

***Title: A Pilot Randomized Controlled Trial of Vaginal Estrogen on Postpartum Atrophy, Perineal Pain,  
and Sexual Function***

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## **ABSTRACT (157)**

Dyspareunia and vaginal/perineal pain are well-known sequelae after vaginal delivery. However, the contribution of postpartum vaginal atrophy to these issues is largely unknown. Although the relationship between lactation, relative estrogen deprivation, and vulvovaginal atrophy has been established, there is a paucity of data regarding the prevalence of vulvovaginal symptoms in the postpartum period and treatment options. We plan to evaluate the feasibility and preliminary efficacy of local estrogen on postpartum genitourinary symptoms by performing a pilot randomized, placebo-controlled trial of nulliparous postpartum women with a perineal laceration following a term vaginal delivery. The primary aim of this study is to compare vulvovaginal atrophy symptoms between women using vaginal estrogen in the postpartum period with those using placebo. Secondary aims of this study include assessment and comparison of vaginal/perineal pain, quality of life, incontinence and sexual function between the two groups as well as treatment satisfaction. Patients will report adverse reactions in all groups for evaluation of safety.

### **SPECIFIC AIMS**

The overall goal of this study is to determine whether there are benefits to use of low-dose vaginal estrogen in the postpartum period. Dyspareunia and vaginal/perineal pain are well-known sequelae after vaginal delivery. However, the contribution of postpartum vaginal atrophy to these issues is largely unknown. Although the relationship between lactation, relative estrogen deprivation, and vulvovaginal atrophy has been established, there is a paucity of data regarding on the prevalence of vulvovaginal atrophy symptoms in the postpartum period. Additionally, although the benefits of vaginal estrogen in postmenopausal atrophy are well-established, the benefits in the postpartum period are unknown.

Recent studies investigating postpartum dyspareunia and pelvic pain have largely gathered data from patient questionnaires, timing of return to coitus, and measures of pelvic floor muscle function including vaginal resting pressure and pelvic floor muscle strength.<sup>1</sup> Only few studies have commented on the prevalence of postpartum vulvovaginal atrophy. Wisniewski and Wilkinson described a 17.2% prevalence of vulvovaginal atrophy in a prospective study of women at 4 weeks postpartum.<sup>2</sup> The authors noted dyspareunia was present in 80% of atrophic patients attempting coitus as compared to 12.9% of controls with mode of delivery comparable in both groups. While the study was not designed to determine efficacy, the authors described a therapeutic response with application of conjugated estrogen vaginal cream. Vaginal estrogen has been utilized in clinical practice for patients undergoing atrophic changes postpartum with pain and dyspareunia despite lack of data on its efficacy. Vaginal estrogen has also been used to treat persistent granulation present in vaginal repairs. Although anecdotally this treatment is beneficial, there are very few descriptions of its use in the postpartum period and no published comparative trials. It remains unclear whether the use of vaginal estrogen in the postpartum period is truly beneficial. Questions remaining to be answered include: Does vaginal estrogen improve postpartum vaginal atrophy? Does it improve healing of obstetrical lacerations? If so, does it also improve pain, incontinence and sexual function during this period? We seek to perform a randomized placebo-controlled trial to evaluate the effect of local vaginal estrogen in the postpartum period to answer these questions.

**Specific Aim 1: To evaluate the feasibility (recruitment, retention and adherence to therapy) and preliminary efficacy of local estrogen on vulvovaginal atrophy in the postpartum period.**

**Hypothesis: Use of low-dose vaginal estrogen in the postpartum period will decrease postpartum vaginal atrophy and associated symptoms.**

We chose a validated measurement of vulvovaginal symptoms as our primary measure of vulvar atrophy. The Vaginal Vulvar Assessment Scale tools will be utilized during an exam at 6 weeks and 12 weeks. The tool also has a scale for physical exam findings associated with atrophy that will be recorded as well. Given most postpartum visits are scheduled at four to six weeks following a vaginal delivery for an uncomplicated

pregnancy and acute surgical wounds usually complete healing within two to four weeks, six weeks was deemed appropriate timing for vulvar assessment. The primary outcome for the study is Vulvar Assessment Scale (VuAS) at 6 weeks. Vaginal pH and maturation index will be obtained at follow up postpartum visits to further assess atrophy. Vaginal pH will be obtained in a standardized manner by swabbing indicator strips with pH range of 4.0 to 7.5 against the distal posterior vagina and interpreted by the examiner. Vaginal maturation will also be obtained via vaginal smears at the introitus and sent for quantitative assessment. Presence of granulation tissue and visible healing abnormalities such as suture line disruption, visible sutures, abscess, hematoma, and need for reoperation will be noted.

**Specific Aim 2: To estimate the effect of local vaginal estrogen in the postpartum period on perineal pain, quality of life, and sexual function.**

**Hypothesis: Use of low-dose vaginal estrogen in the postpartum period will improve vaginal and perineal pain, quality of life measures and sexual function.**

These will be assessed using validated questionnaires consisting of a visual analog scale for pain (VAS), Edinburgh Postnatal Depression Scale (EPDS), the Urinary Distress Inventory-6 (UDI-6), the Fecal Incontinence Severity Index for bowel symptoms (FISI), and the Female Sexual Function Index (FSFI). These questionnaires will be completed on day of randomization and postpartum visits at 6 weeks and 12 weeks.

**Specific Aim 3: To compare patient satisfaction, ease of product use, likelihood of continued use, and rates of adverse events for the vaginal estrogen and placebo groups.**

**Hypothesis: Use of low-dose vaginal estrogen in the postpartum period will have a higher treatment satisfaction rate when compared with placebo. The rate of adverse events between the groups will be similarly minimal.**

We will use a Likert scale to assess patient satisfaction, ease of product use, comfort, and likelihood of continued use. We will monitor for adverse events related or possibly related to local estrogen. All local estrogen and non-local estrogen adverse events will be recorded.

**Impact:** There is limited knowledge of dyspareunia and perineal pain postpartum and the role of vulvar and vaginal atrophy. Increased efforts to measure and improve postpartum sexual functioning can impact a substantial number of women suffering from these oftentimes lengthy symptoms. Given the psychological burden a patient can endure from pelvic floor pain, it is important investigate treatment options for women with perineal trauma in the postpartum period.

## **RESEARCH STRATEGY**

### **A.SIGNIFICANCE**

The postpartum period is a challenging time that requires a balance of physical, social, and psychological changes. It is characterized by such challenges as lack of sleep, fatigue, pain, breastfeeding, depression, stress, lack of sexual desire and urinary incontinence.<sup>3</sup> The majority of women in the United States do not interact with a health care provider after discharge until the first postpartum visit 4 to 6 weeks following delivery. Because of this, many postpartum complaints may not be addressed in the limited time available. The postpartum period is not well defined but considered to last between 4 to 6 weeks following delivery during which anatomical and physiological changes return to the non-pregnant state.<sup>4</sup> This time frame likely represents historical traditions, as studies have demonstrated peripartum effects are present months after delivery.<sup>5</sup> Evidence-based studies of optimal maternal postpartum management are lacking and clinical recommendations are often based on expert opinion and observational studies.<sup>6</sup> Recent data on urinary and

sexual functioning postpartum have been important in investigating some of the health domains significant to women during this period.<sup>7</sup>

The prevalence of postpartum sexual dysfunction in women has been noted to be 41-83% in the first 2 to 3 months after delivery.<sup>8,9</sup> In addition to obstetrical factors, fatigue, stress, partner, body image, breastfeeding, and hormonal changes contribute to sexual functioning postpartum.<sup>10</sup> In a secondary analysis of 2,748 primiparous women, specific risk factors for dyspareunia identified at 6 months were breastfeeding, perineal pain, fatigue and stress.<sup>11</sup> Women breastfeeding at 6 months were 2.89 times more likely (95% confidence interval [CI] 2.33-3.59,  $P < .001$ ) to report dyspareunia compared to non-breastfeeding women. These results underscore the potential impact of lactation on vulvovaginal atrophy and sexual functioning postpartum. Furthermore, 32.5% of participants reporting perineal pain at 1 month were 2.45 times more likely (95% CI 1.93-3.10,  $P < .001$ ) to report dyspareunia at 6 months. Increased efforts to measure and improve postpartum sexual functioning can impact a substantial number of women suffering from these oftentimes persistent symptoms. While studies have aimed at improving the understanding of postpartum maternal morbidities as well as severity and persistence of symptoms contributing to sexual function, few studies have evaluated treatment options.

Clinical use of vaginal estrogen and associated research have been limited mostly to the genitourinary syndrome of menopause, described as the symptoms and signs of the genital system resulting from decreased estrogen levels, including vaginal or vulvar dryness, burning, dyspareunia, or dysuria, urgency or frequency.<sup>12</sup> A 2014 systematic review of 44 studies of vaginal estrogen for women with genitourinary syndrome of menopause described improved dryness, dyspareunia, urinary urgency, frequency, stress urinary incontinence, and urgency urinary incontinence compared with placebo.<sup>13</sup> In addition, the authors found that vaginal estrogen also decreased urinary tract infection rates. While there is minimal research regarding the use of vaginal estrogen in the postpartum period, it is commonly done in obstetric practice. Because vulvovaginal atrophy can be present in both menopausal and postpartum states, it is reasonable to assume that many of the benefits seen with vaginal estrogen use in menopausal women may translate to postpartum use as well.

As a pilot intervention study for vulvovaginal symptoms in postpartum women with perineal injury, we seek to study the effects of local estrogen on postpartum vulvar symptoms utilizing validated scales and objective biomarkers. Ultimately, we anticipate this study will contribute to treatment of dyspareunia and vulvar atrophy.

## **B.INNOVATION**

The mechanisms of estrogen deficiency and local estrogen on vulvar and vaginal tissue have been described previously. Local vaginal estrogen has been accepted for treatment vulvovaginal symptoms in postmenopausal patients. By applying local estrogen to postpartum patients with a similar physiological state of estrogen deficiency, we anticipate improvements in symptoms of vulvovaginal atrophy. In our pilot randomized controlled trial of a commonly used vaginal estrogen cream, we will gather initial rigorous evidence to evaluate if this treatment is appropriate for resolution of vulvar symptoms in the immediate postpartum period.

## **C.APPROACHES**

**C.1. Specific Aim 1: To evaluate the feasibility (recruitment, retention and adherence to therapy) and preliminary efficacy of local estrogen on vulvovaginal atrophy in the postpartum period**

### **Background, preliminary results and rationale**

In a 2014 systematic review of local estrogen use for genitourinary symptoms in postmenopausal women, no differences were found in efficacy or safety between different vaginal estrogen preparations at typical dose and frequencies for vaginal dryness, itching or burning, atrophy-related dyspareunia, dysuria, urgency, frequency, nocturia, and incontinence (Rahn et al). Estrogen vaginal delivery methods including cream, tablet, ovule, suppository or ring are typically influenced by cost, ease of application, and patient preference. Estradiol

(Estrace®) cream will be utilized for the study given its extended use at the clinic sites. Participants will be given instructions for estradiol (Estrace®) cream at the initial clinical starting dose of 1g twice weekly. To our knowledge there has been no previous rigorous evaluation of local estrogen in the postpartum period.

## Research Design

This is a pilot randomized, placebo-controlled trial at a single academic center to examine the feasibility of use and preliminary efficacy of local estrogen in women with perineal injury in the immediate postpartum period. We will be assessing symptoms and physical findings associated with vulvovaginal atrophy, perineal pain, quality of life, and sexual function at 6 weeks and 12 weeks. Prior to enrollment, all patients with a term pregnancy will have been admitted to Ohio State University Wexner Medical Center and will have undergone obstetrical care as provided by their primary care team for a vaginal delivery at term. Once the patient has been cleared for transfer to the postpartum unit, a member of the study team (study nurse or coordinator) will introduce the study and, if the patient agrees, will assess her for eligibility and enrollment prior to discharge. If the participant is eligible and agrees to participate, written consent will be obtained and she will be enrolled in the study.

**Inclusion criteria:** females  $\geq 18$  years old with at least one prior prenatal care appointment affiliated with The Ohio State University Wexner Medical Center; nulliparous; 1-2 days status post  $\geq 37$  weeks and 0 day vaginal delivery with at least a second degree perineal laceration; English-speaking and able to provide informed consent.

**Exclusion criteria:** allergies to estradiol cream or its constituents; a current or previous diagnosis of estrogen-dependent breast cancer; inability to complete questionnaires in English or comply with study protocol; and inability to apply vaginal cream independently.

## Randomization

Randomization to either Estrace® cream for use 1g twice weekly or placebo cream for use 1g twice weekly will be implemented in the study's electronic data capture system, REDCap. Participants will be randomly allocated to the treatment arms in a 1:1 ratio. The randomization scheme will be stratified by degree of obstetrical laceration: 2<sup>nd</sup> degree laceration or 3<sup>rd</sup>/4<sup>th</sup> degree laceration. Third and fourth degree lacerations, referred to as obstetric anal sphincter injuries, are less frequent but more often associated with increased risk of fecal and urinary incontinence, pain, and sexual dysfunction, potentially impacting study outcomes. The allocation scheme will be balanced between treatment groups by permuted blocks of varying size. The scheme will be developed by the study statisticians (Dr. Hade and Mr. McLaughlin) and will remain blinded to study PIs, treating physicians, and those collecting final outcome measures, and study staff where possible.

The **primary outcome** will be a comparison of the clinical scores as assessed by the Vulvar Assessment Scale (VuAS) at 12 weeks postpartum in the vaginal estrogen and placebo groups. The VuAS has been utilized as a brief clinical measurement to identify vulvovaginal symptoms in patients with atrophic vaginitis and genitourinary symptoms of cancer survivors.<sup>14,15</sup> The VuAS is a four-item measurement administered by a clinical provider that quantifies and rates the patient's responses to questions of dryness, soreness, irritation and pain to external stimulation. Patients are asked whether they have experienced specific symptoms ("yes/no") during the past 4 weeks and rate symptom severity ("none," "mild," "moderate," "severe"). The first 3 items assess dryness, soreness, and irritation during routine activities excluding sexual intercourse and the fourth item assesses pain with external manual stimulation. An option for "no attempt" indicates a patient has not been sexually active within the past 4 weeks. The VuAS also contains a physical exam component that evaluates the external genitalia, including the labia minora, labia majora, clitoral hood, clitoris, and perineum. The administering physician can provide clarification as needed and a diagram can be used to educate patients regarding anatomy. Each item in the VuAS is scored from 0 (none) to 3 (severe) with composite scores calculated by taking the mean of the items when at least two of four items are not missing.

Higher scores indicate worse symptoms. Considering the first three items focus on vulvar health as compared to sexual function specifically, two composite scores will exist for each group. The alternative score will only include a composite score of items 1 to 3 as patients may have missing scores if answering “no attempt” for item 4. The VuAS has been demonstrated to assess change in self-reported measurement of atrophic symptoms. In a randomized trial of estradiol vaginal tablets and hyaluronic acid sodium salt in symptomatic postmenopausal women with atrophic vaginitis, the VuAS noted a significant decrease in symptoms after an 8-week treatment course. In a validation study of VuAS as well as the Vaginal Assessment Scale (VAS) in cancer survivors, a strong correlation was observed between VAS dyspareunia and Female Sexual Function Index (FSFI) pain with intercourse. Additionally, increased severity of symptoms on VAS and VuAS were correlated with worse pain on exam, worse functioning on FSFI pain, lubrication, worse vulvar irritation, and worse total scores. The VAS tool is a secondary measure that will be scored at the same time points: 6 weeks and 12 weeks. In addition to the VuAS, a pelvic exam will be performed and will include obtaining vaginal pH and maturation index in a standardized manner as it is a validated measure of urogenital atrophy and vaginal health.<sup>16</sup> Presence of granulation tissue and visible healing abnormalities such as suture line disruption, visible sutures, abscess, hematoma, and need for reoperation will be noted.

**Other patient characteristics to be collected** will include baseline demographics and delivery characteristics, gathered from the patient's electronic medical record including: age, race, past medical, surgical obstetric and gynecologic history, and delivery variables including infant birth weight at delivery, chorioamnionitis, duration of ruptured membranes, duration of second stage, operative delivery, degree of laceration, and plan for breastfeeding.

### **Treatment administration**

Instructions will be given to patients at the time of their hospital admission following their delivery but prior to hospital discharge. Only Estrace® cream will be used to avoid influence of different types of estradiol products available. They will be asked to follow directions of cream application 1g twice weekly to simulate “real world use.” Participants in the **vaginal estrogen protocol** will be given instructions to administer Estrace® cream 1g as measured by plastic applicator calibrated to 1g increments to a maximum of 2g. The Estrace® cream will be placed intravaginally twice weekly manually. Refill tubes will be given at follow up visits. Participants will return to the office at 6 weeks and 12 weeks and evaluated by a Female Pelvic Medicine and Reconstructive Surgery specialist part of the research team. Participants in the **placebo protocol** will be given a vaginal cream alongside a plastic applicator calibrated to 1g increments with instructions to administer 1g intravaginally twice weekly. Refill tubes will be given at follow up visits. Participants will return to the office at 6 weeks and 12 weeks and evaluated by a Female Pelvic Medicine and Reconstructive Surgery specialist part of the research team.

### **Statistical Methods**

#### *Sample size determination and recruitment*

Based on preliminary data, it is expected that approximately 560 nulliparous births with at least a 2<sup>nd</sup> degree laceration will be observed at the Wexner Medical Center from our generalist clinic in one year providing nearly 50 potentially eligible births to screen each month. Recruitment is expected to last 4-6 months. Consistent with our goals to evaluate preliminary efficacy and the feasibility of recruiting, retaining and monitoring of patient adherence to therapy our study sample size is based on more lenient criteria than would be expected in a definitive randomized trial. Very preliminary evidence for the primary endpoint, VuAS suggests that the average scores in those untreated would be on average 0.8 (sd=0.8) (Eaton et al). We reasonably expect to be able to recruit and fund the treatment for up to **70 participants, randomized, 1:1**. Assuming 20% attrition of those initially randomized at the 6 week follow-up, 35 patients will complete their 6-week follow-up visit. We would have 80% power to reject the null hypothesis of equal means with 10% two-sided type I error for a 50% reduction in the VuAS score. This larger type I and II error rates are reasonable for a pilot efficacy evaluation.

#### *Analysis plan*

Demographic and baseline characteristics of all participants will be summarized and presented overall and by assigned treatment group. We would expect approximate balance of observed and unobserved participant characteristics between study groups. Any chance imbalance in characteristics known to be related to primary or secondary outcomes will be considered as adjustment variables in outcomes analyses. Analysis of the primary outcome, VuAS at 6 weeks, will be compared regardless of treatment adherence or dose of intervention received (intent to treat analysis, (ITT)). Primary efficacy analysis comparing VuAS scores at 6 weeks between the randomized groups will be estimated via linear regression, adjusting for stratification factor of laceration degree. Further analysis will consider adjustment for chance imbalances in key patient characteristics. Secondary analyses will investigate the VuAS at later time points, through linear mixed models or linear generalized estimating equation models (GEE), accounting for correlation over time. Recruitment screening counts, refusal rates, and retention rates will be reported overall and by treatment group. All statistical analysis will be performed using SAS or STATA. Data will be presented according to CONSORT 2010 guidelines for randomized controlled trials.

#### *Data capture*

All study data will be collected using standardized electronic case report forms (CRF)s in REDCap. The study team (PIs and study statisticians) will develop CRFs for data capture for both patient reported and data abstracted from the medical record. Dr. Hade and Mr. McLaughlin will monitor all incoming data, with particular attention to: 1) enrollment and follow-up reports as entered into the database, 2) potential adverse events, and 3) missing data (for complete visits and for particular items) or extreme values. Regular reporting to the study team will work to reconcile or report issues as needed and to monitor participant retention.

#### **Pitfalls and Solutions**

Study limitations include retention difficulties and compliance issues. Dropout will be minimized by telephone or text reminders one week prior to patients' scheduled postpartum visit and attempts will be made to schedule study visits on same day of routine obstetrical postpartum visits for the first follow up visit. Eligible patients will also include only patients with a history regular prenatal care by an obstetrician with offices affiliated with the Wexner Medical Center. If participants are unable to attend their scheduled visit, a phone interview will be conducted to fill out questionnaires. In addition, patient adherence to twice weekly application in vaginal estrogen and placebo groups will be noted. Again text reminders will be used to encourage compliance. Patients will be asked about adherence at each follow up visits and reasons for discontinuation or deviation from instructions will be noted.

#### **Specific Aim 2: To estimate the effect of local vaginal estrogen in the postpartum period on perineal pain, quality of life, and sexual function.**

#### **Background, preliminary results and rationale**

In order to effectively evaluate the impact of each group on perineal pain, quality of life, and sexual function in the early postpartum period, we will administer baseline and follow-up questionnaires. Changes will be assessed using validated questionnaires consisting of a visual analog scale for pain (VAS) and Edinburgh Postnatal Depression Scale (EPDS). Researchers in the field of Female Pelvic Medicine and Reconstructive Surgery have also created several validated questionnaires to assess these measures. We will be able to objectively assess quality of life by using the following validated questionnaires: The Urinary Distress Inventory (UDI-6), the Fecal Incontinence Severity Index for bowel symptoms (FISI), and the Female Sexual Function Index (FSFI). These questionnaires have consistently been used in landmarks trials in the assessment of female pelvic floor disorders.

#### **Research Design**

1. *Perineal pain*: The **VAS** scale ranges from 0 to 100 with 100 indicating maximum pain.



2. *Quality of Life measures*: The **EPDS** is a validated 10-question depression assessment for postpartum women, which includes anxiety symptoms and excludes constitutional symptoms associated with depression common in the postpartum period, such as changes in sleeping patterns. Each question is given a score of 0 to 3 and a total score of at least 10 indicates minor or major depression at the time of the patient's follow-up; The **UDI-6** is a questionnaire that includes 6 items evaluating bother from urinary symptoms with higher scores indicating more bothersome symptoms; The **FISI** evaluates patient responses symptom severity to fecal incontinence with higher scores indicating more bothersome anal incontinence symptoms.

3. *Sexual function*: The **FSFI** is a validated questionnaire to assess sexual function in six domains of sexual function, including desire, arousal, lubrication, orgasm, satisfaction, and pain over the 4 weeks prior to administration of questionnaire with lower scores indicating more sexual dysfunction.

**Questionnaires will be administered to all groups at baseline enrollment and clinic encounters at 6 weeks and 12 weeks. See Fig 1.**

### **Statistical Analysis**

Similar to analyses proposed in Aim 1, secondary endpoints will be analyzed via generalized linear mixed models or linear generalized estimating equation models (GEE), adjusting for stratification factors and accounting for correlation over time.

### **Anticipated results**

Assuming an improvement in perineal symptoms associated with vulvar atrophy with local estrogen use, patients will have a significant improvement in perineal pain, quality of life, and sexual function.

### **Pitfalls and Solutions**

Again retention and compliance is a concern in the postpartum period. Strategies including telephone and text reminders will be utilized. If patients are unable to attend their follow-up visit, a study member will call the patient and record the patient's responses.

**Specific Aim 3: To compare patient satisfaction, ease of product use, likelihood of continued use, and rates of adverse events for the vaginal estrogen and placebo groups.**

### **Background, preliminary results and rationale**

In order to effectively evaluate the impact of each group on satisfaction and ease of product use and likelihood of continued use of vaginal estrogen and placebo group, we will administer global rating scales. Global ratings of satisfaction have previously been found to have acceptable validity for measuring outcomes in studies of treatment for urinary incontinence.

### **Research Design**

1. *Satisfaction and ease of use*: These outcomes will be assessed with Likert scales collected via RedCap at weeks 6 and 12. Satisfaction will be assessed using the patient satisfaction questionnaire, with responses of "completely," "somewhat," and "not at all," in response to the question, "How satisfied were you with your progress with this treatment?" In a similar fashion, ease of usability will be scored be assessed on a score of 0, 1, 2, 3, 4, 5, and 6, correlating to the following responses of "strongly disagree," "disagree," "slightly disagree," "neither agree nor disagree", "slightly agree," "agree," "strongly agree" to the statement, "This product was easy to use."

2. *Likelihood of continued use*: This will be assessed at the end of the study intervention with a 7-point Likert scale at weeks 6 and 12. This will be assessed on a score of 0, 1, 2, 3, 4, 5, and 6, correlating to the following responses of "strongly disagree," "disagree," "slightly disagree," "neither agree nor disagree", "slightly agree," "agree," "strongly agree" to the statement, "I plan to continue using this product."

3. *Adverse events (AEs)*: Potential AEs of interest include vaginal pain attributed to cream placement, vaginal infection, wound separation, and urinary tract infection. Breast myalgia and breastfeeding practices will be noted. Participants will be instructed to call and report any/all adverse events to research personnel and clinical staff. All AEs will be reported to the IRB of the institution at which the AE occurred, recorded in the research database and if needed the patient will be seen for a clinical assessment. At each clinical/research visit the participant will be asked about any adverse events. AEs will be reported with study outcomes.

**Questionnaires will be administered to vaginal estrogen and placebo groups at clinic encounters at 6 weeks and 12 weeks. See Fig 1.**

### **Statistical Analysis**

Similar to analyses proposed in Aim 1, secondary endpoints will be analyzed via generalized linear mixed models or linear generalized estimating equation models (GEE), adjusting for stratification factors and accounting for correlation over time.

### **Anticipated results**

Assuming an improvement in perineal symptoms associated with vulvar atrophy with local estrogen use, patients will have higher scores in satisfaction and likelihood of continued use compared to placebo group. Ease of use global rating will likely be similar in vaginal estrogen and placebo groups.

### **Pitfalls and Solutions**

Again retention and compliance is a concern in the postpartum period. Strategies including telephone and text reminders will be utilized. If patients are unable to attend their follow-up visit, a study member will call the patient and record the patient's responses.

## **D. RIGOR AND REPRODUCIBILITY**

All participants will be postpartum women with a perineal laceration following a vaginal delivery at Wexner Medical Center. Wexner Medical Center has approximately 5,000 deliveries per year. It is a large, multidisciplinary academic medical center that delivers superior quality care to a diverse urban population of patients. Columbus, Ohio is the fifteenth largest city in the United States and is home to a population representing 134 nations and speaking 105 languages. In addition, The Ohio State University (OSU) Divisions of Obstetrics and Gynecology represents a diverse team of faculty, residents, and fellows dedicated towards improving women's health through evidence-based care, research, and education. As an institution, OSU Wexner Medical Center has long been supportive of leadership in research and excellence in patient care.

Estrace® cream is currently available for the treatment of genitourinary symptoms of menopause. We anticipate other clinicians will have similar results in their population.

## **E. HUMAN SUBJECTS**

The three main commercially available preparations for vaginal estrogen in the United States are cream, ring, and tablet. Vaginal creams include a 17 $\beta$ -estradiol vaginal cream and a conjugated estrogen cream. The use of the Estrace® cream or estradiol vaginal cream has FDA-approved for the treatment of vulvovaginal symptoms of atrophy due to menopause. In regards to this study, Estrace® cream has not been FDA-approved for the use of genitourinary symptoms of atrophy in postpartum women with perineal lacerations. However, vaginal estrogen has been utilized in clinical practice to improve vulvovaginal atrophy and wound healing postoperatively in vaginal reconstructive surgery and cases of mesh erosion and exposure. As compared to its alternatives, a 2014 systematic review of 44 studies of vaginal estrogen for women with genitourinary syndrome of menopause found various local estrogen preparations had similar efficacy and safety with extremely rare cases of hyperplasia and adenocarcinoma with up to 1 years of use in postmenopausal women. There were no cases of venous thromboembolism or breast cancer reported

comparing vaginal estrogen with placebo. Studies demonstrate low-dose vaginal estrogen use does not result in sustained serum estrogen levels exceeding normal menopausal range.<sup>17</sup> Studies have also not demonstrated an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or prior history of breast cancer who use vaginal estrogen for genitourinary symptoms.<sup>18</sup> However, given vaginal estrogen is considered second-line treatment for urogenital symptoms of menopause in patients with breast cancer or prior history of breast cancer, these patients will be excluded from our study. Topical vaginal estrogen cream has demonstrated low levels of systemic absorption with no detectable effect on coagulation proteins or incidence of venous thromboembolism. Local estrogens bypass the gastrointestinal conversion of estradiol to estrone with less increase in triglyceride levels, clotting factors, and globulins.<sup>19</sup>

We do not anticipate an impact on lactation supply or practices given the lack of sustained increased serum estradiol levels in prior studies. Furthermore, in a systematic review of estrogen-containing contraceptives among breastfeeding women, the authors note an inconsistent impact of estrogen-containing contraceptives on breastfeeding when initiated prior to 6 weeks postpartum. In fact, the authors highlight a fair quality study demonstrating no impact on supplementation or breastfeeding continuation of estrogen-containing contraceptives when compared to progesterone-only pills.<sup>20</sup>

This study will only include female participants who are at least 18 years old. We will not limit the study based on race, unless unable to provide consent in English, as all patients who will undergo a vaginal delivery with subsequent perineal laceration at Wexner Medical Center will be taken into consideration for eligibility

### **IRB Approval**

This study is currently approved by the Ohio State University Wexner Medical Center IRB.

## **F. EVALUATION CRITERIA AND PROGRESS**

### **Study Visits**

The participants will be randomly assigned to estrogen cream or placebo for 12. The primary outcome is difference in tissue quality via the VuAS at 6 weeks between patients randomly assigned to vaginal estrogen versus placebo cream. Secondary outcomes will compare the effect of local estrogen on: VuAS at 6 and 12 weeks, the VAS at 6 weeks and 12 weeks, perineal pain, quality of life, and sexual function as measured by validated questionnaires in the field of Female Pelvic Medicine and Reconstructive Surgery at 6 weeks and 12 weeks. Patient satisfaction and treatment continuation will be measured at each follow up visit. (Table 2: Study Assessment by Visit).

## **G.POINT OF CONTACT**

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<b>Aims</b>	<b>Evaluation</b>	<b>Baseline</b>	<b>Week 6</b>	<b>Week 12</b>
	Consent	X		
	Demographics	X		
<b>Aim 1</b>	Pelvic Exam		X	X

	VuAS		X	X
	VAS		X	X
	Vaginal pH		X	X
	MI		X	X
<b>Aim 2</b>	EPDS		X	X
	UDI-6		X	X
	FISI		X	X
	FSFI		X	X
<b>Aim 3</b>	Patient satisfaction		X	X
	Continued use		X	X

## STUDY TIMELINE

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14
IRB approval														
Recruitment														
Data Collection														
Data analysis														
Preparation of results														
Study Closeout														

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