BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

DOI: 10.1111/1471-0528.16894
www.bjog.org

Randomised controlled trial

Does preoperative locally applied estrogen treatment facilitate prolapse-associated symptoms in postmenopausal women with symptomatic pelvic organ prolapse? A randomised controlled double-masked, placebo-controlled, multicentre study

M-L Marschalek,[a] K Bodner,[a] O Kimberger,[b] S Zehetmayer,[c] R Morgenbesser,[a] W Dietrich,[d] C Obruca,[d] H Husslein,[a] W Umek,[a,e] H Koelbl,[a] B Bodner-Adler[a,e]

[a] Department of General Gynaecology and Gynaecologic Oncology, Medical University of Vienna, Vienna, Austria [b] Department of Anaesthesiology, Medical University of Vienna, Vienna, Austria [c] Centre for Medical Statistics, Informatics and Intelligent Systems (Institute of Medical Statistics), Medical University of Vienna, Vienna, Austria [d] Department of Gynaecology and Obstetrics, University Hospital Tulln, Karl Landsteiner University of Health Sciences, Tulln, Austria [e] Department of Special Gynaecology and Obstetrics, Karl Landsteiner Institute, Währinger Gürtel, Austria

Correspondence: B Bodner-Adler, Department of General Gynaecology and Gynaecologic Oncology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. Email: barbara.bodner-adler@meduniwien.ac.at

Accepted 28 May 2021.

Objective To evaluate whether locally applied vaginal estrogen affects prolapse-associated complaints compared with placebo treatment in postmenopausal women prior to surgical prolapse repair.

Design Randomised, double-masked, placebo-controlled, multicentre study.

Setting Urogynaecology unit at the Medical University of Vienna and University Hospital of Tulln.

Population Postmenopausal women with symptomatic pelvic organ prolapse and planned surgical prolapse repair.

Methods Women were randomly assigned local estrogen cream or placebo cream 6 weeks preoperatively.

Main outcome measures The primary outcome was differences in subjective prolapse-associated complaints after 6 weeks of treatment prior to surgery, assessed with the comprehensive German pelvic floor questionnaire. Secondary outcomes included differences in other pelvic floor-associated complaints (bladder, bowel or sexual function).

Results Out of 120 women randomised, 103 (86%) remained for the final analysis. After 6 weeks of treatment the prolapse domain score did not differ between the estrogen and the placebo groups (4.4 ± 0.19 versus 4.6 ± 0.19; mean difference, −0.21; 95% CI −0.74 to 0.33; $P = 0.445$). Multivariate analysis, including only women receiving the intervention, showed that none of the confounding factors modified the response to estradiol.

Conclusions These results demonstrate that preoperative locally applied estrogen does not ameliorate prolapse-associated symptoms in postmenopausal women with symptomatic pelvic organ prolapse.

Keywords Local estrogen therapy, pelvic organ prolapse, postmenopausal women.

Tweetable abstract Preoperative local estrogen does not ameliorate prolapse-associated symptoms in postmenopausal women with pelvic organ prolapse.

Please cite this paper as: Marschalek M-L, Bodner K, Kimberger O, Zehetmayer S, Morgenbesser R, Dietrich W, Obruca C, Husslein H, Umek W, Koelbl H, Bodner-Adler B. Does preoperative locally applied estrogen treatment facilitate prolapse-associated symptoms in postmenopausal women with symptomatic pelvic organ prolapse? A randomised controlled double-masked, placebo-controlled, multicentre study. BJOG 2021; https://doi.org/10.1111/1471-0528.16894.

Introduction

Pelvic organ prolapse (POP) represents a major health issue worldwide, affecting up to 50% of postmenopausal women. Treatment options for POP include observation, pelvic floor muscle training, pessary use and surgery. Surgical solutions considered as 'one-off' treatments rather than nonsurgical treatments seemed to be preferred by women with POP.[1] Surgery for POP currently has a lifetime risk of 11.1%, which is expected to increase in the future.[2] The pelvic organs, as well as the surrounding muscular and connective tissue, are sensitive to estrogen. The presence of estradiol receptors α and β (ESR1/2) in the urinary bladder, urethra, vagina and pelvic floor musculature suggest that estrogen levels have a significant effect on the function of the genital and lower urinary tract.[3] The risk of developing pelvic floor disorders of any kind increases significantly after menopause and can be connected to the decline in available estrogen.

For some time, local estrogen therapy (LET) has become a focus of interest in the treatment of pelvic floor disorders. Although oral hormonal replacement worsens urinary incontinence, LET seems to have beneficial effects. There is evidence that LET reduces symptoms of the lower urinary tract, including frequency, urgency and urinary incontinence.[4] Similarly, LET seems to be effective and safe in the treatment of vaginal atrophy.[5–8] Concerning the effectiveness of LET in treating or preventing POP, there is currently no evidence and it is uncertain whether preoperative and/or postoperative LET in postmenopausal women undergoing POP surgery is beneficial.[9]

In an opinion paper the research and development committee of the International Urogynecology Association (IUGA) summarised that most of the recommendations concerning LET and vulvovaginal symptoms, as well as urinary incontinence, correspond to evidence level 2C. Regarding POP, the available evidence is even more scarce, and at this stage no benefit from LET could be demonstrated.[10,11] However, none of the available studies reported symptoms and signs associated with POP, but mainly reported symptoms that are associated with vaginal atrophy.

In summary, there is a need for adequately powered and randomised controlled trials to investigate the effect of LET and its impact on prolapse-associated symptoms, in order to be able to define evidence-based practical guidelines or recommendations for clinical practice in the future.

Therefore, we conducted a randomised double-masked placebo-controlled trial to evaluate whether 6 weeks of LET influences subjective prolapse-associated complaints in postmenopausal women with symptomatic POP and planned prolapse surgery.

Methods

Study design

This was a prospective randomised, double-masked, placebo-controlled multicentre study conducted at the Department of General Gynaecology and Gynaecologic Oncology of the Medical University of Vienna (MUVI) (main study centre), as well as at the Department of Obstetrics and Gynaecology of the University Hospital of Tulln (second centre), Austria. The study was approved by the institutional review board at both centres (IRB number: 1706/2016), and each participant provided written informed consent to participate. All eligible patients were referred by a gynaecologist and were seen by an urogynaecologist at the respective centre. Patients were not involved in the development of the research.

Patient selection

Postmenopausal women with symptomatic POP and planned surgical prolapse repair were eligible participants. In addition, eligible participants needed to be capable of applying a vaginal cream and comprehend the informed consent as well as the delivered questionnaire. Patients with a suspicion or history of malignancies, postmenopausal bleeding, a history of deep vein thrombosis, inherited or acquired blood clotting disorders, a history of transient ischaemic attack, myocardial infarction or ischaemic heart disease, hypersensitivity or contraindications to estrogen were excluded. Further exclusion criteria were treatment with oral hormonal replacement, vaginal moisturiser or herbs. All patients included received information and instruction for pelvic floor muscle training, as this is a standard first-line treatment at our institution. Definitive surgical correction was planned in cases who desired a surgical treatment.

Measurement

The primary outcome was the evaluation of the participants' subjective prolapse-associated complaints according to the prolapse domain score (PDS) of the Comprehensive Pelvic Floor Questionnaire (see below) at enrolment to the trial and after 6 weeks of treatment prior to the planned prolapse surgery. The prolapse domain within the Pelvic Floor Questionnaire consists of the following five questions: 'Do you have a foreign body sensation in the vagina?', 'Do you have the feeling something is falling out of the vagina?', 'Do you have to push back your prolapse to be able to urinate?', 'Do you have to push back your prolapse to have a bowel movement?' and 'How much are you bothered by your prolapse?'. Secondary outcome measures assessed with the comprehensive German pelvic floor questionnaire between groups were differences in other pelvic

floor-associated complaints (bladder, bowel or sexual function).

Comprehensive Pelvic Floor Questionnaire

After written informed consent was obtained, 103 of the original 120 participants randomised completed the German version of the validated pelvic floor questionnaire at the point of recruitment as well as after 6 weeks of treatment prior to surgery (total return rate, 85.8%). Participants filled out the questionnaire by themselves. If a question was unclear and the patient was unsure about how to answer, patients were able to ask medical personnel for assistance.

The German Pelvic Floor Questionnaire is a validated, self-administered questionnaire that integrates bladder, bowel and sexual function, pelvic organ prolapse severity, irritability and condition-specific quality of life in women with urinary incontinence (UI) and/or POP.[12] The questionnaire is divided into four domains (bladder, bowel, pelvic organ prolapse and sexual function) and each question is scored from zero to three. The summed scores are divided by the maximum total score giving a value ranging between zero (0 = no symptoms) and 1 for each of the domains. The scores are then multiplied by 10, for ease of reference, giving a value between 0 and 10 for each of the four domains and a maximum global pelvic floor dysfunction score of 40.

Physical and pelvic examination

All study participants underwent a standardized urogynaecological interview, including a complete physical and pelvic examination to check for genital prolapse according to the International Continence Society (ICS) POP-Q system.[13] Urodynamics were not performed routinely.

Funding

This study was funded by Montavit Ges.m.b.H., Salzbergstraße 96, A-6067 Absam/Tirol, Austria. The sponsor had no role in the design and conduct of the study, collection, analysis and interpretation of the results as well as the submission process for this article.

Intervention and study procedures

Women were randomly assigned 1:1 to receive either estradiol containing Linoladiol® cream or placebo cream. The active ingredient of the Linoladiol® estradiol-containing emulsion is 0.10 mg of estradiol in 1 g of cream and is chemically and biologically identical to endogenous human estradiol. The Linoladiol® cream contained estradiol, cetyl alcohol, probylene glycol, triglycerides, hostacerin T3, polysorbate, almond oil, benzyl alcohol and purified water. The placebo cream contained the same ingredients apart from estradiol. Both creams were white and odourless. This means that the estrogen and the placebo cream were visually identical and were not distinguishable by either doctors or patients. The study medication was provided by the pharmaceutical company Montavit Ges.m.b.H. (Absam, Austria).

Women were instructed to use the cream (estrogen or placebo) intravaginally with the enclosed applicator once daily for 1 week, every 48 hours for the following week and then twice weekly for the remaining 4 weeks (total treatment duration, 6 weeks). Participants documented the self-administered application in a patient diary. Adherence was assessed at the follow-up visit after 6 weeks by the trial coordinators. For the final analysis, all remaining patients used the cream as advised and as planned per protocol, meaning that medication adherence was satisfactory and plausible.

Randomisation

Patients who had consented to participate and met the eligibility criteria were randomly allocated to either receive the estradiol-containing cream or the placebo cream in a 1:1 ratio. The randomisation was conducted by the pharmaceutical company Montavit. The allocation sequence was computer-generated by RANCODE PROFESSIONAL 3.6. A randomisation to blocks of four was performed and carried out from numbers 1 to 400. On the basis of the randomisation list, all labels were produced and information of the principal investigator as well as the randomisation number was included. The research team was unaware of each participant's allocated treatment group. The only unblinded person was the study coordinator at Montavit.

Follow-up visit after 6 weeks

The follow-up visit was conducted 6 weeks after treatment and prior to the planned surgical prolapse repair. The German pelvic floor questionnaire was completed once more by the patients to evaluate changes of prolapse-associated symptoms after 6 weeks of treatment. Furthermore, all women underwent a gynaecological examination including POP-Q assessment at this follow-up visit.

Statistical analysis and sample size calculation

An intention-to-treat analysis was performed for all analyses. For the primary analysis we compared the alteration of the prolapse domain score obtained from the pelvic floor questionnaire before and after intervention (between baseline and 6 weeks follow-up) between the placebo and the treatment groups. Schoenfeld et al. observed a mean prolapse domain score of 3.33 with a standard deviation of 2.2.[14] We assumed that the placebo group would have no change in the prolapse domain score, whereas the treatment group would improve by two points. We further assumed that the standard deviation of the pre- and the

post-intervention values are equal and that the correlation between the pre- and the post-intervention values is 0.5, and thus the standard deviation of the differences is 3.8. Then a two-sided Student's *t*-test with 60 patients per group would have more than 80% power (significance level 0.05). For the sample-size calculation NQUERY XXX was used.[15]

Primary end point analysis

An analysis of covariance (ANCOVA) was computed with the dependent variable prolapse domain score after 6 weeks and the independent variables group (treatment versus placebo) and prolapse domain score at baseline. The baseline variables, the follow-up variables and the differences were described via mean values and standard deviations or 95% confidence intervals. The chi-square test was used for the comparison of categorical variables between the two groups and the Student's *t*-test was used for continuous variables. Multivariate stepwise logistic regression was performed to identify parameters associated with improved prolapse domain score in the intervention group. $P < 0.05$ was considered statistically significant. SPSS 23 (IBM, Armonk, NY, USA) was used for the calculations.

Results

Recruitment took place over a 31-month period between January 2017 and August 2020 in two urogynaecology centres in eastern Austria (Medical University of Vienna and University Hospital Tulln). One hundred and twenty women were randomised to receive either vaginal estrogen cream ($n = 60$) or placebo cream ($n = 60$). Once the target sample size was reached, the study stopped randomising treatment for women. Study retention was high: 103 of 120 (86%) women provided primary analysis data.

No serious adverse events were recorded, neither in the estrogen group nor in the placebo group.

A patient flow chart is presented in Figure 1. Baseline characteristics were comparable between treatment groups and no statistically significant differences could be

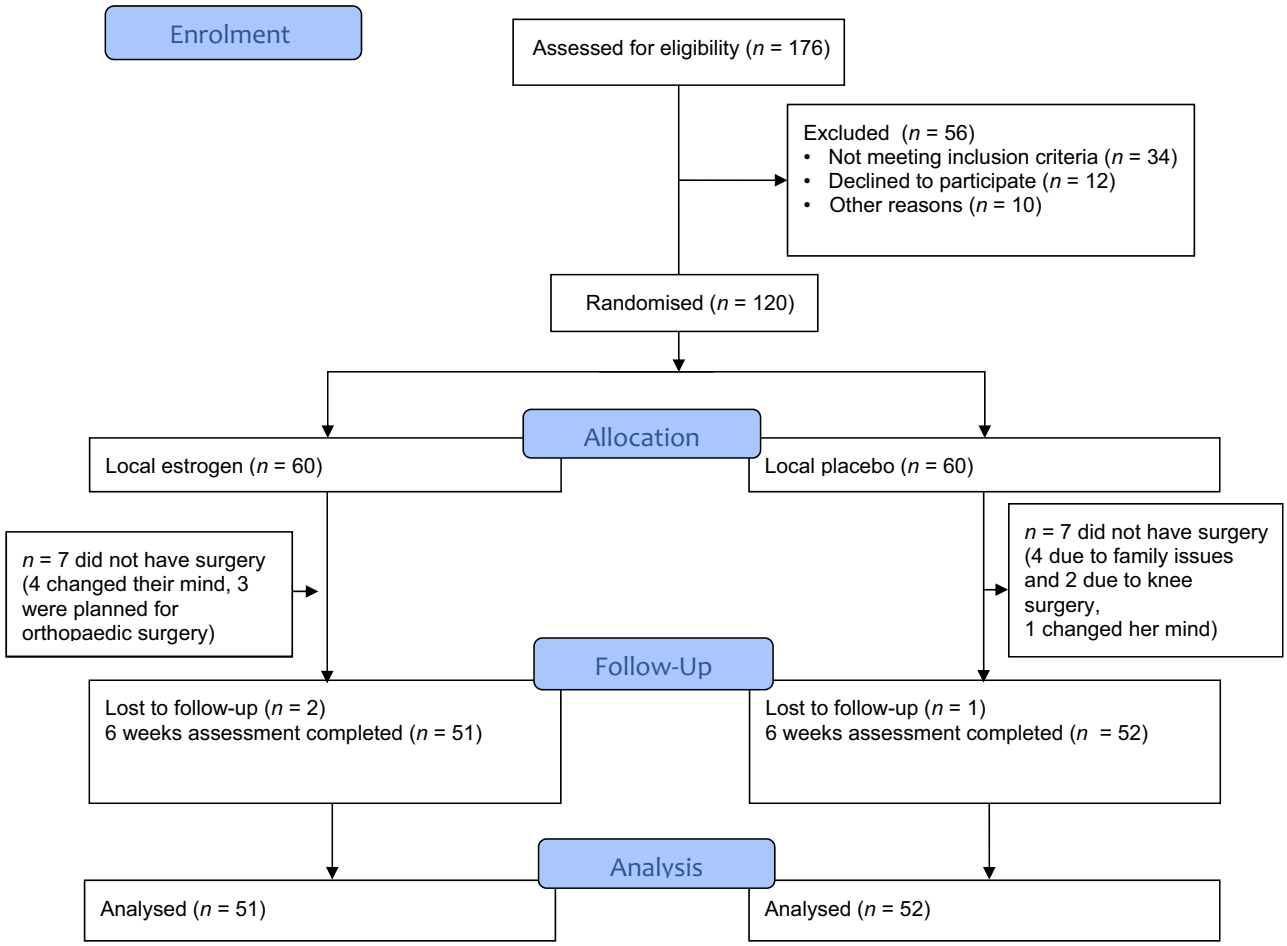

Figure 1. Flow of participants through the trial.

documented between the two groups ($P > 0.05$) (Table 1). Women were between 45 and 86 years old and 76% were married or partnered; 66/103 (64%) women were sexually active.

As calculated by ANCOVA, there was no significant difference between the estrogen and the placebo group in all domains of the Pelvic Floor Questionnaire (Table 2). Prolapse-associated symptoms appeared to be similar in both groups at baseline.

Differences of prolapse-associated symptoms after 6 weeks of estrogen or placebo treatment

After 6 weeks of treatment with either estrogen or placebo no significant reduction of prolapse-associated complaints could be observed according to the prolapse domain score of the Comprehensive Pelvic Floor Questionnaire (mean difference between groups, −0.21; 95% CI −0.74 to 0.33; $P = 0.445$) (Table 2). Likewise, all other domain scores (bladder, bowel, sexual function and global pelvic floor score) did not significantly differ between the intervention and the placebo group after 6 weeks (Table 2).

Differences of prolapse-associated complaints after 6 weeks of estrogen treatment compared with baseline

No statistically significant variations between baseline score and the score after 6 weeks of treatment with local estrogen could be observed (Table 3). None of the domains showed a significant difference between the scores at baseline and at 6 weeks.

In the placebo group, the prolapse domain score similarly did not significantly differ after 6 weeks (mean difference, 0.01; 95% CI −0.03 to 0.05; $P = 0.62$).

Multivariate analysis including only women with intervention

When controlled for age, POP-Q stage, parity, menopausal age, body mass index (BMI) and smoking through multivariate logistic regression, none of the above parameters modified the response to estradiol (Table 4).

Table 1. Baseline characteristics of the study population ($n = 103$)

Characteristic	Estrogen ($n = 51$)	Placebo ($n = 52$)	All patients ($n = 103$)
Age (years)	64.3 ± 9.7	61.2 ± 10.1	62.8 ± 10.0
Age at menopause (years)	48.9 ± 6.2	49.5 ± 5.9	49.2 ± 6.0
Parity	2.4 ± 2.1	2.3 ± 1.1	2.4 ± 1.7
BMI (kg/m^2)	26.9 ± 4.0	27.3 ± 4.8	27.1 ± 4.4
Diabetes	4 (7.8)	4 (7.8)	8 (7.8)
COPD	5 (9.8)	1 (1.9)	6 (5.8)
Smoking	11 (21.6)	8 (15.4)	19 (18.4)
POP-Q stage baseline	2.8 ± 0.4	2.7 ± 0.5	2.8 ± 0.5
Stage II	9 (17)	13 (25)	
Stage III	41 (80)	38 (73)	
Stage IV	1 (0.02)	1 (0.02)	
POP-Q stage after 6 weeks	2.8 ± 0.4	2.7 ± 0.5	2.8 ± 0.5
Stage II	9 (17)	13 (25)	
Stage III	41 (80)	38 (73)	
Stage IV	1 (0.02)	1 (0.02)	

BMI, body mass index; COPD, chronic obstructive pulmonary disease; POP-Q, Pelvic Organ Prolapse Quantification System.
Data are means ± SDs or *n* (%).

Table 3. Difference of prolapse domain score and other pelvic floor domain scores Baseline minus 6 weeks of estrogen treatment

Difference of scores baseline minus 6 weeks of estrogen treatment	Mean difference (baseline minus 6 weeks of treatment)	*P*
Prolapse domain score	0.025 (−0.02 to 0.06)	0.22
Bladder domain score	0.012 (−0.02 to 0.04)	0.38
Bowel domain score	0.002 (−0.02 to 0.02)	0.83
Sexual domain score	0.013 (−0.03 to 0.06)	0.54
Global pelvic floor score	−0.004 (−0.06 to 0.06)	0.88

Data are means (95% CIs).

Table 2. The German Pelvic Floor Questionnaire domains after 6 weeks of treatment with estrogen or placebo, according to ANCOVA

Scores after 6 weeks of treatment	Estrogen ($n = 51$)	Placebo ($n = 52$)	Mean difference between groups	*P*
Prolapse domain score	4.4 ± 0.19	4.6 ± 0.19	−0.21 (−0.74 to 0.33)	0.445
Bladder domain score	2.7 ± 1.1	2.6 ± 1.1	0.03 (−0.35 to 0.3)	0.868
Bowel domain score	1.8 ± 0.09	1.8 ± 0.09	0.04 (−0.28 to 0.21)	0.765
Sexual domain score	1.3 ± 0.14	1.5 ± 0.14	−0.22 (−0.6 to 0.17)	0.265
Global pelvic floor score	6.9 ± 0.22	7.0 ± 0.22	−0.06 (−0.69 to 0.56)	0.838

Data are means ± SDs or means (95% CIs).

Table 4. Multivariate logistic regression analysis of prolapse-associated complaints after 6 weeks of estrogen treatment

Variable	Regression coefficient (95% CI)	*P*
Age (years)	−0.01 (−0.08 to 0.06)	0.827
BMI (kg/m^2)	−0.08 (−0.24 to 0.08)	0.330
Parity	0.17 (−0.14 to 0.47)	0.270
POP-Q	−0.22 (−1.71 to 1.27)	0.765
Smoking	1.52 (−0.11 to 3.15)	0.068

BMI, body mass index; POP-Q, Pelvic Organ Prolapse Quantification System.
Data are means (95% CIs).

Discussion

Main findings

The results of this randomised, double-masked, placebo-controlled, multicentre study demonstrated that preoperative locally applied estrogen has no effect on prolapse-associated symptoms in postmenopausal women with symptomatic POP. Multivariate analysis, including only women in the intervention group, showed that none of the confounding factors modified the response to estradiol. Interestingly, women younger than 60 years demonstrated a greater improvement with the placebo than with estrogen.

Strengths and limitations

To the best of our knowledge, this study is the first trial evaluating prolapse-associated complaints in postmenopausal patients receiving either local estrogen therapy or placebo for symptomatic POP before planned surgical prolapse repair. We conducted a prospective, randomised, double-masked, placebo-controlled, multicentre study in a large population with excellent participant follow-up and medication compliance. Moreover, the study was adequately powered to draw serious conclusions from our results, albeit that the predetermined sample size of 60 per group was not reached. We realise that the generalisability of our trial results is limited by the homogenous population, despite enrolling at two centres. A further limitation of our study could be the fact that our patients received vaginal estrogen for a limited treatment duration of 6 weeks. With the wide variation of treatment duration in the literature (2–12 weeks), the authors decided on an average time period of 6 weeks. We are aware that this might not be long enough to see the impact of estrogen. Furthermore, the lack of an objective control of the local estrogen effect via vaginal maturation index or Meisels index could also be considered a limitation of this study.

Interpretation

Local estrogen treatment was protective in cases of pelvic floor disorders in several studies.[16–18] However, it is uncertain whether LET is beneficial in postmenopausal women with POP. With the lack of evidence and as none of the available studies reported symptoms and signs associated with POP, but mainly reported symptoms associated with vaginal atrophy, our research dealt with exactly this unresearched area.

It is well known that the extracellular matrix (ECM) is a key constituent of the supportive tissue of the vagina, and alterations in ECM metabolism have been demonstrated in women with POP.[19] Similarly, abnormalities in collagen metabolism such as elevated matrix metalloproteinase (MMP) activity have been identified in association with POP.[20] Other studies have shown that MMP synthesis and activity were suppressed in the presence of estrogen, leading to decreased collagen degradation in pelvic floor connective tissue.[21]

Although estrogen supplementation has not been established as an effective preventive or therapeutic measure for POP, vaginal estrogen is widely used to reduce side effects associated with conservative treatments (like pessaries) and surgically implanted materials.[22] Although studies support the use of local estrogen in women using pessaries,[23,24] it is unclear how estrogen exerts its positive effect. In our study we only included women with POP and planned pelvic floor surgery, and therefore we cannot comment on the effect of local estrogen in pessary users. The group of patients was chosen in order to observe solely the estrogen effect on the wellbeing of the patients in a homogenous patient group.

Similar to our study, Vaccaro et al. evaluated the role of 2–12 weeks of preoperative local estrogen in increasing vaginal wall thickness prior to POP surgery. Their results could not demonstrate a statistically significant increase in the treatment group compared with the group that received no intervention.[25] Although Rahn et al. observed an increased synthesis of mature collagen and epithelial thickness of the vaginal wall as a result of preoperative vaginal estrogen treatment, in a systematic review the same authors later summarised that it is uncertain whether LET is beneficial before prolapse repair, as an increase in vaginal thickness could not be observed.[21,26] As the main outcome variables of our study were possible changes of subjective prolapse-associated complaints after 6 weeks of preoperative treatment with estrogen or placebo, we cannot comment on changes in vaginal thickness after treatment.

Regarding prolapse symptoms, a Cochrane Review conducted by Ismail et al. did not find any clear evidence to suggest that estrogen helps in reducing the symptoms of POP, and concluded that an adequately powered

randomised controlled trial (RCT) is needed to identify the benefits or risks associated with estrogen supplementation in the prevention and management of POP.[27] The aim of our study was to identify possible changes in subjective prolapse-associated symptoms after 6 weeks of treatment with estrogen. Our data showed that prolapse-specific complaints were not ameliorated by local estrogen treatment, as neither prolapse nor other domain scores (bladder, bowel, sexual function or global pelvic floor score) differed between the intervention and the placebo group.

Moreover, recently, Verghese et al.[28] performed a pilot study to assess the feasibility of a multicentre RCT comparing estrogen versus no treatment in women undergoing POP surgery and reported good compliance within the study cohort. The authors would like to corroborate this hypothesis as the compliance rate within our study population was also satisfactorily high (176 patients were assessed for eligibility and 120 were randomised, with a retention rate of 86%).

In this study the following potential confounding factors were included: age, POP-Q stage, parity, menopausal age, BMI and smoking. Our results showed that none of these confounding factors modified the response to estradiol. A recent study identified an association of higher serum estradiol levels with higher body mass index, surgical menopause, alcohol use and antihypertensive medication among postmenopausal women with oral hormone therapy. Smoking was associated with lower estradiol levels.[29] Concerning local estrogen treatment, we were unable to find any comparable studies in the literature.

In summary, our results suggest that preoperative locally applied estrogen does not ameliorate prolapse-associated symptoms in postmenopausal women with symptomatic POP. Furthermore, and in light of the rising population affected by POP, which imposes a substantial health care and financial burden, there is a demand for supportive therapeutic options in order to alleviate the discomforting experience of prolapse symptoms.

Conclusion

This RCT was not able to detect any benefits of LET with regards to prolapse-associated symptoms, such as sensation of a vaginal bulge or something falling out of the vagina, and its encroachment on urinary or defecatory function. Our results strongly imply that prolapse-associated complaints cannot be improved solely by preoperative LET in postmenopausal women with symptomatic POP. Other factors, such as defects in the pelvic floor anatomy and damaged connective tissues causing POP are apparently not influenced by LET.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

M-LM participated in the project conception, data management, manuscript writing and editing. KB participated in the project conception, manuscript writing and editing. OK analysed and interpreted the data and participated in manuscript editing. SZ carried out the power analyses and participated in manuscript editing. RM participated in data collection and data management. WD and CO participated in data collection, data management and manuscript editing. HH and WU participated in manuscript writing and editing. HK participated in the project conception and manuscript editing. BB-A conceptualized and designed the study, coordinated and supervised the intervention, collected data and participated in manuscript writing and editing.

Details of ethics approval

The study was approved by the institutional review board of the Medical University of Vienna on 26 September 2016, and by the institutional review board of the University Hospital of Tulln, Austria (IRB no. 1706/2016). Clinical Trial Registration EudraCT no. 2016-000410-30. ClinicalTrials.gov identifier: Preoperative Oestrogen in Postmenopausal Women with Pelvic Organ Prolapse, NCT03779633.

Funding

This study was funded by Montavit Ges.m.b.H., Salzbergstraße 96, A-6067 Absam/Tirol, Austria. The sponsor had no role in the design and conduct of the study, collection, analysis and interpretation of result as well as submission process.

Acknowledgements

We acknowledge the support of this trial by Engelbert Hanzal, Martina Veit, Maria Jimenez, Ksenia Kröglер-Halpern.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

References

1 Basu M, Wise B, Duckett J. A qualitative study of women's preferences for treatment of pelvic floor disorders. *BJOG* 2011;118:338–44.

2 Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 1997;89:501–6.
3 Iosif CS, Batra S, Ek A, Astedt B. Estrogen receptors in the human female lower uninary tract. *Am J Obstet Gynecol* 1981;141:817–20.
4 Robinson D, Cardozo L. Estrogens and the lower urinary tract. *Neurourol Urodyn* 2011;30:754–7.
5 Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. *Obstet Gynecol* 2008;112:1053–60.
6 Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. *Obstet Gynecol* 2008;111:67–76.
7 Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998;92:722–7.
8 Goldstein I. Recognizing and treating urogenital atrophy in postmenopausal women. *J Womens Health (Larchmt)* 2010;19:425–32.
9 Trutnovsky G, Guzman-Rojas R, Martin A, Dietz HP. Pelvic floor dysfunction–does menopause duration matter? *Maturitas* 2013;76:134–8.
10 Bodner-Adler B, Alarab M, Ruiz-Zapata AM, Latthe P. Effectiveness of hormones in postmenopausal pelvic floor dysfunction-International Urogynecological Association research and development-committee opinion. *Int Urogynecol J* 2020;31:1577–82.
11 Felding C, Mikkelsen AL, Clausen HV, Loft A, Larsen LG. Preoperative treatment with oestradiol in women scheduled for vaginal operation for genital prolapse. A randomised, double-blind trial. *Maturitas* 1992;15:241–9.
12 Baessler K, Junginger B. [Validation of a pelvic floor questionnaire with improvement and satisfaction scales to assess symptom severity, bothersomeness and quality of life before and after pelvic floor therapy]. *Aktuelle Urologie* 2011;42:316–22.
13 Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JOL, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10–7.
14 Schoenfeld M, Fuermetz A, Muenster M, Ennemoser S, von Bodungen V, Friese K, et al. Sexuality in German urogynecological patients and healthy controls: is there a difference with respect to the diagnosis? *Eur J Obstet Gynecol Reprod Biol* 2013;170:567–70.
15 Elashoff JD. nQuery Advisor. Version 7.0 User's Guide. Los Angeles, CA; 2007.
16 Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I. Economic burden of urgency urinary incontinence in the United States: a systematic review. *J Manag Care Pharm* 2014;20:130–40.
17 Cardozo L, Lose G, McClish D, Versi E. A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder. *Acta Obstet Gynecol Scand* 2004;83:892–7.
18 Hanna-Mitchell AT, Robinson D, Cardozo L, Everaert K, Petkov GV. Do we need to know more about the effects of hormones on lower urinary tract dysfunction? ICI-RS 2014. *Neurourol Urodyn* 2016;35:299–303.
19 Alperin M, Moalli PA. Remodeling of vaginal connective tissue in patients with prolapse. *Curr Opin Obstet Gynecol* 2006;18:544–50.
20 Phillips CH, Anthony F, Benyon C, Monga AK. Collagen metabolism in the uterosacral ligaments and vaginal skin of women with uterine prolapse. *BJOG* 2006;113:39–46.
21 Rahn DD, Good MM, Roshanravan SM, Shi H, Schaffer JI, Singh RJ, et al. Effects of preoperative local estrogen in postmenopausal women with prolapse: a randomized trial. *J Clin Endocrinol Metab* 2014;99:3728–36.
22 Alperin M, Burnett L, Lukacz E, Brubaker L. The mysteries of menopause and urogynecologic health: clinical and scientific gaps. *Menopause* 2019;26:103–11.
23 Bulchandani S, Toozs-Hobson P, Verghese T, Latthe P. Does vaginal estrogen treatment with support pessaries in vaginal prolapse reduce complications? *Post Reprod Health* 2015;21:141–5.
24 Dessie SG, Armstrong K, Modest AM, Hacker MR, Hota LS. Effect of vaginal estrogen on pessary use. *Int Urogynecol J* 2016;27:1423–9.
25 Vaccaro CM, Mutema GK, Fellner AN, Crisp CC, Estanol MV, Kleeman SD, et al. Histologic and cytologic effects of vaginal estrogen in women with pelvic organ prolapse: a randomized controlled trial. *Female Pelvic Med Reconstr Surg* 2013;19:34–9.
26 Rahn DD, Ward RM, Sanses TV, Carberry C, Mamik MM, Meriwether KV, et al. Vaginal estrogen use in postmenopausal women with pelvic floor disorders: systematic review and practice guidelines. *Int Urogynecol J* 2015;26:3–13.
27 Ismail SI, Bain C, Hagen S. Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women. *Cochrane Database Syst Rev* 2010(9):CD007063.
28 Verghese TS, Middleton L, Cheed V, Leighton L, Daniels J, Latthe PM, et al. 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* 2020;10:e025141.
29 Sriprasert I, Kono N, Karim R, Hodis HN, Stanczyk FZ, Shoupe D, et al. Factors associated with serum estradiol levels among postmenopausal women using hormone therapy. *Obstet Gynecol* 2020;136:675–84.