Periurethral versus Intravaginal Application of Vaginal Estrogen for the Prevention of Urinary Tract Infections in Postmenopausal Women: Design of a Randomized Non-inferiority Trial

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1.1 Overview

The TAPER trial was approved by the IRB at the University of Pittsburgh Medical Center (UPMC) (STUDY22010147) and registered on Clinicaltrials.gov (NCT05472779) prior to study initiation and patient recruitment.

1.2 Study Population

Postmenopausal women assigned female sex at birth with a history of recurrent UTIs not currently using and/or not having used vaginal estrogen for at least 3 months were recruited from urogynecology, urology, women's health, and infectious disease specialty clinics, as well as by other marketing methods. The inclusion and exclusion criteria are detailed in Table 1. We defined postmenopausal status as having had a bilateral oophorectomy or no menses for at least one year, unless the patient had a history of a prior hysterectomy or was amenorrheic due to other surgical or medical means (e.g., endometrial ablation, intrauterine device). In these women, the patient was considered menopausal if they were at or above the 95th percentile for age at menopause (age 56) or had a documented follicle stimulating hormone level >30 IU/L. We defined UTI as dysuria, urinary frequency, or other UTI symptoms with either a positive urine culture or urinalysis with positive nitrites, moderate or many bacteria, and/or 2+/large leukocyte esterase. Although leukocyte esterase is not as specific as nitrites for the detection of UTI, it is often present as pyuria in the setting of an infection.[21] A level of at least 2+ or large leukocyte esterase in the setting of UTI symptoms was specified in order to maximize the likelihood of an actual UTI. We required laboratory evidence within the past year of recurrent UTI (≥2 UTI in the prior 6 months or ≥3 UTIs in the prior year) with these criteria. We included patients who were currently taking alternative non-antibiotic medications for UTI prevention, such as methenamine hippurate, D-mannose, probiotics, and cranberry extract supplements. We excluded any patient

who was taking a daily antibiotic or was undergoing at least weekly bladder instillations containing an antibiotic for indications of bladder pain or UTI prophylaxis. Other notable exclusion criteria include indwelling bladder catheterization or the use of intermittent catheterization, active treatment of an estrogen-responsive malignancy (e.g., breast cancer, uterine cancer), and significant vaginal stenosis or shortening that would prohibit appropriate use of a vaginal applicator.

Table 1: Inclusion and Exclusion Criteria in the TAPER Trial

Inclusion Criteria

- Female sex
- Postmenopausal
    - No menses for 1 or more years
    - OR status post bilateral oophorectomy without hormonal replacement
    - OR if status post hysterectomy or amenorrheic due to endometrial ablation/medication (e.g., Levonorgestrel releasing intrauterine device), patient must be age ≥56 years (95%ile for age at menopause) or have a documented follicle stimulating hormone (FSH) >30 IU/L
- Meets criteria for recurrent UTI with ≥2 UTIs in the prior 6 months or ≥3 UTIs in the prior year
    - Definition of UTI: symptoms WITH a positive urine culture OR urinalysis findings suspicious for UTI
        - Positive nitrites
        - Moderate or large bacteria
        - Large/2+ leukocyte esterase
- May include patients who used vaginal estrogen previously if they stopped use for ≥3 months prior to inclusion in study

Exclusion Criteria

- Current use of vaginal or oral estrogen products or use within the previous 3 months
- Inability or refusal to use vaginal estrogen
- Daily antibiotic use
- Frequent (at least weekly) bladder instillations containing an antibiotic
- Intermittent catheterization or indwelling bladder catheter
- Active treatment of an estrogen-responsive malignancy
- Known hydronephrosis due to incomplete bladder emptying
- Known bladder stones, mesh erosion into bladder, or foreign body in bladder
- Significant vaginal stenosis or shortening (e.g., due to lichen sclerosis, radiation, vaginal septum, or obliterative prolapse surgery) that would prohibit use of a vaginal applicator (i.e., genital hiatus <1 cm and/or total vaginal length <2 cm)

- Inability to use a vaginal applicator and without a caregiver who can administer vaginal estrogen (e.g., provider-managed space-filling pessary use (e.g. Gelhorn, cube), significant arthritis)
- Unable to consent for self
- Non-English speaking

1.3 Recruitment Sites

There were two main research sites for this study: UPMC Magee-Womens Hospital (Pittsburgh, PA) and UPMC Hamot Hospital (Erie, PA). Additional recruitment occurred at the University of Pittsburgh Physicians clinical offices of urogynecology, urology, internal medicine, and infectious disease and a urology office at a different institution within a 100-mile radius of the two main research hubs. Further recruitment efforts included targeted emails sent to the Pitt+Me community, a registry of over 300,000 participants interested in research run by the University of Pittsburgh's Clinical and Translational Science Institute.

Sites were grouped into "Pittsburgh" or "Erie" for randomization stratification purposes. The proximity of the location of the baseline visit was used to determine to which site a participant belonged. Remotely enrolled participants were assigned to the "Erie" site.

1.4 Study Intervention

The study drug for all women was estradiol 0.01% vaginal cream (brand name: Estrace), supplied in a 42.5-gram tube. Estradiol cream was chosen over other estrogen cream preparations due to estradiol being the primary intracellular human estrogen and the availability of generic options for purchase.

Participants were randomly assigned to one of two medication application assignments. The intravaginal drug administration arm followed the standard protocol of 1.0 g estradiol 0.01% cream instilled into the vagina using an applicator. The periurethral drug administration arm followed the protocol of 0.5 g dosage applied with a finger to the periurethral tissues. In both

study arms, participants applied vaginal estrogen nightly for two weeks, followed by maintenance dosing twice weekly at night.

All participants assigned to the intravaginal administration arm were taught to use the calibrated plastic applicator to measure the correct amount of vaginal cream. Anatomical depictions were used to show study participants the amount of cream used and the location where the cream should be applied (see Appendices A and B). Participants were asked to demonstrate their ability to appropriately dispense and measure the study drug at their baseline visit by way of the "teach-back" technique.[22,23] This is a non-blinded study given the need for study participants to apply the study drug appropriately and for the study team to teach them how to do so.

1.5 Baseline Assessments

The schedule of study encounters during participants' 6-month involvement in the TAPER trial is presented in Table 2. Once eligibility was confirmed and a patient provided written informed consent, baseline demographics (age, self-reported race/ethnicity), medical history (obstetric history, sexual activity, smoking status, relevant medical conditions, medication use, prior urogynecologic or urologic surgical history) and physical exam findings (body mass index, pelvic organ prolapse quantification and post-void residual, if available) were obtained through patient interview and chart review.

Table 2: Timeline of Study Encounters for TAPER Trial

Measure	**Screening**	**Baseline**	**2-week call**	**3-month visit**	**6-month visit**
Window (+/- week)			**±1 week**	**+2 weeks/-1 week**	**± 2 weeks**
Eligibility	X				
Consent	X				
Demographics		X			

Medical History		X			
Randomization		X			
Adverse Events Assessment			X	X	X
UDI-6		X		X	X
FSFI-6		X		X	X
Vulvovaginal symptoms questionnaire		X		X	X
Patient experience with estrogen questionnaire				X	X
Clean-catch urine specimen†		X		X	X
Vaginal flocked swab†		X		X	X
Vaginal Maturation Index*†		X		X	
Estradiol tube weight†		X		X	X

UDI-6: Urinary Distress Index-Short Form; FSFI-6: Female Sexual Function Index-6
*Vaginal maturation index was collected only for the first 21 participants in each arm
†Remotely enrolled participants did not have any collection of specimens or estrogen tube weights.

1.6 Randomization

Patients were randomized 1:1 to intravaginal application or periurethral application of estradiol cream using a fixed block size of 4 and stratified by study site ("Pittsburgh" or "Erie"). Randomization was performed through a secure web-based application that used a random allocation sequence generated prior to the start of the study. To reduce bias, only the randomization system programmer and study statistician had access to this sequence.

1.7 Remote Enrollment

Research staff met patients at clinical offices for in-person research visits. However, during the early recruitment phase, recruitment was noted to be low for patients traveling long distances for clinical care. Therefore, we introduced a remote enrollment option to improve generalizability and reduce barriers to enrollment. Remote enrollment would only be discussed if a participant expressed interest in the study but were unwilling to attend in-person research

visits. Eligibility was assessed by phone, and consent was obtained online through a secure web application or on paper by mail. The study drug was then delivered by mail. Once the study drug was received by the patient, the patient was randomized, and baseline information demographics and medical history was collected over phone call. Participant instruction of the vaginal estrogen application method was performed over the phone or via video application, with the participant following along using instructional handouts that were also sent by mail (see Appendices A and B). The participant was then asked to repeat these instructions to the study team member using the "teach-back" method. Questionnaires were sent to participants for self-completion by email via a secure web application or by mail. At 3 and 6 months, the study team called remote participants to confirm appropriate application of the study drug, to assess for need for additional study drug, and to address any concerns or questions. Adverse events were reviewed to ensure appropriate follow-up or notification of the IRB, if necessary.

1.8 Outcome Measures

Primary Outcome Measure

The primary outcome was the proportion of participants found to be UTI-free 6 months after the initiation of study drug use. Any UTI diagnosed within the first 4 weeks of study drug use was not counted towards this outcome given the known delay of approximately 3-4 weeks in the effects of vaginal estrogen therapy after initiation.[24–26] The primary outcome was assessed by chart review and confirmed by patient report 6 months after the initiation of vaginal estradiol therapy. Standing urine culture orders were provided to study participants for use when they experienced UTI symptoms (e.g., dysuria, frequency, urgency). Research staff sought to obtain copies of culture results if performed at an outside laboratory. To reduce recall bias, participants were queried at each research encounter about the occurrence and frequency of UTIs they had experienced in the prior 3 months.

Patient-Reported Measures

At baseline, 3 months, and 6 months, urinary symptoms and sexual function were assessed using two validated patient questionnaires. The Urogenital Distress Inventory Short Form (UDI-6) assesses bother related to both stress and urge urinary incontinence and has been validated in older adults.[27] The Female Sexual Function Index-6 (FSFI-6) is a shortened 6-item version of the FSFI that has excellent specificity and sensitivity for detecting female sexual dysfunction.[28] Two additional questionnaires were developed by the research team and administered at baseline, 3 months and 6 months timepoints. A four-question survey on vaginal irritative symptoms using a 5-point Likert scale was developed based on previous studies[29,30] and the expert opinions of two fellowship-trained urogynecologists (see Appendix C). A ten-question non-validated survey assessing patient experience with the cream using binary (yes/no) or 5-point Likert scale questions was developed and refined by the research team after consultation with two fellowship-trained urogynecologists and a dissemination and implementation scientist (see Appendix D). Questionnaires were administered on paper or online using a secure web-based application and were completed without the presence of study team members to reduce potential bias.

Translational Outcomes

To assess the potentially differential effects of application technique on the vaginal microbiome and vaginal epithelium, we included several exploratory translational aims for participants who could present for in-person research visits.

Vaginal pH typically increases after menopause to >4.5 and has been shown to decrease with local estrogen therapy.[9,31] Vaginal pH was assessed 2 cm proximal to the vaginal hymen using pH paper at baseline, 3-month and 6-month visits.

The estrogen status of the vaginal epithelium was assessed using the Vaginal Maturation Index (VMI), a vaginal cytology measure.[32] The VMI quantifies the distribution of parabasal, intermediate and superficial epithelial cells, with superficial cells being the most mature type of epithelial cell and indicating adequate vaginal estrogenization. For the purposes of comparison, the VMI (proportions of cell types) can be distilled into a single weighted score known as the Maturation Value (MV). The MV is calculated using the following equation: MV = % superficial cells + (0.5 x % intermediate cells).[33] The MV ranges from 0 to 100 with higher values indicating greater vaginal estrogenization. Specimens were collected without a speculum using a spatula and ThinPrep® kit.[34] The specimen was collected by a study team member to ensure appropriate collection from the mid-vagina. Specimens for VMI were collected at baseline and 3 months for the first 21 participants in each arm, based on a second power analysis (described in a later section). Specimens were processed by trained cytologists at the Magee-Womens Hospital Cytology Laboratory.

Local estrogen therapy has been shown to change the vaginal microbiome of postmenopausal women and increase the relative abundance of *Lactobacillus* species.[35] We sought to evaluate the change from baseline in both *Lactobacillus* and *E. coli* levels (the most common uropathogen) in the vagina and urine in the two trial arms. A vaginal flocked swab was collected from the mid-vagina, and participants provided a clean-catch, mid-stream urine sample at baseline, 3 months, and 6 months. For *Lactobacillus* quantification, DNA was extracted, and polymerase chain reaction (PCR) primers specific for *L. crispatus*, *L. iners*, *L. jensenii*, *L. gasseri,* and *Limosilactobacillus vaginalis* (*Lactobacillus* species known to be increased with exposure to vaginal estrogen) were used to amplify sequences for quantification.[36,37] For *E. coli* quantification, samples were inoculated on blood agar plates, streaked into four zones, and

incubated aerobically at 37°C in 5-6% carbon dioxide for a minimum of 48 hours.[38] Semiquantitative growth of *E. coli* was assessed, and phenotypic tests were performed to confirm bacterial identity.

Adherence to Study Drug Use

Adherence to the study drug use was assessed by estradiol tube weights at baseline, 3 months, and 6 months. Tubes of study drug were weighed using digital scales accurate up to 0.01 grams. The total amount of study drug used over the 6 months were calculated based on the measured weights at each research visit. Additionally, questions about adherence (5-point Likert scale questions: "I used the estrogen cream with the recommended frequency" and "I always apply the recommended amount of estrogen cream, based on my randomization in the study," as well as binary question: "If not, did you use more or less cream?") were used to assess subjective adherence to the study drug (Appendix D).

Adverse Event Assessment

Participants completed an adverse events assessment at the 3- and 6-month visits. All emergency room visits, hospitalizations, and urgent outpatient appointments were documented from patient report and confirmed by chart review. Symptoms potentially related to study drug use (ranging from vulvar rash to mood changes and joint pain) were listed, and participants were asked whether they believed the symptom was related to study drug use (Appendix E). All serious adverse events were reported to the IRB. A formal Data Safety Monitoring Board was not required for this study given the low-risk side-effect profile of vaginal estradiol cream.

1.9 Statistical Analysis

The primary analysis for non-inferiority between the two arms will be an intention-to-treat analysis. We will also perform a secondary per-protocol analysis, which will exclude participants who fail to follow their assigned arm for >50% of study involvement or who are required to

initiate bladder catheterization, daily prophylactic antibiotic, or frequent bladder instillations containing an antibiotic during their study enrollment. We will perform a Kaplan-Meier curve to compare survival experiences between the groups and use Student's t-test to compare the time to first UTI between the two groups. Group differences in survey scores, vaginal pH, vaginal maturation value, and *Lactobacillus* and *E. coli* levels will be explored using two-sample t-tests for secondary outcomes.

1.10 Sample Size and Power Calculations

Sample size calculations were performed *a priori* based on a non-inferiority test of two independent proportions with a type 1 error of 5% and 80% power. Based on the prior study of women using an estradiol ring by Eriksen et al., a 45% UTI-free rate at 6 months was applied.[39] Assuming a non-inferiority margin of 25% and a 45% UTI-free rate in each arm, 49 participants were needed per arm to provide 80% power to demonstrate noninferiority. To maintain planned power with an anticipated 14% loss to follow-up, a sample size of 57 participants per arm were required, for a total of 114 participants.

A second power analysis was conducted to determine the number of VMI samples needed to determine a group difference in change in MV, the weighted score for quantifying vaginal estrogenization. We hypothesized that due to longer exposure of the vaginal tissue to estrogen with instillation of cream intravaginally, the intravaginal application arm would be superior to the periurethral application arm with respect to improvement in MV scores over 3 months. Using a power of 0.80 with an alpha of 0.05 and predicting a mean change of 21 in the MV based on a 2022 study comparing a placebo ring to vaginal estrogen ring, we would require 21 participants per arm or 42 participants total to be able to determine superiority of intravaginal application in change in MV score.[40]