-36.
21. Sun Z, Zhu L, Xu T, Shi X, Lang J (2016). Effects of preoperative vaginal estrogen therapy for the incidence of mesh complication after pelvic organ prolapse surgery in postmenopausal women: is it helpful or a myth? A 1-year randomized controlled trial. *Menopause,* 23:740-8.
22. Tontivuthikul P, Sanmee U, Wongtra-Ngan S, Pongnarisorn C (2016). Effect of Local Estrogen Cream on Vaginal Health after Pessary Use for Prolapsed Pelvic Organ: A Randomized Controlled Trial. *J Med Assoc Thai,* 99:757-63.
23. Vaccaro CM, Mutema GK, Fellner AN, et al (2013). Histologic and cytologic effects of vaginal estrogen in women with pelvic organ prolapse: a randomized controlled trial. *Female Pelvic Med Reconstr Surg,* 19:34-9.
24. Verghese TS, Middleton L, Cheed V, et al (2020). Randomised controlled trial to investigate the effectiveness of local oestrogen treatment in postmenopausal women undergoing pelvic organ prolapse surgery (LOTUS): a pilot study to assess feasibility of a large multicentre trial. *BMJ Open,* 10(9):e025141.
25. Chiengthong K, Ruanphoo P, Chatsuwan T, Bunyavejchevin S (2022). Effect of vaginal estrogen in postmenopausal women using

vaginal pessary for pelvic organ prolapse treatment: a randomized controlled trial. *Int Urogynecol J*, 33(7):1833-1838.
26. Marschalek ML, Bodner K, Kimberger O, et al (2021). Surgical Assessment of Tissue Quality during Pelvic Organ Prolapse Repair in Postmenopausal Women Pre-Treated Either with Locally Applied Estrogen or Placebo: Results of a Double-Masked, Placebo-Controlled, Multicenter Trial. *J Clin Med,* 10(11):2531.
27. de Albuquerque Coelho SC, Giraldo PC, et al (2021). ESTROgen use for complications in women treating pelvic organ prolapse with vaginal PESSaries (ESTRO-PESS)-a randomized clinical trial. *Int Urogynecol J,* 32:1571-1578.
28. Weber MA, Diedrich CM, Ince C, Roovers JP (2016). Focal depth measurements of the vaginal wall: a new method to noninvasively quantify vaginal wall thickness in the diagnosis and treatment of vaginal atrophy. *Menopause,* 23:833-8.
29. Crandall CJ, Hovey KM, Andrews CA, et al (2018). Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause,* 25:11-20.
30. Zbucka-Kretowska M, Marcus-Braun N, Eboue C, et al (2011). Expression of estrogen receptors in the pelvic floor of pre- and post-menopausal women presenting pelvic organ prolapse. *Folia Histochem Cytobiol,* 49:521-7.
31. Fuermetz A, Schoenfeld M, Ennemoser S, et al (2015). Change of steroid receptor expression in the posterior vaginal wall after local estrogen therapy. *Eur J Obstet Gynecol Reprod Biol,* 187:45-50.
32. Weber MA, Limpens J, Roovers JP (2015). Assessment of vaginal atrophy: a review. *Int Urogynecol J,* 26:15-28.
33. Mitchell CM, Reed SD, Diem S, et al (2018). Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. *JAMA Intern Med,* 178:681-690.
34. Manzini C, van den Noort F, Grob ATM, et al (2021). The effect of pessary treatment on puborectalis muscle function. *Int Urogynecol J,* 32:1409-1417.
35. Barber MD, Kuchibhatla MN, Pieper CF, Bump RC (2001). Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. *Am J Obstet Gynecol,* 185:1388-95.
36. Rogers RG, Kammerer-Doak D, Villarreal A, et al (2001). A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. *Am J Obstet Gynecol,* 184:552-8.
37. Barber MD, Walters MD, Bump RC (2005). Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol,* 193:103-13.
38. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C (2003). A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). *Int Urogynecol J Pelvic Floor Dysfunct,* 14:164-8; discussion 168.
39. Mattsson NK, Karjalainen PK, Tolppanen AM, et al (2020). Pelvic organ prolapse surgery and quality of life-a nationwide cohort study. *Am J Obstet Gynecol,* 222:588. e1-588.e10.
40. Srikrishna S, Robinson D, Cardozo L (2010). Validation of the Patient Global Impression of Improvement (PGI-I) for urogenital prolapse. *Int Urogynecol J,* 21:523-8.
41. Rahkola-Soisalo P, Mikkola TS, Altman D, Falconer C (2019). Pelvic Organ Prolapse Repair Using the Uphold Vaginal Support System: 5-Year Follow-Up. *Female Pelvic Med Reconstr Surg,* 25:200-205.