COVER PAGE

TITLE: Vaginal Estrogen and Pelvic Floor Physical Therapy in Women with Symptomatic Mild Prolapse

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SPECIFIC AIMS

Pelvic organ prolapse (POP) is a common disorder among women. It has been estimated that 200,000 women in the United States undergo inpatient procedures to repair pelvic floor disorders each year,[1] and by the year 2030, over 7 million surgeries will be performed annually.[2] Women have an 11% lifetime risk of undergoing surgery for pelvic floor disorders, and a 30% risk for re-operation.[3] Vaginal birth is considered a major risk factor since most parous women have mild asymptomatic prolapse.[4] However, the factors that lead to prolapse progression and symptom development are not clear. Currently, there is a lack of research correlating patient symptoms and degree of prolapse with biochemical data, such as collagen content and collagenase activity. POP has traditionally been managed either conservatively, with a pessary, or through surgical intervention. Recent studies suggest that Pelvic Floor Physical Therapy (PFPT) may also be beneficial.[5,6] The role of vaginal estrogen is unclear, and to date, limited data exist on its use in the treatment of prolapse.[7]

Prior studies in our lab confirm that the degradation of the pelvic connective tissues is regulated by estrogen and progesterone.[8,9] Data from animal models suggest that hormones given to women with normal support or with mild prolapse will prevent vaginal connective tissue breakdown and preserve mechanical integrity. Currently, it is our clinical practice to offer patients with symptomatic mild pelvic organ prolapse conservative treatment with pelvic floor physical therapy (PFPT) and vaginal estrogen. **We hypothesize that restoration of the vaginal support complex through re-alignment and muscle strengthening by way of PFPT, and improved tissue integrity through the use of vaginally delivered hormones, will lead to decreased symptoms and improved patient satisfaction with her treatment outcome.** We propose to test this hypothesis in a randomized trial in which women with symptomatic mild prolapse (stage I-III) who have opted to undergo PFPT, receive treatment with PFPT in combination with vaginal estrogen versus placebo. Ultimately, we hope to use this data as a foundation for instituting a larger trial in which prolapse progression strategies are tested in women with mild to moderate prolapse.

Aim 1: To determine the impact of vaginally delivered estrogen on global impression of improvement in women with symptomatic stage I-III pelvic organ prolapse who are undergoing pelvic floor physical therapy. Women will be randomized to PFPT in combination with vaginal estrogen versus placebo, and will be administered questionnaires at baseline and 6 months after treatment. The primary outcome is global impression of her improvement, measured via administration of the validated Patient Global Impression of Improvement questionnaire (PGI-I).[10] Other validated questionnaires will be used to assess symptoms, sexual function, and quality of life. Results will be compared between groups.

Aim 2: To determine the impact of vaginal estrogen on POP stage, as measured by the Pelvic Organ Prolapse Quantification (POP-Q) exam. The POP-Q exam is an objective validated clinical tool that is used to assess prolapse stage.[11] POP-Q exam will be performed at baseline and 6 months after treatment.

Aim 3: To evaluate the effect of PFPT and vaginal estrogen on biomarkers of prolapse, and to correlate this data with patient symptoms and anatomical changes. Vaginal tissue swabs will be collected at baseline and 6 months. Collagenase activity will be analyzed.

BACKGROUND

Estrogen receptors are present throughout the female pelvic floor and have been detected in the levator ani muscles and urogenital ligaments.[12,13] This biological finding provides a basis for the suggestion that estrogen may play a role in the development of pelvic organ prolapse, and in turn, may be beneficial in the prevention and treatment of this condition. Several studies have confirmed that the degradation of pelvic connective tissues is regulated by hormones. In primates, estradiol given to ovariectomized animals increased collagen synthesis[14] and the expression of vaginal cystatin C, an inhibitor of collagen proteases.[15] In human studies, biopsy specimens of the arcus tendineous fasciae pelvis in postmenopausal women who were not on hormones showed a decrease in type I collagen and collagen ratios compared to biopsies from premenopausal women, whereas no decrease was found in postmenopausal women who were on hormone therapy.[16]

Additional studies on human tissue and in rats also suggest that hormones may have a protective effect against supportive tissue degradation[8,9] and may lead to restoration of biomechanical properties.[17]

To date, limited data exist from randomized controlled trials and the role estrogen in the prevention and treatment of prolapse remains unclear.[7] One small randomized placebo-controlled trial compared the effects of raloxifene, tamoxifen, and oral conjugated equine estrogen (CEE) on the pelvic floor, and was part of a larger osteoporosis trial.[18] The patients were taught Kegel exercises and encouraged to perform home exercises daily, but did not undergo formal pelvic floor physical therapy. Patients with prior hysterectomy were excluded, but those using pessaries were not. In this trial, 2 of 8 patients in the oral CEE group demonstrated worsening prolapse, and 2 or 8 showed an improvement. More evidence is needed to determine the impact of estrogen and pelvic floor muscle exercises on the treatment and possibly prevention of pelvic organ prolapse.

We believe that the optimal approach to improving prolapse symptoms in the patient with mild prolapse requires both re-alignment and strengthening of the levator muscles via pelvic floor physical therapy (PFPT), and optimization of tissue integrity via local estrogen therapy. Although recent studies suggest a reduction in prolpase symptoms with PFPT,[5,6] the impact of complementary therapy with vaginally delivered hormones remains unknown. It is our current clinical practice to offer patients with mild symptomatic pelvic organ prolapse conservative treatment with PFPT and vaginal estrogen. We do not suggest this treatment regimen for women with more severe prolapse, as we believe that it will have little clinical benefit. In the proposed trial, we plan to evaluate the effect of vaginal estrogen on the treatment of symptomatic mild prolapse with PFPT.

SIGNIFICANCE

The estimated annual direct cost for pelvic organ prolapse surgery is over $1 billion dollars.[19] As the population ages and the demand for care of pelvic floor disorders increases,[20] it is critical that we investigate alternatives to surgical intervention and develop new strategies for prevention. To date, few studies have compared the effectiveness of our current treatments for mild prolapse. Thus, it is difficult to counsel women on their risk for prolapse progression or whether a specific treatment is beneficial. This study provides a unique opportunity to explore a commonly prescribed treatment alternative to pessaries and surgery for patients with mild symptomatic prolapse, and to correlate patient symptoms and anatomical findings with biochemical data. We believe that the results of this study will improve our comprehension of the disease mechanism of prolapse, and will have future implications for averting or delaying disease progression. Moreover, this study will serve as critical content for a future larger study in which we compare the effectiveness of therapies for mild prolapse.

RESEARCH DESIGN AND METHODS

Overview: This is a randomized placebo-controlled trial in which women with symptomatic mild prolapse who have opted to undergo Pelvic Floor Physical Therapy (PFPT), receive treatment with PFPT in combination with vaginal estrogen versus placebo. Patients will be followed for a 6-month timeframe. This study has been approved by the University of Pittsburgh Institutional Review Board.

Study Location: Patient recruitment and exams will take place at the Women's Center for Bladder and Pelvic Health at Magee-Womens Hospital, which is part of the University of Pittsburgh Medical Center (UPMC). Additional recruitment sites at Magee include: the Midlife Health Center and Western PA Women's Healthcare Associates. Pelvic Floor Physical Therapy will take place at UPMC Centers for Rehab Services. Biochemical analysis of the vaginal swabs will take place at the Magee-Womens Research Institute in Dr. Moalli's laboratory.

Sample size: Given the lack of data on PFPT and vaginal estrogen in the treatment of prolapse, the decision was made to conduct a pilot study, with plans to use this data as a foundation for instituting a larger clinical trial in the future. A convenience sample size of 53 patients (27 in the treatment group and 26 controls) was chosen to comply with the budget. Based on prior data from our lab evaluating collagen alignment and

collagenase activity in primates with mild versus no prolapse,[21,22] we estimate that 53 patients will have 99.6% power to detect a 48% difference between groups at the 2-sided 0.05 significance level.

Recruitment: Patients will be recruited from the Women's Center for Bladder and Pelvic Health, the Midlife Health Center, and Western PA Women's Healthcare Associates. Women will be approached for study participation if they have symptomatic mild (stage I-III) POP, as measured by POP-Q exam,[11] and have chosen to proceed with PFPT for management. Inclusion/exclusion criteria are listed below.

Inclusion criteria:

- Women in good health aged 40-80
- Has symptoms of pelvic organ prolapse; answers "yes" to at least 1 of the following questions:
    - Do you feel or see a vaginal bulge?
    - Do you feel pressure in the vagina?
- Meets POP-Q criteria on exam for stage I, II, or III prolapse
- Interested in PFPT for management of POP
- Normal mammogram within 1 year of enrollment

Exclusion criteria:

- Prior surgery for prolapse
- Other prior interventions for prolapse (e.g. pessary, PFPT)
- Connective tissue diseases known to affect collagen or elastin remodeling
- Known liver dysfunction
- Unevaluated abnormal vaginal bleeding or abnormal pap smear in the previous year
- BMI > 35 kg/m^2
- History of estrogen therapy (including birth control) in the previous year
- Current or prior breast or pelvic malignancy (ovarian, tubal, uterine, cervical or vaginal)
- Contraindication to hormone use (e.g. thromboembolic disorder, use of anti-coagulants, coronary artery disease, history of stroke)

Interventions - Baseline Visit:

I. Demographic data will be abstracted from the medical record by the research staff. Research variables include: age, race, ethnicity, BMI, age at menarche, history of oral contraceptive use, gravidity, parity, vaginal parity, number of cesarean sections, age at first full term pregnancy, age at last full term pregnancy, weight of largest baby, date of last/final menstrual period, age at menopause, time since menopause, current medications, smoking status, bowel habits, questions related to urinary and fecal incontinence, medical co-morbidities (obesity, diabetes, chronic lung disease, constipation and irritable bowel syndrome), and surgical history (focusing on abdominopelvic surgeries and hernia repairs).

II. All subjects will complete self-administered questionnaires. Pelvic floor symptoms will be assessed with the Pelvic Floor Distress Inventory (PFDI-20).[23] Sexual activity will be evaluated with the Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire (PISQ-12).[24] Impact on quality of life will be measured with the Pelvic Floor Impact Questionnaire (PFIQ-7).[23] All of these questionnaires have been validated in women with pelvic organ prolapse.

III. POP-Q exam[11] and prolapse stage will be recorded. POP-Q exam, as described by the International Continence Society, is performed on all patients at their initial visit to the Women's Center for Bladder and Pelvic Health. As stated in the inclusion criteria above, only those patients who have stage I, II, or III prolapse on POP-Q exam will be approached for study participation.

IV. A vaginal maturation index will be obtained on all patients in order to assess baseline estrogen status.

V. Vaginal swabs will be collected from the posterior fornix for biochemical analysis. The vaginal swabs will be sent to Dr. Moalli's laboratory where collagenase activity will be measured.

VI. Subjects will be randomized to receive either PFPT plus vaginal estrogen or placebo. A random allocation sequence will be achieved by generating a random number list using a computer.

VII. Subjects will be given a 6 month supply of either vaginal estrogen or placebo and instructed on proper use (1 gram every night for 7 days, then 1 gram twice weekly thereafter for a total duration of 6 months). Handouts will be given which include these instructions and the potential side effects of vaginal estrogen therapy. The dose of hormones used in this study is the same as what we commonly prescribe in our office during routine clinical care. Several trials have evaluated the safety of vaginally delivered estrogen and reports of endometrial hyperplasia or cancer are rare.[25-30]

VIII. All patients will be referred to the UPMC Centers for Rehab Services for PFPT for a treatment duration of 6 months. All women will undergo the standard PFPT program used in the treatment of prolapse. This includes weekly sessions for the first 4 weeks, followed by 1 session per month thereafter, with instructions for home practice.

Interventions – Follow-up:

I. Phone call at 3 months: Subjects will receive a phone call from the research staff at 3 months following the initial baseline visit to assess compliance with therapy and to address questions.

II. Follow-up visit at 6 months: Patients will be seen at the Women's Center for Bladder and Pelvic Health 6 months after initiation of therapy. The following activities will take place:

a. Questionnaire completion: Subjects will complete the same 3 questionnaires that they completed at their baseline visit (PFDI-20,[23] PISQ-12,[24] and PFIQ-7 [23]). The Patient Global Impression of Improvement questionnaire (PGI-I) will also be completed, which is a global assessment tool that has been validated in women undergoing treatment for prolapse.[10]

b. Patients will be asked to complete a brief confidential survey about the number of PFPT visits that they attended and the reason for any PFPT visits that were missed. This survey will also ask about vaginal symptoms over the course of the study, and about compliance with study drug therapy. In order to maintain blinding of the research staff, patients will fill out this survey in private and will place it in a sealed envelope when finished.

c. POP-Q examination will be performed

d. Vaginal maturation index and vaginal swabs for biochemical analysis will be collected

Primary outcome: Global impression of improvement with treatment, as measured by the PGI-I[10]

Secondary outcomes:

- Pelvic floor symptoms – as measured by the PFDI-20 [23]
- Sexual complaints – as measured by the PISQ-12 [24]
- Impact on quality of life – as measured by the PFIQ-7 [23]
- POP-Q stage
- Biochemical markers - collagenase activity

Data analysis:

Baseline characteristics will be analyzed using chi-square, Student's t-, or Mann-Whitney U test, as appropriate. Paired Student's t-test or Wilcoxon signed-rank test will be used to compare baseline and 6-month questionnaire scores, biochemical endpoints, and POP-Q measurements, as appropriate based on the distributions of the data. Student's t- or Mann-Whitney U test will be used to compare the change between the baseline and 6-month measurements between groups. Pearson's correlation coefficient and multivariable linear regression models will be used to examine the associations between clinical and biochemical outcomes. Statistical tests will be evaluated at the 0.05 significance level.

Safety Monitoring:

The risks associated with the use of vaginal estrogen are small,[25-30] and in this study, patients will be on hormones for only 6 months. Patients will be instructed to contact the research team in the event of any symptoms, such as breast tenderness, perineal pain, vaginal discharge, or bleeding. Persistent breast or perineal pain may require a decrease in the frequency of vaginal estrogen use. All bleeding will be evaluated by standard clinical guidelines. Several trials have evaluated the safety of vaginally delivered estrogen and reports of endometrial hyperplasia or cancer are rare.[25-30] At the discretion of the investigators, if continued study participation is felt to be unsafe for any woman, she will be withdrawn from the study. Drs. Skoczylas and Moalli will be responsible for monitoring for adverse events and side effects. Formal monitoring will take place at monthly research meetings which the investigators attend. Informal monitoring will occur more frequently and will be based upon need. All deviations from the normal course will be reported to the IRB.

Subject compensation:

Subjects will be provided with enough vaginal medication for the 6-month study duration. Study subjects will be compensated $50 at their baseline visit and $50 at their 6-month follow-up visit, for a total of $100. Patients will also be reimbursed $25 for each PFPT session attended, up to 9 sessions (for a total of $225). A grant has been received from the American Urogynecologic Society which will cover the cost of this compensation.

Timetable:

The study duration for each patient is 6 months. We hope to finish recruitment by February 2014 and to complete data collection by August 2014. We anticipate that data analysis and report preparation will be completed by December 2014.

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